CHARACTERISING THE QUALITY OF CLINICAL GUIDELINES, EPIDEMIOLOGY AND HEALTHCARE RESOURCE UTILISATION OF NEUROGENIC BLADDER

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ABSTRACT

Background and Aims: Knowledge on several key aspects of the neurogenic bladder (NGB) patient journey remain unknown. Accordingly, the aim of this research was to conduct an in-depth analysis of the prominent NGB clinical guidelines (CGs) and characterise the descriptive epidemiology and healthcare resource utilisation (HRU) of NGB in the UK.

Methods: (1) The AGREE II tool was used to appraise the quality of the National Institute for Health and Care Excellence (NICE), European Association of Urology (EAU) and International Consultation on Incontinence (ICI) CGs for NGB and the concordance of their recommendations were assessed. (2) Adults (≥19 years) with a definitive or probable diagnosis of NGB between 1st January 2004 and 31st December 2016 were included into a study using the Clinical Practice Research Datalink (CPRD) GOLD and Hospital Episode Statistics (HES) databases in order to determine their real-world patient characteristics and drug utilisation patterns. Furthermore, the level of HRU over 12 months and associated costs were calculated via a bottom-up approach (ISAC protocol number 17_207RMn).

Results: NICE scored 92%, the EAU scored 83% and the ICI scored 75% in the AGREE II appraisal. The CGs place differing emphasis on costs and expert opinion, which translated in notably different recommendations. Amongst many important findings, the CPRD study revealed evidence of diagnosis error in NGB, a high level of comorbidities 8.6 (SD,7.6), polypharmacy 5.2 (SD,4.8), an Anticholinergic Cognitive Burden (ACB) score of 6.6 (SD,5.9), and substantial HRU (overall costs £2,395 per annum).

Conclusions: Improving the applicability and incorporation of comparative effectiveness research (CER) is crucial to ensure uptake of CGs and efficiency in clinical practice. It is also imperative that the underlying evidence base is strengthened, and cross-speciality interactions enhanced in order to guide more robust and consistent recommendations in future publications. Furthermore, policy makers should be aware of the substantial burden of complications, polypharmacy, comorbidity, anticholinergic burden and HRU associated

with NGB, and modifications to CGs should be introduced to aid in optimal management of these issues.

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ABBREVIATIONS

5-ARIs: 5α-Reductase Inhibitor

ACB: Anticholinergic Cognitive Burden

AD: Alzheimer's disease

AE: Adverse event

AEC: Anticholinergic Effect on Cognitive

AGREE: Appraisal for Guidelines Research and Evaluation

AMR: Antimicrobial resistance

APC: Admitted Patient Care

APN: Acute pyelonephritis

AUS: Artificial urinary sphincter

BBB: Blood Brain Barrier

BC: Base case

BMM: Bladder Management Method

BNF: British National Formulary

BOO: Bladder outlet obstruction

BPH: Benign prostatic hyperplasia

BTX-A: Botulinum toxin A

CAUTI: Catheter associated urinary tract infection

CCG: Clinical Care Commissioning Group

GDG: Guideline Development Group

CDSS: Clinical Decision Support Systems

CEA: Cost Effectiveness Analysis

CER: Comparative Effectiveness Research

CG: Clinical guideline

CKD: Chronic kidney disease

CNS: Central Nervous System

COI: Cost of Illness

CPRD: Clinical Practice Research Datalink

DELBI: Deutsches Instrument zur methodischen Leitlinien-Bewertung

DSD: Detrusor sphincter dysynergia

DUR: Drug utilisation research

EAU: European Association of Urology

EBM: Evidence Based Medicine

EHR: Electronic healthcare record

EMA: European Medicines Agency

ER: Extended release

FCE: Finished Consultant Episode

GLIA: GuideLine Implementability Appraisal

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HCAI: Healthcare associated infections

HCP: Healthcare professional

HES: Hospital Episode Statistics

HRG: Healthcare Resource Group

HRU: Healthcare resource utilisation

HRQoL: Health Related Quality of Life

HTA: Health Technology Assessment

IC: Intermittent catheter

ICC: Intraclass sorrelation

ICI: International Consultation on Incontinence

ICS: International Continence Society

ICUD: International Consultation on Urological Disease

IDUC: Indwelling catheterisation

IndUC: Indwelling urethral catheterisation

IMAGINE: Impact Assessment of Clinical Guidelines Implementation and Education

IR: Immediate release

ISAC: Independent Scientific Advisory Committee

LOS: Length of stay

LUTD: Lower urinary tract dysfunction

M (receptor): Muscarinic

MA: Marketing authorisation

MCI: Mild cognitive impairment

MESH: Medical Subject Headings

MHRA: Medicines and Healthcare Products Regulatory Agency

MMSE: Mini Mental State Examination

MS: Multiple sclerosis

MSA: Multiple system atrophy

NDO: Neurogenic detrusor overactivity

NGB: Neurogenic bladder

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NLUTD: Neurogenic lower urinary tract dysfunction

OAB: Overactive bladder

OCEBM: Oxford Centre of Evidence-Based Medicine Levels of Evidence

OPCS: Surgical Operations and Procedures

OTC: Over-the-counter

PD: Parkinson's disease

PDD: Parkinson's disease dementia

PFMT: Pelvic floor muscle training

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: Prospective Register of Systematic Reviews

QALY: Quality Adjusted Life Year

QoL: Quality of Life

QUOROM: Quality Reporting of Meta-Analysis

RCT: Randomised Controlled Trial

RV: Reflex voiding

RWD: Real World Data

RWE: Real World Evidence

SA: Sensitivity analysis

SARS: Sacral anterior root stimulation

SB: Spina bifida

SCI: Spinal cord injuries

SD: Standard deviation

SPC: Suprapubic catheter

SOC: Standard of care

SoMe: Social Media working group

SR: Systematic review

STK: Stroke

SUI: Stress urinary incontinence

SNM: Sacral neuromodulation

SNOMED CT: Systematised Nomenclature of Medicine Clinical Terms

UI: Urinary incontinence

UK: United Kingdom

USA: United States

USD: United States dollars

UTA: Urology Trade Association

UTI: Urinary Tract Infection

UTS: Up-to-Standard

VUR: Vesicouteral reflux

WHO: World Health Organisation

1) Chapter One - Background to the Study

1.1 Neurogenic Bladder

Neurological disorders are caused by damage or dysfunction to the central nervous system (CNS). They can cause major disability, premature death and cost a monumental amount to the healthcare system (Raggi and Leonardi, 2015; Thornton, 2018). Some of the common disorders and the typical phenotypic manifestations are described in Table 1.1. There is a great deal of heterogeneity within each disease, owing to differences in patient characteristics and varying disease stages and severity.

Table 1.1 Common neurological conditions and the typical symptoms

Neurological disorder	**Symptoms**
Parkinson's disease	Tremor, rigidity, bradykinesia, (slowness of movement), hypokinesia (decreased body movement), and akinesia (impaired unconscious movement).
Multiple sclerosis	Weakness, sensory loss, ataxia (voluntary coordination of muscle movements)
Stroke	Hemiparesis (numbness on one side of the body), confusion, speech problems, trouble walking, severe headache, sight problems
Spinal cord injury	Pain, fatigue, weakness or total paralysis of arms and/or legs
Spina bifida	Weakness or total paralysis of the legs

Adapted from (Dauer and Przedborski, 2003; Ben-Zacharia, 2011; Centre for Disease Control, 2018; Jensen et al., 2007)

Normal micturition involves a process of passive, low pressure filling of the bladder during the urine storage phase, whilst voiding necessitates bladder contraction. The process is fundamentally dependent upon the hierarchical neural circuitry, involving interaction

between the sympathetic, parasympathetic and somatic nervous systems. The neural signalling pathway mediating this process can become dysfunctional due to neurological diseases, such as those listed in Table 1.1; this is termed neurogenic bladder (NGB) (or neurogenic lower urinary tract dysfunction (NLUTD)) (Dorsher and McIntosh, 2012). NGB also occurs in numerous other neurological conditions including dementia, cerebral palsy and multiple system atrophy (MSA), amongst others (Bloc et al., 2017). The concept of NGB is relatively new, being known to medical professionals for around thirty years and consequently, knowledge in this field is constantly evolving (Persu, 2014).

Although NGB patients share the same diagnosis, they are notably unique in their urological symptoms and risk profiles because of differences in their underlying condition, location of neurological lesion, and stage and severity of disease (Apostolidis et al., 2017). Symptoms of NGB result from a complex interplay of pathophysiological features. The main manifestations include neurogenic detrusor overactivity (NDO), where individuals experience increased frequency of micturition, urinary urgency and urinary incontinence. This is usually the result of spastic, unexpected bladder contractions occurring through a lack of inhibition of the motor pathway or augmentation of sensory input and/or motor output (Cocos and Przydacz, 2018). Alternatively, the bladder may become flaccid and distended, ceasing to contract fully. In this case, patients experience problems in voiding, with symptoms including hesitancy, a slow urinary stream, straining and urinary retention. In some instances, both retention and voiding symptoms can arise in combination (Ginsberg, 2013).

1.1.1 Impact of Neurogenic Bladder to Patients and the Healthcare System

The multi-faceted and disabling nature of NGB has far-reaching effects, impacting many aspects of patient life. Serious systemic illnesses such as hydronephrosis (blockage of the renal collection system causing distention of the renal calyces), renal failure and septicaemia are amongst the multiple detrimental sequela associated with NGB (Patel et al., 2015; NHS, 2011; Gormley, 2010). The risk of renal dysfunction has lessened since the 1940's and 50's, however a recent study found that the incidence of chronic kidney disease

(CKD) was still three times higher in NGB patients in comparison to their healthy counterparts (Sung, 2016). This reveals that despite recent advances in medical care, serious complications remain an ominous threat to patients' health.

Bladder symptoms can be embarrassing and isolating, which has a substantial impact on health-related quality of life (HRQoL). Patients with multiple sclerosis (MS), spinal cord injuries (SCI), and Parkinson's disease (PD) have reported negative effects in physical function, emotional well-being and social relationships (Tapia et al., 2013). Furthermore, the symptoms and associated complications poses an economic burden across all realms of the healthcare sector; at an individual level and in primary, specialist, hospital and social care (Davis et al., 2016; Flack and Powell, 2015).

1.2 Clinical Guidelines in Neurogenic Bladder

The National Academy of Medicine (NAM) (formerly known as the Institute of Medicine (IOM)) was founded in 1970, under the charter of the National Academy of Sciences. The organisation comprises of 80 prominent members in the field of medicine and related disciplines (IOM, 2011). The NAM defined clinical guidelines (CGs) in 2011 as:

Statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options (Sox, 2014: 200).

Evidence-based medicine (EBM) involves the conscientious and reasonable application of the best modern evidence in clinical decisions. CGs are an important vehicle to introducing and establishing up-to-date EBM in clinical practice as well as reducing unwarranted variation in care (Masic et al., 2008). Accordingly, CGs are used by clinicians to keep abreast of new scientific advances and devise optimal management strategies for patients. They are also useful in empowering patients to upkeep their own health by allowing them to enhance their understanding of available treatments and the associated harms (Fearns et al., 2016).

Most CGs for NGB are developed by special interest groups for neurological conditions, for example those developed in the UK by Abrams et al (2008) for patients with SCI, and those by the Consortium for Spinal Cord Medicine (CFSCM) in the USA (CFSCM, 2006). Recommendations have also featured in scientific journal publications, such as the UK recommendations for NGB secondary to MS (Fowler, 2011). The most prominent and most utilised NGB CGs are those by the National Institute of Clinical Excellence (NICE) (NICE, 2012), the European Association of Urology (EAU) (Bloc et al., 2017), and the International Consultation on Incontinence (ICI) (Apostolidis et al., 2017) (Table 1.2). These CGs cover all types of underlying neurological conditions; therefore, can be applied in a wide range of clinical circumstances.

Table 1.2 Clinical guidelines for neurogenic bladder

Guideline Title	Institution	Year	Region
Neurologic Urinary and Faecal Incontinence	International Consultation on Incontinence (ICI)	2017	International scope
Clinical Guidelines on Neuro-Urology	European Association of Urology (EAU)	2017	European scope
Urinary Incontinence in Neurological Disease: Management of Lower Urinary Tract Dysfunction in Neurological Disease	National Institute for Health and Care Excellence (NICE)	2012	National scope (United Kingdom)

Developed from: NICE, 2012; Bloc, 2017; Apostolidis, 2017

In order to derive the most benefit for stakeholders and reduce the chances of harm to patients, it is important to appraise CGs to ensure they meet the key characteristics of what constitutes 'high quality'. In particular, assessing the comprehensiveness of the underlying evidence base, the process by which recommendations are created, and the feasibility of applying them to clinical practice is essential (Brouwers et al., 2010).

1.3 The Evidence Gap in Neurogenic Bladder

Randomised controlled trials (RCTs) are considered the gold standard for testing the efficacy of interventions because special effort is made to reduce multiple forms of confounding and bias. This means they are highly internally valid and allow for the sole investigation of the cause-effect relationship (Akobeng, 2005; Spieth et al., 2016). A recent systematic review (SR) showed a very low number of RCTs conducted from 1976 (earliest recorded NGB RCT) to 2014, furthermore, the studies were too heterogenous to derive solid conclusions on optimal management practices (Persu, 2014) (Section 4.7.1).

Despite the merits, RCTs also beset with a number of problems, one of the principal issues being their low external validity (generalisability outside of the study setting), arising as a result of the constricted patient inclusion criteria and artificial study settings (Jones et al., 2017). As CGs are designed to be applied in real-world practice, it has been argued that the concern for external validity should be equally as great as that for internal validity. Therefore, real world evidence (RWE) (observational data), which represents the reality of healthcare delivery should be given elevated importance when formulating recommendations (Rosner, 2012). Accordingly, in order to strengthen the recommendations that appear in the NGB CGs, increased research effort should be focused on generating knowledge beyond the traditional sphere of RCTs. This is especially apt in this disease area, where there are obstacles to conducting RCTs because of the vulnerable patient populations, for example, children, the elderly and patients with cognitive deficits and comorbidities (Apostolidis et al., 2017; Denys et al., 2006).

Descriptive epidemiological studies, a particular type of RWE, are an important gateway into more hypothesis driven real-world research in a disease area where little evidence exists. They also provide initial insights into how the management of the disease can be improved. Descriptive epidemiology includes prevalence estimates and frequency counts, which demonstrate the scale of the disease and can guide efforts towards supply management, and the targeting of education regarding diagnosis and treatment of urological complications (Gomelsky et al., 2018). Drug treatment patterns provide an insight into the care and attention physicians give to a particular group, acting as an indicator of physician attitudes towards the disease. They are also important in understanding how well recommendations are implemented in real world practice and thus, how CGs could potentially be improved. Furthermore, highlighting the current burden of disease (including rates of healthcare resource utilisation (HRU), complications and associated costs) aids in quantifying the magnitude of burden in NGB. This information can enlighten policy-makers on the resource intensive aspects of the disease, helping them to consider how healthcare budgets could be allocated efficiently and equitably to avoid unnecessary costs and ensure optimal outcomes for patients. Unfortunately, the only truly large-scale epidemiological study focusing on the NGB population was conducted in the USA, using data between 2002-2007 (Manack et al., 2011) (Section 4.7.1).

The comprehensiveness of the underlying evidence base is instrumental to the formation of high-quality recommendations; however, this chapter has established that there is a paucity of research conducted in NGB, both from a clinical and epidemiological research point of view. Consequently, the question arises as to whether this translates in implications for the quality of the current CGs. Many other factors also dictate whether CGs can be reliably applied in clinical practice, including the rigour of development, whether relevant stakeholders were involved in their creation and the clarity with which recommendations and supporting evidence is presented. A quality appraisal of NGB CGs has never been conducted, thus their potential value and effectiveness in current clinical practice remain unknown. Two previous studies have assessed the quality of similar CGs in the area of urology, however they exclude NGB, which has a distinct evidence base. There

may also be possible differences in development, and a calculation of interclass correlation, which is important to assess the level of agreement between appraisers, is not included.

With all of this in mind, this thesis will assess the quality of current NGB CGs to elucidate how well-equipped clinicians are to manage patients. A descriptive epidemiological study will also be carried out as the first step to characterising the UK NGB population. Through this research potential areas of improvements in the CGs and treatment pathway can be identified, which can incentivise further research, enhance health outcomes and introduce improved economic efficiencies in this critical patient group.

1.4 Aims of Research

There are two main aims to the proposed research, where the ultimate goal is to improve the awareness and understanding of this currently under-researched population and advance patient management through making recommendations for alterations to CGs and treatment practices.

Primary aim: Enhance the understanding of the current treatment landscape in NGB through the following objectives:

1. To critically appraise NGB CGs developed by NICE, EAU and ICI, using the Appraisal of CGs for Research and Evaluation (AGREE) II instrument (a specific tool designed to assess the quality of CGs).

2. To compare the treatment recommendations in NGB CGs in order to uncover the similarities and differences between the three institutions.

3. To undertake a SR to describe and characterise the treatment patterns and management strategies of NGB in real-world settings.

4. Conduct an epidemiological study using the UK Clinical Practice Research Datalink (CPRD) to describe the NGB patient demographics, comorbidities, complications, current patterns of drug use over 12 months.

Secondary aim: Enhance the understanding of current burden of disease of the NGB population through the following objectives:

1. To undertake a literature review to describe the HRU of NGB related to the symptomology, secondary complications of disease and management strategies.
2. Conduct an epidemiological study using the UK CPRD database to describe NGB related HRU and costs over 12 months.

1.5 Thesis Overview

Chapter 1 discussed the current gaps in knowledge in the NGB disease area. This included highlighting the impetus for quality appraisal of the current prominent CGs and a discussion of the dearth of clinical and epidemiological research. Accordingly, the aims of the research related to these topics were outlined.

Chapter 2 provides a detailed overview of NGB. The chapter begins by presenting prevalence estimates from around the world. It then proceeds to review the clinical classifications of NGB followed by complications related to the condition. Next, the particular importance of anticholinergic burden in patients with neurological conditions is discussed at length. The concepts of drug utilisation research (DUR) and HRU are introduced, as well as presenting a literature review of HRU in NGB.

Chapter 3 first includes an overview of CGs and their importance in clinical practice, and then presents a completely novel critical quality appraisal of the three most prominent CGs available for NGB (NICE, EAU and ICI) using the AGREE II instrument.

Chapter 4 compares and contrasts the treatment recommendations in the NICE, EAU and ICI NGB CGs and provides in-depth discussion around the evidence gap that currently exists in this disease area.

Chapter 5 presents a SR describing the real-world treatment patterns of NGB. The aim of this SR is to determine changes in practices over time, as well as compare the results to the recommendations in the current NICE, EAU and ICI CGs.

Chapter 6 presents the methodology for a descriptive epidemiological study using the CPRD database. This study aims to elucidate the patient characteristics, drug utilisation patterns and HRU in a UK patient population.

Chapter 7 exclusively presents the results from the CPRD study.

Chapter 8 discusses the findings from the CPRD study, particularly in the context of similar research and considers the strengths and limitations of the research.

Chapter 9 contains the summary, recommendations for future research and conclusions taking into account all of the research presented in this thesis.

2) Chapter Two - Background to the Disease Area

2.1 Introduction

The main objective of this thesis is to develop a comprehensive picture of the neurogenic bladder (NGB) population. In line with this, the following chapter gives a concise overview of several relevant aspects of NGB. Firstly, prevalence estimates from the literature are reported. Secondly, the clinical features and classifications are discussed; in particular, the most renowned classification system by the International Continence Society (ICS) is described in detail. Third, the major clinical complications related to NGB are described. Fourth, a brief overview of the impact NGB has on health-related quality of life (HRQoL) is presented. Fifth, the use of bladder muscarinic drugs as first-line treatment of NGB are discussed along with an assessment of risks and benefits of their use. Sixth, the concept of healthcare resource utilisation (HRU) is introduced and a literature review of the HRU and economic burden of NGB is presented. Lastly, the concept of drug utilisation research (DUR), a prominent theme in this thesis, is introduced.

2.2 Prevalence of Neurogenic Bladder

2.2.1 Definition and Importance

Prevalence is defined as:

The proportion of persons in a population who have a particular disease or attribute at a specified point in time or over a specified period of time (Centre for Disease Control [CDC], 2012: online).

This is distinct from the incidence rate, which only provides information on the number of new diseases or attributable cases (CDC, 2012). Chronic conditions such as NGB are best described using prevalence figures, as incidence underestimates the magnitude of the problem (Yamamoto, 2003).

Although it is true that estimates of the scale of disease can never directly equate to need, they are crudely but inexorably linked to issues connected with funding and effective healthcare planning (Ward, 2013). There is normally a relationship between the size of a population and the demand for healthcare, for this reason prevalence estimates are useful for defining actual or potential markets for the delivery of pharmaceuticals and healthcare services (Morris et al., 2007). Demographic descriptions of a population also can aid in market segmentation. For example, in the case of NGB stratifying the population by age, sex, and underlying neurological condition would be useful for targeting delivery of healthcare services accordingly, given the differing needs between these populations.

2.2.2 Prevalence of Neurogenic Bladder

The global aging population means that there is an increasing number of people living well into their 70s and beyond. In the UK, the population aged 85 and over has increased by 31% since mid-2005 (Henderson and Thilagarjah, 2016).

Despite the advancements in modern medicine, as population age increases the number of chronic conditions also continues to surge. According to the World Health Organisation (WHO), chronic diseases have surpassed infectious and parasitic diseases in becoming the leading cause of mortality and morbidity worldwide (a phenomenon known as the epidemiological transition) (McKeown, 2009). Over the years, we will continue to witness an increase in neurological conditions such as Parkinson's disease (PD), multiple sclerosis (MS), and stroke, and the rate of NGB will follow suit. The scale of elderly patients with multiple chronic conditions requiring long-term care will challenge healthcare systems across the globe, putting invariable pressure on budgets and resources. Accordingly, economic analyses of interventions and careful allocation of resources will become increasingly crucial as time goes on (MacLeod et al., 2017).

Neurological conditions currently account for between 4.5 to 11% of global disease burden. A lack of large-scale epidemiological research means that the overall prevalence of NGB within that population remains poorly understood (Ruffion et al., 2013). The small number

of estimates that do exist are highly variable, which is likely a reflection of a mix of limiting factors, such as the difference in populations sampled (different geographical areas) and the heterogeneity of patient samples (including variations in age, sex, disease severity etc.). The only large-scale real-world study conducted to address the epidemiology of NGB was in 2011 (study period between 2002-07), using a US claims database, containing over 30 million patient records. The researchers observed 46,271 patients with NGB and of those patients 9,315 patients had MS and 4,168 had spinal cord injuries (SCI) (Manack et al., 2011). The absence of data on the UK NGB population highlights the need for epidemiological research using data from a UK electronic healthcare record (EHR).

Rather than overall estimates, several epidemiological studies have reported the prevalence of NGB within specific neurological conditions. The studies have been conducted over differing periods and geographical regions. The prevalence estimates of the main neurological conditions that cause NGB are presented in the following sections and summarised in Table 2.1.

2.2.2.1 Multiple Sclerosis

The median prevalence of MS is highest in North America (140/100,000 population) and Europe (108/100,000), and lowest in East Asia (2.2/100,000), and Sub-Saharan Africa (2.1/100,000) (Leray et al., 2016). Estimates are also low in Ecuador, Colombia and Panama where 0.75–6.5/100,000 individuals live with MS (Przydacz et al., 2017). Consequently, the rate of NGB is also lower in developing nations in comparison to the Western hemisphere.

A systematic review (SR) conducted in 2007, reported a large variance in the occurrence of NGB amongst MS patients (32% to 96.8%). The varying times of examination from onset of MS and diagnosis was cited as a reason for the variance (de Seze et al., 2007). A separate SR found that prevalence of urinary incontinence (UI) amongst MS patients was 51% (Przydacz et al., 2017).

2.2.2.2 Parkinson's Disease

The prevalence of PD within the UK is 27.4 per 10,000 people, which when applied to the UK population as a whole is equivalent to 126,893 individuals (Parkinson's UK, 2009). Like MS, the prevalence of PD in developing countries tends to be a lot lower, subsequently, the occurrence of NGB will also be lower in these countries. For example, the rate is 16–27/100,000 in India and 7/100,000 in Nigeria (Przydacz et al., 2017).

Lower urinary tract dysfunction (LUTD) is present in 27-63.9% of PD individuals worldwide (Ruffion et al., 2013). The review also estimates that Multiple System Atrophy (MSA), which is often confused for PD in the early stages, has a virtually 100% prevalence rate of UI (Yeo et al., 2012).

2.2.2.3 Stroke

Stroke is one of the leading causes of adult physical disability worldwide (Murray et al., 2012). The stroke association estimated that 100,000 strokes occur every year in the UK (Stroke Association, 2016) Estimates of stroke in the developing world are scarce; however, occurrence is generally thought to be lower than in developed nations (Przydacz et al., 2017).

An SR estimated 22-47% of patients had urinary retention within 72 hours of acute stroke (Sayed, 2008). It is important to note that the studies included into the SR were heterogeneous, and prevalence of bladder dysfunction was dependent on the study group, the interval after stroke, and the criteria used to define retention (Sayed, 2008). Another SR found that 23.6% individuals that had experienced stroke subsequently developed UI (Ruffion et al., 2013).

2.2.2.4 Dementia

An SR found a 5%–7% prevalence of dementia in individuals aged 60 or over, in most regions of the world. The major anomalies were Latin America (8.5%), and sub-Saharan Africa (2%–4%) (Prince et al., 2013).

A study including 464 patients with probable Alzheimer's disease (AD) found a prevalence of 24.8% of incontinence in AD and more than 25% in other dementias, namely; Lewy body, Normal Pressure Hydrocephalus (NPH), Binswanger, Nasu-Hakola and Pick Disease (Na et al., 2015).

2.2.2.5 Spina Bifida and Spinal Cord Injuries

The prevalence of those with spina bifida and other congenital disease in the UK is 8-9 cases per 10,000 in patients aged between 10-69, with the highest prevalence in those aged between 25-29 years (Lawrenson et al., 2000). A cross-sectional study in the Netherlands found that 60.9% young adults with spina bifida suffered from UI (Verhoef et al., 2005).

The prevalence of traumatic SCI in some Asian countries is estimated to be between 236 and 464/1,000,000 (Przydacz et al., 2017). In the UK, 12–16 per million of the population live with SCI (NHS, 2013).

An SR identified 52.3% of individuals with SCI in the UK suffered from UI (Ruffion et al., 2013). In a prospective cross-sectional study conducted in India, researchers found the prevalence of UI in patients with non-traumatic SCI to be 31.25% (Gupta et al., 2009).

Table 2.1 Prevalence of common neurological disorders and bladder symptoms

Neurological disorder	Prevalence of neurological disorder	Prevalence of bladder symptoms
Multiple sclerosis	North America: 140/100,000 population, Europe: 108/100,000, East Asia: 2.2/100,000 population, Sub-Saharan Africa: 2.1/100,000, Ecuador, Colombia and Panama: 0.75–6.5/100,000	NGB: 32% to 96.8%, UI: 52%

Parkinson's disease	UK: 27.4 per 10,000, India: 16–27/100,000, Nigeria: 7/100,000	NGB: 27-63.9%, UI: 57-83%
Multiple System Atrophy	-	100%
Stroke	UK: 100,000 strokes per year	Urinary retention within 72 hours of acute stroke: 22-47%, within this group, detrusor areflexia: 75%, hyper-flexia: 25%. UI: 23.6%
Dementia	Most countries: 5%–7%, Latin America: 8.5%, Sub-Saharan Africa: 2%–4%	UI: 24.8%
Spina bifida	UK: 8-9 cases per 10,000	UI: 60.9%
Spinal cord injuries	UK: 12 – 16 per million Some Asian countries: between 236 and 464/1,000,000	UI: 52.3% India (non-traumatic SCI) UI: 31.25%

UI, urinary incontinence; NGB, neurogenic bladder; SCI, spinal cord injuries
Adapted from: Leray et al., 2016; Przydacz et al., 2017; de Seze et al., 2007; UK, 2009; Ruffion et al., 2013; Murray et al., 2012; Stroke Association, 2016; Na et al., 2015; Lawrenson et al., 2000; Gupta et al., 2009.

2.3 Clinical Features and Classifications

A good classification system ensures that patients are diagnosed accurately and therefore are recipients of appropriate care. Additionally, classification systems are a valuable tool in providing a structured framework for introducing new scientific findings and observations into the existing sphere of knowledge (Staskin and Wein, 2017).

Multiple classification systems exist to describe the distinct manifestations of NGB; some are based on urodynamic findings (functional tests that are used to determine the nature of LUTD) whilst others are based on neurological criteria. The most utilised and reputable

systems include the Krane and Siroky's, Lapide's, and Maddersbacher's. All systems come with their inherent advantages and disadvantages and at present, no system is advocated over another. These systems will continue to evolve and improve as greater evidence is generated on the complex interactions of the phases of micturition, bladder physiology and neurological processes (Staskin and Wein, 2017).

The current classification system created by the ICS and used in the International Consultation on Incontinence (ICI) clinical guidelines (CGs) focus on the nature of lesion and its location (Apostolidis et al., 2017) (Figure 2.1). This classification system provides an intuitive way to categorise the various types of NGB. From the descriptions below, it clear to see that NGB is a diverse and complicated condition, where symptomology is heavily influenced by the lesion of damage.

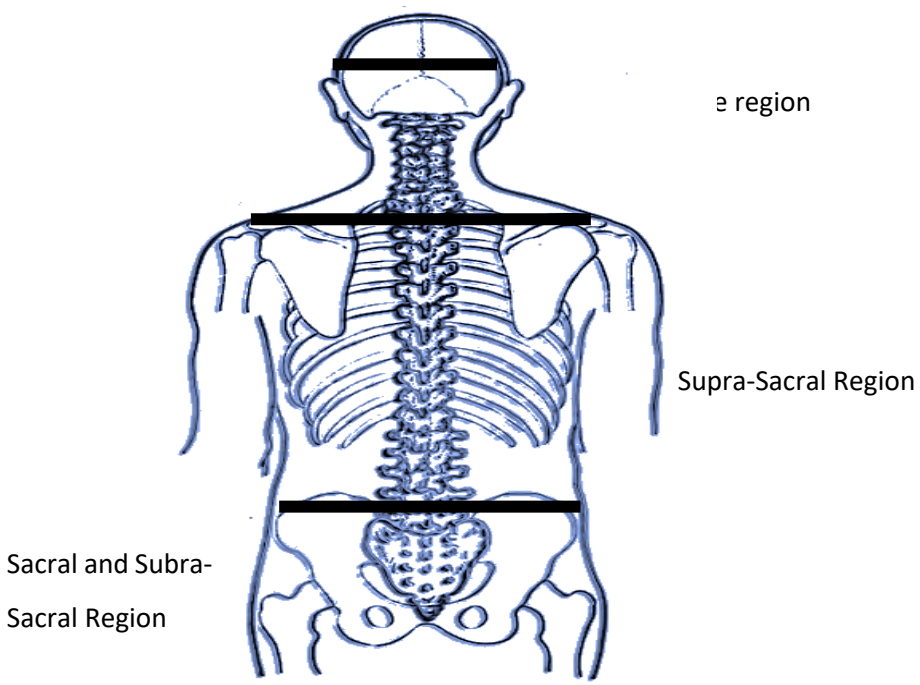


Figure 2.1 Regions of neurological lesion (Adapted from ThinkFirst, 2015)

2.3.1 Pontine Region

Lesions that occur in the pontine region, such as MSA are a rare occurrence. Urological dysfunction typically presents as neurogenic detrusor overactivity (NDO), where symptoms of frequency, nocturia, urgency and urge incontinence are common, and/or detrusor sphincter dyssynergia (DSD), where the urethral sphincter contracts at the same time as the bladder. The most frequent symptom is voiding (79%), followed by nocturia (74%), urgency (63%), urgency incontinence (63%) and urinary retention (8%) (Ciolli et al., 2014).

2.3.2 Supra-Pontine Region

Lesions that occur in the supra-pontine (above the pontine micturition center (PMC) located in the brainstem), may be as a result of progressive diseases such as dementia, MS and PD or stable conditions such as stroke (Game, 2010; Hashim and Dasgupta, 2017). Typically, lesions in this area cause NDO however detrusor underactivity in conjunction with NDO has also been reported (Apostolidis et al., 2017). Additionally, older men may experience bladder outlet obstruction (BOO) in conjunction with NDO, which simultaneously reduces or stops the flow of urine into the urethra (Oelke et al., 2008).

Urological symptoms are dynamic and tend to worsen with increasing decline in cognition and mobility, reflecting the advancing severity of the underlying neurological condition (Araki and Kuno, 2000; Game, 2010). For example, in the four stages of dementia, each of which represent a distinct decline in cognition, incontinence normally begins to develop in the third stage (moderate dementia) (Han, 2008). Relapsing-remitting MS (RRMS) accounts for around 85% to 90% of all cases of MS (Canadian Agency for Drugs and Technologies in Health, 2013). The pattern of LUTD is different within each period of disease; during periods of remission, urinary symptoms may be less severe or completely absent, however during a period of relapse, urinary symptoms worsen (Phé et al., 2016).

2.3.3 Supra-Sacral Spinal Region

Lesions which occur in the supra-sacral region, located between the pons and sacral cord and panel are either SCI or spina bidifa. Lesions may be either complete (total lack of sensory and motor function) or incomplete in nature (Apostolidis et al., 2017). Despite abnormal urodynamic tests, because of the lesser severity, patients with incomplete lesions tend to experience fewer urinary tract symptoms than individuals with complete lesions.

Complete lesions describe a state when the spinal reflex becomes unmodulated; causing NDO (Apostolidis et al., 2017). In conjunction to this, instead of the normal synchronisation of sphincter relaxation with bladder contraction, DSD occurs (Lawrenson et al., 2000). Bladder contractions are poorly sustained and voluntary control of the micturition reflex is lost (Apostolidis et al., 2017).

Anterior cord syndrome is another condition occurring in this region. It causes reduced or absent motor activity. In this type of injury, NDO is most likely to occur, and depending on the severity and location of cord injury, DSD may also be present (Apostolidis et al., 2017).

2.3.4 Sacral and Subra-Sacral Region

Sacral SCI is caused by lesions at the sacral region. Damage to the parasympathetic system is common and results in weak or absent detrusor contraction, known as detrusor areflexia (Yoshimura and Chancellor, 2004). Incontinence or stress urinary incontinence (SUI) may also result (Madersbacher, 2005; Apostolidis et al., 2017).

Similar symptoms can be seen when lesions occur in the subra-sacral regions, which include cauda equina syndrome or damage to the peripheral nerves as a result of infections such as cytomegalovirus and herpes, fractures or surgery. Peripheral neuropathies can occur in diabetes, alcohol abuse and Guillain-Barré syndrome and impairment to both the parasympathetic and somatic motor function are possible (Apostolidis et al., 2017).

2.4 Health Related Quality of Life in Neurogenic Bladder

HRQoL measures an individual's perception of their own health in relation to their social, psychological and physical well-being (Flokstra-de Blok et al., 2009). Understanding the additional dimension of burden that NGB has on several health-related aspects of an individual's life, can aid in devising better management strategies. This is especially important in a climate where patient-centred care is accumulating greater weight in healthcare decision-making (King and Hoppe, 2013).

In a study using the Kings Health questionnaire (KHQ) which measures attributes such as general health, physical limitations and personal relationships, HRQoL was found to be more negatively impacted in individuals with NGB in comparison to the idiopathic OAB population. Participants were also asked to complete the Incontinence Quality of Life questionnaire (I-QOL), which again demonstrated lower scores for NGB patients. This study shows that those with NGB view their LUTD differently to those with idiopathic OAB, hence management of these patients should also be distinct (Burks, 2011). A separate study showed that incontinence also has a detrimental impact on HRQoL. Incontinent NGB patients scored significantly lower on several OAB symptom scales and measures of activity impairment in comparison to their continent counterparts (Tang et al., 2014).

Studies have also demonstrated changes in Quality of Life (QoL) as a result of treatment strategies employed. One study showed that bladder augmentation resulted in significant improvements in QoL due to the perception of better health and resolution of UI (Lima et al., 2015). A separate study demonstrated improvements in QoL scores after intradetrusor injections of Onabotulinum-A (Kalsi et al., 2006).

2.5 The Clinical Burden of Complications of Neurogenic Bladder

A number of adverse sequelae can occur as a consequence of NGB, either as a result of the natural progression of the disease or due to side effects of treatments. The severity and nature of complications are often dependent upon the prominence of the underlying neurological condition. Complications increase morbidity, lower QoL and represent a

significant economic burden to both the patient and the healthcare provider, thus utmost effort should be made to reduce their occurrence and manage them appropriately (Gormley, 2010). This section will cover the clinical burden of complications, and the economic burden will be addressed separately (Section 2.7.1.4.1).

Vesicoureteral reflux (VUR) is one of the most frequent complications of NGB, observed in 20% of cases (Gormley, 2010). The condition is caused by high intravesical pressures as a result of the retrograde flow of urine from the bladder to the kidneys, leading to a number of further serious complications such as pyelonephritis, urinary tract calculi and hydronephrosis (Sillen, 2008; Wu and Franco, 2017). VUR in NGB is less likely to spontaneously resolve as it often does in idiopathic cases, therefore, to avoid long-term damage, it should be managed by restoring the intravesical pressure early on through management methods such as intermittent catheter (IC), anticholinergics or bladder augmentation (Santiago-Lastra and Stoffel, 2015; Wu and Franco, 2017).

Hydronephrosis is another serious complication of NGB, characterised by dilation of the renal collecting system that occurs because of a blockage (Groth, 2012). A study of 178 patients with myelomeningocele found a correlation between hydronephrosis and renal deterioration as well as the increased need for surgical intervention (Alpajaro, 2015).

Chronic urinary tract infections (UTIs) are another significant, and well-documented problem in NGB patients. High bladder pressures, immunocompromised status, and inadequate management with catheters put patients at particular risk. In the worst-case scenario, chronic infections can lead to renal insufficiency (Hsiao et al., 2015). MS patients in particular are at increased risk due to the immunosuppressive treatment regime used to manage their condition (Palma-Zamora and Atiemo, 2017).

Chronic UTI can disrupt the detrusor's normal anti-reflex mechanisms and lead to acute pyelonephritis (APN), a severe type of UTI emanating in the kidney (Paz, 2014). Complications can often exacerbate one another, and VUR in APN causes the reflux of infected urine which increases the risk for permanent renal scarring (Jakobsson et al., 1994; Ghoniem, 2006). Raz et al (2003) showed that 46% of women that were hospitalised for

APN had evidence of renal scarring. Urolithiasis (stone formation) is also potentiated by chronic UTI. Once a kidney stone has developed, the risk of developing a second stone within 5-7 years is around 50% (Parmar, 2004). Symptoms include fatigue, dysuria (painful micturition) and renal pain (Institute for the Study of Urologic Diseases, N.D.).

All of the complications described above are risk factors for renal failure (end stage CKD). Renal failure was the leading cause of mortality for SCI patients in the 1950's, when treatment and surveillance techniques strategies were less advanced (Donovan, 2007). Despite vast improvements in patient management, 3-12% of NGB patients still die from renal-related dysfunction. Those at highest risk are individuals with SCI, transverse myelitis, spina bifida, and men with MS (Nseyo, 2017).

Although a relatively rare outcome, the risk of developing bladder cancer is up to 28 times higher in individuals with NGB compared to the general population (Kalisvaart et al., 2010). In addition to this, malignancy tends to present on average 25 years earlier, and at a more advanced pathological stage (Welk et al., 2013). Risk factors include chronic bladder infection, long-term use of indwelling catheterisation (IndUC) and urolithiasis (Austin et al., 2007; Yu et al., 2018).

2.6 Anticholinergic Burden in Neurogenic Bladder

Anticholinergics are a class of drugs prescribed to manage numerous conditions including PD, depression, certain allergies and chronic obstructive pulmonary disorder (COPD) (Ruxton et al., 2015). For a number of years, anticholinergic drugs have also represented the mainstay of pharmacological treatment for patients with NDO (henceforth referred to as 'bladder muscarinics'). A systematic review of trials including various bladder muscarinics demonstrated favourable patient-reported cure/improvement rates and significant reduction of maximum detrusor pressure when compared to placebo (Madhuvrata et al, 2012). Various bladder muscarinics are available on the market, with the most prominent including oxybutynin, solifenacin, and tolterodine (Abrams and

Andersson, 2007). Evidence from clinical trials has not effectively differentiated the these drugs in terms of efficacy (Madhuvrata et al, 2012).

Anticholinergic burden is defined as the cumulative effect of using one or more drugs with the potential to cause anticholinergic adverse effects (Chaplin, 2013). The most serious and irreversible adverse event culminating from a high anticholinergic burden is dementia (Rudolph et al., 2008). Patients with neurological conditions are particularly vulnerable to these adverse events given the neuropathological changes that occur in the brain and high levels of cognitive and functional dysfunction accompanying their condition (Dauphinot et al., 2017).

This section serves as a useful introduction to anticholinergic burden in neurological disorders, which is one of the central themes in this thesis. It discusses the implications of and the role of bladder muscarinics in the NGB treatment pathway. This dialogue is essential in raising awareness of this issue amongst prescribers and payers and deciphering whether modifications to clinical practice may be necessary to ensure optimal patient outcomes.

2.6.1 Propensity of Bladder Muscarinics to Cause Secondary Organ Effects

The beneficial effects of bladder muscarinics are primarily exerted via the blockade of the muscarinic M_2 and M_3 receptors located on the detrusor muscle. This inhibits binding of the primary detrusor contractile neurotransmitter, acetylcholine, decreasing the ability of the bladder to contract and therefore alleviating the symptoms of urge and incontinence (Athanasopoulos and Giannitsas, 2011).

Some bladder muscarinics have low muscarinic receptor selectivity, which means that as well as binding to the muscarinic receptors on the detrusor, they may indiscriminately bind to other muscarinic receptors (M_1-M_5), which are widely distributed throughout the body. This can cause a range of undesirable systemic effects, affecting both cognitive and physiological function (Klausner and Steers, 2007).

Blockade of M_1 and M_3 salivary receptors causes significant dry mouth; a particularly burdensome symptom extensively reported in the literature. A recent meta-analysis found that 25% of subjects taking bladder muscarinics experienced symptoms of dry mouth compared to just 5.3% of those receiving placebo. When considering specific drugs, the highest rate of dry mouth was in the fesoterodine group (29.45%), followed by solifenacin (26.0%), darifenacin (23.8%), and lastly tolterodine ER (6.1%) (Vouri et al., 2017). There is also a distinct difference between the rates of dry mouth between immediate-release (IR) oxybutynin and extended release (ER) oxybutynin (Appell, 2002).

Some evidence suggests that interference with cardiac M_2 receptor function may be associated with electrocardiogram (ECG) changes, such as bradycardia anarrhythmias. There is currently a lack of clinical data differentiating the risk profiles of the various bladder muscarinics in causing cardiovascular effects (Andersson et al., 2011).

2.6.2 Propensity of Anticholinergics to Cause Cognitive Impairment

The blood-brain barrier (BBB) is a diffusion barrier made up of endothelial cells, pericytes, and astroglial processes (Pagoria et al., 2011). The main purpose of the BBB is to prevent the influx of compounds from the blood to the brain in order to preserve the healthy brain microenvironment and normal functioning of the central nervous system (CNS) (Ballabh et al., 2004). A number of therapeutic agents are obstructed by the BBB to protect against undesirable cognitive side effects; examples include antibiotics, antineoplastic agents and neuropeptides. It is however essential that certain drugs are able to enter the brain in order to deliver their intended health benefit (Pardridge, 2005). These drugs are carefully designed to penetrate the membrane through drug delivery systems such as drug carriers (prodrugs), or through cellular mechanisms for drug targeting (Upadhyay, 2014).

The passage of bladder muscarinics across the BBB is not necessary for their impact on bladder function, despite this, many of them possess the ability to pass through into the brain. Once there, these drugs can cause a spectrum of CNS adverse events (AEs) such as delirium, hallucinations and confusion (Staskin and Zoltan, 2007; Chancellor and Boone,

2012). Some anticholinergics for PD, depression and insomnia, are supposed to pass the BBB, but nonetheless they can still cause similar undesirable secondary cognitive effects. Historically, the general view has been that any impact on cognition was reversible; however, a hypothesis has recently emerged connecting the chronic antagonism of muscarinic receptors by anticholinergics to the pathogenesis of AD (Carrière et al., 2009; Gray et al., 2015). A pivotal study, deemed methodologically superior to similar previous studies, uncovered a ten-year dose-response relationship between common anticholinergics (tricyclic antidepressants, antihistamines and bladder muscarinics) and AD (Gray et al., 2015). The potentiality of dementia is of particular concern considering the severity, irreversibility and substantial economic and humanistic burden (Madersbacher, 2005).

It is thought that the antagonism of anticholinergics to the M_1 and M_2 receptors situated in the neocortex, hippocampus and neostriatum, which are involved in higher cognitive processing, is responsible for CNS AEs (Abrams et al., 2006; Yamamoto et al., 2011). Certain pharmacological properties including non-polarity, high lipophilicity, small molecular size, lack of efflux-pump affinity and long half-life can enhance the drug's ability to cross the BBB and subsequently increase chances of binding to the muscarinic receptors and causing CNS AEs (Kay, 2008) (Table 2.2).

Table 2.2 Pharmacokinetic profile of common bladder muscarinics used in neurogenic bladder

Bladder Muscarinic	**M_3 Receptor Affinity**	**Size**	**Lipophilicity**	**Polarity**	**Efflux Pump**	**Half-Life (Hours)**
Oxybutynin	Poorly M3 selective	357 kDa	Lipophilic	Neutral	None	2/13
Tolderodine	Poorly M3 selective	475.6 kDa	Lipophilic	Positive	None	2/8

Solifenacin	Moderately M3 selective	480.6 kDa	Lipophilic	N/A	None	45-68
Darifenacin	M3 selective	507.5 kDa	Lipophilic	Positive	P-glycoprotein	12
Trospium	Poorly M3 selective	428 kDa	Hydrophilic	Positive	P-glycoprotein	20

kDa, kilodaltons

Developed from: Abrams and Andersson, 2007; Cetinel and Onal, 2013; Kay, 2008; Klausner and Steers, 2007; Pagoria et al., 2011

Amongst the bladder muscarinic agents, oxybutynin (in particular the IR formulation) has the highest potential for causing CNS AEs, due to its low M_3 muscarinic receptor selectivity and other pharmacological properties that increase its ability to cross the BBB. Gray et al (2015) demonstrated that the consumption of oxybutynin consecutively for three years increased the risk of dementia. No other bladder muscarinic has been exclusively implicated in the onset of dementia. Unfortunately, as oxybutynin is the cheapest and the oldest drug available, it is one of the most utilised in clinical practice (Donovan, 2007; Game, 2010). Other bladder muscarinics have varying degrees of potency, with darifenacin considered to be one of the safest drugs due to its favourable pharmacokinetic properties and no documented evidence of CNS AEs in trials (Table 2.2) (Zinner, 2007).

Some of the most potent anticholinergic drugs of other classes are summarised in Table 2.3 below, although by no means should be considered an exhaustive list. These drugs also significantly contribute towards anticholinergic burden and possess an enhanced ability to cross the BBB and cause CNS AEs.

Table 2.3 Medications with definite anticholinergic activity (potent anticholinergics)

Class	Specific medication
Antidiarrheals	diphenoxylate/atropine.
Antihistamines	cyproheptadine, chlorpheniramine, dexchlorpheniramine, hydroxyzine, clemastine, diphenhydramine.
Antidepressants	amitriptyline, amoxapine, clomipramine, doxepin, imipramine, mirtazapine, nortriptyline, protriptyline, trazodone, paroxetine
Antipsychotics	chlorpromazine, clozapine, fluphenazine, haloperidol, mesoridazine, olanzapine, thioridazine, thiothixene, prochlorperazine, promethazine.
Antiemetics	dimenhydrinate, meclizine, prochlorperazine, promethazine, trimethobenzamide.
Anti-Parkinson's agents	amantadine, benztropine, biperiden, trihexyphenidyl, hyoscyamine.
Antiarrhythmics	disopyramide, quinidine, procainamide.
Cardiovascular agents	dipyridamole
Antispasmotics	belladonna alkaloids, clidinium/chlordiazepoxide, dicyclomine, flavoxate, hyoscyamine, oxybutynin, propantheline, tolterodine

Adapted from Lakey et al., 2009 and Campbell et al., 2016

An individual's overall anticholinergic burden can be calculated using an anticholinergic burden scale, where the resulting score gives an indication as to how 'at risk' an individual is to CNS AEs (Section 6.2.14.1.6 and Section 8.6.3). It is important to note that not only 'potent' anticholinergics can contribute towards anticholinergic burden, in fact most of the anticholinergic burden (over 70%) seen in general practice comes from multiple 'low potency' anticholinergic medications (in particular cardiovascular drugs) (Magin et al., 2016).

2.6.3 Use of Anticholinergic Drugs in Patients with Neurological Conditions

The pathophysiological changes in the brain that accompany increasing severity of certain neurological conditions make these individuals particularly susceptible to the potential CNS AEs of anticholinergic drugs (Gao et al., 2017; Spencer et al., 2018). Most studies in the literature documenting the effects of anticholinergics on cognition have focused on older individuals. It is important that patients with neurological conditions are assessed separately, as they represent a younger, clinically distinct patient group and pose unique management challenges compared to older individuals. This section aims to summarise notable studies that have investigated cognitive impairment and the use of anticholinergic drugs in neurological conditions.

Although PD is predominantly a motor condition, around 20–50% of individuals also experience mild cognitive impairment (MCI) (Goldman and Litvan, 2011). MCI includes symptoms of memory decline, disorientation, or reduced cognition, which tends to increase parallel to neurodegeneration (Meireles and Massano, 2012). MCI is a further risk factor for dementia (clinically referred to as Parkinson's disease dementia (PDD)), which affects 30-40% of individuals. PDD significantly contributes towards morbidity and mortality (Poewe, 2005; Pandya et al., 2016).

Anticholinergic drugs have shown to increase the rate of cognitive dysfunction in PD (McKenzie, 2017). Importantly, common anti-Parkinson's drugs consist of anticholinergics, consequently putting patients at high risk of exposure (Crispo et al., 2016). The relationship between anticholinergic burden and cognition was measured in a community-based cohort of patients with PD (n=235) using the mini-mental state examination (MMSE), one of the most widely used screening tools for dementia (Ehrt et al., 2010). During an 8-year follow-up, the cognitive decline was higher in those taking anticholinergic drugs (median decline on MMSE 6.5 points) in comparison to those not taking them (median decline 1 point; p=0.025). In order to avoid the progression of cognitive decline, the researchers go so far as to suggest avoiding anticholinergic drugs in PD patients altogether (Ehrt et al., 2010). The impact anticholinergics have on cognition was confirmed in a functional imaging study;

Perry et al (2003) found that hallmark signifiers of AD; amyloid plaque and neurofibrillary tangle densities were much higher in long-term anticholinergic drug users compared to short-term and non-users. These observations provide tangible evidence to suggest that anticholinergics contribute towards AD-type pathology in PD.

In contrast, in a longitudinal observational study by Yarnall et al (2015) demonstrated that anticholinergic drug use in PD patients was in fact not associated with a decrease in cognitive scores. This result is surprising, as it goes against the broad consensus of other studies in this area that suggest the contrary. Despite this, the authors of the study still recommend avoiding these drugs in the PD population and warn that the results should be interpreted with caution due to a number of intrinsic limitations in the study design, including the short follow-up duration and the young average age of participants.

Like PD, MS is also defined as a neurodegenerative disease (Hague et al., 2005; Gironi et al., 2016). Forty to sixty percent of MS patients experience some degree of cognitive impairment and in the same manner as PD, the progression seems to be associated with advancement of the underlying condition (Rahn et al., 2012; Højsgaard Chow et al., 2018). Cognitive impairment is most prevalent and severe in secondary progressive MS (SPMS) (Højsgaard Chow et al., 2018). Although the occurrence of dementia is much rarer, it still exhibits in 20–30% of individuals, emerging primarily at end stages of disease (Guimaraes and Sa, 2012). Cognitive dysfunction in all its forms is an arbiter of large societal burden in MS, constituting one of the primary reason's patients cannot return to employment (Coyne et al., 2015).

There is scarce data on the impact of high anticholinergic burden in MS patients. A small observational study including 42 patients revealed that bladder muscarinic drug use resulted in consistently lower scores on the two separate cognitive functioning tests; the Symbol Digit Modality Test (SDMT) and the Selective Reminding Test (SRT) compared to individuals not taking anticholinergics (Cruce et al., 2012). Another study including 70 patients, covering not only anticholinergics, but also a broad range of CNS active medications found that individuals taking these medications experienced greater

impairment on measures of processing speed, sustained attention, and fatigue compared to non-users (Oken et al., 2006).

Cognitive impairment is also an issue in stroke patients. The chances of an individual becoming cognitively impaired increases threefold after experiencing a stroke. What is more alarming is that, 25% of individuals go on to develop dementia (Danovska, 2012). Healthcare costs are increased threefold for stroke patients with cognitive impairment, and the ability to perform activities of daily living (ADL) is severely diminished (Claesson et al., 2005).

As in PD and MS, the use of anticholinergics is directly implicated in exacerbating cognitive deficits. A preliminary study found that anticholinergic drugs play a role in the pathogenesis of delirium in acute stroke patients (Caeiro et al., 2004). Delirium is characterised by reduced ability to focus, sustain, or shift attention and is often accompanied by perceptual or cognitive dysfunction (Fong et al., 2009). Although there is some evidence to suggest bladder muscarinics do not cause cognitive impairment, the studies are marred with limitations such as small cohort numbers and short follow up periods (Park, 2013).

The literature presented in this section clearly indicates there is an association between neurological disorders and the onset of cognitive impairment and dementia, which is further exacerbated by high anticholinergic burden. Given the significant level of comorbidity, neurological patients tend to be prescribed anticholinergic drugs to manage a number of different conditions (Novy and Sander, 2016; McLean et al., 2017) (Section 8.2.1). In addition, a sizable proportion of patients that suffer from bladder dysfunction will be receiving bladder muscarinics as first-line management (Manack et al., 2011) (Section 2.6 and Section 8.4.1). This puts patients at particularly great risk of exposure. Furthermore, due to their pre-existing cognitive impairment as a consequence of their neurological condition, subtle changes in cognitive functionality induced by anticholinergics may be overlooked. This can be dangerous as the additional anticholinergic load can have a major impact on patient's daily functioning and potentially cause irreversible changes to brain structure (Perry et al., 2003).

Despite the incentive for further inquiry, much of the research into the impact of using anticholinergics in this patient population is preliminary, based on small sample sizes, and the results can often be conflicting. Additional research is imperative to extend our understanding in this crucial area to prevent avoidable harm to patients. An important first step would be to determine the baseline anticholinergic burden in NGB patients.

2.7 Marketing Authorisation and Reimbursement of Bladder Muscarinics

The evidence requirements between marketing authorisation (MA) authorities (for example, The European Medicines Agency (EMA)) and Health Technology Assessment (HTA) bodies (for example, the National Institute for Health and Care Excellence (NICE) in the UK) differ. MA authorities are principally concerned with assessing the safety and efficacy of a new intervention through rigorously controlled double-blind randomised clinical trials (RCTs). All pharmaceutical companies legally require MA for every product they wish to distribute (Permanand et al., 2006).

HTA is defined as:

a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner (Sacchini et al., 2009: 453).

As the remit of HTA bodies is a lot more extensive than MA authorities, companies are asked to provide additional evidence requirements, including the presentation of the unmet medical needs, the relative effectiveness and safety of the drug, drug price, budget impact and cost-effectiveness (Tafuri et al., 2016). Progressively, MA authorities are also becoming more receptive to the holistic effects of interventions.

Although bladder muscarinics are advocated as first-line management in CGs, their use in neurological populations has not been thoroughly assessed. Manufactures have only sought MA for idiopathic OAB therefore most use of bladder muscarinics in clinical practice is off-label (Cameron, 2016). Subsequently, the efficacy and safety evidence from the

idiopathic population tends to be ‘carried over’ to the NGB population (Kennelly and Devoe, 2008). The transfer of evidence from OAB to NGB is largely inappropriate, as despite similar symptoms, NGB tends to be more diffuse and dynamic than the idiopathic kind because severity increases with underlying neurological disease progression (Aharony et al., 2017; McDonald et al., 2017). The same also holds true for many other treatments such as neuromodulation and the β3-adrenoceptor agonist, mirabegron (these treatment options are discussed further in Chapter 4).

The limited evidence that does exist in the NGB population pertains mostly to adults with MS and SCI, and children and young adults with myelodysplasia (Fowler, 2011). Due to the magnitude of population diversity, it is difficult to apply evidence across neurological conditions; however, it is still common practice to do so given the paucity of adequate research. In addition, only the older generation of bladder muscarinics (propiverine, trospium, oxybutynin, propantheline and tolterodine) have studies supporting their use, which means the use of the newer generation of bladder muscarinic drugs is not evidence-based (Fowler, 2011). A meta-analysis revealed 'there is still uncertainty about which bladder muscarinics are most effective, at which dose, and by which route of administration' (Madhuvrata et al., 2012: 823).

The median cost of RCTs is $3.4 million USD for phase I, $8.6 million for phase II and $21.4 million for phase III (Martin et al., 2017). Furthermore, applications to the EMA cost upwards of €286,900. Therefore, pharmaceutical companies generally do not wish to incur the costs of pursuing MA for drugs that are already extensively used in clinical practice unless they expect it to encourage further uptake of the drug. In a disease area such as NGB where there are no other viable alternatives to idiopathic OAB drugs, the incentive for seeking MA approval is very low (Institute of Medicine, 2010). On the other hand, gaining reimbursement for use in non-licenced indications is desirable for pharmaceutical companies in the UK because once a technology has been recommended by NICE, National Health Service (NHS) trusts are ‘legally obliged to fund and resource medicines and treatments recommended by NICE’s technology appraisals’, thus encouraging uptake of

the intervention (Lawrence, 2016). Furthermore, from a government perspective, in order to promote the efficient use of bladder muscarinics, and indeed other forms of management in NGB, there needs to be a formal process by which the available treatments are assessed for their cost-effectiveness, based upon the value demonstrated in RCTs and real-world settings, which should be used by HTA bodies for priority setting.

2.8 Healthcare Resource Utilisation in Neurogenic Bladder

2.8.1 Cost of Illness Studies

Cost-of-illness (COI) studies represent an important preliminary step in lowering the total burden of disease by identifying and measuring all of the associated costs. They are valuable for policy makers for evidence-based planning of services and the introduction of new interventions. One of the most notable COI studies is the 'Global Burden of Disease' program, launched in 1991 by the WHO, which is the largest of its kind in the world, providing information on the burden of a number of diseases, injuries and risk factors (Murray and Lopez, 2013). When focusing only on direct medical costs, these studies are known as healthcare resource utilisation (HRU) studies.

Scarcity is intrinsic to the healthcare system therefore there is invariable pressure on governments to utilise financial resources as efficiently as possible (de Joncheere, 2003; Parkin, 2017). Accordingly, cost-containment strategies are used across jurisdictions to free up resources and generate additional benefits to be used elsewhere in the system (Almarsdottir and Traulsen, 2005). COI studies are able to highlight the major cost components of disease, and hence act as an important tool in demonstrating where cost-containment policies could have the greatest impact (Jo, 2014; Zannetos et al., 2017). COI studies can also be utilised to justify more resources to be devoted to diseases with higher economic burden (Drummond, 1992). Whilst both of these uses are valid, in reality, the role of COI studies has changed significantly since their inception and early use. Because of their descriptive nature, rather than actively directing healthcare decisions, these studies have adopted an increasingly complimentary role, mainly in raising the cost-consciousness

of consumers. They are typically used as educational tools, in public advocacy, to encourage policy debate and evaluation, and contribute towards the planning of services in conjunction with more sophisticated measures of healthcare evaluation (Larg and Moss, 2011).

The amount of pharmaceutical innovation directly relates to the burden of disease (Lichtenberg, 2005). Therefore, as well as being useful for guiding policy decisions, COI studies are valuable to pharmaceutical companies in guiding their Research and Development (R&D) focus. The target product profile (TPP) is an all-encompassing document, outlining the goals and expectations of the drug development process. The economic burden of a disease is calculated as part of the initial environmental scanning in order to highlight the unmet need and possible areas where cost savings can be made through the introduction of new interventions (Tyndall, 2017). Well-differentiated products in established disease areas are more likely to be successful (Ahlawat, 2013). It is therefore important for pharmaceutical companies to invest resources in elucidating and publishing evidence on the burden of disease in order to increase the likelihood commercial success.

2.8.2 Debate on the Use of Cost of Illness Studies

There is no shortage of debate amongst health economists on the value of COI studies in guiding healthcare decisions. Some criticisms relate to the methods involved in calculating indirect and productivity costs, however since the research presented in this thesis is only concerned with direct medical costs (HRU), other types of costs will not be discussed. This section will instead focus on the broad concerns pertaining to flaws in design and rationale of use.

Welfare economists argue that health is a multi-dimensional concept that cannot simply be measured in monetary gains and losses. They propose that a patient's judgement of their own health reveals a great deal on the burden of disease, for example the psychological distress and social isolation that is not captured in direct or indirect measures

of cost (Shiell, 1987). Accordingly, these critics, suggest that the lack of attention given to HRQoL is a major limitation of COI studies.

COI studies are often presented in a way that suggests vast cost savings could be made from eradicating the disease in question, however, in reality, few diseases could be completely eliminated therefore the costs of treatments presented will not all be saved (Byford et al., 2000). In addition, whilst COI studies could indeed reveal that treatment costs are high, they often fail to account for the costs of preventing disease, which could also be costly, if not more so (Byford et al., 2000). It is therefore important that the conclusions derived from COI studies are presented in a way that is purely informative and raises awareness of the disease, rather than making bold inferences about cost savings.

It is evident that the descriptive nature of COI studies, limits their practical use in healthcare decision-making (Wiseman and Mooney, 1998). Other, more sophisticated forms of economic analyses such as cost-effectiveness analysis (CEA) have considerably more weight in priority setting because they make valid comparisons between alternative interventions of the cost versus the expected health gain (Hutubessy et al., 2003). However, with limited resources for HTA, and almost one novel chemical entity introduced per week, decisions need to be made around which disease areas are worth focusing on (Gabbay and Walley, 2006). This is particularly necessary in low-income countries with a lessened ability to conduct expensive assessments of all new interventions (Baltussen et al., 2005; Drummond et al., 2011). In this sense, COI studies can help to educate, inform and enlighten HTA bodies and policy-makers, and guide the focus onto diseases that are resource intensive, have a high rate of complications, and are in need of new cost-effective interventions.

Furthermore, it is also important to consider that the economic models submitted to HTA bodies can only be as reliable as the evidence used to inform their parameters. Outputs from COI studies improve the reliability of the underlying evidence in economic models as the full disease pathway can be accurately elucidated, including the costs and occurrence of iatrogenic and disease related AEs, costs for medical services and, if taking a societal perspective, broader parameters such as the level of work absenteeism (Gao et al., 2016).

Ultimately, it is inapt to compare COI studies to more sophisticated types of economic evaluation as they have their own unique place in healthcare research, representing an essential, descriptive type of economic evaluation. They should be used in combination with population frequency, morbidity and mortality estimates to derive the best possible value. These studies are exceedingly important in the under-researched and unrepresented area of NGB, where it is important to raise the profile of the disease and generate further hypotheses to encourage more research and innovation.

2.8.3 Literature Review - Healthcare Resource Utilisation in Neurogenic Bladder

A literature review was conducted to summarise evidence of HRU in NGB. Literature reviews differ from systematic literature reviews in that there is no specific question that needs to be addressed, rather, the topics covered are general and aim to provide an overall summary of the pertinent data in the area. This means that papers are sought through a random process, without the use of pre-defined search terms, and without the conduction of a pilot study to determine feasibility of article detection (Robinson and Lowe, 2015). Furthermore, a quality assessment of individual studies is not conducted.

NGB is associated with a number of widespread indirect and direct costs, spanning further than the resources required to manage the condition. When adopting the perspective of the patient and/or their family, costs include trips to hospital appointments, the income lost from a partner taking on the role of a carer, and in more advanced stages of disability, nursing home and end of life costs (Palma-Zamora and Atiemo, 2017). When considering the societal perspective, reduction in work productivity and work absenteeism as a result of NGB related morbidity represent a substantial burden (Boccuzzi, 2003).

Although a number of different costs from various perspectives could be considered, HRU (direct medical costs) will be discussed in this section. It is recognised that a number of factors dictate the level of HRU and associated costs in NGB including complications, access to healthcare, symptomology and management strategies employed, however the

economic burden on the healthcare system still remains poorly characterised (Palma-Zamora and Atiemo, 2017). Most studies in the literature pertain to idiopathic OAB patients, and owing to the lack of data, these estimates are often extrapolated to the NGB population.

Across multiple disease areas, significant proportions of healthcare spending are wasted on complications that could have been prevented with the right care and planning. A study using hospital claims data for California and Maryland in the USA found that 9.63% of all hospital spending ($6,504,557,501) was associated with potentially avoidable complications (Fuller et al., 2009). In NGB, preventing complications such as those detailed in Section 2.3 can help reduce potentially avoidable medical costs and free up resources to be used in other parts of the healthcare sector.

UTI is a common complication of NGB and also one of the most common healthcare associated infections (HCAIs), accounting for 17.2% of all cases. In the USA, UTI accounted for nearly 7 million office visits, 1 million emergency department (ED) visits, and 100,000 hospitalisations in 1997, mostly associated to APN (Foxman, 2002). These conditions are also expensive, generating medical costs of $1.30 billion USD and $1.6 billion USD per year respectively (Brown et al., 2005). Evidence suggests there is a direct relationship between the length of time a patient resides in a healthcare setting and their chances of contracting a HCAI (Mantle, 2015). The average length of hospital stay is longer for NGB patients in comparison to idiopathic OAB patients, consequently putting them at increased risk for contracting nosocomial UTIs (Sauerwein, 2002). The risk of infection also increases with the duration of catheterisation, and in the UK, around 43%-56% of overall UTI cases are caused by IndUC, which stays in the bladder longer than IC (Mantle, 2015; Hallam, 2017). From a UK perspective, every catheter associated urinary tract infection (CAUTI) case increases hospital stay by 10 days and costs an average of £2523 per patient (Prieto et al., 2015).

Antibiotics are the mainstay of treatment for UTIs, and currently there are no alternative treatments in existence. Worryingly, antimicrobial resistance (AMR) is emerging as a major threat to the effectiveness of antibiotics and consequently to global population health. The

drugs are slowly proving ineffective against many common strains of bacteria, including E.coli, which is responsible for 70-80% of all community acquired infections (McLellan and Hunstad, 2016). Unless antibiotic stewardship is adopted across the globe, the possibility of a post-antibiotic era may become a reality, and common infections such as UTIs could cause much longer duration and severity of illness, and inevitable mortality for a lot more people. The WHO predict this will put a much higher economic strain on healthcare resources, families and societies (WHO, 2014). An instance of AMR has been estimated to cost more than $55,000 USD per patient episode. Furthermore, mortality from infections as a result of AMR are predicted to result in a reduction of 2%-3.5% of global gross domestic product (GDP) by 2050, equating to around $60-100 trillion USD (Allcock, 2017).

Renal related complications also pose a large burden on the healthcare system. CKD cost the NHS £1.45 billion in 2009-2010, accounting for around 1.3% of all spending that year (Kerr, 2012). When considering per-person costs, a study using Medicare data in the USA estimated the costs reached up to $12,700 for stage 4 patients (adjusted to 2010 dollars) (Honeycutt et al., 2013). Kidney transplantation is more cost effective than dialysis in managing CKD, leading to a cost benefit in the second and subsequent years of £25,800 per annum, however the lack of organ donation remains a prominent barrier to carrying out more transplantations (National Kidney Federation., 2010). VUR, is another common complication in NGB and correspondingly the costs are also substantial. A retrospective study found that since 2000, hospital charges for inpatient VUR management have gradually increased, and in the last year of analysis, charges were $18,798 USD per hospitalisation (Spencer et al., 2011).

The link between incontinence and HRU has been well established in the idiopathic OAB population. Two large-scale studies showed average annual per capita costs of $65.7 billion in the US and £4.2 billion in the five largest western European countries (Germany, Italy, Spain, Sweden, and the UK), spent in managing OAB (Ganz et al., 2010; Reeves et al., 2006). Another study conducted from the perspective of a payer in the USA estimated an annual cost of $12,357.43 per patient for incontinence related hospitalisations, clinician office

visits, outpatient, and emergency department (ED) services (Thom et al., 2005). There is also evidence to suggest that NGB patients with NDO are more healthcare resource intensive than their continent counterparts. A retrospective, cross-sectional study utilising a multinational survey of patient and physician reported data, demonstrated higher rates of OAB-related hospitalisations, OAB-related surgery, pad use and bladder muscarinic treatment switching amongst incontinent NDO patients in comparison to continent patients (Tang et al., 2014).

A study estimated the overall treatment costs in idiopathic OAB to be $27,98990 USD (Hu et al., 2003). Investment of resources and enhancement of initial treatment capabilities should theoretically reduce the costs of treating late-stage disease and the associated consequences, therefore justifying initial high treatment costs (Hu et al., 2003). However, certain management techniques and situations can prove an unfounded cost burden. A US claims database showed that all-cause and OAB-related costs were higher in a treatment-switch group than persistent patients six months after the index date (all-cause $7,017 vs. $8,806, OAB-related $642 vs. $797) (Ivanova, 2014). Therefore, considering that many NGB patients do not remain persistent on their first line bladder muscarinic, all of the costs associated with bladder muscarinics may not be justified. Better strategies should be employed to consider the optimal management method from the onset, in order to avoid switching and save costs (Tijnagel et al., 2017).

A cost analysis in the USA comparing 12 common treatments for idiopathic OAB found that costs ranged from $500 USD for oxybutynin to $19,443 for sacral nerve stimulation (SNS). The cost for onabotulinumtoxin A was $1892 and was found to be the least costly option throughout the duration of the study when compared to SNS and percutaneous tibial nerve stimulation (PNS) (Yehoshua, 2018). Although generic bladder muscarinics were the cheapest in this study, it is essential to consider the persistence rates and risk of AEs, which tend be higher with this form of management (Tijnagel et al., 2017). Accordingly, the choice and sequence of treatments are typically guided by cost-effectiveness analysis (CEA), where the ratio of costs incurred by the new intervention relative to the comparator to the

cost per health benefit gained is used to determine whether the intervention in question is cost-effective or not (depending on the available national or local budget) (Giannitsas and Athanasopoulos, 2015).

A CEA comparing onabotulinumtoxin A to best supportive care (BSC) in individuals with MS and SCI, resulted in an additional 0.4 Quality Adjusted Life Years (QALYs), at an increased cost of £1,689 over 5 years. The authors of the study considered onabotulinumtoxin A to be more cost-effective than BSC. Another CEA, projecting the 10-year costs for onabotulinumtoxin A, deemed it more cost-effective than clam cystoplasty (Flack and Powell, 2015). At present, most CEA has been primarily conducted in the OAB population, signifying an unmet need in the NGB population.

2.8.3.1 Access to Healthcare

Access to healthcare services is a key attributor towards the health of the NGB population. Access is simply defined as the 'ability to obtain health services when needed' (Bodenheimer, 2012: 17). In many parts of the world, the opportunity to reach services is impeded by barriers such as poor healthcare infrastructure, economic deprivation, and physical restrictions (Levesque et al., 2013). Delayed or restricted access to services ultimately results in higher long-term resource use and costs.

In countries that lack universal healthcare coverage, the price of services conditions the individual's willingness to pay (WTP) for necessary interventions and consequently, out-of-pocket payments often inhibits access to healthcare for the poorest in society (Peters et al., 2008). When there are high costs attached to lifesaving treatments such as dialysis in renal failure, patients may be compelled to forgo treatment and risk increased morbidity or even death because of the lack of affordability. Thus, NGB patients with lower ability to pay are at risk of being inappropriately managed, consequently increasing their risk of further complications, morbidity, morality, and associated costs (Rahmqvist et al., 2016; Przydacz et al., 2017). This notion is supported in a retrospective database study in the USA,

which found that NGB patients with low annual incomes and without insurance or self-pay were more likely to be discharged from hospital earlier (Sood et al., 2017).

In countries with underdeveloped health infrastructure, the necessary services may be entirely absent. Urodynamic testing is often considered essential for diagnosis and guiding subsequent treatment choices, however countries in the developing world may lack the sophisticated equipment and/or the medical expertise required to carry out these tests (Przydacz et al., 2017). Undiagnosed or poorly diagnosed NGB can have devastating consequences for healthcare outcomes and costs.

Even in countries such as the UK with the well-established NHS, barriers to care remain persistent. Waiting times are an all-too-familiar problem in publicly funded services (Willis et al., 2011). 'Non-urgent' patients wait an average of 13 weeks to see a urologist, much longer than what is considered clinically reasonable (Witherspoon et al., 2017). Long wait times have been proven to lead to poor patient outcomes, increased risk of mortality and increased medical costs due to the delay in accurate diagnosis and treatment (Schaafsma, 2006).

The cost of incontinence products such as pads and diapers typically represent an ongoing out-of-pocket expense for patients even in countries where state funding often covers most forms of management. A study demonstrated that absorbent pads represented nearly two thirds of the annual per patient costs of idiopathic OAB management in five European countries (Reeves et al., 2006). In the UK, provision of these products by the NHS depends on criteria set out by local clinical care commissioning groups (CCGs), which can introduce inequity in access (Guimaraes and Sa, 2012). In the USA, absorbent products are not covered by health plans (Palma-Zamora and Atiemo, 2017). A notable exception to this trend is Denmark, where the Danish National Health Service (DNHS) fully reimburses incontinence pads and the major manufacturers even send nurses to the patients' homes to help with adjustment (Cornago and Garattini, 2001).

2.8.3.2 Conclusions

It is unmistakable from the evidence presented in this section that NGB represents a large economic burden to healthcare systems, which is amplified by multiple barriers to access. The literature also revealed that there is a lack of resource use data in the NGB population, resulting in the necessary extrapolation of data from the OAB population. Other literature reviews into the burden of NGB have resorted to the same extrapolation to make up for the dearth of research (Flack and Powell, 2016). Despite the similarity in symptoms, these two conditions should be considered as distinct clinical entities due to differences in HRQoL, varying patterns of disease, and differences in complications, such as the unique occurrence of autonomic dysreflexia in SCI (Tapia et al., 2013; Truzzi et al., 2016). Despite this, the use of OAB data is the best available alternative until more research efforts are directed towards generating evidence for NGB.

Most of the estimates retrieved were from non-UK populations, calculated at a national level. Therefore, in order to inform prescribers and payers and potentiate informed decisions on optimal care in the UK, there is a need to characterise the impact NGB has on the NHS, particularly at a patient level.

2.9 Drug Utilisation Research

DUR is one of the main themes underpinning the research in this thesis, and this section aims to provide an overview of the topic. Narrow definitions define DUR as 'research or studies related to the prescribing, dispensing and ingesting of drugs' (Brodie, 1971: 1), however it is now widely accepted as being a vast, ever-evolving area of research, encompassing a breadth of aims and methodologies. A broader and more apt definition was coined by the WHO in 1977 describing it as:

the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (WHO, 2003: 33).

In this discussion, special attention is placed on descriptive studies, which undeniably do not allow causal inferences to be drawn but are exceedingly important for new areas of investigation such as NGB, to identify problems which require more in-depth research.

DUR is an important step in the promotion of rational and effective use of drugs (Shalini, 2010). It incorporates quantitative methods to describe the current state (cross-sectional) and trends of treatment use over time (longitudinal), using retrospective databases or prospective studies (Lee, 2012). It is possible to determine utilisation patterns within specific sub-groups of patients (for example different neurological populations), and stratify according to demographic characteristics (for example, age and sex), to explore differences between groups and generate hypotheses. In order to calculate and compare use of drugs both nationally and internationally, a standardised classification system in which drugs are described and sorted is necessary. Drugs can be classified according to their mode of action, indications or chemical structure (WHO, 2003). The reference standard for quantitative DUR is the WHO Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology, however, other coding systems also exist, for example standard coding in the UK is by the British National Formulary (BNF) (Mittal et al., 2014) (Section 6.3.12.1.7).

There has been a proliferation in DUR since its inception in the 1960s due to the intensification of marketing of new drugs, variation in prescribing patterns, differences in attitudes towards drugs, and increasing pressure to adopt cost-containment measures (Gama, 2008). Approaches to DUR vary according to the purpose and needs of the intended user (Lunde and Baksaas, 1988). Perspectives can be of governments, healthcare management, economists, the public, and drug manufacturers, amongst others (Lee, 2012). For example, a single hospital sought to determine whether local CGs were being adhered to in their institution, whereas a nationwide study was focused on the differences in drug utilisation between males and females (Wettermark, 2016). Other studies place a particular focus on identifying inappropriate drug use through validated scales such as the anticholinergic cognitive burden (ACB) scale, which identifies high anticholinergic burden

whilst others focus on identifying Potentially Inappropriate Medicine (PIM) use by using tools such as STOPP/START or the Beer's Criteria (Campbell et al., 2013; Desnoyer et al., 2017). PIM incorporates issues such as over-prescriptions, prescriptions of contra-indicated medications, or incorrect prescribing of an indicated drug, including duplicates or administering an incorrect dose or duration. Inappropriate use of drugs is a public health hazard, causing AEs, considerable morbidity, mortality and increased healthcare costs, thus it is important to identify and correct (Desnoyer et al., 2017). The DUR in this thesis consists of a systematic review (SR) (Chapter 5) which focuses on gathering evidence on real world drug utilisation patterns in NGB. Additionally, a retrospective study using the CPRD database (Chapters 7 and 8) seeks to describe multiple aspects of NGB drug prescribing behaviour in the UK including OAB drug use, polypharmacy and ACB score.

The vast majority of DUR studies are descriptive; therefore, they are designed to pave the way for more focused research and activity such as hypothesis driven pharmacoepidemiological research, that can improve the way drugs are utilised in society. Alternatively, retrospective data can first be employed to detect problems or notable trends in prescribing, then specific patients who are at risk or of interest can be targeted for further enquiry through qualitative means (Truter, 2008). The central theme of qualitative studies is the 'appropriateness of drug prescribing'; thence, quite aptly, these studies are referred to as 'drug use evaluation (DUE)' studies (Lee, 2012). Methods to gather data can include in-depth interviews or focus group discussions (Wettermark, 2016). Ultimately, DUR can lead to modifications to CGs, changes in health policy, educational interventions to improve physician prescribing and patient awareness programmes (Wettermark, 2016).

DUR can also help pharmaceutical companies to demonstrate the value of their product compared to routine clinical practice, identify key target subgroups, and aid in the evaluation of likely commercial success (Navarro, 2009). Expert opinion is often used to construct treatment pathways in economic models for submissions to reimbursement agencies, however, this type of evidence is heavily subject to cognitive bias. CGs could be

used, however they often represent what clinical practice should look like in an ideal sense, thus are an inaccurate reflection of prescribing reality (Tappenden, 2012). Treatment pathways derived from large-scale epidemiological studies are a better indicator of how patients are being managed in the real world thus; this information can improve the reliability and transparency of the economic model, improving chances of reimbursement (Nuijten et al., 2011).

Given that CGs are the main tool by which to promote best practice in and influence prescribing choices, analysis of CG development and recommendations are a useful supplement to DUR to help contextualise the findings and understand how alterations in CG development could improve the treatment landscape.

2.10 Chapter Summary

This chapter provided an in-depth overview of many pertinent aspects relating to NGB. The prevalence of this chronic condition is high; however, current estimates fall short of providing an accurate depiction of real-life rates, especially in a UK population. The clinical burden of complications relating to NGB were also elucidated, revealing that secondary conditions can be severe, thus optimising management should be a priority. The impact of high anticholinergic burden in neurological patients was also discussed at some length. From the research presented it is apparent that further evidence needs to be accumulated on this topic in order to inform current prescribing practices with anticholinergics. A logical first step comes in calculating the ACB score of individuals with NGB. Lastly, HRU and DUR were explored in some detail, including a literature review on the economic burden of NGB, which revealed a dearth of data in a UK population, especially at a patient level. HRU and DUR are important in determining the quality of current management practices and highlighting the resource intensive aspects of the condition, demonstrating to payers and policy makers where improvements are possible.

This chapter ultimately revealed that there is a lack of epidemiological data on NGB patients in the UK. Accordingly, a UK-wide retrospective study utilising the CPRD database is

presented in Chapters 6, 7 and 8 to bridge this evidence gap. The next chapter will focus on developing a comprehensive understanding of the current management landscape for NGB through a critical appraisal of the NICE, EAU and ICI CGs for NGB, which is a useful precursor to conducting DUR.

3) Chapter Three - Clinical Guidelines in Neurogenic Bladder – A Critical Appraisal

3.1 Introduction

High quality clinical guidelines (CGs) influence drug utilisation in clinical practice and adherence to recommendations is positively correlated with improvements in health outcomes (Murad, 2017). Despite this, the application of neurogenic bladder (NGB) CGs in clinical practice remains sub-optimal in the Netherlands, and expert opinion suggests that the same trend is replicated in other European countries (Cruce et al., 2012; Drake and de Ridder, 2017). Low uptake of CGs is most commonly due to the multifaceted barriers in implementation across care practices or inadequacy in the CGs themselves, pertaining to the methods of development and content (Spallek et al., 2010).

It is important to contextualise the prominent NGB CGs, in order to assess their value in the current healthcare setting and discover what may be preventing optimal uptake. In keeping with the theme of drug utilisation research (DUR), the aim of this chapter is to identify potential shortcomings in the CGs and provide suggestions around the means by which they can be addressed. Such investigation paves the way for improvements in the treatment pathway and delivery of care, with the ultimate aim of enhancing health outcomes and introducing increased economic efficiency in the treatment of NGB.

To achieve this aim, the chapter begins with a discussion on the importance of CGs and the impetus for quality assessment. Secondly, the important attributes and activities that steer CG development are explored in the context of NGB. Third, a brief history on the evolution of the National Institute for Health and Care Excellence (NICE), European Association of Urology (EAU) and International Consultation on Incontinence (ICI) CGs is presented. Finally, a critical appraisal of the CG development process using the Appraisal of CGs for Research and Evaluation (AGREE) II instrument is presented.

3.2 Importance of Clinical Guidelines

With burgeoning healthcare expenditures and public spending budgets becoming progressively strained, increasing the value obtained from health care investments has become an emerging priority (Clancy and Cronin, 2005). Consequently, evidence-based medicine (EBM) has gained a lot of traction over the last 20 years, with increased efforts dedicated towards embedding high quality research into clinical decision-making (Fernandez et al., 2015). CGs encapsulate the plethora of complex and dynamic evidence into easy to follow recommendations, as well as (ideally) considering costs, expert opinion and health policy (Oyinlola et al., 2016). Therefore, they represent the model way to introduce EBM into clinical practice and improve efficiency.

The majority of patient care takes place in the primary healthcare setting, where general practitioners (GPs) are faced with various treatment options and may be unaware of all of the associated side effects or merits. It can be near impossible to keep abreast of all existing and new developments in the field of NGB, especially when the body of scientific research is vast, ever expanding, and often conflicting. Thus, one of the primary aims and uses of CGs is guiding GPs towards optimal treatment choices so that they can rest assured with the knowledge that their care decisions are supported by sound evidence (Woolf et al., 1999).

Patients with chronic conditions are notoriously non-adherent to their medications (Yeaw et al., 2009). In NGB there is a medication continuation rate of only 40% after 12 months (Tijnagel et al., 2017). Often, low adherence is the result of a gap that lies between actual medical outcomes and patient expectations (Lateef, 2011). In a survey sent out to idiopathic overactive bladder (OAB) patients prescribed bladder muscarinics, the overwhelming majority (89%) named unmet treatment expectations as the main reason for discontinuation (Benner et al., 2010). ‘Consumer’ CGs, such as leaflets and online versions in lay language can help patients gain a better understanding of all treatment options available to them. Equipped with a better knowledge, patients can feel empowered

to upkeep their own health, adhere to their medications and improve communications with their doctor (King and Hoppe, 2013; Francke et al., 2008; Woolf et al., 1999).

Unwarranted variation in care is generally the result of underuse of 'effective' care, this is problematic because patients in certain geographical areas or particular practices may not be deriving the best possible value from the healthcare system (Wennberg, 2011; Woolf et al., 1999). In many disease areas, standardisation in the application of CGs has been a preeminent step in optimising the efficiency of healthcare resource utilisation (HRU), ensuring that services are more equitably distributed, and thus better outcomes are possible for the vast majority of patients (Woolf et al., 1999). It is however important to consider that complete standardisation is not always desirable due to varying patient characteristics and preferences (Buchan et al., 2016; Alexander, 2017). This is especially true for NGB patients, who are a notably heterogeneous patient group with varying treatment requirements. For example, a young child with spina bifida would require a distinctly different treatment regime than an elderly patient with Parkinson's disease (PD).

3.3 Quality of Clinical Guidelines

The AGREE collaboration, a multidisciplinary team of experts formed in 2003 to address the variability that exists in CG development, defined good quality CGs as:

The confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice (AGREE, 2013: online).

CG quality is essential to derive the best possible benefit for all stakeholders. To this end, the AGREE collaboration developed the AGREE II instrument as means to critically appraise the transparency and methodological rigour of CG development (Brouwers et al., 2010). Some of the pertinent aspects of CG quality they identified relate to the clarity of objectives, general presentation, the systematic review (SR) techniques, level of stakeholder involvement, conflicts of interest and integration of external review. These attributes are explored further in the following sections.

3.3.1 Scope and Purpose of Clinical Guidelines

There should be good rationale for CG creation; ideally, they should fill a gap that exists in clinical practice. Often it is necessary to create new CGs because the condition of interest lacks evidence-based guidance for healthcare professionals (HCPs). In other instances, there may be evidence of inappropriate practice, which the CGs aim to rectify (Rosenfeld and Shiffman, 2009).

The objective of the CGs should specifically describe the overall goals of implementation and the performance expectations should be clearly communicated. This can serve as criteria against which specific improvements in patient health or clinical care can be measured against.

3.3.2 Systematic Review Techniques and Grading of Evidence

The most vital aspect in the formation of evidence-based recommendations is a comprehensive SR of all available evidence (Semlitsch et al., 2015). In order to be truly systematic, reviews should be carried out by experienced researchers, start with clearly formulated research questions, appraise the quality of well selected studies and adequately summarise the evidence (Khan et al., 2003). Explicit SR methodology such as that from the Cochrane collaboration or the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) should be utilised (Moher et al., 2009; Henderson et al., 2010).

The EBM hierarchy, conceptualised in 1995, provides guidance around the relative strength of difference evidence types (Figure 3.1). Its use ensures the totality of high-quality evidence informs recommendations, rather than single studies or expert opinion, which are prone to bias (Møller and Myles, 2016). Moving up the hierarchy implies increasing validity and applicability in making clinical decisions (Murad et al., 2016). By default, randomised controlled trials (RCTs) are ranked as ‘high’ and observational studies are ranked as ‘low’.

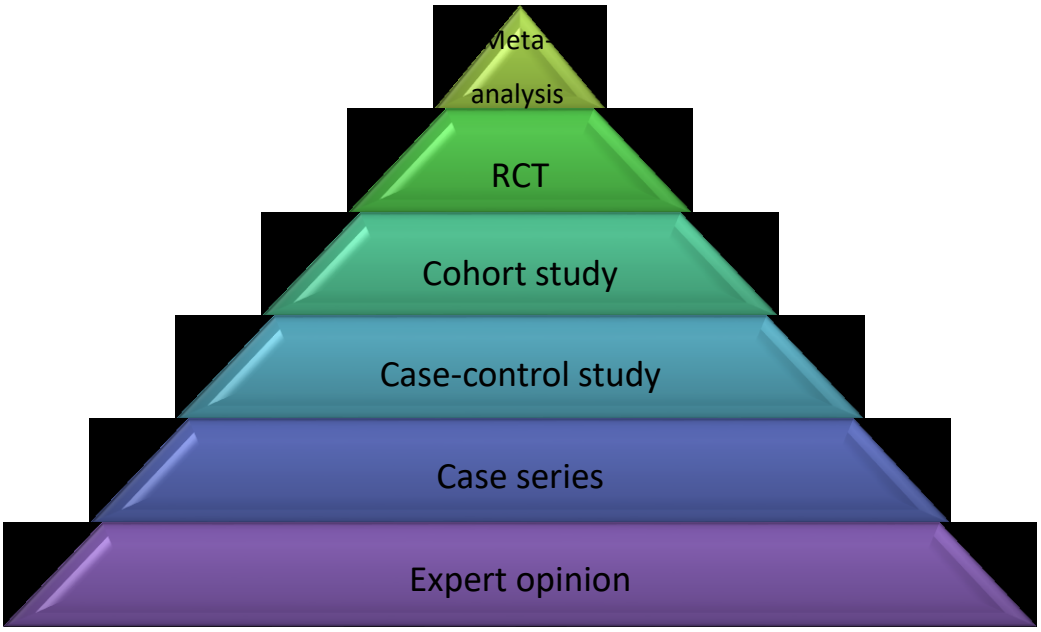


Figure 3.1 The evidence-based medicine hierarchy (Guyatt et al., 1995)

Meta-analyses involve the quantitative aggregation of several high quality and homogenous RCTs to provide a precise overall treatment effect; it is therefore considered the optimal analytical method to appraise the underlying evidence (Figure 3.1) (Kanters et al., 2016; Haidich, 2010). High-quality RCTs should be double blinded, as this prevents doctors and patients acting on any preconceived notions they have of the interventions in question (Misra, 2012). Other attributes of a well-designed trial include randomisation, which reduces selection bias, large sample sizes, which increase the power to detect a relevant outcome, and following an intention to treat (ITT) analysis, which reduces the risk of breaking the random assignment of patients (Kendall, 2003). Outcomes normally relate to proving the efficacy of a new intervention compared to the current standard of care (SOC). Safety, patient reported outcomes (PROs), and economic outcomes are often sought as secondary outcomes (Revicki and Frank, 1999). Most RCTs compare an active intervention to an inert placebo, although in some instances head-to-head trials are also conducted (Ioannidis, 2006).

Expert opinion is considered the lowest level of evidence within the EBM hierarchy, due to the inability of experts to detach themselves from their personal experiences, thus making their opinions subject to cognitive bias (Burns et al., 2011). The excessive use of expert opinion in place of scientific research can jeopardise the integrity of the recommendations by allowing the experts' conflict of interest to potentially direct decisions (Eibling et al., 2014; Grilli et al., 2000). There is however an important distinction between expert opinion and expert knowledge (which is not made in the hierarchy), with the latter being grounded in extensive and shared experiential knowledge between multiple experts (Fernandez, 2015). Nevertheless, clinicians need to exercise additional caution when considering recommendations not supported by substantial evidence.

Grading the underlying strength of the body of evidence (the methodological quality) allows users to determine how much confidence they can place in the resulting recommendation. The strength of the recommendation is determined separately and is not solely dependent upon the quality of the underlying evidence base; it necessitates multifaceted judgments of the clinical context in combination with the developer's experiential knowledge. If the recommendation is based on high-quality evidence, as further evidence accumulates it is unlikely to change, however if it is based on low-quality evidence, then it has the potential to change subject to new evidence generation (Guyatt et al., 2012). It is therefore important that the strength of evidence is reported transparently, so that users are aware of the changeability of recommendations.

There are a number of evidence appraisal systems available to facilitate grading, the most common being the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCEBM 2011). Both are validated and posited as highly credible and reliable systems, however based on a recent high-quality SR, the GRADE system was considered the most useful, as it goes beyond just rating evidence, providing a framework to guide SR (Atkins et al., 2004). Furthermore, it is comprehensive and flexible in nature, and includes all consumers' views and preferences (Johnston and Dijkers, 2012).

The notion of the EBM hierarchy is somewhat contentious because CGs are designed to be applied in real world practice, thus external validity (highest in observational studies) should be of particular importance. This issue is particularly apposite in NGB where there is dearth of high-quality research, thus a need for new evidence generation, however RCTs are difficult to conduct because of the vulnerability of the patient population (Section 4.7). Despite this, the explicit use of grading systems underpinned by the philosophical concept of the EBM hierarchy (i.e. the GRADE and OCEBM) garners high marks in the AGREE II appraisal.

3.3.3 Stakeholder Involvement

A stakeholder is anyone with a legitimate interest in the CG (Cluzeau et al., 2012). The involvement of a broad range of stakeholders allows the integration of several unique perspectives on optimal healthcare, aids in the prioritisation of important topics, and minimises bias towards certain treatment options caused by conflict of interest (Rosenfeld and Shiffman, 2009). In order to integrate stakeholder views successfully, their involvement needs to be 'inclusive, equitable, and adequately resourced' (Cluzeau et al., 2012: 269).

Experts working in the field of neuro-urology, such as urologists, gynaecologists, urology nurses as well as neurologists have superior knowledge of disease pathological processes and possess vital experiential knowledge of managing patients in clinical practice. Their involvement in the development group is integral, both in assessing objective evidence and in providing expert opinion in the absence of high-level evidence (Eibling et al., 2014).

As the recommendations will ultimately affect patients, it is internationally recognised that their involvement is a critical component of CG development (Armstrong et al., 2017; Boivin et al., 2010). Active participation of patients encourages public confidence and acceptance, which can in turn increase the likelihood of adherence to recommendations.

There are a number of ways to assimilate the patient voice into recommendations. At the macro-level, patients could be involved in topic selection for the CG via passive means such as submitting topics for discussion. Alternatively, they may have direct input into the SR,

however the relevance of patient involvement is debated due to the scientific complexity of the task (van de Bovenkamp and Trappenburg, 2009). At the micro-level, CGs can be used to stimulate consideration of individual patient values and preferences during their interactions with their healthcare provider (van der Weijden et al., 2010). Out of all methods, active involvement in the development team is considered the optimal way to integrate the patient voice into CGs (Armstrong and Bloom, 2017).

Primary care is where the bulk of prescribing normally takes place therefore it is also necessary to glean insights from GPs, who are at the forefront of patient care. Limited involvement from this stakeholder group can result in a reluctance to utilise the CGs due to the inevitable limited applicability in primary care (McKinlay et al., 2004).

There are some important barriers that must be overcome to ensure the optimal inclusion of patients and GPs. This includes reconciling their views with experts, gaining clarity around their roles in the development team, and ensuring adequate representation. An additional requirement to integrate patients is finding the resources for training to aid them in their evaluation (van der Ham et al., 2016).

3.3.4 Implementation and Dissemination Techniques

Implementation refers to the promotion of the systematic uptake of EBM into routine practice. Dissemination is closely linked, referring to the spread of new practices to target audiences through planned strategies (Schillinger, 2010). Even if CGs are created with the highest possible scientific and methodological rigour, it is still not possible to ensure the translation of EBM into routine practice without superior and targeted implementation and dissemination strategies. Unfortunately, many best efforts to improve CG uptake often go unfulfilled, with non-compliance reaching as high as 70% across many countries and disease areas (Barth et al., 2016). Furthermore, around 30–40% of patients still receive care that is not in line with up-to-date research, and more alarmingly, 20-25% receive care that is unnecessary or potentially harmful (Fischer et al., 2016). Poor implementation and dissemination can also have a negative impact on timely rates of correct diagnosis.

Common barriers to uptake of CGs pertain to a lack of available resources, resistance to changing long-established clinical practices, and the difficulty of implementing complex recommendations. Uptake can be improved through the formulation of tailored approaches, based on an assessment of local barriers and available resources (Carey et al., 2009; Grimshaw et al., 2012). Additionally, interactive education and training for HCPs has been found to enhance knowledge, skills, attitudes and clinical behaviour, thus increasing chances of them utilising the CGs (Kastner et al., 2015).

Clinical Decision Support Systems (CDSS) represent a sophisticated computational means by which CGs can be fully integrated into clinical practice. CDSS are defined as:

Software that are designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base and patient-specific assessments or recommendations are then presented to the clinician or the patient for a decision (Sim et al., 2001: 528).

They are flexible enough to provide individual patient-specific advice, whilst allowing the clinician to exercise their personal judgement where they feel the recommendation is not applicable. Clinicians are able to input reasons for deviation into the system, as well as which alternatives were employed instead, adding to the body of knowledge around management pathways (Fox et al., 2009). Although CDSS are not the magic bullet to implementation, and several challenges in information technology (IT) infrastructure impede full success (O'Sullivan et al., 2014), recent meta-analyses have demonstrated promising improvements in health outcomes (Bright et al., 2012; Fillmore et al., 2013).

3.3.4.1 Health Economics

Burgeoning healthcare expenditure coupled with the expansion of new technologies and healthcare innovation means that integration of economic analyses within CGs and consideration of the wider impact on population health and inequalities are essential (Eccles et al., 2000; Da'ar and Al Shehri, 2015). Healthcare systems, policy makers and payers often depend on CGs to maximise the cost-effectiveness of healthcare (Eccles and

Mason, 2001). However, despite the proliferation in CGs over the last two decades, incorporation of resource implications and costs remains low. A study conducted in the USA found that only 26% CGs incorporated at least one economic analysis of above-average quality (Wallace et al., 2002).

Moreover, clinicians are often resistant to the uptake of CGs, and are seldom swayed by economic arguments (Tunis et al., 1994; Ramsey, 2002). This is primarily due to a lack of understanding around the fundamentals of health economics, and a sense of moral responsibility towards their patients, causing them to be less inclined to choose less-effective, but cheaper interventions (Wailoo et al., 2004).

Without systematic implementation of cost-effectiveness at a regional or national level, clinicians inevitably end up making their own subjective choices on how to best manage budgets, which introduces inconsistency and variation across practices. Treatments are applied until there is no more health to be gained, which will ultimately lead to the exhaustion of resources (Ramsey, 2002). The acceptance of health economics is contingent upon training and education; helping clinicians to develop an appreciation for the fine balance between the human aspect of healthcare and scarcity of resources (Eddy, 1999; Oladokun, 2016). This will encourage both clinicians and budget allocators to accept the principle which advocates the application of treatments continually until health returns diminish in relation to costs so as to improve the efficiency of care (Oladokun, 2016).

3.3.5 External Review

According to Shekelle et al (2012), criticism from external reviewers can enhance CG quality in four ways:

1) Checking the accuracy, comprehensiveness, and balance of the scientific evidence
2) Checking the validity of the rationale for recommendations
3) Feedback on the clarity and feasibility of recommendations
4) Engagement of stakeholders

The external reviewers may identify additional studies that were previously overlooked and issues with ambiguity or methodological/statistical errors. External review also provides an additional opportunity to eliminate any specialty or society bias that may exist (Fulda, 2014).

Views can be sought either through invited peer review, where individuals or groups are chosen based on their perceived ability to contribute valuable criticism, or they may be sought via public consultation, where anyone with an interest in the CGs can provide comments (Shekelle et al., 2012).

3.3.6 Clarity and Presentation

Recommendations should be easily identifiable, specific and unambiguous. Ease of information visualisation is intrinsically linked to the applicability of CGs, thus it is important that due attention is given to presentation (Kastner et al., 2015).

3.3.7 Conflict of Interest and Funding Bias

In order to preserve the integrity of CGs and ensure confidence in the resulting recommendations, organisations should make every effort possible to ensure editorial independence. This is only possible with a commitment to openness, transparency and communication (Matias-Guiu and Garcia-Ramos, 2010).

Funding bias refers to the tendency of CGs to support the interests of the financial sponsor. Electing unbiased sponsors or erecting a firewall between developers and the sponsor can mitigate against this type of bias (Lexchin, 2012).

Research suggests that CG developers are more likely to positively favour the commercial products being evaluated if they have vested financial, personal or family interests with the pharmaceutical company responsible for developing the intervention; this is known as conflict of interest (Lenzer et al., 2013; Shnier et al., 2016). This can pose an ethical dilemma for clinicians who may reluctantly follow recommendations despite the knowledge that

they are compromised by conflict of interest, potentially putting patients at undue harm (Lenzer, 2013). The way that conflicts are handled is of utmost importance, for example individuals with relevant conflicts may not be permitted to participate in the formulation of certain recommendations.

It is perhaps naïve to assume that key opinion leaders (KOLs) can ever be truly free of conflict of interest. It has been postulated that even if individuals genuinely do not have any conflict, they may be biased by their desire to work in industry in the future, although of course this is a type of conflict that cannot be avoided by any measures (Garrison, 2016). Some alternative opinion suggests that financial relationships with industry could provide unique and important expertise into the input of CG development (Institute of Medicine, 2009).

3.4 Evolution of Neurogenic Bladder Clinical Guidelines

The three most prominent CGs in NGB are those produced by the NICE, EAU and ICI. This section will provide background information on the institutions and detail the methodological evolution of the CGs.

The International Consultation on Urologic Disease (ICUD) is a non-governmental organisation registered with the World Health Organisation (WHO). The ICI is a sub-committee of the ICUD, tasked with developing recommendations with worldwide relevance for lower urinary tract dysfunction (LUTD) (Khoury et al., 2000).

Under the initiative of the WHO, the Scientific Committee of the First International Consultation on Incontinence gathered in 1998. Based on conclusions drawn at this meeting, the 'neurogenic incontinence' sub-committee devised the earliest recommendations for NGB in 2000, which were published in the Lancet scientific journal (ICI, 2000). The recommendations were top level; confined to just initial management in exclusively incontinence issues. Only two paragraphs worth of recommendations and one treatment algorithm were presented. Although the methodology involved systematic reviewing of literature, the recommendations were not graded using a validated system.

The second international conference took place a year later and resulted in a more comprehensive set of recommendations, published in the form of a book in 2002 (Abrams et al., 2002). The CGs tackled a wider range issues not covered in the initial publication; this included urinary retention, adverse events (AEs) of treatments, and patient education. This demonstrates the increased effort towards better quality CGs, which only enhanced in forthcoming years of publication. The committee sought evidence to answer particular questions relating to interventions:

1) How and when to do it?
2) Is it effective?
3) Is it safe?
4) Is it cost-effective?
5) Complications and how to treat them

They also provided conclusions (with levels to signify the strength of underlying evidence), as well as graded recommendations (to signify the strength with which the authors recommend interventions).

In the latest CGs, a broad range of urological dysfunctions are covered. Members of the working group performed SRs and updates to compile the CGs. The most recent recommendations are based on evidence and conclusions drawn in the 2013 meeting in Tokyo and were published in 2017 (Apostolidis et al., 2017).

The EAU is a non-profit organisation that formed in 1973, with the aim of improving urological practice, research and education across Europe and beyond. They develop CGs on a wide range of urological topics, including in 'neuro-urology' (NGB). The first NGB CGs were released in 2003, shortly after the second edition of the ICI CGs. Unlike the ICI, who explicitly stated their publication is not to be considered as CGs or SOC, the EAU CGs were designed to be applied directly in clinical practice. The first edition of the EAU CGs were not graded, instead, they reflected the current opinion of experts, rendering them less superior in rigour of development than the ICI CGs at this point in time. The most recent edition of

the EAU CGs, published in 2017, are of a substantially higher quality, using a validated grading system and incorporating comprehensive systematic reviewing techniques.

NICE was founded in 1999 with the aim of reducing unwarranted variation in care and encourage the fast uptake of innovations in clinical practice across the UK (Chalkidou, 2009). The institute provides evidence-based clinical care guidance for the National Health Service (NHS) through multiple initiatives. They pioneered their CG development programme in 2002 (NICE, 2018c). The first (and thus far, the only) NICE CGs for NGB entitled 'urinary incontinence (UI) related to neurological disease' were developed in 2012, considerably later than the ICI and EAU. As the name implies, the CGs are only concerned with UI, purposefully omitting urinary retention issues. They target both children and adults and were specifically designed for application to clinical practice in UK healthcare settings. As the field of EBM had made considerable strides by this time, the first NICE NGB CGs were significantly more robust than the earlier versions of the ICI and EAU.

With each new edition of the EAU and ICI CGs, the organisations adopted a more systematic and structured processes of development, which has seen the scientific rigour and consequently, their credibility also improve. Today, all three CGs have evolved to become well-respected and consulted documents for urologists, other HCPs and patients alike. Their influence reaches internationally and are often used as the basis for many national CGs.

3.5 Critical Appraisal of the NICE, EAU, and ICI Clinical Guidelines for Neurogenic Bladder Using the AGREE II Instrument.

3.5.1 Introduction

The development process (Section 3.3) differs between CGs, primarily on account of the differing goals and objectives of the institutions, the amount of financial resources available and disparate organisation membership. For example, some developers employ rigorous SR techniques whilst others weigh more heavily on expert opinion. Another key differentiating factor is the weight given to health economics, whereas some CGs include

well-integrated economic analysis to determine the most cost-effective management strategies, others focus solely on clinical outcomes. Consequently, the quality of resulting CGs also varies, which can have implications for clinical practice.

The history and growth of the NICE, EAU and ICI CGs for NGB was described in Section 3.4. In order to determine their current value in clinical practice and decipher where improvements are necessary, their quality was assessed using the AGREE II instrument. The following section describes the methods utilised and results from the study.

3.5.2 Aim

The aim of this study was to critically appraise the quality of three principal CGs for NGB using the AGREE II instrument.

3.5.3 Methods

3.5.3.1 Instrument Selection

In order to avoid the duplication of efforts an SR by Siering et al (2013) was the main source of information for instrument selection, supplemented by other evidence from the literature. Siering et al (2013) identified 40 different appraisal instruments, exemplifying the sheer amount of choice researchers are faced with when planning a quality appraisal. Options include the AGREE II instrument, the Deutsches Instrument zur methodischen Leitlinien-Bewertung (DELBI) and GuideLine Implementability Appraisal (GLIA), amongst others. The choice of appraisal instrument ultimately depends on the type of assessment that needs to be carried out. Many instruments provide an intricate assessment of quality, specifically targeted towards CG developers and decision makers in health policy. These instruments often contain multiple assessment criteria, which can be too burdensome to use within clinical practice and as a result more rapid assessment instruments with primarily busy clinicians in mind have also been developed (Siebenhofer et al., 2016).

Most of the appraisal instruments identified in the SR by Siering et al (2013), were concerned with assessing the technical aspects of CG development, principally pertaining

to the evaluation and synthesis of evidence and the formation of recommendations (88% of appraisal systems looked at the evidence evaluation process). Only 50% of the appraisal tools covered dissemination, and 45% covered implementation and final evaluation, highlighting an issue around the exclusion of many pertinent aspects affecting CG development (Qaseem et al., 2012).

An appraisal instrument that adopts a mixed methods approach provides the most effective assessment. This includes a scoring system that enables a formal quantification of the assessors' opinions thus allowing systematic cross-comparison, as well as a qualitative assessment as a means to contextualise the scoring decision (Qaseem et al., 2012). The SR by Siering et al (2013) found that only 20 (50%) of the instruments identified incorporated a scoring system, which severely limits their ability to provide a trustworthy appraisal.

The most renowned appraisal instruments for comprehensive assessment are the DELBI and AGREE II, with the latter being the internationally preferred instrument for developing and assessing CGs (Grimmer et al., 2014). The AGREE II instrument replaces the original AGREE instrument that was created in 2003 and contains modifications to items in several domains such as 'scope and purpose' and 'applicability'. The DELBI instrument contains 34 items, organised into eight domains (Beyer, 2006). The developers state that the instrument represents what high quality CGs should look like within the German healthcare system, and accordingly have a domain named "Applicability to the German Healthcare System". Omitting this domain allows the DELBI to have international relevance.

The AGREE II and DELBI both cover pertinent aspects of CG development, contain quantitative and qualitative assessment, and can be applied across a broad-range of settings. The AGREE II has been evaluated for reliability, whereas the DELBI tool has not (Siering et al., 2013). Validation is essential to verify the instrument is measuring what it is supposed to measure (Lai, 2013).

If more emphasis should be given to clinical content, then the ADAPTE (assessment module from the ADAPTE Manual and Toolkit) is a trustworthy choice. The instrument is unique, as it was developed for the adaption of local CGs from one cultural setting to another.

Although this instrument has been validated, its use is limited to appraisers who are highly skilled in EBM (Siering et al., 2013). If the main purpose is to assess the implementability of CGs in clinical practice then the GLIA instrument, developed by the Yale Centre for Medical informatics should be utilised. Some 'global questions' relate to the wider quality of the CGs but there is no scoring system attached to these items (Shiffman et al., 2005).

Based on this mini-review of the literature, it was concluded that whilst there are clear merits in all appraisal instruments, the AGREE II is the only previously validated instrument that covers all pertinent aspects of CG development. The instrument uses a scoring system and incorporates a qualitative assessment, allowing the most accurate and interpretable scoring of results. In addition, the aim of this review was to provide a comprehensive evaluation of NGB CGs therefore rapid assessment tools were not suitable.

A newer systematic review of appraisal instruments was also available (Buccheri & Sharifi, 2017). This was only discovered after conduction of the present study; therefore, it was not considered during selection of an instrument. This could be considered a limitation. Furthermore, not conducting a novel review for the purposes of instrument selection may also be considered a limitation.

3.5.3.2 The AGREE II Instrument

The present author (AJ) and a second reviewer (ES), independently assessed the quality of the NGB CGs using the AGREE II instrument. One of the appraisers (AJ) is experienced in the field of EBM, urology and health economics. The second appraiser (ES) is a urologist by training with advanced knowledge in EBM. The appraisers underwent the official AGREE II training available online (AGREE, N.D).

The AGREE II instrument has proven to have acceptable reliability and construct validity, with statistically significant ($p \leq 0.05$) differences found between high and low quality CGs in 20 of the 23 items it is composed of (Brouwers et al., 2010). The items are grouped into six domains: (1) scope and purpose (items 1-3), (2) stakeholder involvement (items 4-6), (3) rigor of development (items 7-14), (4) clarity and presentation (items 15-17), (5)

applicability (items 18-21), and (6) editorial independence (items 22-23). Table 3.1 displays the instrument domains including the questions (items) that comprise them.

Table 3.1 The Appraisal of Clinical Guidelines for Research and Evaluation (AGREE) II instrument

Domain	Questions
One – scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described. 2. The health question(s) covered by the guideline is (are) specifically described. 3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Two – stakeholder involvement	4. The guideline development group includes individuals from all relevant professional groups. 5. The views and preferences of the target population (patients, public, etc.) have been sought. 6. The target users of the guideline are clearly defined.
Three – rigour of development	7. Systematic methods were used to search for evidence. 8. The criteria for selecting the evidence are clearly described. 9. The strengths and limitations of the body of evidence are clearly described. 10. The methods for formulating the recommendations are clearly described. 11. The health benefits, side effects, and risks have been considered in formulating the recommendations. 12. There is an explicit link between the recommendations and the supporting evidence. 13. The guideline has been externally reviewed by experts prior to its publication. 14. A procedure for updating the guideline is provided.

Four – clarity of presentation	15. The recommendations are specific and unambiguous. 16. The different options for management of the condition or health issue are clearly presented. 17. Key recommendations are easily identifiable.
Five – applicability	18. The guideline describes facilitators and barriers to its application. 19. The guideline provides advice and/or tools on how the recommendations can be put into practice. 20. The potential resource implications of applying the recommendations have been considered. 21. The guideline presents monitoring and/or auditing criteria.
Six – editorial independence	22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed.

Each item is rated on a seven-point Likert scale, where the score increases as more criteria are fulfilled (seven correlates to strongly agree) (Figure 3.2). It is important to note that a score of 1 does not necessarily mean that the item criteria was not fulfilled, instead this could represent a lack of relevant information available to the appraiser to assign an appropriate score. However, this in itself could be considered a limitation as it indicates the development methodology is not transparent enough. The information used to appraise the instrument can be derived from the CG itself or supplementary information such as a technical development document. There is the chance for the appraiser to input qualitative reasoning for the score of any item.

Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree

No information/poorly reported Full criteria has been met

Figure 3.2 Likert scale AGREE II rating system

The domain scores were calculated by the following equation, formulated by the AGREE II developers:

$$\frac{\text{(Obtained score – Minimum possible score)}}{\text{(Maximum possible score – Minimum possible score)}}$$

Where the:

- Obtained score is the sum of the individual all possible item scores by all appraisers
- Minimum possible score is the minimum possible score by any appraiser x n items x n appraisers
- Maximum possible score is the maximum possible score by any appraiser x n items x n appraisers (AGREE, 2013)

The instrument also asks appraisers to make two additional assessments; on the overall CG quality, using the Likert scoring system, and on whether they would recommend the CGs for use in clinical practice, whilst taking into account their appraisals from the main six-domain review. The options for the latter question are 'Yes', 'Yes with modifications' or 'No'. The overall assessments are calculated independent of the main six-domain review.

3.5.3.3 Interrater Reliability

Given that the AGREE II appraisal is ultimately a subjective exercise, it is highly likely that the appraisers assigning scores interpret the evidence relating to each domain differently. In order to demonstrate the degree of confidence in the study results the interrater reliability was calculated in two ways; the intraclass correlation (ICC) and the Cohen's Kappa

statistic (McHugh, 2012). The IBM SPSS Statistics v. 24 (IBM Corporation) package was used to calculate these statistics.

3.5.3.3.1 Intraclass Correlation

The ICC reflects the degree of correlation and agreement between measurements and is deemed an appropriate choice of statistic in evaluating the interrater reliability of reviewers (Burton, 2000). The range of ICC is between 0 and 1, where the closer to 1 a score is, the smaller the variation between scores of raters on each item (Koo and Li, 2016). The ICC score is interpreted as per Table 3.2 below.

Table 3.2 Interpretation of intraclass correlation scores

Reliability	**Values**
Poor	$\geq$0.49
Moderate	0.5-0.74
Good	0.75-0.89
Excellent	0.9-1

Values derived from: Koo and Li, 2016

The same two independent appraisers rated each domain, and the sample of raters were selected from a larger population, therefore a two-way random effects model, based on a single rater was chosen. The level of absolute agreement between raters was measured.

Based on the overall form of the chosen model, the following calculation was used to calculate the ICC (McGraw and Wong, 1996):

$$\frac{MS_R - MS_E}{MS_R + (k-1)MS_E + \frac{k}{n}(MS_C - MS_E)}$$

MS_R= mean square for rows; MS_E = mean square for error; MS_C= mean square for columns, k= observations per object of measurement

3.5.3.3.2 Cohen's Kappa Statistic

There are some inherent limitations in using the ICC in the context of this study. The ICC relies on the underlying assumption of normality, however the AGREE II items are scored using a Likert scale, which does not produce normally distributed data, making its use questionable. This statistic was incorporated into this analysis as an overwhelming number of publications using the AGREE II instrument have made use of the ICC, thus comparability is made easier by using the same statistic (Zhang et al., 2013; Smith et al., 2015; Lucendo et al., 2017).

The Cohen's kappa statistic was calculated in addition to the ICC, to improve the statistical integrity of the interrater reliability analysis. This statistic is often used to calculate the interrater reliability when using categorical data and was developed to account for the possibility that raters guess on some variables due to uncertainty (McHugh, 2012). Similar to the ICC, the range is between 0-1, although occasionally negative scores are observed (Kvalseth, 2015). The interpretation of Cohen's Kappa can be found in Table 3.3.

Table 3.3 Interpretation of Cohen's Kappa Statistic

Reliability	**Values**
No agreement	≤0
Slight	0.01-0.2
Fair	0.21–0.40
Moderate	0.41– 0.60

Substantial	0.61–0.80
Almost perfect	0.81–1.00

Values derived from: McHugh, 2012

The Cohen's Kappa is based on the chi-square table, and is derived through the following formula:

$$\mathrm{k} = \frac{Pr(a) - \Pr(e)}{1 - \Pr(e)}$$

Pr(a), actual observed agreement; Pr(e), chance agreement

The expected chance agreement, or Pr(e) is calculated via the following calculation:

$$\frac{\left(\frac{(cm1) \times (rm1)}{n}\right) + \left(\frac{(cm2) \times (rm2)}{n}\right)}{n}$$

m^1 =column 1 marginal; cm^2 =column 2 marginal; rm^1 =row 1 marginal; rm^2 =row 2 marginal; n=the number of observations (not the number of raters) (McHugh, 2012)

3.5.3.3.3 Confidence Intervals

95% confidence intervals (CIs) were used to measure the level of uncertainty around the results. If the CI crossed zero, the result was considered non-significant, and the CI was not reported in such an instance.

3.5.3.4 Data Management

All appraisals were conducted using the online AGREE II appraisal platform, named 'My AGREE PLUS'. The system automatically calculates the scaled domain percentage scores

using the calculation displayed in Section 3.5.3.2. These scores were then copied into an SPSS document to calculate the ICC and Cohen's statistic.

3.5.3.5 Ethical Considerations

Ethical considerations were not applicable as this study utilised CGs that have already been published and there was no handling of and patient sensitive data.

3.5.4 Results

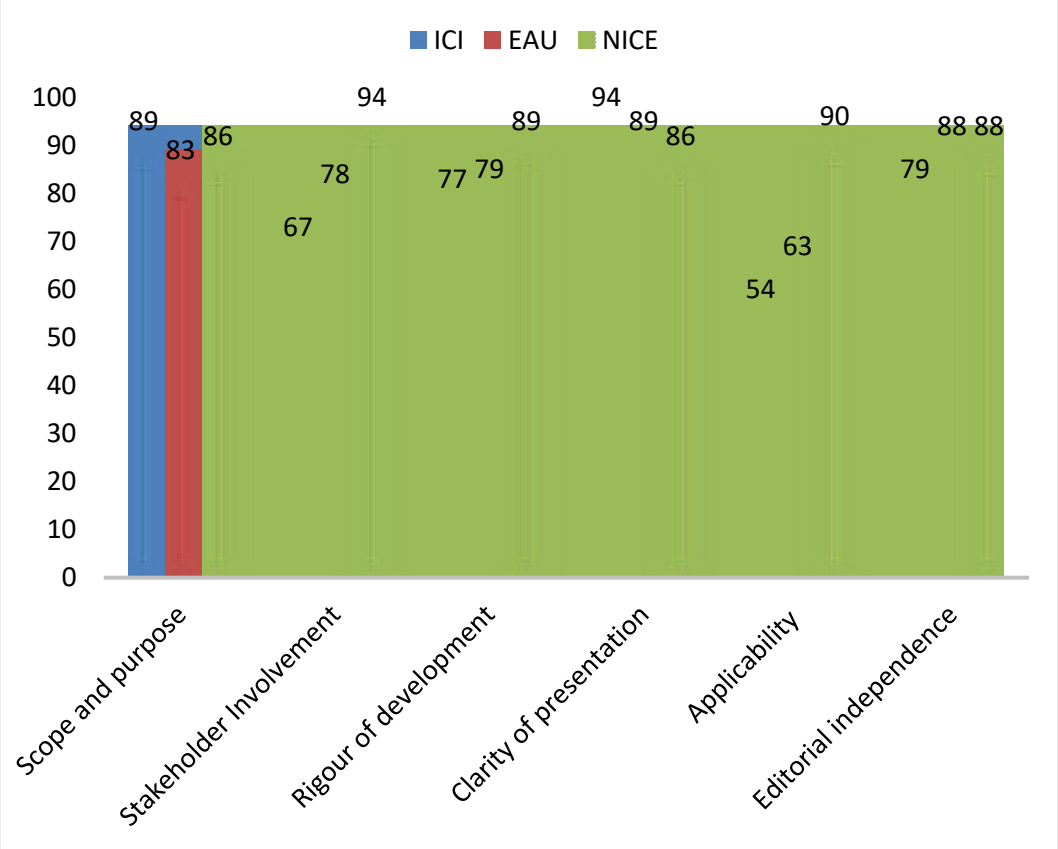
The NICE CGs were deemed highly compliant to the AGREE II domains and received an overall score of 92%. They scored highest in stakeholder involvement domain (94%), and the lowest scoring domains were clarity of presentation and scope and purpose (86% in both domains). The EAU CGs received an overall score of 83%, the highest scoring domain was clarity of presentation (89%) and the lowest scoring domain was the applicability domain (63%). The ICI CGs achieved the lowest overall score (75%) amongst the CGs. The highest scoring domain in this CG was clarity of presentation (94%) and the lowest scoring domain was applicability (54%) (Table 3.4 and Figure 3.3). The individual appraisal results for each CG can be found in Appendix 6.

Table 3.4 Scaled domain percentages for AGREE II domains in the appraisal of neurogenic bladder clinical guidelines

	Scope and purpose	**Stakeholder involvement**	**Rigour of development**	**Clarity of presentation**	**Applicability**	**Editorial independence**	**Overall score**	**Recommended for use?**
ICI	89%	67%	77%	94%	54%	79%	75%	Yes, with modifications - 2
EAU	83%	78%	79%	89%	63%	88%	83%	Yes, with modifications - 2

NICE	86%	94%	89%	86%	90%	88%	92%	Yes - 1, Yes, with modifications - 1
Average (95% CI)	86% (82.6%-89.5%)	79.7% (64.3%-95.1%)	81.7% (74.4%-89%)	89.7% (85.1%-94.3%)	69% (47.8%-83.2%)	85% (79.1%-90.9%)	83.3% (73.7%-92.9%)	

NICE, National Institute for Health and Care Excellence; EAU, European Association of Urology; ICI, International Consultation on Incontinence; CI, confidence interval



NICE, National Institute for Health and Care Excellence; EAU, European Association of Urology; ICI, International Consultation on Incontinence

Figure 3.3 AGREE II appraisal of neurogenic bladder clinical guidelines (domains 1-6)

The ICC varied from low to excellent reliability; however, CIs were not significant in some domains, and very wide in the stakeholder involvement and applicability domains (Table 3.5). The Cohens Kappa statistic varied from no agreement to substantial agreement, however most results were not significant (Table 3.6).

Table 3.5 Intraclass correlation between two appraisers of neurogenic bladder clinical guidelines

Domain	ICC (95% CI)	Degree of agreement
Scope and purpose	0.4	Poor
Stakeholder involvement	0.8 (0.4-1)	Good
Rigour of development	0.5	Moderate
Clarity of presentation	0.7 (0.1-0.9)	Moderate
Applicability	1 (0.9-1)	Excellent
Editorial independence	0.3	Poor

Where the 95% confidence interval (CI) is not presented this indicates that the CI crossed 0, therefore the result is not significant.
Degree of agreement from Koo and Li, 2016

Table 3.6 Level of agreement between two appraisers of neurogenic bladder clinical guidelines - Cohen's kappa statistic

Domain	Cohen's Kappa (95% CI)	Degree of agreement
Scope and purpose	0.3	Fair
Stakeholder involvement	0.6 (0.2-0.9)	Moderate
Rigour of development	0.2	Slight

Clarity of presentation	0.5	Moderate
Applicability	0.9	Almost perfect
Editorial independence	-0.2	No agreement

Where the 95% confidence interval (CI) is not presented this indicates that the CI crossed 0, therefore the result is not significant.
Degree of agreement from Landis and Koch, 1977

3.5.5 Discussion

The study demonstrated that quality varied moderately across the AGREE II domains as well as between the NGB CGs. Amongst all CGs, the highest scoring domain was clarity of presentation and the lowest scoring was applicability. NICE achieved the highest overall score and the ICI achieved the lowest overall score, however all CGs were deemed to be of high quality and were recommended for use in clinical practice (mostly with some modifications, apart from one appraiser that deemed the NICE CGs did not require modifications).

To the best of the researcher's knowledge, this is the first study that assesses the quality of currently available NGB CGs. The aim of the following discussion is to provide an in-depth analysis, considering how well the NICE, EAU and ICI CGs fulfilled the requirements of the AGREE II domains.

3.5.5.1 Level of Agreement Between Appraisers

The level of agreement between reviewers varied substantially between poor to excellent in the ICC and no agreement to substantial in the Cohen's kappa statistic. The two statistics were similar in terms of degree of agreement.

The lowest level of agreement was observed in the editorial independence domain, where an ICC level of 0.3 (poor) and Kappa score of -0.2 (no agreement) was reached. The Kappa score demonstrated slight agreement (0.2) in the rigour of development domain compared

to moderate agreement (0.5) in the ICC. The applicability domain demonstrated full agreement between the appraisers (ICC=1), and almost perfect agreement (0.9) in the Kappa statistic. This was also the most significant result in the ICC, with a narrow confidence interval of 0.9-1.

3.5.5.2 Scope and Purpose (Domain One)

This domain reviews whether the overall aim of the CG, specific health questions and target population are described in a sufficient level of detail (Section 3.4.1) (Brouwers et al., 2010). All CGs scored highly in this domain. The ICI scored the highest (89%) due to the comprehensive way in which the patient population was described and the detailed aims of development. This was followed by NICE (86%) and the EAU (83%).

Before the NICE CGs were created, the UK lacked national CGs for NGB, thus they filled an important gap in clinical practice. The objective of the EAU and ICI is to standardise urological practice across European and International spheres respectively, thus given that many CGs for NGB are limited to a national scope and often confined to management in one neurological condition, these CGs also fill a very important gap.

According to EAU CGs, there are four aims that are of paramount importance when treating NGB, regardless of aetiology. Clinicians must choose the best course of management to ensure these aims are met. The aims, in order of priority are:

1) Protection of the upper urinary tract
2) Improvement of UI
3) Restoration of some lower urinary tract function
4) Improvement of the patient's Quality of Life (QoL)

These recommendations delineate the specific health benefits the EAU hope to achieve with implementation of their recommendations. The aims of NICE and the ICI are not as detailed. NICE's objectives for their NGB CGs are 'to improve care by recommending specific treatments based on what symptoms and neurological conditions people have'. They do not make reference to any specific improvements in patients' health. The ICI's

objectives also do not specifically relate to NGB, instead they provide overarching aims for all of their CGs relating to LUTD. The aims of the ICUD are:

1) To update present knowledge and modern management of the thematic disease and assess the cost-effectiveness of various diagnostic and therapeutic options.
2) To prepare recommendations, based on the most convincing information available, for a number of selected topics.
3) To prepare, whenever possible, consensus or a widely accepted strategy concerning diagnosis and treatment according to evidence based medicine.

Information on patients' demographics, signs and symptoms, clinical results and typical comorbidities should be included to ensure precision in describing the target population (Rosenfeld and Shiffman, 2009). The ICI CGs in particular did an excellent job of accurately describing the NGB population. They provided context around how complex and heterogeneous this population is and how this introduces obstacles in proficient management. None of the CGs considered the common comorbidities patients may have. This is an important omission because comorbidities can influence the neurological condition, urological dysfunction, as well as modifying treatment effects.

Both NICE and the ICI CGs present the specific health questions covered. NICE have unique healthcare questions for every sub-topic, relating to efficacy, safety and costs. For every sub-section the ICI provide a comprehensive overview of the safety and efficacy of treatment options. The EAU have only provided health questions sporadically, thus it is unclear in which manner the information in sub-sections without health questions has been sought.

3.5.5.3 Stakeholder Involvement (Domain Two)

The stakeholder representation domain evaluates the extent to which CGs have accurate representation from all relevant intended users (Section 3.4.3). The appraisal revealed that the individuals responsible for developing and providing input into the NGB CGs are notably dissimilar between the three organisations. Due to the exceptional consideration given to

stakeholder involvement, NICE scored the highest in this domain (94%). The EAU and ICI achieved lower scores in this domain (78% and 67% respectively).

NICE's principles of openness and transparency are symbiotic with their role as a public body (Chidgey et al., 2007). This means that their guidance is developed, not only with experts in the field but through a rigorous process of cross-collaboration with specialist and/or general physicians, as well as lay representatives. These representatives make up the Guideline Development Group (GDG). NICE also engages with stakeholders who may be affected by the CG recommendations, this includes, but is not limited to; patients, practitioners, local Healthwatch organisations and commercial industries related to public health. Registered stakeholders such as these have a considerable part to play in the providing feedback on the draft CGs through their highly personalised and relevant experiences.

In contrast to NICE, the development groups for both the EAU and ICI NGB CGs are made up almost exclusively of neuro-urological experts. To their credit, the two CGs made considerable effort to ensure global representation of experts, which increased their applicability. The EAU scored slightly higher than the ICI, as where possible, they sought input from patients during the development of the SR questions and drafting of recommendations. Further information pertaining to the exact process by which the patient input is incorporated is not provided, which could be an indication that it is not done in a structured manner. In the ICI CGs some consideration given to QoL in the discussion of treatments; however, at present, very little input is directly sought from patients. The developers acknowledge that increased efforts to incorporate the patient voice into their CGs is necessary.

NICE and the EAU need to improve the transparency with which the stakeholder's comments are incorporated into recommendations. In other words, more information could have been made available on the issues patients/GPs raised and how these shaped the resulting recommendations.

It is widely accepted that broad stakeholder representation, in particular, that of patients is necessary in the development of CGs (Section 3.4.3.2). However, some alternative judgement suggests that there is in fact no empirical evidence supporting the idea that patient participation enhances the quality of CGs, particularly owing to the unstructured way in which their opinions are incorporated, and the lack of support offered to them (van de Bovenkamp and Trappenburg, 2009). NICE have taken measures to ensure that all members of the GDG have equal chance to contribute, and that lay members are offered training to improve their capabilities in critical evidence appraisal. This suggests that patient involvement has a well-integrated and accommodated for role, ensuring that their participation has the ability to enhance CG quality. However, despite measures to improve patient input, there remains some risk that the individuals involved are not accurately representative of that patient population as a whole. One of the requirements NICE advertises to participate in a GDG is the ability to understand scientific articles, which would suggest this opportunity is only available to highly educated individuals who represent a small segment of a wider lay group (van de Bovenkamp and Trappenburg, 2009).

Neurologists are also an important, yet uninvited addition to the development group of all the NGB CGs. Neurologists can provide valuable insight into the issues patient's face because of their primary condition, and how these interplay with their LUTD. The inclusion of UK neurologists into NGB CG development may however be a difficult task to achieve. Firstly, despite having one of the highest prevalence rates of conditions such as MS, the UK scores third worst in Europe for numbers of neurologists per person (MS society, 2011). This indicates there may be potential difficulty in recruiting UK neurologists, as their time is limited in a resource-deprived environment. Consequently, organisations may need to focus their recruitment efforts in other parts of the world. Another issue may be the unwillingness of neurologists to offer their time and expertise on this topic, due to a presumed lack of understanding on the importance of urological issues (Drake and de Ridder, 2017).

Benefits in terms of enhancing neurologists understanding of NGB are likely if they are actively involved in CG development. This could encourage increased uptake of the CGs by neurologists working in clinical practice, owing to an increased sense of ownership over the CGs. The development process also encourages active dialogue between neurologists and urologists. Communication and consensus are especially important when constructing recommendations for contentious issues that affect both these stakeholders. One such example of this is the use of central acethylcholinesterase (ACE) inhibitors that are often prescribed by neurologists for amelioration of cognitive functioning in patients with Alzheimer's disease (AD) (Gao et al., 2013). There remains controversy over whether these drugs can exacerbate UI and/or cognitive impairment (Demaagd and Davenport, 2012). By considering the evidence and constructing these recommendations together, both expert opinions can be integrated and given due credence.

3.5.5.4 Rigour of Development (Domain Three)

This domain relates to the thoroughness with which the SR was conducted, and how results were synthesised. It also evaluates the link between recommendations and the supporting evidence, whilst asking appraisers to determine whether key concerns such as health benefits and risk profile were considered. The NICE SR process was deemed the most superior, thus achieved the highest score in this domain (score 89%). This was followed by the EAU (79%), the ICI (77%).

The NICE process involves a specific team for evidence review, made up of an information specialist, systematic reviewer and (in most cases) an economist, who independently and systematically review all available evidence from RCTs and observational studies. Searches are conducted using a wide range of sources, including grey literature. Although the broadest possible search is employed, effort is also made to strike a balance between specificity and sensitivity of the search strategy.

The EAU previously employed a condensed process of evidence review due to the sheer scale of reviewing all available literature for the 20 separate CGs that the organisation

develops (Aus et al., 2009). Young clinicians known as Guideline Associates (supported by methodologists and statisticians) appraised SRs, meta-analysis and some RCTs (as opposed to original research papers included by NICE). The institution recently announced a gradual implementation of the Cochrane methodology across their CG panels. The 2017 version of the NGB CGs contained three new SRs using the Cochrane methodology, thus elevating their score for this domain. There are plans for further SRs to be conducted where the appointed CGs panel will select the clinical questions. Although a step in the right direction, there will continue to be inconsistencies in the level of rigour for each health question until complete implementation of the Cochrane methodology is achieved.

The recommendations of the ICI CGs are based mainly on the subjective knowledge of the experts, using evidence from a comprehensive literature search from multiple sources (Syan and Brucker, 2016). The topic of interest is studied collaboratively by ten international committee members over email and face-to-face meetings, for a period of two years. Members submit their conclusions and recommendations at the end of the two years for discussion with thousands of other colleagues at a plenary session. The committee members then edit a consensual summary of the recommendations, which are submitted to WHO and subsequently published. The consultation takes place again every 2-3 years (Khoury et al., 2000). Although still deemed to be of high quality, this method of development was considered to be less rigorous than the NICE and the EAU, and consequently the ICI scored the least in this domain.

Recommendations in all three NGB CGs occasionally relied on expert opinion, which is evidenced by the often-conflicting guidance between them (Chapter 4). Unfortunately, as the evidence base underlying NGB is sparse and mostly composed of trials with perceived weak methodological design, such inconsistency cannot be avoided.

All three CGs used a validated grading system to assess the strengths and limitations of the underlying body of evidence. In the NICE review, the GDG make the ultimate decision on the content of recommendations through considering both the evidence and their own experiences and knowledge of the disease area. Quality assurance is integrated throughout

the duration of the development process, ensuring there are few deviations from the pre-determined development process and that the evidence incorporated is 'up-to-date, credible, robust and relevant', with a clear link to the resulting recommendations. Recommendations are based on the highest-level of evidence available.

NICE use the GRADE appraisal system for rating the overall quality of evidence and grading of recommendations, however the terminology used differs slightly to the use of levels and grades. If there is a strong body of empirical evidence to support a recommendation, clinicians should 'offer' the treatment. If evidence is weak, then the clinician should 'consider' the treatment. EAU and ICI use distinct modified versions of OCEBM 2011. In the EAU CGs, recommendations are given a level of evidence ranging from 1-4, as well as a grade from A-C to represent the strength of the recommendation. Contrastingly, the ICI assign a level of evidence to conclusions drawn from the literature, and then further award a grade to recommendations. All grading systems are viable; however, the GRADE methodology is generally considered superior to other grading systems (Section 3.4.2).

External review from experts (and in some cases patients), that were not involved in the development of the CGs and having an explicit procedure for updating the CGs also garners high scores within this domain. The NICE CGs invite feedback on their draft CGs from stakeholders via their website for a 6-week period of public consultation. Changes may be made to the CGs in light of comments received. Although there is a process for external review, NICE do not routinely commission peer review by external experts such as practitioners or academics. In contrast, the ICI and EAU CGs are not crosschecked and validated via external means, leaving room for unimpeded error, and thus causing them to lose points in this domain.

3.5.5.5 Clarity of Presentation (Domain Four)

The clarity of presentation domain pertains to the quality of presentation of the CG and whether all relevant interventions have been considered. The extensive list of treatments analysed and compared, as well as good aesthetic considerations helped the ICI CGs

achieve the highest score in this domain (94%). This was followed by the EAU (89%) and then NICE (86%).

All CGs developers gave apposite attention to the proper placement of visual elements, including diagrams and visuals where necessary. The NICE CGs are structured with the following headings: treatments to improve bladder storage, stress incontinence, bladder emptying, catheter valves, ileal conduit diversion, and treatments to prevent UTI. The recommendations are based on symptoms, whereas the EAU and ICI base their recommendations on urodynamics. The EAU and ICI CGs are structured more simply, with the management of NGB split between 'Non-invasive treatment' and 'Surgical treatment'. The EAU feature further subheadings and provide additional recommendations for urinary tract dysfunction and sexual dysfunction. All CGs presented their final graded recommendations in an easily identifiable table below a comprehensive discussion of the evidence, which was deemed to be an informative and intuitive choice of display.

In addition to aesthetic considerations, it is important that all possible management options are presented, so that end users can make fully informed clinical decisions. The ICI do not promote their CGs to be directly applied in clinical practice, instead they are endorsed as the reference document for the condition of interest (in reality however they may still be interpreted as CGs and be applied in clinical practice). Because of their broad objective, the ICI consider an exhaustive number of management strategies, many of which were not mentioned in the other CGs such as oestrogens, certain types of electrical neuromodulation, and several surgical techniques (ICUD, 2015).

NICE did not consider an exhaustive list of treatment options which could be due to their narrow remit, focusing specifically on UI, consequently, they scored the lowest in this domain. The EAU lost points, as despite providing a thorough discussion on behavioural techniques, no graded recommendations were made for this type of management. the developers of the CG do not disclose the definite reason however the limited evidence base may have precluded the formation of solid recommendations.

3.5.5.6 Applicability (Domain Five)

The applicability domain assesses the measures taken to improve uptake, how well uptake is monitored, and the consideration given to the resource implications. Implementation into clinical practice is considered throughout the duration of the NICE CG development process, thus they scored exceptionally high in this domain (90%). Scores were much lower for the EAU and ICI, awarded 63% and 54% respectively. Discussion of this domain is subdivided into implementation and dissemination, health economics, and auditing and monitoring.

3.5.5.6.1 Implementation and Dissemination

NICE consider the most important populations and the feasibility of implementation for the most challenging institutions during the initial scoping. This ensures their recommendations could be applicable to across all possible institutions, including the most resource deprived.

Both NICE and the EAU have dedicated teams to promote implementation of the CGs. NICE's implementation team work with local organisations to develop strategies for adapting recommendations locally, using two important tools, the 'baseline assessment tool' and the 'costing statement', which help health authorities estimate the likely financial impact of adopting the recommendations. The EAU strives for harmonisation in urological care across all EU Member States, thus they have a much larger task than NICE in achieving optimal implementation of their CGs. The EAU's 'IMpact Assessment of CGs Implementation and Education (IMAGINE)' team is tasked with overcoming barriers to implementation and education of key stakeholders. Unfortunately, there is little information freely available online that explains the exact activities of the IMAGINE group. Perhaps due to their worldwide relevance, the ICI CGs do not have a dedicated implementation team. In the early years of development, a sub-committee named 'Faecal Incontinence and Incontinence in the Developing World', created tailor-made recommendations for countries with underdeveloped or resource-deprived healthcare

systems; however, this committee has not featured in the CGs, nor made recommendations since the second edition of publication.

A multi-faceted approach to dissemination is necessary in order to reach the widest possible audience, and achieve the greatest impact (Suman et al., 2016). The EAU and NICE publish abridged versions of their CGs to reach a diverse range of stakeholders. The EAU's abridged CGs, named 'pocket CGs', are aimed at busy urologists. NICE's version is published on their website, which makes them easier for various stakeholders to access. Recommendations also appear in the 'NICE pathways', which are interactive flowcharts that provide an intuitive way to read recommendations, reaching a population that may otherwise have little time to read the full edition (NICE, 2018e). In contrast, the ICI do not actively promote dissemination of their recommendations, as they are foremost targeted towards ICI members and urologists. Their guidance is published as a book which is available for a fee from their website. A publication is also made in the journal 'Neurourology and Urodynamics'. The publication allows users to view the recommendations in a shorter, easier-to-read format; however, it is still not as accessible as the EAU's pocket-guideline, or NICE's online versions. Furthermore, passive methods of publication in professional journals are unlikely to change practice (Hoecke and Cauwenberge, 2007). Furthermore, the level of complexity of CGs has proven to be inversely proportional to its adoption and compliance (Scott, 2008; Gurses, 2010). Therefore, although the ICI CGs could be directly applied to clinical practice, their comprehensiveness may in fact impede the possibility of this.

The EAU is unique from the other CGs in that it also has a designated team named the 'Social Media (SoMe) working group', who are responsible for promoting the CGs on Facebook and Twitter by creating polls and updates highlighting key recommendations (Loeb et al., 2017). This is a particularly impactful means of dissemination, in an age where SoMe has become a frequent vehicle to disseminate medical information. The EAU is also endorsed by 41 National Urological Societies worldwide, who promote the CGs.

It is not clear whether any of the CGs are disseminated via means of CDSS, but this would most likely depend on individual institutions or national policies.

3.5.5.6.2 Health Economics

NICE are the only CG to incorporate economic evaluations into their recommendations. Importantly, costs are integrated during the recommendation development process (Eccles et al., 2000). This approach ensures that costs are not calculated in isolation of clinical efficacy, which would derive erroneous results (Mason, 1998).

De-novo economic analysis is conducted where necessary, but in most cases previously published economic literature and relevant technology appraisals are utilised (Drummond, 2016). One could argue that the economic evidence that was not formulated de-novo lacks applicability to the specific health questions asked because previously published evaluations are conducted from a wide range of perspectives, analytic techniques, using disparate baseline data (Woolf et al., 2012).

In the UK, only certain medicines and medical devices are invited by NICE to submit health economic data for reimbursement, which means many new technologies are not reviewed (Parvizi and Parvizi, 2017). In addition, interventions introduced pre-NICE's technology appraisal system have not been evaluated for their cost-effectiveness. This could introduce a distortion in health care policy, where newer technologies are evaluated with greater scrutiny than those existing in the pre-NICE technological appraisal era (Mason, 1998). In theory, the integrated cost-effectiveness in CGs can remedy this by providing an oversight of the whole disease area; reviewing all current treatments available. However, in order for this to happen, NICE would need to consider wider studies of multiple competing interventions (Drummond, 2016). Ranking interventions in order of cost-effectiveness and working down until the budget is completely spent has been proposed as the superior way to create a truly cost-effective CG (Brockis, 2016). However, this method is not feasible because the number and variety of interventions, patients, settings and other variables is too large and the resources necessary to conduct such a monumental task would be difficult to procure (Drummond, 2016; Birch and Gafni, 2004)

The CG economic evaluation is conducted in complete isolation from the NICE Health Technology Assessment (HTA) program via a distinct methodology, in fact the GDG is not permitted to access health economic data from the programme (Wilsdon, 2013; Brockis, 2016). This lack of coordination can result in potential discrepancies in the recommendations made in the NICE NGs CGs and reimbursement decisions, consequently leading to inefficiencies for the NHS, and confusion amongst prescribers (Wilsdon, 2013).

Due to their broad country remits, no cost assessment or consideration to resource constraints are given in the EAU or ICI CGs. It would be difficult to generalise costs, access conditions and resources across multiple countries as they have notably different healthcare systems and face unique challenges when it comes to resource allocation and cost containment. This reality casts uncertainty on EAU's mission to harmonise urological care across Europe. There are however some technical solutions to transferring cost data that were not considered by these CGs. A study focusing on three chronic diseases; type 2 diabetes mellitus, epilepsy and schizophrenia across multiple countries concluded that calculating the raw cost data into percentage of gross domestic product (GDP)/capita of individual country was a feasible approach to transfer the direct medical cost across countries (Gao et al., 2016).

Another possible reason that the EAU and ICI did not include economic analyses is the paucity of high-level economic analyses in the literature. This is particularly true for NGB, where there is also a scarcity in basic cost data preventing de-novo analyses. Whilst charge data may be available, the analytical steps and assumptions required to transform it to cost data can be complex (Eccles et al., 2000). Large scale epidemiological studies such as the one presented in Chapter 6, 7 and 8 of this thesis are necessary to fill this gap.

Alternatively, the EAU and ICI CGs may have not included economic analyses because interventions that demonstrate benefits in the future (for example, smoking cessation), rather than having immediate impact such as NGB, are more likely to include economic analysis, as there may be greater rationale to justify program benefits economically (Wallace et al., 2002).

Unlike the ICI CGs, the EAU CGs are intended to be directly applied to clinical practice, which may in fact not be possible due to the lack of attention given to costs. In particular, when considering a country with a weak economy, adopting costly technologies would be near impossible. Countries that are looking to adapt these CGs to their local healthcare systems should conduct their own economic assessment, taking account the issues specific to their country (Wise and Billi, 1995). This could nonetheless be challenging to execute, as the skills required for economic analysis are unlikely to be available in every local setting, and can also prove expensive (Drummond et al., 2003; Silagy et al., 2002).

3.5.5.6.3 Auditing and Monitoring

Auditing and monitoring uptake are essential to highlight whether additional implementation and dissemination efforts are necessary. NICE have a dedicated programme for monitoring CG uptake; however, this is limited to some selected CGs. Upon checking the 'NICE uptake data' page in 2018, data on the uptake of the NGB CGs was not available (NICE, 2018b).

The EAU Twitter platform has been used to estimate adherence to recommendations, but this is not an accurate measure. The ICI CGs are used as the basis for other national CGs; however, they do not provide monitoring data around which institutions have utilised their CGs in this way.

3.5.5.7 Editorial Independence (Domain Six)

This domain seeks to assess how well the CGs have achieved editorial independence. In the first iteration of the AGREE instrument, appraisers were only asked to assess whether potential conflict of interest had been recorded. The AGREE II instrument goes one step further and asks whether provisions have been made to address the potential conflict. The NICE and EAU CGs have specific and detailed policies on how to manage conflict of interest; hence, they scored highly in this domain (88% in both CGs). The ICI scored much lower (79%).

When analysing funding sources, there seems to be little risk of bias. NICE is funded by the NHS, whose main goal is to provide good healthcare to all individuals in the UK, irrespective of wealth (NHS, 2015b). The EAU and ICI both are independent, self-funded bodies with the ultimate goal of improving urological care.

None of the CGs included into this study were pharmaceutical industry funded; however, some of the developers did declare financial relationships with the industry, which could have skewed their perspectives about certain interventions. The NICE and EAU CGs place high emphasis on the importance of managing conflict of interest effectively. Cautionary measures are employed such as routinely collecting conflict of interest information (rather than the standard single collection at the beginning of development) and excluding development members from developing recommendations related to their area of conflict (NICE, 2014b; EAU, 2017). As with all stages of the CG development process, transparency in the conflict of interest process is of paramount importance. Although the ICI CG developers are under obligation to disclose all likely conflicts, procedures for managing them could not be identified, which implies their process is less rigorous than NICE and the EAU. For this reason, the CGs achieved a lower score in this domain.

Despite the adoption of cautionary measures, there remain disadvantages to the current conflict of interest management processes. Relying upon a process of self-reporting runs the risk of making important omissions, and there is no other choice but to rely upon the honesty of all parties involved (Graham et al., 2015). Some have argued that a public database listing payment made to experts by the industry would increase transparency, however even with such a measure, it would remain difficult to list all potential conflicts (Norris et al., 2011).

3.5.6 Comparison to Previous AGREE II Appraisals of Similar Clinical Guidelines

Two studies that measured the quality of the NICE, EAU and ICI CGs in the disease area of urology using the AGREE II instrument were identified. Whereas one study assessing the quality of the CGs on urinary incontinence was more liberal in their judgement (Syan and

Brucker, 2016), the other study focusing on CGs for non-neurogenic male LUTD reported fairly similar results to the present study (Chua et al., 2015).

In the present study and the study by Chua et al (2015), none of the CGs scored 100% in any domain. Conversely, all three CGs in the study by Syan et al (2016) received 100% in the scope and purpose, stakeholder involvement, and clarity of presentation domains. Furthermore, Syan et al (2016) deemed all three CGs to have excellent (100%) quality overall. Given there were intrinsic differences in development, and obvious issues such as a clear lack of stakeholder representation in the EAU and ICI CGs, the perfect scores awarded by Syan et al (2016) do not seem apt.

Both our study and the study by Chua et al (2015) deemed the applicability of the ICI CGs to be very low, scoring them 54% and 45% respectively. In contrast, Syan et al (2016) judged the applicability of these CGs in clinical practice to be feasible with little to no modification to current development procedures, scoring them 83%. This is surprising considering the ICI gave very little attention to implementation and dissemination techniques.

In some domains, such as clarity of presentation the study by Syan et al (2016) mirrored the results of this study more so than Chua et al (2015). In the present study, the ICI CGs were deemed very high quality for clarity of presentation (94%), similarly Syan et al (2016) gave them a perfect score (100%). Conversely Chua et al (2015) only scored the ICI CGs 64% in this domain.

This comparison to other studies in this area highlights the immense subjectivity that comes with assessment of quality. The appraiser's perceptions could have been conditioned by a number of factors such as their experience in the EBM field, the weight they give to each domain in the AGREE II instrument, and even the day on which they conducted the appraisal. These findings suggest that although inter-rater reliability may prove to be high within any given a study (although, both of these studies did not report statistics of interrater reliability), when looking across studies this may not be the case.

3.5.7 Limitations

A major limitation when conducting quality appraisals pertains to the ambiguous definition of quality. The AGREE II developers do not provide thresholds for what should be considered 'low quality' and 'high quality', thus interpretation of the resulting scores was ultimately based on capricious human judgement. A third of AGREE II users have specified their own threshold level to indicate 'high quality' (Hoffmann-Esser et al., 2017), however the level is largely inconsistent across studies. Some have used the threshold of 50% to indicate acceptable quality, with any domain that scores <50% considered to be of limited use (Lo Vecchio et al., 2011). Other studies have chosen a threshold of 60% in at least three domains to indicate high quality (Fehlings and Nater, 2015). A valid basis for thresholds would require a detailed and transparent approach, whereas many studies utilising them did not report their rationale for choosing a particular cut-off. The inconsistency and lack of evidence surrounding threshold values is the reason they were not incorporated into this study.

The overall assessments are scored completely independently of the main six-domain scores; however, the results from the main-domain assessment are still expected to be considered. Alonso-Coello et al (2010) noted that:

… the validity of the overall assessment may be limited, as there were no clear rules on how to weigh the different domain scores in making a decision about whether or not to recommend the CGs (Alonso-Coello et al., 2010: e58)

Due to the of the lack of clarity, many authors using the AGREE II instrument have erroneously calculated a weighted average of the six domains to comprise their overall assessment (Hoffmann-Esser et al., 2018). In other cases, domains three (rigour of development) and five (applicability) had a greater influence than the other domains in determining the overall score.

Although the number of appraisers in this study was in line with the recommendations from the AGREE collaboration (they recommend at least two, but preferably four appraisers), increasing this number could have improved the interrater reliability. The number of appraisers necessary to reach an ICC of 0.7 ranges from two to five across domains (Zeraatkar et al., 2016). Furthermore, the external validity of quality appraisal studies may be low due to the subjectivity of the appraisal exercise. Repetition of the assessment several times by multiple appraisers, and pooling together the results could remedy this issue.

More information was publicly available on the NICE method; therefore, it may have been useful to request additional information from the EAU and ICI on their development process. However, given that the published CG remains the only practical source of information for most stakeholders, the results are most relevant without grey sources of information.

One of the authors of this study (MJD) was involved in the development of the ICI CGs, which could have introduced an element of bias. However, they were not involved in the appraisal of any of the CGs, thus their involvement did not risk the study results immensely. In addition, three authors work in Urology Research and Development (R&D) based roles for a pharmaceutical company (AJ, ES & JN), which raises an important conflict of interest, although the fact that they are in non-promotional roles mitigated some of this bias. All authors are based in the UK, which could also have affected the reliability of conclusions. Steps that were taken to reduce bias include the same two appraisers assessed all domains using the AGREE II tool, and the anonymisation of results, meaning there was no communication during the appraisal process.

3.5.8 Further Considerations

Mainstream opinion suggests that attention to the quality of CGs is undoubtedly an important facet of development because this is what usability is ultimately dependent upon; however, there is some opinion to suggest otherwise.

A modified Delphi panel was conducted in 2008 to determine whether good technical quality translated into CGs that providers will find acceptable (Nuckols et al., 2008). Of the five CGs deemed to have excellent technical quality as determined by the AGREE II instrument, according to the providers, four CGs were considered moderately comprehensive and valid, and one CG was deemed invalid overall.

This study highlights the current misconception that high quality CGs will automatically be applicable to experts working in the field. Even if feasibility issues have been addressed, there still remains questions around how well the CGs relate to clinical practice. This also challenges the significance of the EBM hierarchy, and how applicable RCTs are in real world decision making. The perception that observational research and expert opinion is always inherently of lower value should be challenged.

3.5.9 Conclusions and Recommendations

This study demonstrated that quality varied moderately across the AGREE II domains as well as between the NGB CGs. Amongst all CGs, the highest scoring domain was clarity of presentation and the lowest scoring was applicability. NICE achieved the highest overall score and the ICI achieved the lowest overall score, however all CGs were deemed to be of high quality and were recommended for use (mostly with some modifications).

The lower score overall for the ICI CGs could partly be attributed to their contrasting purpose of development and intention of use as an international guidance document. NICE CGs were deemed to be of the highest quality due to characteristics such as the involvement of multiple stakeholders and economic evaluation of treatment options. It is important to note that NICE has steady funding from the UK government, which makes fulfilment of many of the AGREE II domains a lot easier. The EAU has some promising initiatives such as increased involvement of patient groups and gradual implementation of Cochrane methodology that will elevate the quality in coming years.

The findings support the importance of enhanced cross-speciality interactions, which will result in increased harmonisation of development methodologies, and ultimately improve and standardise outcomes for NGB internationally. One of the most challenging barriers will be ensuring the clinical and economic applicability of recommendations to a diverse range of healthcare systems across the globe. This will require considerable resources in order to conduct the distinct SRs and economic analyses for each country. Alternatively, aiding countries, and in some instances, states or hospitals to carry out adaptions to their local settings present a viable option. Considering there will be three sources of funding in this tripartite, resourcing will likely be manageable. NICE's remit is to only provide guidance for the UK, therefore it may seem as if their resolve to be involved in an international venture may be missing. However, it could align with their initiative 'NICE international', which offers advice to governments around improving health policy through enhancing their evidence synthesis and review capabilities (NICE, 2009).

Increased collaboration between not only experts, but also a wider range of stakeholders is necessary to ensure external validity of the CGs to target healthcare systems. Nevertheless, it is important to consider that with additional collaboration, there is a risk that reaching consensus may become more difficult, especially amongst institutions with contrasting objectives.

3.6 Chapter Summary

This chapter involved a novel and thorough assessment of the prominent CGs currently available for use in NGB, using the AGREE II instrument. The study gives assurance to users of the CG that they are evidence-based and follow high-quality methodological process of development. It also highlights several shortcomings which should be addressed to enhance the quality of care for NGB patients.

The next chapter tackles a separate but indubitably connected topic of recommendations made in the CGs. A CG with high methodological quality production is more likely to have relevant and appropriate recommendations. Given that the CGs utilised distinct methods

of development and often relied on expert opinion, this may translate in differing recommendations, which can cause varying drug utilisation patterns and therefore variations in clinical practice.

4) Chapter Four - Differences and Similarities in the NICE, EAU and ICI Neurogenic Bladder Guidelines Treatment Recommendations

4.1 Introduction

The previous chapter presented the Appraisal of Guidelines for Research & Evaluation (AGREE) II critical appraisal of the most prominent clinical guidelines (CGs) for neurogenic bladder (NGB). The appraisal demonstrated variations in the development processes of the different institutions. Given that there is only one evidence base for NGB, it is of interest to determine whether as a consequence of the differing development processes, the institutions have interpreted the data differently and whether this translated in contrasting recommendations.

In this chapter, the recommendations for the management of NGB were compared between the CGs, to determine the level of concordance. This research provides further insight into how sufficient the current management of NGB patients is in clinical practice. Additionally, the evidence gap that persists in this disease area is investigated and possible solutions to closing it are put forward.

4.2 Contrasting Recommendations in Clinical Guidelines and the Implications

There are myriad treatment options for the management of NGB, supported by a substantial corpus of evidence (Dorsher and McIntosh, 2012). The evidence base is however composed mainly of trials with perceived weak methodological design, leaving room for subjective expert opinion and personal judgements to influence the resulting recommendations. This could lead to conflicting recommendations between institutions. Notably, the AGREE II appraisal uncovered the use of different evidence appraisal systems

(GRADE and OCEBM), which can often result in contradictory interpretations of the underlying evidence base. Furthermore, the incorporation of health economics in some CGs (NICE) and omission in others (EAU and ICI) is bound to result in divergent conclusions. Research in other disease areas has demonstrated that CG developers will arrive at different conclusions, even within national borders and despite a common evidence base (Burgers et al., 2002).

Contrasting recommendations between CGs create uncertainty for healthcare professionals (HCPs) and patients when devising management strategies, ultimately leading to sub-optimal standards of care (SOC). Where one CG may advocate for the use of a certain technique, another may prohibit it, consequently the dilemma arises of which recommendation should be followed. For clinicians fearing the risk of medical negligence litigation, this situation can prove onerous (Samanta et al., 2006). For patients, this confusion can imperil their right to make informed decisions regarding treatment options. Contrasting recommendations can also affect the standardisation of care, which can cause the overuse of certain medical procedures and techniques in some geographical areas and underuse in others (Brownlee et al., 2017) This threatens patient health and hinders the ability to appropriately allocate budgets (Wallace et al., 2002).

4.3 Aims

The aim of this study was to assess the concordance of prominent NGB CGs. The similarities and differences of treatment recommendations made in the NICE, EAU and ICI CGs were assessed.

4.4 Ethical Considerations

The CGs considered in this study have already been published, additionally, there was no handling of and patient sensitive data. Therefore, given the descriptive nature of this study, ethical considerations were not applicable.

4.5 Methods

The recommendations made in the three most prominent CGs for NGB were assessed through rigorous content analysis, incorporating a process of constant comparison of each recommendation appearing in the CGs. The recommendations were tabulated to aid in cross-comparisons and identifying similarities and discrepancies.

4.6 Results

4.6.1 Behavioural Management

Behavioural techniques are summarised in Table 4.1 below. They are often used as a first line technique by virtue of their conservative nature (Ginsberg, 2013). Whilst no graded recommendations are made in the EAU CGs, they are advocated in both the NICE and ICI CGs, though recommendations are based on a lack of clinical evidence. The EAU may lack recommendations for behavioural management either due to the dearth in evidence or because it is often deemed unsuitable to manage patients with NGB solely through this method (Manack et al., 2011). Similarly, level 2 evidence in the ICI states behavioural management techniques should be used in conjunction with other therapies, as administered alone, they are not sufficient for symptom control.

NICE advises the consideration of timed voiding (toilet breaks at timed intervals), bladder retraining (developing a personalised toileting schedule) and habit retraining (patient is encouraged to initiate own voiding through positive reinforcement). The committee makes this recommendation using evidence from the general elderly idiopathic population, on the basis that no relevant evidence exists for patients with neurological disorders. As both habit retraining and prompted voiding involve encouragement and reinforcement by the caregiver, they are especially useful techniques for patients with cognitive difficulties, which is a predominant symptom in neurological conditions (NICE, 2012). The ICI and NICE both advocate prompted voiding and NICE recommends habit retraining as an additional option. These techniques can be supported with behavioural modification such as purging

of diuretics from the diet and controlled fluid intake, but this is not specifically mentioned in either of the CGs (Hashim and Abrams, 2008).

NICE recommends pelvic floor muscle training (PFMT) in potential combination with electrical stimulation or biofeedback in SCI or MS, or other conditions in which the ability to voluntarily contract the pelvic floor is present. The procedure involves repeated contractions and relaxations of the pelvic floor musculature, stimulating urethral closure (Zhu et al., 2016). In patients who have difficulty in identifying and contracting the correct pelvic floor muscle, electrical stimulation can be used (Yamanishi et al., 2008). Although not providing an explicit recommendation, the EAU mention that peripheral temporary electrostimulation, which involves the use of surface electrodes, combined with PFMT and biofeedback to control the correct contraction of the PFMT, can reduce symptoms in MS. The ICI make a grade C/D recommendation for electrical stimulation of the pelvic floor muscle in all NGB patients.

ICI and EAU endorse expression techniques such as the Crede manoeuvre (manual compression of the lower abdomen) and Valsalva manoeuvre (abdominal straining), only if it is urodynamically safe to do so. Both CGs stress the manoeuvres are potentially hazardous due to potential creation of high intra-vesical pressures, and therefore where possible the use of these procedures should be avoided. NICE CGs do not mention expression techniques.

Both the ICI and EAU provide cautionary statements on autonomic dysreflexia, a serious condition that can arise in patients with SCI with lesions above T6 region. Autonomic dysreflexia is characterised by a dramatic increase in blood pressure, and if patients do not receive immediate attention it can cause hypertensive encephalopathy, stroke, cardiac arrest, seizure and even death (Eldahan and Rabchevsky, 2018). Iatrogenic causes include invasive urodynamic testing and triggered voiding. The ICI specifically recommend that SCI units should have the capability to manage potential cases of autonomic dysreflexia.

Table 4.1 Behavioural management recommendations in the neurogenic bladder clinical guidelines by the European Association of Urology, National Institute for Health and Care Excellence and the International Consultation on Incontinence

NICE	EAU	ICI
Recommendations which are similar for the three guidelines		
Consider a behavioural management programme (for example, timed voiding, bladder retraining or habit retraining) for people with NLUTD Consider PFMT in SCI and MS and in neurological conditions where voluntarily contraction of pelvic floor is preserved. Consider combining with biofeedback and/or electrical stimulation	No graded recommendations	Behavioural techniques are a suitable component of the rehabilitation program for each individual (C) In patients with incomplete denervation and some voluntary contraction of the pelvic floor muscle and the striated sphincter, electrical stimulation may be an option to improve pelvic floor function, thus improve incontinence (C/D)
Recommendations differing between the three guidelines		
	No graded recommendations	Before recommending bladder expression by Valsalva or Credé, it must be proven that the LUT is urodynamically safe (B) Triggered voiding could be recommended only for

		patients whose situation has proven to be urodynamically safe and stable, and who can manage reflex incontinence Reflex voiding can be recommended only if an adequate follow-up is guaranteed (C)

PFMT, pelvic floor muscle training; SCI, spinal cord injuries; MS, multiple sclerosis; NULTD, neurogenic urinary lower tract dysfunction
Grade of recommendations displayed in brackets

4.6.2 Oral Pharmacotherapy

Oral pharmacotherapy is summarised in Table 4.2 below. All CGs agree that bladder muscarinics are the preferred pharmacological treatment for neurogenic detrusor overactivity (NDO). NICE make the distinction between offering bladder muscarinics for SCI and MS and considering their use in brain conditions. On the other hand, the EAU and ICI recommend bladder muscarinics indiscriminate of underlying neurological condition. NICE also suggest that these strategies should only be employed if more conservative treatments such as bladder training have proved unsuccessful, which is in direct contrast to the ICI, who only advocate behavioural training in conjunction with other treatments.

All CGs advise cautionary use of bladder muscarinics due to the increased possibility of adverse effects such as urinary tract infections (UTIs) and constipation (Macdiarmid, 2008). These drugs also have the potential to cause cognitive dysfunction by binding to the M_1 and M_2 receptors in the brain (Svoboda et al., 2017) (Section 2.5.1). Therefore, the ICI and NICE CGs express concern of use in patients with pre-existing cognitive impairment with the ICI accordingly advocating the use of bladder muscarinics that are less likely to have further impact on cognition. Level 1 evidence states tolterodine, propiverine, trospium and

extended release (ER) oxybutynin have significantly less side effects compared to immediate release (IR) oxybutynin. Contrastingly, due to the lack of evidence differentiating bladder muscarinics, NICE recommend balancing the side effect profile with cost, rather than advocating the use of one drug over another. The EAU do not necessarily advocate the use of one drug over the other but present a brief evidence profile of the bladder muscarinics currently available on the market.

Due to the additional increased severity of symptoms in the NGB population in comparison to the idiopathic overactive bladder (OAB) population the EAU suggests employing bladder muscarinics in combinations, and in higher doses in order to achieve optimal treatment effectiveness. Based on level 2 evidence, the ICI states that dual therapy (with combinations of oxybutynin, tolterodine and trospium) have shown positive results in some patients, but a graded recommendation is not given.

At present, most bladder muscarinics do not have marketing authorisation (MA) for use in NGB, thus there is not a manufacturer's recommended dose to follow, instead, it is carefully selected through a 'trial and error' approach (Kennelly and Devoe, 2008). A warning is featured in the EAU CGs implicating higher doses to increased rates of adverse events and consequently potential low adherence to medication due to lack of tolerance, however there was no underlying evidence to support this, suggesting this recommendation is based on expert opinion.

None of the CGs describe the manner in which bladder muscarinics should be administered, which leaves some room for clinical discretion. In an interview with an expert, they described a method of administering one bladder muscarinic that acts as the principal method of management, and a second bladder muscarinic prescribed to consume on a pro re nata (PRN) basis (as and when is needed) (Drake and de Ridder, 2017). One example of when an individual may consume their second bladder muscarinic is when additional support is required in social situations where a toilet may not be easy to locate. This technique is not outlined in any, CGs nonetheless; it may still be widely applied by physicians to suit patients' individual lifestyle requirements.

Although graded recommendations are not made (presumably due to the lack of evidence), if bladder muscarinics are not tolerated or prove ineffective, the ICI suggest the β3-adrenoceptor agonist mirabegron as a viable alternative, as it has demonstrated a favourable efficacy-tolerability profile in randomised controlled trials (RCTs), particularly involving idiopathic OAB patients. The drug works via a different pharmacological mechanism to bladder muscarinics, although the exact means by which beneficial effects are exerted are yet to be elucidated. What is known is that the distinct mechanism of mirabegron avoids the systemic side effects associated with bladder muscarinics such as dry mouth and cognitive impairment (Chen et al., 2018). The EAU suggest combination therapy with mirabegron and bladder muscarinics may be an option in the future, as trials have demonstrated efficacy in idiopathic OAB patients (in particular with solifenacin) (Xu et al., 2017).

The ICI and EAU recommend α-adrenergic antagonists for bladder outlet obstruction (BOO) resistance. Although previously confined for use in benign prostatic hyperplasia (BPH), a selective α-1 adrenoreceptor antagonist such as terazosin is effective in treatment other lower urinary tract dysfunction (LUTD) (Nitti, 2005). The EAU give this form of treatment a grade A, whereas it is a grade B/C in the ICI CGs. Conversely, α-adrenergic antagonists are recommended against in the NICE CGs for bladder emptying problems, as they are deemed not cost-effective. The GDG group also noted that patients were unlikely to experience better Quality of Life (QoL) from improved flow rate.

For stress incontinence, EAU and NICE CGs both recommend against the administration of drugs. Conversely, the ICI state that α-adrenergic antagonists could increase stress incontinence.

Table 4.2 Oral pharmacotherapy recommendations in the neurogenic bladder clinical guidelines by the European Association of Urology, National Institute for Health and Care Excellence and the International Consultation on Incontinence

NICE	EAU	ICI
Recommendations which are similar for the three guidelines		
	Use bladder muscarinic therapy as the first-line medical treatment for NDO (A) Prescribe α-adrenergic antagonists to decrease BOO resistance (A)	Bladder muscarinic drugs should be recommended for the treatment of NDO (A) For decreasing BOO in NGB a-adrenergic antagonists may be used (B/C)
Recommendations differing between the three guidelines		
Offer bladder muscarinics to people with spinal cord disease (e.g. MS or SCI) and symptoms of OAB Consider bladder muscarinic drug treatment in people with conditions affecting the brain (for example, cerebral palsy, head injury or stroke) and symptoms of OAB Consider bladder muscarinic drug treatment in people with urodynamic investigations showing impaired bladder	Maximise outcomes for NDO by considering a combination of bladder muscarinic agents (B) Do not prescribe drug treatment in neurogenic SUI (A) Do not prescribe parasympathomimetics for underactive detrusor (A)	

storage Do not offer α-adrenergic antagonists for bladder emptying problems caused by neurological disease		

OAB, overactive bladder; NDO, neurogenic detrusor overactivity; BOO, bladder outlet obstruction; SCI, spinal cord injuries; MS, multiple sclerosis; NGB, neurogenic bladder
Grade of recommendations displayed in brackets

4.6.3 Minimally Invasive Techniques

Minimally invasive techniques are summarised in Table 4.3 below. Despite the fact that several trials have proven its efficacy, intradetrusor injections of Onabotulinum-A do not have an indication for NGB (except in Switzerland), meaning that use is off label (Weckx et al., 2016). The treatment represents a minimally invasive strategy to control symptoms in patients who do not tolerate or do not experience efficacy from bladder muscarinics (Orasanu and Mahajan, 2013). On account of high-level evidence, the EAU and NICE advocate Onabotulinum-A in NDO as a consequence of SCI and MS. In contrast, the ICI recommends Onabotulinum-A for NDO in any underlying neurological condition. The ICI again diverges from EAU and NICE when it recommends Onabotulinum-A for detrusor sphincter dyssynergia (DSD) in SCI.

Based on level 2 evidence, the EAU recommend alternative (non-oral) routes of administration of bladder muscarinic drugs including intravesical injections or intradermal patches. In contrast, the evidence underpinning intravesical instillation of oxybutynin is classified as low (level 4) by the ICI. Intravesical implant or rectal suppository are not mentioned in any CGs (Lai et al., 2002). Both the ICI and NICE do not provide graded recommendations for alternative forms of bladder muscarinic administration.

The ICI CGs provide a grade C/D recommendation for electrical neuromodulation techniques including sacral neuromodulation (SNM), anogenital stimulation, pudendal nerve stimulation, dorsal genital nerve stimulation, percutaneous tibial nerve stimulation, magnetic stimulation and deep brain stimulation. Both the EAU and ICI agree there are limited reports proving efficacy.

Table 4.3 Minimally invasive treatment recommendations in the neurogenic bladder clinical guidelines by the European Association of Urology, National Institute for Health and Care Excellence and the International Consultation on Incontinence

NICE	**EAU**	**ICI**
Recommendations which are similar for the three guidelines		
Offer bladder wall injection with BTX-A with spinal cord disease (e.g. MS or SCI) and with symptoms of OAB and in whom bladder muscarinic drugs have proved to be ineffective or poorly tolerated. Offer bladder wall injection with BTX-A to adults with spinal cord disease and with urodynamic investigations showing impaired bladder storage and in whom bladder muscarinic drugs have proved to be ineffective or poorly tolerated.	Use BTX-A injection in the detrusor to reduce NDO in MS or SCI if bladder muscarinic therapy is ineffective (A)	

Recommendations differing between the three guidelines		
	Alternative routes of administration (i.e., transdermal or intravesical) of bladder muscarinic agents may be used (A)	BTX-A should be offered as a treatment option for incontinence associated with NDO (A). BTX-A may be considered for DSD in SCI patients (B) If pharmacotherapy fails to relax the overactive detrusor, electrical neuromodulation (sacral neuromodulation (SNM), anogenital stimulation, pudendal nerve stimulation, dorsal genital nerve stimulation, percutaneous tibial nerve stimulation, magnetic stimulation and deep brain stimulation) may be optional in patients with neurogenic DO (C/D)

BTX-A, botulinum toxin A; SCI, spinal cord injuries; MS, multiple sclerosis; NDO, neurogenic detrusor overactivity

Grade of recommendations displayed in brackets

4.6.4 Catheters and Appliances

Catheters and appliances are summarised in Table 4.4 below. Retention symptoms in most cases co-exist with storage symptoms, thus catheterisation is often necessary in conjunction with bladder muscarinics or Onabotulinum-A injections (Phé et al., 2016). The practice involves the insertion of a catheter through the urethra into the bladder to allow the dispel of urine. All CGs recommend intermittent catheters (IC) over indwelling catheter (IndUC) due to decreased risk of attributable infections, calculi and in severe cases, bladder carcinoma (Moussa et al., 2009).

The use of IC is impeded by the fact that use requires a high level of manual dexterity to frequently insert and remove the catheter (Seth et al., 2014). This can be an issue for patients with certain neurological conditions, for example, those with PD often have symptoms of bradykinesia, severely affecting regular movement (Mazzoni et al., 2012). In such cases, unless assisted IC is an option, use of indwelling catheters is unavoidable. The ICI do not completely preclude use of IndUC, stating that short-term use is safe during the acute phase of neurological injury. NICE also recognise that in some instances the choice of management technique is limited by what the patient can manage. Patient education in catheterisation is encouraged by NICE and EAU CGs.

When considering appliances to expel the urine from the catheter, NICE recommend the use of catheter valves over drainage bags. The ICI and EAU CGs advocate the use of condom catheters with a collection device in men. The ICI advises awareness on skin breakdown, and the EAU ask clinicians to closely monitor infection risk.

Table 4.4 Catheters and appliances recommendations in the neurogenic bladder clinical guidelines by the European Association of Urology, National Institute for Health and Care Excellence and the International Consultation on Incontinence.

NICE	EAU	ICI
Recommendations which are similar for the three guidelines		
When discussing treatment options, tell the person that IndUC may be associated with higher risks of renal complications (such as kidney stones and scarring) than other forms of bladder management (such as intermittent self-catheterisation)	Use IC, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder (A) Avoid IndUC and SPC whenever possible (A)	IC is first choice treatment for inability to empty the bladder adequately and safely in neurogenic voiding dysfunction (A) Long-term IndUC should be the last resort and may be safe only if a careful check-up of urodynamic, renal function, and upper and lower tract imaging are performed (B)
Recommendations differing between the three guidelines		
In people for whom it is appropriate a catheter valve may be used as an alternative to a drainage bag		Short-term IndUC during the acute phase of neurological injury is a safe management for neurologic patients (B) Regular bladder emptying with low bladder pressures and low post void residual should be confirmed with

		condom catheters and external appliances (B)

IndUC, indwelling catheterisation; SPC, suprapubic catheterisation; IC, intermittent catheterisation
Grade of recommendations displayed in brackets

4.6.5 Surgical Management

Surgical management is summarised in Table 4.5 below. If conservative measures have failed, then surgery is a viable option. All CGs recommend augmentation, a surgical technique designed to enlarge the bladder, using intestinal segment in refractory NDO. NICE consider augmentation to be more cost-effective than Onabotulinum-A in patients likely to benefit from treatment for more than 10 years. Therefore, although a step-wise approach to treatment is generally recommended, in such an instance, they recommend that augmentation be carried out earlier on in the treatment pathway.

All CGs recommend use of autologous urethral slings for neurogenic SUI, which aim to restore the urethral support during sudden movement thus avoiding the involuntary leakage of urine. A lack of evidence prevents endorsement of synthetic tapes. In addition, there are concerns about the need for placement under tension for neurogenic SUI, due to sphincter deficiency. In contrast to the other CGs, the EAU recommend autologous sling use in female patients only due to anatomical differences to males. The ICI make further surgical recommendations for SUI which are not covered by the other CGs, including bulking agents and bladder neck reconstruction. They also present bladder neck closure as a last resort if all possible alternatives are unsuitable or have failed to relieve symptoms.

Artificial urinary sphincter (AUS) works by simulating the biological urinary sphincter. It is the gold standard procedure for men with neurogenic sphincter deficiency, Both the ICI and NICE recognise the paucity of research in using this procedure in women, but do not exclude use in this group, conversely, the EAU only recommend use in men. NICE only

recommend AUS use after autologous sling procedures have failed, due to the high rate of re-operation within 10 years.

According to the EAU, continent cystostomy is the preferable urinary diversion technique (redirect the stream of urine) in refractory NGB. Conversely, NICE do not consider evidence for continent cystostomy, and only provide recommendations for ileal conduit diversion. The ICI do not advocate one type of urinary diversion technique over the other.

The ICI recommend urethral stenting (insertion of permeant thin tube in urthera) or surgical sphincterotomy (incision of sphincter) to lower bladder pressure for patients with DSD, in whom IC is not an option. Graded recommendations for these techniques are not provided by the EAU, however they state that sphincterotomy is safe and does not cause severe adverse events. On the other hand, although stenting has comparable efficacy, possible complications and re-interventions limit its use.

Sacral rhizotomy in conjunction with sacral anterior root stimulation (SARS), which aims to producing detrusor contractions is given a graded recommendation by the ICI, and advocated in the EAU CGs, in highly selected individuals.

Table 4.5 Surgical procedure recommendations in the neurogenic bladder clinical guidelines by the European Association of Urology, National Institute for Health and Care Excellence and the International Consultation on Incontinence

NICE	EAU	ICI
Recommendations which are similar for the three guidelines		
Consider autologous fascial sling surgery for people with SUI Do not routinely use synthetic tapes and slings in people with		Autologous slings can be used to treat SUI (B) Artificial urinary sphincter can be used to treat SUI (A)

SUI because of the risk of urethral erosion Consider surgery to insert an AUS for people with SUI only if an alternative procedure, such as insertion of an autologous fascial sling, is less likely to control incontinence		Due to the limited evidence base, possible sphincter deficiency, perceived risk of complications and potential consequences on future management options, the Committee is unable to recommend routine use of synthetic slings and tapes to treat SUI in neurogenic patients (D)
Recommendations differing between the three guidelines		
Consider augmentation cystoplasty using an intestinal segment for people with non-progressive neurological disorders and complications of impaired bladder storage (for example, hydronephrosis or incontinence) For people with neurogenic lower urinary tract dysfunction who have intractable, major problems with urinary tract management, such as incontinence or renal	Perform bladder augmentation to treat refractory NDO (A) Place an autologous urethral sling in female patients with SUI who are able to self-catheterise. (B) Insert an AUS in male patients with SUI (A)	Any segment of the gastrointestinal tract may be used for bladder augmentation, but the ileum seems to give the best results in terms of ease of use, risk of complications and efficacy (B) Synthetic tapes could be recommended in older women with stable neurological conditions and SUI due to urethral hypermobility (C)

deterioration consider ileal conduit diversion		Bulking agents can be used to treat SUI when there is a demand for a minimally invasive treatment (D) Bladder neck reconstruction can be used to treat SUI (D) Bladder neck closure should be offered to patients who have persistent neurogenic stress incontinence where alternative treatments have either failed or are likely to fail (B) Non-continent urinary diversion is the last resort for patients with NGB (A) Ileal conduit urinary diversion has the best long-term results for non-continent diversion, if the following pre- and peri-operative precautions are taken (B)

		Where clean IC is not possible, the use of a urethral stent is possible (in DSD (B) Although surgical sphincterotomy is the accepted reference treatment for neurogenic DSD, analysis of the literature highlights the lack of reliable efficacy and reproducibility criteria for the technique (B) In certain situations, dorsal rhizotomies can be undertaken in association with ventral root stimulators (Brindley's technique) or even with continent cystostomy (B)

SUI, stress urinary incontinence; AUS, artificial urinary sphincter; NDO, neurogenic detrusor overactivity; NGB, neurogenic bladder; DSD, detrusor sphincter dysynergia
Grade of recommendations displayed in brackets

4.6.6 Stem Cell Treatment and Tissue Engineering

The NICE, EAU and ICI CGs do not mention the potential of stem cell or tissue engineering techniques to manage bladder dysfunction subsequent to neurological disease. In contrast to the treatment options currently available that are only able to provide symptomatic

relief and are often associated with severe side effects and high rates of non-response, stem cell therapy and tissue engineering have the ability to halt disease progression and reverse the underlying pathology (Tran and Damaser, 2015; Kim et al., 2014). One example of regenerative medicine in the bladder is during the augmentation process. Gastrointestinal segment used for bladder augmentation can increase the chances of metabolic disturbances, urolithiasis, infection, perforation and increased mucus production because of differing composition and permeability compared to the bladder tissue (Soler et al., 2009). Utilising autologous bladder tissue provides a promising solution to this issue.

Although regenerative medicine in bladder dysfunction has been conceptualised for some time, research into it is scarce, which could be the reason it is not mentioned in any of the NGB CGs. It likely to be a number of years before the clinical and funding challenges relating to the implementation of stem cell therapies are addressed and it is routinely used for the resolution of bladder dysfunction (Adamowicz et al., 2017).

4.7 Discussion

CGs are crucial in establishing up-to-date evidence-based medicine (EBM) in clinical practice. Adequate management in NGB offers benefits to the patient in terms of protection of the upper urinary tract, reduction in the rate of adverse sequelae and promotion of good QoL (Bloc et al., 2017). Additionally, widespread adoption of best effective practice avoids unnecessary costs to the healthcare system linked to treatment related adverse events. Due to varying development processes (Chapter 3), the NGB CGs contain discordant treatment recommendations, which can cause variation in care amongst patients, and across practices. Dissimilarities arose as a result of the differing interpretation of the underlying evidence base, varying considerations given to cost, and the weight given to expert opinion. Since the ICI CGs attempt worldwide relevance, they were most comprehensive. For example, the CGs provide extensive recommendations for patients with SUI, considering treatments that were not assessed in the NICE or EAU CGs.

The CGs generally agree on their approach to conservative management, including for behavioural therapies and catheterisation techniques. However, the EAU CGs lacked graded recommendations for behavioural management, the reason for which is unclear. When considering oral pharmacotherapy, all three CGs place bladder muscarinics as first line for NDO. Despite highlighting the potential adverse effects of these drugs, none of the CGs clearly acknowledges the particular concern of use in progressive neurological conditions (although NICE asks clinicians to 'consider' their use in brain conditions). Even if notable impairment does not already exist, the blood brain barrier (BBB) can become compromised, increasing the susceptibility of experiencing cognitive side effects (Section 2.5.1). The ICI and NICE recommend further research into the use of newer bladder muscarinics in NGB. It is interesting to note that although the ICI CGs were published five years after the NICE CGs; the same recommendation is made, indicating that little progress has been made in the way of this particular research. This further fuels the belief that major institutions are not aware of the differences between bladder muscarinics that influence their ability to cause cognitive deficits. This has a direct influence on the knowledge and behaviour of prescribers and payers.

When it comes to using a combination of bladder muscarinics, only the EAU provided graded recommendations. Expert consensus may have had a large influence in formulating this recommendation, as only evidence generated from a few small-scale RCTs currently exists.

The CGs contain contrasting recommendations on α-adrenergic antagonists and Onabotulinum-A. Although some evidence exists demonstrating efficacy of α-adrenergic antagonists in NGB patients with BOO, the need for large-scale RCTs remains (Nitti, 2005). Despite this, they are advocated for use in the EAU and ICI CGs. Onabotulinum-A is only licensed for NDO in SCI and MS due to the paucity of adequate research in other neurological conditions. The ICI CGs still recommend Onabotulinum-A in all patients with NDO, regardless of underlying aetiology, thus it is evident that the EAU and NICE CGs more accurately reflect the evaluated patient population in this instance. In the absence of high-

quality clinical evidence, recommendations for α-adrenergic antagonists and Onabotulinum-A were primarily reliant upon expert opinion.

Disparities were most apparent in surgical treatments. One major difference between the EAU CGs and the other CGs were the presence of some sex-specific recommendations. Male autologous slings are relatively new interventions, with consequently less data supporting their use than female autologous slings (Groen et al., 2012). For this reason, use in males is not advocated the EAU CGs. On the other hand, AUS is not recommended in females, as physiological barriers introduce technical difficulties in implantation (Phé et al., 2014). All CGs also differed in recommendations for urinary diversion. Whereas continent cystostomy is advocated in the EAU CGs, NICE recommend ileal conduit diversion. The ICI do not advocate any one kind of urinary diversion, which is perhaps most suitable, as superiority of one type of technique in terms of functionality and health related quality of life (HRQoL) has not yet been proven (Evans et al., 2010). The discrepancy between the NICE and EAU CGs is again most likely because of differing expert opinion.

An advantage of the NICE CGs was the well-integrated economic evaluation, which aims to improve national healthcare efficiency in the UK. As a result, certain recommendations diverged from what is recommended by the EAU and ICI, for example, the option to introduce bladder augmentation earlier than Onabotulinum-A in the treatment pathway in patients likely to benefit for more than 10 years. Traditionally, invasive techniques to control bladder dysfunction are only carried out if non-invasive measures have failed to provide adequate relief. However, in such instances health economic analyses may conclude that breaching the traditional sequence is in fact more cost-effective in certain patient groups. Another analysis conducted in the UK healthcare system derived a similar conclusion to NICE. This study compared the 10-year costs of Onabotulinum-A to 10-year costs of clam cystoplasty and deemed that if symptoms were severe enough to require 4 or more catheterisations per day, cystoplasty was the less costly choice (Lamb et al., 2010).

It would be of interest to determine whether this recommendation is actually adopted in real world practice given that the health translation process is exceedingly slow, with

multiple sources estimating a 17-year time lag between research evidence generation and its enactment in clinical practice (Morris et al., 2011). This means it could take a long time before this recommendation is fully embedded in clinical practice. Taking an even more pessimistic stance, this recommendation may in fact never be adopted by clinicians. There may be significant resistance to abandoning a step-wise approach in favour of conducting invasive bladder augmentation before administering Onabotulinum-A injections; a considerably more conservative technique. In essence, clinicians are expected to 'un-learn' the most basic tenets of patient management practices, which is to leave surgery until absolutely necessary (Gupta et al., 2017). This resistance is further exacerbated by clinicians' distrust of health economics (Section 3.3.7) (Wailoo et al., 2004; Gupta et al., 2017). Due to their broad country remit, cost assessment and/or consideration of resource utilisation is not conducted in the EAU and ICI CGs (Section 3.6.5.6.2).

4.7.1 Filling the Neurogenic Bladder Evidence Gap

The underlying evidence base of a disease dictates the trustworthiness of the recommendations featuring in CGs (McAlister et al., 2007). In the absence of high-quality clinical evidence, many of the recommendations made across all three NGB CGs were unavoidably based on expert opinion and/or knowledge. One of the main ways in which the dearth in research is remedied is through the extrapolation of evidence pertaining to the use of treatments in idiopathic OAB to justify management practices in NGB. This was evident in the recommendations for behavioural techniques in the NICE CGs. Such extrapolation is often inappropriate, as NGB patients are distinct from the idiopathic OAB population; they tend to have a lower health related quality of life (HRQoL), substantial disability, and high rates of complications including recurrent infection, autonomic dysreflexia, chronic disease of the urinary tract, and sexual dysfunction (Tapia et al., 2013; Bodner, 2006).

A recent systematic review (SR) showed that despite an increase in the number of RCTs in NGB conducted from 1976 to 2014, most of the trials contained a small number of subjects, thus were not adequately powered; extended over short periods, therefore were

insufficient to assess long-term outcomes and included heterogeneous populations, preventing the ability to aggregate results (Persu, 2014). The authors of the SR also noted that the numbers of RCTs were still low, especially when considering the review's 30-year long search window, and when compared to research in other disease areas. In addition, the majority of research was concentrated in SCI (Figure 4.1), which creates a gap in our understanding of NGB related to other neurological conditions (applying evidence across different conditions is typically insufficient due to the vast patient heterogeneity) (Apostolidis et al., 2017). Ultimately, the trials were considered inadequate to reach solid conclusions on the optimal management and care of patients. Other reviews since 2014 focusing on specific treatments also derived similar conclusions. One SLR on the use of alpha-blockers and another on the use of bladder augmentation in NGB determined that further RCTs are necessary in this area to determine efficacy of interventions (Schneider et al., 2019 and Hoen, 2017). Thus, it is evident that research efforts in NGB need to be enhanced.

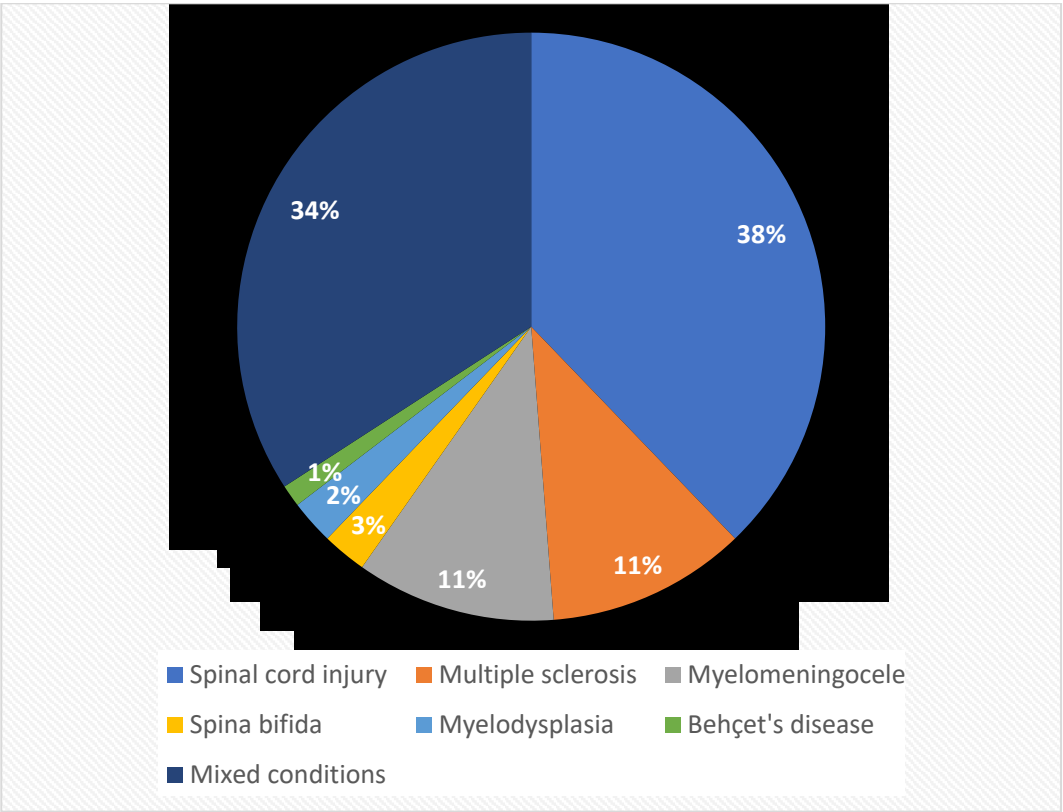


Figure 4.1 Trials conducted in neurogenic bladder from the years 1976-2014 (Persu, 2014).

In beginning to construct an understanding of the evidence gap that exists in NGB, it is first important to consider the inherent limitations associated with RCTs. Most NGB trials are industry sponsored (as is the case with all RCTs), which means they are meticulously designed to demonstrate benefit in an ideal environment (i.e. they possess high internal validity) (Persu, 2014). They are carried out by highly specialised researchers, and every effort is made to adhere to strict protocols (Perez-Gomez et al., 2016). Moreover, the inclusion and exclusion criteria are very specific; selecting a narrow section of the population that are most likely to derive benefit from the treatment (van Spall et al., 2007). An SR found that industry sponsored trials were likely to exclude women, patients with high rates of comorbidities, high polypharmacy and low socioeconomic status, thus are not representative of the real-world patient population (van Spall et al., 2007). These stringent

controls are in place to meet the requirements of the regulatory agencies, namely the European Medicines Agency (EMA) and the Food and Drugs Approval Body (FDA) in the USA, which necessitate high quality trials demonstrating efficacy and safety, in order to approve a drug to market. This does however mean that outcomes are often not relevant, appropriate or of importance to patients in real world clinical settings (i.e. the trials have low external validity) (Booth and Tannock, 2014). Austin Bradford Hill in 1984 proclaimed:

At its best such a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use (Hoffman, 2015: 673).

Due to these shortcomings of RCTs and evolving attitudes towards observational research, decision makers are increasingly demanding Real-World Evidence (RWE) in order to manage uncertainty when making reimbursement and policy decisions. The International Society of Pharmacoeconomics (ISPOR) defined RWE as 'everything that goes beyond what is normally collected in the Phase III clinical trials program in terms of efficacy' (Annemans, 2012: online). RWE is created from the analysis of real-world data (RWD), which is derived from a number of sources including electronic healthcare records (EHRs), claims databases, disease registries, and health monitoring devices (Wilk et al., 2017; Ha et al., 2018). In contrast to RCTs, RWE represents the actuality of healthcare delivery in clinical practice, where patients are notably heterogeneous in terms of characteristics such as age, sex, ethnicity, comorbidity and polypharmacy than the patients recruited in the trials where interventions were tested (Cohen et al., 2015).

Similar to the dearth in adequate clinical research in NGB, the generation of RWE also falls short in comparison to the plethora of research conducted for many other chronic conditions. With the recent progression in technology, EHRs in particular provide an excellent, yet untapped opportunity to uncover longer term safety and tolerability outcomes of NGB patients, something that is not possible through RCTs (Poon et al., 2006). Furthermore, observational studies are easier to access, cheaper and can often include much larger patient populations (Poon et al., 2006). Disease registries also contain

observational data; however, they are especially set up for patients with shared characteristics and clinicians collect data as per a pre-defined protocol to support specific health questions (Yörük, 2015).

Analysing RWD from EHRs and registries does come with its intrinsic limitations, with the potential to undermine the validity of results. Selection bias is one of the most difficult issues that occur in the analysis of RWD, arising when there are systematic differences in patient groups that can influence the outcomes of interest. Due to the lack of randomisation in observational studies, all confounding factors cannot be accounted for. Techniques for controlling missing data such as last observation carried forward, mixed models and multiple imputation techniques may help mitigate some of the risk related to selection bias, however it is largely unavoidable, thus the impact this form of bias can have on the resulting outcomes should always be acknowledged. Another form of bias common in observational studies is when the association between the exposure and the outcome is confounded by indication. Techniques including multivariable regression modelling and propensity score matching help to reduce this form of bias however unknown confounders of course cannot be controlled for (Hammer et al., 2009).

Pragmatic trials arose from the realisation that traditional RCTs fail to inform real life practice, and accordingly, there are several dimensions which position these trials as better tools to demonstrate effectiveness. Firstly, participants are similar to patients who would receive the intervention in real world practice, as opposed to the highly selected patients recruited into RCTs (Ford and Norrie, 2016). Furthermore, rather than highly specialised experts, a variety of investigators with varying experience administer the interventions, which is also true of the real-life clinical situation. Other differences include the lack of blinding, no artificial expectation of follow up and the selection of outcomes that are important to patients (Zuidgeest et al., 2017). Pragmatic studies normally fall on a continuum between purely explanatory (traditional RCTs) and purely pragmatic (RWE), although few tend to meet all of the criteria of the latter, thus they are said to represent *close* to real-life practice conditions (Patsopoulos, 2011).

A certain level of pragmatism needs to be adopted when determining the optimal type of evidence required to bridge an evidence gap such as the one that exists in NGB, because as established above, 'better evidence', according to the EBM hierarchy (i.e. RCTs) is not the most generalisable (Rosner, 2012). Further than this, management practices in NGB have become well established over the years, often without the backing of formalised trials. Some international experts suspect that many aspects of patient care in NGB will in fact never be tested in RCTs due to their apparent self-evident nature (Apostolidis et al., 2017). Moreover, there is a high cost attached to trials and lack of incentive for developers to seek marketing authorisation (MA) given that many of the interventions are already being applied in clinical practice. They can also be challenging to conduct due to the difficult patient populations (children, the elderly, patients with comorbidities and cognitive dysfunction). Thus, it is clear that in order to promote evidence-based practice in NGB, increased research effort should be focused on generating knowledge beyond the traditional sphere of clinical research. RWE has been paramount in providing much needed empirical evidence and strengthening recommendations in a number of CGs outside of NGB (Gores, 2018). In NGB, EHRs, pragmatic trials, and prospective registries conducted at centres managing a diverse range of neurological conditions represent excellent solutions to bridge the lacuna between efficiency and real-world effectiveness and provide rich and comprehensive evidence on which to base future CG recommendations (Patsopoulos, 2011).

It is in some sense vital that recommendations, at least in part, are formulated using RWE because they will be applied to patients in the real world who do not fit into the contrived categories of RCTs. Although evidence appraisal systems such as the GRADE promote a multidisciplinary approach and do a good job ensuring clinical discretion and assimilation of the patient perspective, grading the strength of the underlying evidence is still skewed towards RCTs as the optimum. In order for RWE studies to be readily accepted, and consequently for the NGB CGs to become more inclusive of patient diversity, the EBM hierarchy requires transformation. In its current state it is inflexible, failing to take into account the inter-connected non-linear nature of health that is best analysed using a

variety of study designs and techniques. Therefore, the notion that external validity is equally as important as internally validity in the formation of recommendations needs to be promoted, whilst taking into account the compromise that sometimes needs to be made between randomisation which mitigates several forms of bias, and the applicability of evidence which is only possible through observational studies (Fernandez et al., 2015).

4.8 Conclusions

There is relative unanimity between the NICE, EAU and ICI CGs despite the fact that they are developed independently of each other via distinct methodological processes (Chapter 3). However, they do provide differing emphasis on costs and expert opinion, which translated in some notably different recommendations. This is not surprising in the absence of high-quality clinical evidence for NGB. Varying recommendations can cause unwarranted variations in care, leading to inequity in urological care for NGB patients.

Increased efforts in enriching the underlying evidence for NGB are necessary to ensure recommendations are grounded in tested theory and promote evidence-based practice. Given that conducting RCTs is difficult in this patient population and recommendations are to be applied in the real-world, research efforts should focus on generating RWE. Generation of such data poses fewer ethical challenges and represents an expedited path to evidence collection.

Coordinated collaboration between organisations will also aid in great concordance between the resulting recommendations (Chapter 3). If differences do exist, it is recommended that CGs acknowledge other CGs in the same area and explain these differences, so to be as transparent as possible for users.

4.9 Chapter Summary

This study demonstrated that divergent development methodologies, as well as differing emphasis on costs and expert opinion results in notably different recommendations within the three most prominent guidelines for NGB. The research in this chapter falls short of

understanding how patients are actually managed in the real-world. Accordingly, the next chapter outlines an SR that to identify the real-world treatment patterns in NGB, which will elucidate whether CGs are applied in clinical practice, as well as dispel further gaps that remain in our understanding of the management pathway in NGB.

5) Chapter Five - Real world Treatment Patterns in the Neurogenic Bladder Population - A Systematic Literature Review

5.1 Introduction and Rationale

The results of the study detailed in Chapter Three and Four of this thesis demonstrated that on account of the varying developmental processes, the treatment recommendations made in the National Institute for Health and Care Excellence (NICE), European Association of Urology (EAU) and International Consultation on Incontinence (ICI) clinical guidelines (CGs) for neurogenic bladder (NGB), can often be contradictory. This inconsistency spans across conservative methods, such as behavioural techniques as well as more invasive forms of management, such as surgery. This can have implications for the standardisation of care for NGB patients across different care settings.

This systematic review (SR) aims to collate evidence on the management strategies that are employed in the real world and determine which CGs, if any, practices are aligned with. This gives indication as to how well recommendations are followed. In theory, because CGs represent the optimum, if real world practices are broadly consistent with the suggestions in CGs, then it can be assumed that management is of high quality. This exercise of comparison is useful because it indicates where CGs could potentially be modified to better reflect real life conditions. Furthermore, dangerous or disadvantageous practices can be identified in the real world, and the accompanying information in the CGs evaluated to determine whether it is comprehensive enough to adequately inform care providers and patients.

As the EAU and ICI CGs have a broad geographic scope, studies conducted in all corners of the globe were included. By casting a wide geographical net, potential variation in practices across the world can be distinguished and the possible reasons discussed. Through employing a wide time-frame, this research also aims to demonstrate the evolution of management strategies over time, and the changes that occur with the introduction of CGs.

To the author's knowledge, this is the first attempt to collate information on the real-world treatment practices in NGB.

5.2 Aim

The aim of this SR was to describe the treatment patterns and management strategies of NGB in real world clinical practice.

5.3 Protocol Registration

Prospective registration of SRs is important to increase transparency, reduce bias, and avoid duplication of efforts for researchers seeking to address the same question (Stewart et al., 2012). To address this, the University of York centre for reviews and dissemination manage the international Prospective Register of Systematic Reviews (PROSPERO) database. The Unique IQ number for this SR is: 42017055499 and is available in full at: https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017055499

5.4 Methods

5.4.1 Eligibility Criteria

The following studies were eligible for inclusion to this study:

- Studies that included patients with any neurological condition. The National NGB CGs (UK) aided in selecting qualifying conditions. These included; Parkinson's disease (PD), multiple sclerosis (MS), stroke, spinal cord injuries (SCI), spina bifida, diabetes mellitus, cerebral palsy, head injury, dementia's, spinal dysraphism, cervical spondylosis with myelopathy, ano-rectal anomalies, sacral agenesis, cauda equine syndrome, peripheral nerve injury from radical pelvic surgery and peripheral neuropathy (NICE, 2012).
- Studies that measure treatments and management strategies, specifically related to managing urological symptoms (i.e. not for other end-organ effects or treatment related adverse events (AEs) such as antibiotics to treat urinary tract infection (UTI) as a result of catheterisation). Qualifying studies could present and calculate treatment in

a number of ways, for example percentage use, duration of use, treatment switching or combination use.

- Real world studies, with any period follow-up, which could be either retrospective or prospective and be designed as cohort, case-control, cross-sectional or chart reviews.

5.4.2 Inclusion/Exclusion Criteria

The full inclusion and exclusion criteria for studies in this review are listed in Table 5.1.

Table 5.1 Inclusion and exclusion criteria

Inclusion	Exclusion
• Published in English • Includes human subjects • Reporting the treatment patterns/use in NGB • Conducted in a real-world setting	• Non-English publications • In vitro, pre-clinical or animal studies • RCTs, SRs, case-report/series, editorials, questionnaires, letters, commentaries, legal cases, newspaper articles or patient education materials

NGB, neurogenic bladder; RCTs, Randomised Controlled Trials; SRs, systematic reviews

5.4.2.1 Modification to Inclusion/Criteria

This SR had originally aimed to explicate the treatment patterns in adult NGB patients only. However, upon conducting a pilot search of the literature, no articles that focused solely on adults were retrieved. For this reason, the researchers of this SR decided to broaden the remit of the search to include patients of all ages. Upon reflection, it was decided that this was a positive move, as the scope of all NGB CGs also do not discriminate by age. This modification to inclusion criteria is reflected in the PROSPERO protocol dated, January 18th, 2017.

5.4.3 Eligibility Assessment

Eligibility assessment of articles was conducted in two stages. In the first stage, an independent reviewer (AJ) screened titles and abstracts for alignment with pre-defined inclusion and exclusion criteria, defined in Table 5.1. Ten percent of included articles were cross-examined by a second independent reviewer (FF). In the second stage, full versions of the included texts, compliant with the inclusion criteria, were screened by both reviewers. Any disagreements were mediated by discussion.

5.4.4 Databases

The MEDLINE® and EMBASE® databases were used to retrieve papers for this study. The USA National Library of Medicine (NLM) biomedical journal articles database, MEDLINE®, contains surplus of 22 million articles, spanning from the year 1946 to present. One of the special features of this database is the use of Medical Subject Headings (MeSH) controlled terms, used to index the articles (NLM, 2016).

EMBASE® is a biomedical journal articles database produced by Elsevier. EMBASE® gathers its papers from over 8,500 journals from over 90 countries, with 29 million records overall, including all citations included in MEDLINE®. It is important to note that journals from EMBASE® have less coverage of American journals (33.8%) in comparison to MEDLINE®, (40.5%). The indexing in EMBASE® is recorded by controlled Emtree terms (NLM, 2016).

5.4.5 Data Management

Data management was fulfilled by using EndNote reference management system (X7 version, Thomson Reuters). This software is ideal for storing, sorting and grouping large numbers of references and removing duplicates.

5.4.6 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

This SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA guidelines evolved from the QUOROM (quality of reporting of meta-analysis) statement, which was first published in 1999. The original QUOROM was conceptualised in response to abundant SRs that were of poor quality and were being poorly presented. The developers hoped these CGs would help standardise and improve the quality and reporting. Since the first iteration of the QUOROM, many conceptual, methodological, and practical advances have been made. This expansion in knowledge incentivised the development of an updated set of guidelines, and in 2009 a multidisciplinary team of 29 consumers, clinicians, review authors, methodologists, and medical editors developed the PRISMA statement.

The PRISMA statement is a 27-item checklist used widely in the scientific research sphere to enhance the transparency of reporting in SRs and meta-analyses (Moher et al., 2009). The checklist includes seven major headings: title; abstract; introduction; methods; results; discussion; and funding. Certain expectations of review quality are set out within each heading.

As well as the checklist, the authors provide researchers with a four-phase flow diagram, which guides the researchers through the paper inclusion process, from initial search to the appropriateness and eligibility of full inclusion of papers. PRISMA encourages researchers to add an explanation as to why papers were not included into the study, in order to promote full transparency in the decision-making process.

5.4.7 Search Strategy

Firstly, a list of related words to each of the eligibility criteria were compiled in order to capture the maximum pool of articles, this formed the ‘free form’ text words. In addition, ‘controlled terms’, that indexers could have used when recording citations were also included. Search terms were developed in collaboration with a medical librarian.

A search was run on 15th February 2017 using a combination of free form text words and controlled terms in MEDLINE®, and EMBASE®. Limits were applied for studies published between the years of 1996-2017; this period was chosen to allow a sufficient detection of changes in management techniques over the years. Further papers were sought by hand searching the references of studies meeting the inclusion criteria.

Search terms for NGB & observational studies were first nested before combining search terms for treatment patterns. Without the parentheses, all search terms would have been combined at the same time. While there may be overlap from the different techniques, each method would generate a different set of results. The search strategy employed was found to be more robust than combining all sets at the same time. The complete search strategy can be found in Appendix 7.

5.4.7.1 Use of Limits in EMBASE and MEDLINE

Limits (filters) are often used in SRs to narrow search results to articles that are most relevant to the research question. However, indexing correspondence with the nature and topics of the citation has often proven to be low. Indexers may not have the relevant subject matter expertise, or the objectives and topics of the study may not be clear and therefore cannot be indexed appropriately (Higgins, 2011). Thus, due to inappropriate indexing or missing indexes, using limits such as 'human' or 'English language' may retrieve irrelevant citations as well as running the risk of potential applicable citations being missed out.

There is also the issue of delayed indexing of newer publications. Newer records which have not yet received MeSH term allocation of 'human' will not be retrieved through a search utilising this limit (Sladek et al., 2010). Indexing for MeSH terms can take months for certain journals, meaning many pertinent articles could be missed (Mao and Lu, 2017). In EMBASE®, provisions have been made to automatically allocate Emtree terms using a pre-defined computer algorithm (Embase, 2018). This in theory should by-pass the risk of missing relevant papers; however, candidate terms and subheadings are not indexed

(Embase, 2018). Another important point to note is that the algorithm is a temporary measure until the citations can be manually indexed, suggesting that the precision of indexing by the algorithms may be lower than manual indexing.

In light of this, only one limit for year of publication (1996-2017) was employed in this study. Although only studies published in English and including human subjects were selected, unlike years of publication, limits were not applied for these conditions. Instead, the two researchers (AJ and FF) manually inspected the papers for evidence of non-human or non-English papers, which were subsequently removed.

5.4.8 Data Extraction

To ensure that no significant information was unavailable from the studies, information on the study design, patient characteristics, and treatments in NGB was independently extracted by two researchers (AJ & FF), using a piloted data extraction form. This form was designed in relation to the SR's aims and objectives and summarised the relevant information necessary for the analysis (Appendix 8).

5.4.9 Summary Measures

Treatment patterns were descriptively summarised using narrative review (the descriptive objective meant that meta-analysis was not appropriate). Thematic content webbing was used to categorise and organise the results. This process involves reading the articles several times over, as well as the extracted data in order to conceptualise and explore overarching themes between the results and map them using a spider diagram (Popay et al., 2006). Where possible, percentage of treatment use was summarised using ranges.

5.4.10 Quality Appraisal

Quality appraisal is relevant when the topic of research is concerned with the efficacy or safety of interventions. This SR seeks to determine treatment patterns, which is purely descriptive in nature. For this reason, quality appraisal was not applicable.

5.5 Results

The search yielded a total of 116 publications. In the first stage of review, only titles and abstracts were screened for eligibility in fulfilling the objective of this SR, and further for pre-defined inclusion and exclusion criteria. Any remaining duplicates were also manually removed during this stage (ProQuest Dialog® removed most duplicates during the running of the search). After the first stage of review, ten articles were retrieved, and the full texts were reviewed. Based on full text review, five papers were excluded for reasons according to the study protocol (detailed in Figure 5.1). In total, five papers were retrieved from the search. Upon searching the references of the five included articles, a further three articles were retrieved and included in the final articles for review. Altogether, eight articles were included in this SR.

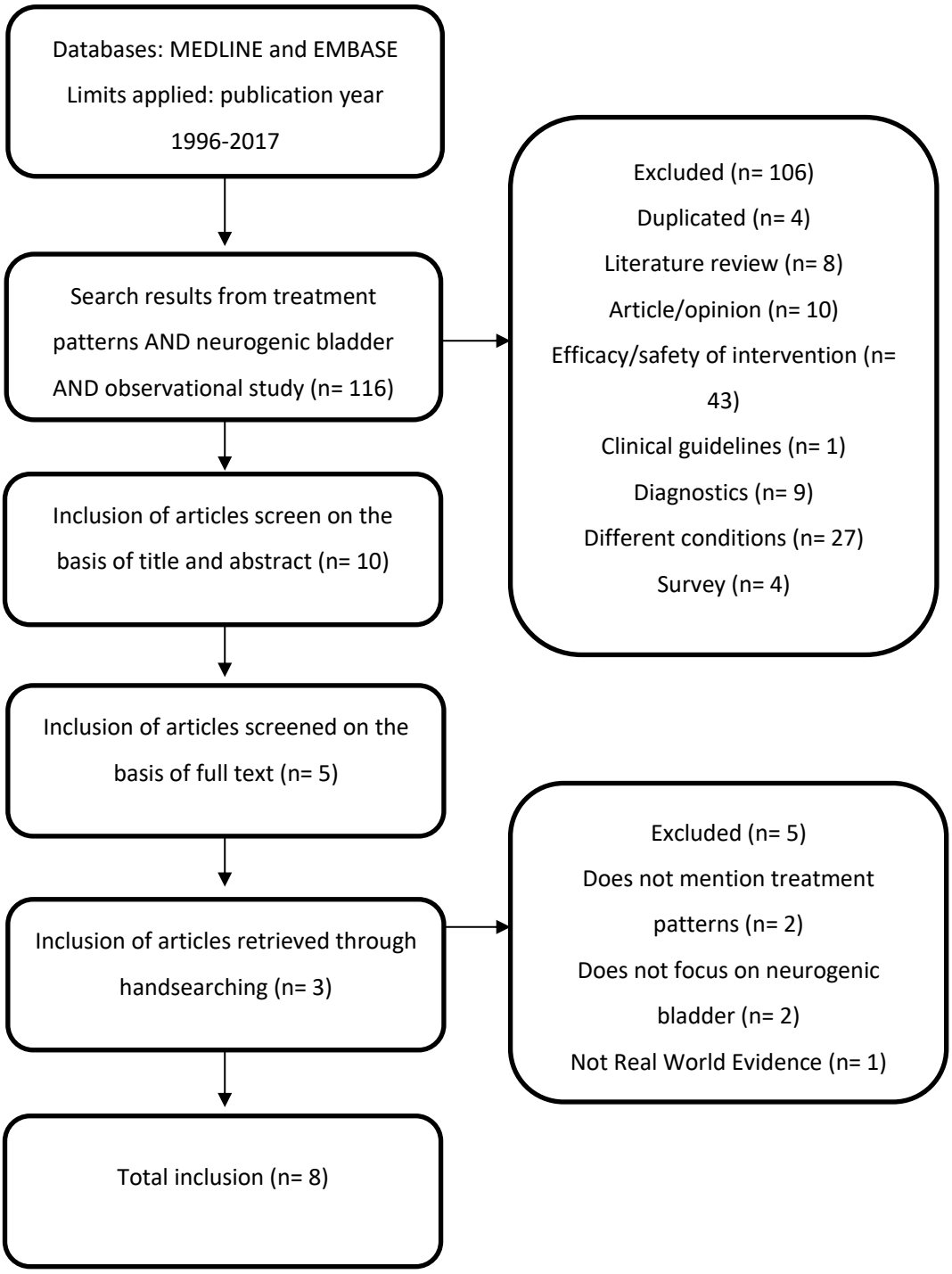


Figure 5.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

5.5.1 Study and Patient Characteristics

From the eight studies included (summarised in Table 5.2), study designs, country, and patient groups were notably heterogeneous. Overall, there were 47,706 patients with NGB and of these, 43.8% were male and the mean age was 42.8. The majority of included patients (46,271) came from two studies. Despite being published at separate times (2009 and 2011), these studies included the same cohort of patients (using the same inclusion criteria and database). Patients included in these studies had mixed underlying neurological conditions including MS, SCI, PD, paralytic syndrome, cerebral palsy and spina bifida. What differentiates the two studies is the 2011 study identified separate sub-cohorts for SCI and MS, including 4,168 and 9,315 patients respectively; thus, due to this additional information, the decision was made to include both studies into the analysis.

Most of the included studies (62.5%) focused on patients with SCI (or included a subgroup), at various levels of neurological injury and varied time since injury. Across the studies, there were a total of 5,182 patients with SCI. One study focused on spina bifida patients, including 421 individuals. The earliest period of data collection began in 1984 and the most recent ended in 2007.

Six studies reviewed retrospective data to gain insight into treatment patterns. Two studies incorporated a longitudinal retrospective study design using a large US medical and a pharmacy claims database (El-Masri et al., 2012; Lemelle et al., 2006). These were the largest studies; all other studies were notably smaller. Three studies used retrospective longitudinal study designs in the UK, France and USA (El-Masri et al., 2012; Lemelle et al., 2006; Manack et al., 2011; Manack et al., 2009). One study was conducted using a large healthcare database based in Taiwan, however in contrast to the other five retrospective studies; a cross-sectional study design was adopted (Chia-Cheng et al., 2012). The remaining two studies prospectively collected data from patients in the UK and US respectively (Anson and Shepherd, 1996; Drake et al., 2005).

The way severity of NGB was described differed between the studies. Of those that focused on SCI, Anson et al, described the severity according to the location of injury (cervical nerves or thoracic nerves) and time since injury. El-Masri et al and Drake et al described severity using the Frankel grade system, which is the most widely used medical classification system, based on the patient evaluation of the location of injury. Weld et al classified SCI according to the level of injury completeness. Lemelle et al classified spina bifida according to mobility. The two remaining studies did not stratify individuals based on level of injury. The different classification systems and heterogeneity of the patient populations made comparisons more tenuous.

Table 5.2 Summary of study and patient characteristics of included studies.

Study	Data collection period	Study design	Country	Patient sample characteristics	Neurogenic condition and severity
Anson and Shepard (1996)	Not reported	Prospective (longitudinal)	USA	348 individuals, 33% aged over 18, mean age 36.6, 82% male and 18% female, 80.2% Caucasian	SCI ● C0-C4: 19.7% ● C5-C8: 36.2% ● T1-T11: 29.4% ● T12-S5: 14.7% Years since injury: ● 1-2 years: 26% ● 3-5 years: 25.2% ● 6-10 years: 29.3% ● 11-15 years: 12% ● 15+ years: 8%

Chia-Cheng et al., (2012)	2006-2008	Retrospective (cross-sectional)	Taiwan	165 patients, mean age 54, 64% male and 46% female	Patients with emergency department visits or hospitalisations for SCI
Drake et al., (2005)	1990-1996	Prospective (longitudinal)	UK	196 individuals, aged 15-55, mean age 57.4, 86% male and 24% female.	SCI for at least 20 years Level of injury: ● Paraplegics with complete SCI (Frankel grade A, B, or C): 49% ● Tetraplegics with complete SCI (Frankel grade A, B, or C): 31.1% ● Incomplete SCI (Frankel grade E): 18.9% ● Mean years since injury: 33.26
El-Masri et al., (2012)	From 1984, with follow up ranging between 8 and 21 years	Retrospective (longitudinal)	UK	119 individuals, aged 16-63, mean age 29, 83.2% males, 16.8% females	SCI ● Paraplegic (two had S3 sacral lesion): 37.3% ● Tetraplegic: 27% ● Frankel grade A: 34% ● Frankel grade B: 4.3% ● Frankel grade C: 7.7% ● Frankel grade D: 18.4% ● Mean years since injury: 29
Lemelle et al., (2006)	2003-2004	Retrospective (longitudinal)	France	421 individuals, aged 10-47.5, mean age 22.1, 140 aged 10-18	Spina bifida (myelomeningocele at the neonatal period,

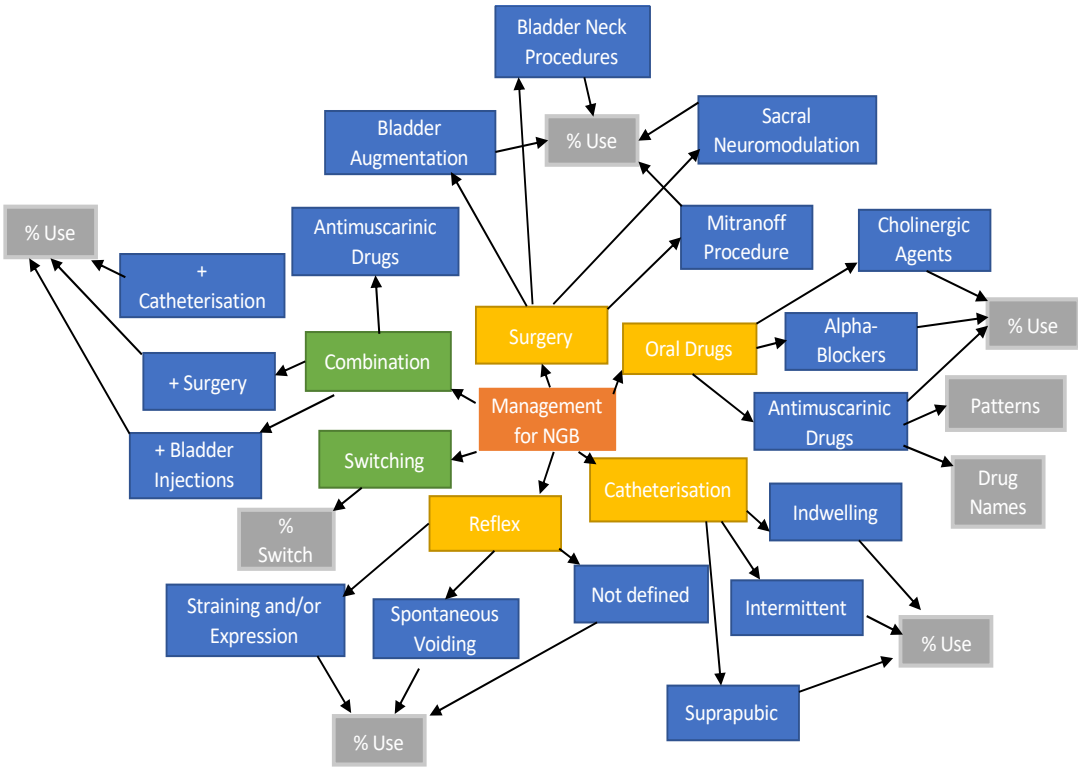
				and 281 aged over 18. 55% male and 45% female.	which was treated surgically) Ability to move: ● Walk with minor aid: 63% ● Walk with walking appliance: 3% ● Wheelchair outside + walk at home: 8% ● Wheelchair most of time: 26%
Manack et al., (2011) & Manack et al., (2009) (NGB cohort only)	April 1, 2002-March 31, 2007	Retrospective (longitudinal)	USA	46,271 individuals in NGB cohort, 9,315 individuals in MS, 4,168 individuals in SCI, aged 0-60+, mean age of NGB cohort was 62.5 years, mean ages in the MS and SCI subcohorts, 53.2 and 61.9 years respectively. 43.6% males and 57.4% females in NGB cohort, 31.3% male and 79.7% female, 41.9% male and 59.1% female in MS and SCI subcohorts respectively.	MS, (SCI (including paraplegia, quadripledia, tetraplegia), spina bifida, Parkinson's disease, cerebral palsy, hemipledia/hemiparesi, late effects of stroke, other paralytic syndromes, and neoplasm of the spinal cord)
Weld and Dmochowski (2000)	Years not reported. Follow up:18.3 years	Retrospective (longitudinal)	USA	316 individuals, mean age- 38 years, 99% male and 1% females	SCI <u>Injury completeness:</u> ● Complete:14.2%

	since injury.				● Incomplete:85.8% <u>Injury level:</u> ● Suprasacral:85.1% ● Sacral:14.9% ● Mean years since injury:18.3 years

C, cervical nerves; T, thoracic nerves; SCI, spinal cord injuries; MS, multiple sclerosis; UK, United Kingdom, NGB, neurogenic bladder

5.5.2 Treatment Patterns

Figure 5.2 below shows the result of the thematic content webbing (Popay et al., 2006). After reading the papers and extracting the data, the various management methods were identified. In line with the objective of this study, these management techniques constituted the main topics of discussion (shown in yellow and then further expanded in blue in Figure 5.2). As well as the management methods, additional topics of 'combination use' and 'switching' were also identified as key themes; these describe the ways in which treatments may be administered (shown in green in Figure 5.2). These key themes were all described in the papers by percentage use of technique (or percentage switch), drug patterns and names. This drug taking information was then used to guide and structure the results and following discussion.



Key

Orange – Theme of spider web (management of NGB)

Yellow – Conservative and interventional management types

Blue – Specific management types (expansion of yellow)

Green – Treatment administration types

Grey – Description of use

Figure 5.2 Thematic content analysis results

5.5.2.1 Oral Pharmacotherapy

Five out of the eight included studies included data on the use of oral pharmacotherapy. Three studies included information on bladder muscarinic drug use, which spanned between 12.6%-86.7%. Results from two studies demonstrated a range of 12.6%-39% patients using oxybutynin.

Lemelle et al reported the lowest recorded bladder muscarinic drug use, where 12.6% of spina bifida patients used oxybutynin regularly. The percentage of patients receiving

bladder muscarinics was almost double in the study by Chia-Cheng et al, where it was used by 26% of SCI patients with neurogenic detrusor overactivity (NDO). Manack et al (2011) reported much higher percentages, with 71.5% of patients in the NGB cohort, 80.9% in the SCI cohort and 86.7% in the MS cohort using this treatment. A prescription of a bladder muscarinic drug, (rather than any form of bladder management method) was one way in which a patient could be included into this study which could explain why percentage use was higher than other studies included into this SR. There is no indication of whether the remaining patients were not on therapy or using some other form of management. The highest use of oxybutynin of all publications was also recorded in this study (39%), followed by tolerodine (36.9%). El-Masri et al, mention that bladder muscarinics were administered to those with NDO, but percentage use is not delineated. Other studies did not report bladder muscarinic use; however, this should not be interpreted as lack of prescription of these medications.

El-Masri et al and Chia-Cheng et al reported the use of α-adrenergic antagonists; however, neither of the authors communicated the names of drugs. In the study by Chia-Cheng et al, the most prevalent drugs amongst SCI patients with NDO were α-adrenergic antagonists, used by 33% of individuals. α-adrenergic antagonists were administered to SCI patients with marked bladder outlet obstruction (BOO) in the study by El-Masri, but as with bladder muscarinic use, percentage use is not described.

The study by Chia-Cheng et al was the only one to mention use of cholinergics, where it was used by 15% of SCI patients with NDO.

5.5.2.1.1 Patterns of Oral Pharmacotherapy Use

Manack et al (2011) provides information on patterns of oral drug use, which is not available from the other studies. 7,782 individuals continued on an OAB drug, 10,110 discontinued and did not start, and a further 9,030 stopped and restarted. The average length of time on drug was 209.1 days for the MS sub-cohort and 195.5 days for the SCI cohort.

5.5.2.2 Catheterisation

Urinary catheter use varied substantially across the studies. Intermittent catheterisation (IC) use was reported in six studies, with a range between 0%-84%. Indwelling catheterisation (IndUC) (in this study, described as both indwelling urethral catheterisation (IDUC) and indwelling suprapubic catheterisation (SPC)) was reported in four studies, with a range of 0% to 100%.

Chia-Cheng et al reported that catheterisation was used by 67% of patients with NDO as a consequence of SCI, however it is unclear whether catheterisation refers to IC or IDC.

5.5.2.2.1 Intermittent Catheterisation

Lemelle et al reported that 71.3% patients with spina bifida were using IC. Anson et al and Weld et al reported much smaller percentages in post-acute phase SCI, with 30.5% and 29.1% respectively.

When considering studies with observations at multiple time points, El-Masri et al reported 27% of SCI patients using assisted IC immediately before admission to the hospital; however, no patients utilised this method upon admission. During hospitalisation, four-hourly IC was the most utilised method, with 84% of patients using it at least once. This is the highest report of IC use from all publications. This markedly declined to 15.1% patients at discharge from hospital. In contrast, the use of IC increased by 10.2% in the study by Drake et al; from 3.6% SCI patients in 1990 to 13.8% in 1996.

The difference in IC use between these two studies could be attributable to the varied follow-up. In the study by Drake et al, changes take place over six years whereas follow up in the study by El-Masri ranged between 8 and 21 years (mean 17.7).

5.5.2.2.2 Indwelling Catheterisation

Weld et al reported 36.1% post-acute SCI patients that utilised IDUC and 11.4% patients had a SPC fitted. In the study by Anson et al, much lower percentages were reported, with

9.8% that used IDUC and 3.2% that used SPC. The lowest recorded use of SPC use amongst the publications was one spina bifida patient in the study by Lemelle et al.

Studies with multiple observations seemed to paint a heterogeneous picture of IDUC use. Overall, IDUC use substantially decreased (by 60.6%) in SCI patients, throughout the duration of the study by El-Masri et al, but the general trend was not a linear decline. SPC use decreased at a much lower rate (0.8%) from hospitalisation to discharge. In contrast to this, the number of SCI patients utilising IDUC increased by 1.6% during the study by Drake et al, and SPC use increased by 7.2%.

In the study by El-Masri et al, 69% were managed with IDUC before admission to hospital and this increased to all patients upon admission. 21% of patients utilised this method at least once during hospitalisation. After discharge, 8.4% patients remained with IDUC. In the study by Drake et al, 12.2% had IDUC in 1990 and this increased to 13.8% in 1996.

The first recorded use of SPC was in the study by El-Masri was during hospitalisation, where 5% of patients utilised this method. After discharge, it was used by 4.2% of patients. Only 2% utilised SPC at study entry in the study by Drake et al, but this increased at a much higher rate than IDUC use, with 9.2% of patients utilising this method at study end.

5.5.2.3 Reflex Voiding

Multiple definitions exist for reflex voiding (RV), including bladder expression (Credé manoeuvre), straining (Valsalva manoeuvre) and triggered RV (Apostolidis et al., 2017). In this SR, RV use was reported in four studies, varying from 2.5% to 53.1%.

RV methods are used by 25% of SCI patients in the study by Anson et al and 23% of SCI patients in the study by Weld et al. Although these percentages are close in range, they cannot be directly compared as Anson et al fail to provide a definition of RV. Weld et al defines spontaneous voiding as ‘reflexive voiding with a post-void residual urine of less than 100 cc and a voiding pressure of less than 40 cm’ (Weld and Dmochowski: 768).

In the study by Drake et al, RV was defined as 'leaving a post void residual <10% and with no upper tract dilation, with or without prior sphincterotomy or urethral stent' (Drake et al.., 2005: 112). Use decreased by 11.8% during the study period, from 53.1% to 41.3%, but it remained the most used method within the study.

El-Masri et al did not specifically define RV, thus it is difficult to compare results to other studies. In this study, a small number of patients (2.5%) were managed with RV prior to admission, and during hospitalisation it was used by 16.8% individuals. It was the most common form of bladder management after patients were discharged from the hospital, where it was utilised by 49.8% of patients.

In the study by Drake et al, straining methods (in this case, defined as either Credé or Valsalva manoeuvres) decreased by 8.2%, from 19.4% to 11.2%. A much lower percentage (2.6%) of patients used expression techniques (defined as the Credé manoeuvre) at the end of the study by El-Masri et al.

5.5.2.4 Surgery

Two authors report the use of surgery to manage bladder symptoms. Manack et al (2009) reports particularly low numbers of bladder augmentation and interstim therapy (0.2% and 0.4% respectively) in NGB patients. This is in contrast to Lemelle et al, where the majority of spina bifida patients (55%) were surgically treated. Of these patients, 21.3% underwent bladder neck surgery, without bladder augmentation (with or without continent diversion), 36% patients underwent intestinal bladder augmentation (with or without bladder neck procedure) and 28.3% patients underwent intestinal bladder augmentation in addition to Mitrofanoff (with or without bladder neck procedure).

5.5.2.5 Other Management Options

Other methods of bladder management related to the collection of urine were also mentioned in one study. In the study by Lemelle et al, some patients used external collection devices, namely 8.3% of people used pads and 1% of patients used a uriseath.

5.5.2.6 Combination Use

Combinations of various procedures are often employed to manage the complex interplay of different symptomology or to control more severe bladder dysfunction. The different combinations of management techniques identified in the included studies are described below.

5.5.2.6.1 Combinations of Oral Pharmacotherapy

Manack et al (2011) reported 8.7% of patients on a combination of two or more bladder muscarinic drugs. 8.3% of patients were on two drugs, 0.4% were on three drugs and a negligible amount were on four or more drugs. A similar pattern was seen in the MS and SCI subcohorts. 9.5% patients in the MS subcohort were on a combination of two or more bladder muscarinics, a further 9% were on two drugs, 0.5% were on three drugs and only two patients were on four or more drugs. When considering the SCI cohort, 9.2% patients were on a combination of two or more bladder muscarinics, 8.9% were on two drugs, 0.3% were on three drugs and no patients were on four of more drugs.

A combination of α-adrenergic antagonists and bladder muscarinics were given to those with detrusor sphincter dyssynergia (DSD) and autonomic dyssynergia in the study by El-Masri et al. Percentages of combination use were not reported in this study.

5.5.2.6.2 Combination of a Therapy with Catheterisation

Lemelle et al states that 12.6% of spina bifida patients regularly utilised IC in combination with oxybutynin. Also, in this study, 90% of patients used IC in addition to undergoing surgery, including 61% through a continent neoconduit and 39% on the abdominal wall.

In the study by Anson et al, 11.5% patients were on a combination of IC and reflex. There is also a report of 3.7% of patients on some combination of treatments between IC, reflex, IDUC, SPC and self-voiding, but actual combinations are not provided.

5.5.2.6.3 Combination of Surgical Procedures and Bladder Neck Injections

Lemelle et al reports 39% of patients undergoing a combination of surgical procedures to achieve adequate reservoir and neck management in spina bifida patients. The most popular combination of procedures is intestinal bladder augmentation + Mitronaff principle + neck closure (Table 5.3).

Table 5.3 Combination of reservoir and neck management in study by Lemelle et al., (2006)

Management Type	Number of Patients
Sling + Mitrofanoff	2
Sling + neck injection	1
Kropp + sling	1
Neck injection + Mitrofanoff	3
Neck closure + Mitrofanoff	3
Neck injection + PippiSalle + Mitrofanoff	1
Intestinal bladder augmentation + urinary artificial sphincter	11
Intestinal bladder augmentation + sling	14
Intestinal bladder augmentation + Kropp	4
Intestinal bladder augmentation + Young-Dees + neck injection	5
Intestinal bladder augmentation + neck injection	10
Intestinal bladder augmentation + sling + neck injection	3
Intestinal bladder augmentation + Kropp + sling	1

Intestinal bladder augmentation + urethral transposition	1
Intestinal bladder augmentation + Young-Dees	1
Intestinal bladder augmentation + Young-Dees + sling + neck injection	1
Intestinal bladder augmentation + Young-Dees + artificial urinary sphincter	1
Intestinal bladder augmentation + PippiSalle	2
Intestinal bladder augmentation + PippiSalle + neck injections	2
Intestinal bladder augmentation + PippiSalle + sling	1
Intestinal bladder augmentation + Mitronaff principle + neck closure	21
Intestinal bladder augmentation + Mitronaff principle + sling	8
Intestinal bladder augmentation + Mitronaff principle + neck injection	7
Intestinal bladder augmentation + Mitronaff principle + sling + neck injection	1
Intestinal bladder augmentation + Mitronaff principle + suprapubic urethral transportation	2
Intestinal bladder augmentation + Mitronaff principle + V-Y neck plasty	1
Intestinal bladder augmentation + Mitronaff principle + artificial sphincter urinary cuff only	1
Intestinal bladder augmentation + Mitronaff principle + pippisale	2
Intestinal bladder augmentation + Mitronaff principle + pippisale + neck injection	1
Intestinal bladder augmentation + Mitronaff principle + Kropp	2

Intestinal bladder augmentation + Mitronaff principle + Young-Dees + sling + neck injection	3
Intestinal bladder augmentation + Mitronaff principle + artificial urinary schincter	2

Adapted from: Lemelle et al., 2006

5.5.2.7 Switching

Weld et al mentions that most post-acute SCI patients switched bladder management methods over the course of the study period; with the most prevalent change being from IC to IDUC, although the percentage is not provided. 14.3% of patients in the study by Drake et al, and one patient in the study by El-Masri also made this particular switch of treatments.

Drake et al provides a table of change in management methods from 1990 to 1996 (Table 5.4). As in the study by Weld et al, most patients switched from their original mode of management (62.8%), however the most prevalent change was straining to IC (28.9%). The most used method in 1990 was RV, and this remained the case in 1996, despite 24% switching to an alternative form of treatment. The second most used method was the straining method in 1990 but changed to IDUC and IC in 1996. SPC remained the least used form of management, along with 'other'.

El-Masri et al also showed a large proportion of patients (39.5%) that switched treatments during hospitalisation (Table 5.5). In contrast to both Weld et al and Drake et al, the most prevalent switch was IC to sphincterotomy and IDUC to IC.

Table 5.4 Change in bladder management methods (BMM) between 1990 and 1996 in study by Drake et al., 2005

	Bladder management method (BMM) in 1996						
BMM IN 1990	**RV**	**Strain**	**IDUC**	**SPC**	**IC**	**Normal**	**Other**

RV 104 (53.1%)	79 (76%)	5 (4.8%)	5 (4.8%)	4 (3.8%)	10 (9.6%)	1 (0.9%)	-
Strain 38 (19.4%)	1 (2.6%)	17 (44.7%)	2 (5.3%)	7 (18.4%)	11 (28.9%)	-	-
IDUC 24 (12.2%)	1 (4.2%)	-	19 (79.2%)	3 (12.5%)	1 (4.2%)	-	-
SPC 4 (2%)	-	-	-	4 (100%)	-	-	-
IC 7 (3.6%)	-	-	1 (14.3%)	-	4 (57.1%)	-	2 (28.6%)
Normal 19 (9.7%)	-	-	-	-	1 (5.3%)	18 (94.7%)	-
Total 196	81 (41.3%)	22 (11.2%)	27 (13.8%)	18 (9.2%)	27 (13.8%)	19 (9.7%)	2 (1%)

BMM, bladder management method; RV, reflex voiding; IC, intermittent catheterisation; IDUC, indwelling urethral catheterisation; SPC, suprapubic catheterisation
Reproduced with permission from Drake et al (2005)

Table 5.5 Bladder management switching during hospitalisation. Adapted from El-Masri et al., 2012

Bladder management switch	**No. of patients**
IC → SPC	4
IC → sphincterotomy → RV	3
IC → RV	7
IndUC → IC	11
IndUC → IC→ RV	3
IC → sphincterotomy	11
IC → SPC → sphincterotomy → RV	1
IC → IndUC	1

IC → IndUC → sphincterotomy → RV	1
IndUC → IC → sphincterotomy	2
IndUC → SPC	1
RV → sphincterotomy	2
Total	47

IC, intermittent catheterisation; IndUC, indwelling catheterisation; RV, reflex voiding; SPC, suprapubic catheterisation

5.6 Discussion

Selecting optimal treatments and employing appropriate management strategies for NGB patients is integral to improving patients' bladder symptoms and Quality of Life (QoL). With passing time, clinicians have moved away from techniques associated with higher rates of complications and mortality, and consequently in recent years, the survival chances of NGB patients have improved considerably (Harrison, 2010). This SR revealed that numerous treatments and management strategies have been used to control the symptoms of NGB throughout the years, mostly consistent with the signs and symptoms of NGB and there has also been a large variance in their use.

The most popular oral pharmacotherapy in this SR were bladder muscarinics, which are correspondingly cited as first line therapy for NDO in the NICE, EAU and ICI CGs (NICE, 2012; Bloc et al., 2017; Drake et al., 2005). This conclusion should however be interpreted with some caution, as many studies in this review did not measure the use of oral pharmacotherapy, instead focusing their attention on other methods of bladder management. It is unclear why oral pharmacotherapy was not as thoroughly documented in the included studies, however it is well known that NDO is frequently observed in SCI (which 62.5% of included studies focused on), and bladder muscarinics have acted as the primary mode of treatment for this condition for a number of years (Madhuvrata et al.,

2012). Speculation therefore suggests that a greater number of patients included into this SR were on some form of bladder muscarinic, but utilisation rates were not recorded.

Most studies did not mention the type of bladder muscarinic drug used. Two studies mentioned a wide range of oxybutynin use. Oxybutynin is one of the oldest and most prescribed bladder muscarinics available on the market for NDO, thus the findings in this SR are as expected (Suguino, 2012). It is also one of the most toxic bladder muscarinics, with the ability to cause various forms of cognitive impairment, including dementia (Gray et al., 2015).

In the study by Manack et al (2011), some patients used a combination of two or more bladder muscarinics. Based on evidence from a few small clinical trials, the EAU provide a grade B recommendation, asking physicians to consider a combination of bladder muscarinic agents. None of the prominent NGB CGs however recommend more than two bladder muscarinics to be prescribed at one time, which was observed in this study, thus demonstrating an example of how real-world practices can deviate from guidance featured in CGs.

In NGB, invasive forms of management such as bladder augmentation are typically only employed once more conservative measures have been exhausted. In spina bifida, two-thirds of patients can become continent through IC and oral pharmacotherapy alone (Frimberger et al., 2012). The minority of spina bifida patients that do not respond to conservative treatments must undergo surgery to improve bladder functionality (Mingin and Baskin, 2003). The one study included in this SR, focusing on spina bifida, reported that the majority of patients underwent surgery. This result is unexpected given that most spina bifida patients should be managed with conservative measures. Possible reasons for this could be the high severity of incontinence in the sample, higher incidence of refractory NGB or a less conservative attitude of physicians towards surgery in France between 2003-2004 (the study period). This result may also imply surgery was the more cost-effective solution in this situation. Although of course these rationalisations are purely speculative.

Many of the studies in this SR have early periods of data collection therefore it is perhaps comprehensible that some practices deviated from what is currently considered safe and effective. One example of such variance is the use of the Credé and Valsalva manoeuvres in studies that collected data in the 1980's and 1990's (El-Masri et al., 2012; Drake et al., 2005). In current CGs, these techniques are contraindicated due to complications including epidydymoorchitis and haemorrhoids (Bloc et al., 2017; Apostolidis et al., 2017). It is thought that these manoeuvres have been progressively phased out in real world practice in the West, and this is supported in the study by Drake et al, where use of these manoeuvres decreased by 8.3% throughout the study duration. In many developing countries these techniques are still endorsed as viable forms of bladder management because they require little to no resources to implement (Przydacz et al., 2017). The ICI CGs aim to modify and improve clinical practice globally however as mentioned in Section 3.6.5.6 the dedicated sub-committee named 'Faecal Incontinence and Incontinence in the Developing World' no long exists, which could make the reduction of detrimental practices such as the Crede and Valsalva manouevers in developing countries less likely.

IndUC was also widely used (up to 100%) despite the fact that this type of catheterisation is associated with an increased risk of UTI, as well as serious sequalae such as bladder cancer (NICE, 2012; Bloc et al., 2017) (Section 2.4). The high frequency of this procedure may again be because of the earlier years of data collection; however, it is also important to consider that SCI can result in limited manual dexterity (for example, in the case of tetraplegia), impeding the ability of intermittent self-catheterisation (ISC) (Taweel and Seyam, 2015). Similarly, the current NICE CGs recognise that in some instances the choice of management technique is limited by what the patient can manage (NICE, 2012).

The latest ICI CGs suggest that assigning causation of urinary tract damage to IndUC may not always be accurate, as the technique is often utilised in patients in whom urinary tract damage has already occurred. Drake et al actually suggest that IndUC might in fact be protective for the upper urinary tract.

There is little evidence-based research supporting SPC use. Some opinion suggests that SPC is generally preferred over IDUC due to a number of advantages including comfort and ease of access for cleaning. In addition, the risk of urethral trauma, necrosis or catheter-induced urethritis and urethral strictures is eliminated (Reitz et al., 2006). Despite these advantages, SPC was used at a much lower rate than IDUC in this SR. This could possibly be because placement of SPC is a more invasive procedure than IDUC or because there are no clear CGs around the choice between SPC and IDUC (Apostolidis et al., 2017). Accordingly, increased research efforts may be necessary in this area to help illuminate optimal catheterisation choice.

This review had a global geographical scope; thus, one may assume that the management methods employed reflect the healthcare system and national CGs in which the study was conducted. At present, the American Urology Association (AUA) lacks any specific CGs for the management of NGB. High bladder muscarinic use in the two US studies by Manack et al are in line with other internationally available CGs, where bladder muscarinics are first line therapy for patients with NDO (Bloc et al., 2017; NICE, 2012; Apostolidis et al., 2017).

In the study by Chia-Cheng et al, conducted in Taiwan, α-adrenergic antagonists were the main method of management for NDO, despite Taiwanese NGB CGs stating there is strong evidence to support the use of bladder muscarinics in NDO (Kuo et al., 2014). The greater use of α-adrenergic antagonists use may indicate patients had retention symptoms, in conjunction to NDO. Alternatively, several small clinical trials have demonstrated efficacy of α-adrenergic antagonists in NDO, which could indicate that clinicians in the real world are making choices in divergence from CG recommendations (Yasuda et al., 1996; Swierzewski et al., 1994). This notion correlates with results from a survey which showed that urologists did not follow CG recommendations meticulously. Nevertheless, this survey also found that despite non-adherence, urologists still tended to make choices in accordance with recommendations (Rikken and Blok, 2008).

Three studies demonstrated notable treatment switching, which could be indicative of the dynamic progression of NGB. Treatment switching has showed to increase costs to the

healthcare system (Ivanova, 2014). Duration of time since injury in SCI can have an impact on bladder compliance that can consequently influence changes in the choice of management strategy (Harrison, 2010). Alternatively, treatment switching may demonstrate that a trial and error approach is necessary to establish an optimal treatment regime (Martinez et al., 2016). A number of factors influence the initial choice of management method, including type of NGB, sex, age, hand dexterity and healthcare access (Taweel and Seyam, 2015). In the study by Drake et al, reasons for switching treatments pertained to complications such as functional decline and UTIs. Some patients included in this review made their own treatment choices, for example, El-Masri et al mention there is the risk of danger 'if the patient chooses RV when bladder overactivity with DSD is not properly dealt with' (El-Masri et al., 2012: 19). This indicates that individual preference plays a large role in the management pathway (Drake et al., 2005; El-Masri et al., 2012; Weld, 2000). Current CGs promote active dialogue between the physician and patient/their carer. In particular, NICE CGs make specific recommendations for education of patients and their carers on the advantages and disadvantages of all available options so they are able to make informed management decisions (NICE, 2012; Engkasan et al., 2013).

The wide variety of methods employed demonstrate that NGB is a notably heterogenous condition. The research presented in this SR can act as an important preliminary step in influencing future CG recommendations to reflect what is working for clinicians in the real world. For example, administration of more than one bladder muscarinic or the use of IndUC over IC. Essentially, CG quality could be improved if they are based on what is already being used to manage patients in the real world and has some clinical evidence to support its use. This is especially important in NGB, due to the infeasibility of conducting RCTs and the supposed self-evident nature of treatment efficacy.

5.6.1 Methodological Limitations

Both the sensitivity (comprehensiveness) and specificity (focus) is important to balance when devising a search strategy (Bramer et al., 2018). In order to decrease the chances of missing relevant citations, a sensitive search strategy is generally preferred (Sutherland,

2001). However, adopting this type of search this will often retrieve thousands of citations, of which a high percentage will be irrelevant. Due to time and resource constraints, specificity was given greater importance in this search over sensitivity. The highly specific search used in this SR may have translated in greater accuracy; however, it could also have meant that relevant publications were potentially missed.

The sensitivity of the search strategy could have been increased in a number of ways. Utmost effort was made to incorporate as many potential terms related to NGB. However, potentially relevant articles may not have mentioned, or indexed terms directly associated with NGB. To account for this, including search terms for underlying neurological conditions in combination with search terms for urinary incontinence (UI) or bladder dysfunction may have retrieved additional relevant citations.

In order to improve the accuracy, this search strategy also included terms to retrieve only real-world studies. The indexing quality of observational studies has proven to be inconsistent in the past (Fraser et al., 2006). Furthermore, the terminology used to describe certain study designs can vary and be used in different ways by different researchers, which can make identifying particular types of studies even more difficult. For these reasons, manually identifying real world studies, rather than including specific search terms may have been a superior search strategy. Search filters also could have been employed, but as mentioned in Section 5.4.7.1, they can often lead to important omissions.

As the purpose of this SR was purely descriptive in nature, the study design (apart from being conducted in a real-world setting) was not of great importance. Inclusion of mixed study designs (retrospective, prospective, cross-sectional etc.) could however, have affected the reliability of results.

Several forms of bias could have affected the results. Publication bias is a well-known phenomenon in scientific research, where studies that do not disprove the pre-specified null-hypothesis are less likely to be published than those with 'positive' results (Dirnagl and Lauritzen, 2010). Although this form of bias is not a pressing issue in the modern day since the introduction of mandatory clinical trial reporting in 2007, it is relevant since this SR

included papers published as far back as 1996. Moreover, most NGB studies are industry-sponsored and publication bias is an even heightened issue in these trials compared to those which are government-funded (Mayo-Wilson et al., 2018). This SR did not make a special attempt to search the 'grey' literature, i.e. literature with limited distribution, where results from 'negative' studies are more likely to be retrieved. Although publication bias is not a real disadvantage in this SR, as it is purely descriptive, omission of grey literature could have meant relevant studies were missed. Furthermore, this SR included English language publications only. This can introduce language bias, as articles are more likely to be published in English if they report significant results (Egger et al., 1997).

In order to minimise bias, eligibility assessment should involve two independent reviewers screening all titles, abstracts, and full-text articles (Moher et al., 2009). Due to time and resource constraints, a restricted method of eligibility assessment was employed in this review, which involved only one reviewer (AJ) conducting the initial abstract screening and the second reviewer (FF) screening a small proportion of those (10%). This could be considered a major source of bias.

This review was completed manually, except during the first stage of de-duplication, which was automatically conducted by ProQuest Dialog®. Although meticulously following the protocol leads to robust analysis, automation could help improve efficiencies. Automation tools are currently available for searching, snowballing, screening, extraction of data, meta-analysis and write-ups (Tsafnat et al., 2014). They allow for more of the reviewer's time to be devoted to producing a high-quality protocol and continual monitoring of the overall quality of the results. Improving efficiency is essential in an age where medicine is progressing at an unprecedented rate, and clinical research questions need to be answered quickly (Tsafnat et al., 2014).

5.7 Conclusions

Many treatments reported in this review are in line with current CG recommendations; however, possibly due to the early years of data collection, some divergence was also

evident. Due to the small number of studies, varied patient baseline characteristics, and selectiveness in the type of treatments and bladder management methods reported, a representative picture of real-world treatment patterns in NGB could not be fully elucidated. Furthermore, only one study was retrieved that included a UK population. Increasing the sensitivity by employing a broader range of search terms, and searching the grey literature could have increased reliability in conclusions drawn from this SR.

It is clear from this review that large epidemiological studies using electronic healthcare records (EHRs) are necessary to advance our understanding of how patients are managed in current practice and determine how well patterns relate to CGs. This information can then be used to enhance current management practices through modifications to CGs and ultimately improve patient outcomes and the allocation of resources.

5.8 Chapter Summary

This chapter sought to identify and describe the real-world treatment patterns in the worldwide NGB population. Some strategies were supported by current NGB CG recommendations but particularly owing to the earlier years of data collection, some practices also diverged.

The next chapter aims to build on the gaps identified in this SR, by generating an understanding of the patient characteristics and treatment patterns in UK NGB patients using the Clinical Practice Research Datalink (CPRD) database. The study will also determine the healthcare resource utilisation (HRU) which is intrinsically linked to the effectiveness of the management pathway.

6) Chapter Six – Clinical Practice Research Datalink (CPRD) Study: Methods

6.1 Introduction

The previous chapters in this thesis have provided an in-depth overview of neurogenic bladder (NGB) by collating and presenting the demographics and healthcare resource utilisation (HRU) (Chapter 2), clinical guideline (CG) quality (Chapters 3 and 4) and drug utilisation patterns (Chapter 5). One of the main findings from the previous chapters was the multiple evidence gaps in NGB, which impedes the optimal quality of CGs. One of the first steps to encouraging research in any disease area is to conduct epidemiological research to characterise the patient population. There are very few studies that effectively describe NGB, and furthermore, none in a UK population. In fact, the only epidemiological study that investigates drug utilisation patterns and HRU was conducted in the USA using data from over ten years ago (Manack et al., 2011). It would be infeasible to transfer this information to a UK population, not only because of the outdated period of data collection, but because patient characteristics, healthcare systems and available treatments differ between countries. With this in mind, there is a pressing need to better distinguish NGB in a UK population; understand how overactive bladder (OAB) drugs (specifically, bladder muscarinics and mirabegron) are used in the real-world setting and discuss the associated economic and health outcomes.

Accordingly, a novel epidemiological study using the Clinical Practice Research Datalink (CPRD) database is presented in the following chapters, providing estimates on important parameters and thus insight into the manifestation of NGB in a UK population. Through answering the objectives set forth in this study, the unmet medical need of this patient population can be elucidated, which can provide direction for future research through the prompting of new hypotheses. These hypotheses can be tested and verified to determine association and ultimately promote the safe and effective use of interventions in clinical practice. Furthermore, the aspects of patient care that are resource intensive and expensive to the National Healthcare System (NHS) demonstrate possible areas where cost savings can be made and the salience of the disease against competing public health

priorities can be determined. This research also aids in elucidating where initial improvements in CGs can be introduced. The methodology to the CPRD study is presented in this chapter, followed by the results (Chapter 7) and discussion (Chapter 8).

6.2 Funding Statement

This study was carried out as part of a Knowledge Transfer Partnership (KTP) program between Astellas Pharma EU and Manchester Metropolitan University. Funding for this research was provided by Astellas Pharma EU and Innovate UK.

6.3 Aims of the Study

Section 1.6 outlined the overall aims of this research, which are to ultimately build a better understanding of the NGB population. The CPRD study was presented as one of the objectives by which to achieve this. The aims of this study are listed below.

Primary Aim: To describe the patient demographics, comorbidities, complications and current patterns of drug use over 12 months in NGB patients, stratified by underlying neurological condition (Parkinson's disease (PD), multiple sclerosis (MS), spinal cord injuries (SCI), spina bifida (SB) and stroke (STK)). Drug use includes:

- Calculation of Anticholinergic Cognitive Burden (ACB) score
- Rates of OAB drug (bladder muscarinic or mirabegron) use including: daily dose, cumulative numbers of days' supply and level of combination use

Secondary Aim: To describe the HRU and NGB related costs in the 12 months post OAB/NGB diagnosis or OAB drug prescription, stratified by underlying neurological condition (PD, MS, SCI, SB and STK).

6.4 Methods

6.4.1 Databases

6.4.1.1 The Clinical Practice Research Database GOLD

The main data source employed in this study was the UK CPRD GP Online Data (GOLD). The database is generally accepted as a reliable resource and is used extensively throughout the world to conduct epidemiological research (Herrett, 2015).

In 2007, the Department of Health's (DoH) National Institute for Health Research (NIHR) launched its pilot 'Research Capability Programme' (RCP), with the aim of reaching a consensus on the use of electronic health record (EHR) data and increasing the availability of such data to researchers in the UK. At the time, the Medicines and Healthcare Products Regulatory Agency (MHRA) had ownership of the General Practice Research Datalink (GPRD), a large longitudinal database collecting primary care data since 1987. An opportunity was recognised for collaboration between these institutions, and resultantly, the CPRD was launched in 2012 with the aim of improving the standard of research within the UK and reducing development time for new interventions (Knight; MHRA, 2012).

The CPRD database is currently the largest longitudinal primary care EHR available in the world. It contains anonymised data from 1987, on over 13.6 million patients from 674 practices which equates to around 20% of the UK population. It is broadly representative of the UK population in terms of age, sex and geographical distribution (Williams, 2012; Herrett, 2015). Data is collected as part of routine primary care practice by healthcare professionals (HCPs) and is recorded into the database. This includes information on demographics (age, sex and registration information), diagnoses (from both primary and secondary care), symptoms, prescriptions (date, formulation, strength, and quantity), specialist referrals, immunisations, behavioural factors and laboratory tests. Overall estimates of diagnostic validity in the CPRD have proven to be high (Herret, 2010).

The standard clinical terminology in UK General Practitioner (GP) practices is the Read code classification; a comprehensive system developed by Dr James Read in 1987, that goes well beyond simply classifying diseases (Spencer et al., 2011). The classification consists of alphanumeric codes encompassing all aspects of patient care such as clinical signs, symptoms and observations; laboratory tests and results; diagnoses; diagnostic, therapeutic or surgical procedures performed; as well as a variety of administrative items. It even covers additional information such as social circumstances and occupation (Strom, 2013). Drug prescriptions are recorded via the product code system, which can be identified by drug substance name or the British National Formulary (BNF) code representing the chapter and section from the BNF (Section 6.3.12.1.7). The CPRD Code Browser (Medical Dictionary and Product Dictionary) is used to identify Read and product codes.

The CPRD is organised into distinct datasets which are combined via each patient's unique identifier to provide information about the patient that is both understandable and analysable (Table 6.1).

Table 6.1 Datasets in the Clinical Practice Research Datalink

Dataset	Description
Patient File	Identification, demographic and registration details
Clinical File	All medical events including symptoms, signs and diagnoses
Additional Clinical Details File	Data linked to events in the Clinical File
Test File	All tests requested for the patient
Referral File	All referrals made to secondary care
Therapy File	All prescriptions issued to patients
Consultation File	The type of consultation entered by the GP

Practice File	Details of the practice (region and collection information)
Staff File	Information on practice staff

Available from: Padmanabhan (2017).

6.4.1.2 Hospital Episode Statistics Admitted Patient Care and Outpatient

A subset of the cohort included into this study were linked to the UK HES Admitted Patient Care (APC) and outpatient databases and utilised for the secondary objective of the research. The original purpose of the HES, which is managed and curated by NHS Digital, was for administration and hospital performance assessment, but it has since evolved into a vital resource for epidemiological research (Herbert, 2017).

The CPRD linkage scheme allows the longitudinal analysis of both primary and secondary care data (Herrett, 2015). Around 75% of patient records in CPRD is linked to the HES APC and outpatient databases which provides data on all inpatient admissions since 1989 and outpatient appointments since 2004 in English NHS Trusts. Linked data is available from April 1997 (Herbert, 2017). Since linkage become available, the use of HES to determine HRU has expanded extensively owing to its comprehensive data capture on diagnoses, surgical procedures and outpatient attendance.

Diagnosis in HES is coded by the International Classification of Disease, 10th revision (ICD-10), a modified medical classification system by the World Health Organisation (WHO). Procedures are coded by the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th edition (OPCS-4.8) (NHS, 2017). Finished consultant episodes (FCEs) are the basic counting units and represent a period of care for a patient under one consultant. FCEs can then be aggregated into 'spells' which represent the complete time a patient spends in one hospital (Aylin, 2004). The strengths and limitations of the two main databases used in this study can be found in Appendix 9.

6.4.2 Ethical Approval, Governance and Patient Confidentiality

Ethics approval for this study was granted from Manchester Metropolitan University (MMU) and can be found in Appendix 10.

Governance approvals were granted by three multi-disciplinary review bodies within Astellas Medical Affairs Europe. The bodies are called the Protocol Review Committee (PRC), the Core Medical Team (CMT) and the Medical Affairs Protocol Advisory Committee (MA-PAC). These bodies included representation from medical, pharmacovigilance and statistics, and they scrutinise the scientific integrity, study design and statistical soundness of the protocol.

Protocol submission to the MHRA's, Independent Scientific Approval Committee (ISAC) prior to the commencement of any analyses is mandatory. The protocol was approved on 29th September 2017 and assigned the ISAC number 17_207R (Appendix 11).

Only anonymised data is used in this research, therefore patient consent was not required for this study. All analysis was conducted in accordance with the Guidelines for Good Pharmacoepidemiological Practice (GPP), which sets out best practice for ensuring data integrity and patient confidentiality (International Society for Pharmacoepidemiology [ISPE], 2008). In order to ensure security, the data for this study was only available to individuals with personalised log in credentials, who have undergone CPRD and Astellas' specific real-world informatics (RWI) training. Furthermore, the data was held and analysed in the secure Amazon Web Services (AWS) platform.

6.4.2.1 Practical Set Back – Governance

As a result of the rigorous governance procedures, there were some setbacks in commencing analysis on the intended start date. Gaining access to the analysis platform was also met with significant delays owing to the long administration process and issues pertaining to the new General Data Protection Regulation (GDPR) guidelines.

6.4.3 Study Design and Aim

This was a descriptive, exploratory study, performed using the CPRD GOLD database, amongst adult patients (≥19) who have NGB, with the aim of characterising the population, describing current treatment patterns, and HRU. The study sample data was drawn from January 1st, 2004 to December 31st, 2016 (12 years).

6.4.4 Quality Control

Before analysis can begin, data must be converted to research-ready status. Analysis was conducted on patients flagged by CPRD as being of 'research acceptable' status, for whom their study observation period occurs during an uninterrupted period of practice registration, where the practice is deemed UTS by CPRD. All data management was done in accordance with Astellas standard operating procedures (SOPs). After reception of the data from CPRD, data management (selection, variable derivation), summarisation, and analyses was conducted using the SAS software, Version 9.4. All data transformations were logged in the SAS coding files.

To determine patients' age, it was necessary to convert the 'year of birth' variable by adding 1800 to the integer value of the number of years since 01/01/1800. Gender (referring to patient sex) is pre-defined with category in the patient table with values of 0, 1, or 2, which map to the labels; "Not entered", "Male", "Female", respectively.

In order to generate the code lists for this study, search terms were first conceptualised by AJ and then reviewed by an in-house (Astellas) urologist. Once search terms had been agreed, the relevant CPRD code dictionary was searched for appropriate codes. The resulting codes were again confirmed by the urologist to ensure applicability and decide whether any changes were required to the original search terms. This was repeated until the final code list was derived. An effort was made throughout the duration of this process to enhance inclusivity but also be as specific as possible.

6.4.5 Missing Data

Routinely collected data such as that from the CPRD, are normally used for administrative purposes, without a-priori research goals. This can introduce inconsistencies and increase the chances of missing data (Farmer et al., 2018). In this study, only data from patients flagged as being of 'research-acceptable' quality was used therefore there was no missing data for age, sex or practice. Due to the descriptive nature of this study, no imputation methods were employed for any data other than prescription data described in the sections below.

6.4.5.1 Missing Values for Prescription Data

In the CPRD data, prescription duration is not a mandatory field, and overall, only 7% of drug prescriptions are recorded with a duration value. Drug quantity (i.e. the number of pills in a pack) is recorded more consistently, with around 99% of all drug prescriptions possessing a valid quantity value.

A CPRD-derived daily quantity field (number of pills per day or numerical daily dose) is provided. Some prescriptions do not clearly specify the numerical daily dose, and instead the physician has provided instructions for the patient to take 'as needed' or 'as directed, making 26% of values invalid (Matcho et al., 2014).

Patients for which duration or information to calculate the duration of treatment was missing were still included in the study population and imputation of the numerical daily dose and duration were performed when missing or invalid.

To estimate the duration, a numeric daily dose (daily quantity) was imputed for all prescriptions with missing or invalid values. This imputation was performed stepwise, using the following set of assumptions, as described by Matcho et al (2014):

1) If the numeric daily dose was missing or invalid, the most common valid numerical daily dose in the data for the same combination of product, quantity and strength was used.

2) If the first step failed to produce a valid daily quantity, then the most common valid numeric daily dose in the data for the product only was used.
3) Otherwise, the daily quantity was set at one per day.

This method utilises the most common quantities, i.e. the mode, to replace missing data via a hot decking approach. This consists of using replacing missing data with observed data from a similar unit, in this case, from the same combination or single product. This is a fast and simple way to make up the missing daily quantity values however utilising the mode does lack accuracy and can potentially underestimate daily quantity. This method can nevertheless be used for drugs with large sample sizes. When considering the hot decking method, the issue of too many missing values being imputed from the same donor can arise (Joenssen & Bankhofer, 2012).

6.4.6 Identification of the Neurogenic Bladder Study Population

Defining the patient cohort was an important first step before beginning analysis. In order to determine appropriate diagnostic codes to identify NGB patients, the search terms shown in in Table 6.2 were inputted into the CPRD code browser, searching the clinical, test and referral files.

Table 6.2 Search terms used to identify Read codes for neurogenic bladder

Condition	Inclusion terms
Neurogenic bladder	*neurogenic*, *neuropathic*bladder*, *neuromuscular*bladder*

* - represents a wild card indicating that any character can take this place.
Words could appear on either side of the 'AND' search term.

Upon conducting the search, read codes were retrieved for neurogenic bladder, neuropathic bladder and neuromuscular bladder, but no Read codes were retrieved for neurogenic detrusor overactivity (NDO) or underactivity (Table 6.3). Neuropathic bladder

and neuromuscular bladder were confirmed to be interchangeable terms with neurogenic bladder (Game, 2010; Drake and de Ridder, 2017). The term 'NGB', is used throughout this study to refer all three of these Read codes.

Table 6.3 Read codes for neurogenic bladder

Search term	Read code label	Read code
neurogenic	Neurogenic bladder	K16V011
	Neurogenic bladder	F246112
neuropathic bladder	Neuropathic bladder	K16V00
	Neuropathic bladder	F246113
	Reflex neuropathic bladder, not elsewhere classified	K16W.00
	Uninhibited neuropathic bladder, NEC	K16X.00
neuromuscular*bladder	Other neuromuscular dysfunction of bladder	Kyu5200
	Neuromuscular dysfunction of bladder, unspecified	Kyu5E00
	Neuromuscular dysfunction of bladder, unspecified	K16V.00

A feasibility count was conducted using the Read codes listed in Table 6.4, with no application of any inclusion/exclusion criteria. It came to light that a small number of patients with NGB were recorded in the CPRD database (Table 6.4). Over the period of 2004-2015, 327 patients were diagnosed neurogenic bladder and 660 patients were diagnosed neuropathic bladder. Taking into consideration the prevalence estimates in Section 2.2 it seemed unlikely that this was representative of the UK NGB population (discussed further in Section 8.2).

Table 6.4 Number of neurogenic bladder patients retrieved per calendar year from the CPRD database

Year of diagnosis	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Patients with a diagnosis of:													
Neurogenic bladder	35	32	28	29	29	28	34	41	27	28	14	10	327
Neuropathic bladder	82	95	78	68	82	71	62	56	42	42	37	8	660
Neuromuscular bladder	0	0	0	0	0	0	0	0	0	0	0	0	0
Neurogenic or Neuropathic bladder	117	127	114	96	110	98	95	97	68	70	51	18	697

Resultantly, a proxy means of identification; combining Read codes for neurological conditions and a diagnosis of OAB or a prescription of an OAB drug (bladder muscarinic or mirabegron from Therapy file) was employed to uncover further patients that most likely have NGB (Table 6.5 and 6.6). Accordingly, in this study, two separate definitions of NGB were employed. 'Definitive NGB' refers to those patients with a Read coded diagnosis of NGB, and 'probable' were those identified via the proxy means of identification. Another feasibility assessment was conducted on 29th July 2016 using both definitions of NGB (Table 6.7).

Table 6.5 Search terms used to identify Read codes for probable neurogenic bladder patients

Condition	Inclusion terms
Overactive bladder	*overactive* *detrusor*
Stroke	*stroke*, *haemorrhage*, *cereb* AND (*infarct* OR *thrombos* OR *embol* OR *occlusion*), *brain* AND *infarct*, *wallenberg*, *lateral medullary*,
Spinal cord injury	*spinal cord injur*
Multiple sclerosis	*multiple sclerosis*, *disseminated sclerosis*
Parkinson's disease	*parkinson*, * paralysis agitans*
Spina bifida	*spina bifida*

* - represents a wild card indicating that any character can take this place.
Words could appear on either side of the 'AND' search term.

Table 6.6 Overactive bladder drugs used to identify probable NGB patients (in combination with search terms for neurological conditions of interest)

Active ingredient	Formulation
Fesoterodine	Oral tablet
Mirabegron	Oral tablet
Oxybutynin ER	Oral extended release tablet
Oxybutynin IR	Oral immediate release tablet
Solifenacin	Oral tablet
Tolterodine ER	Oral extended release capsule
Tolterodine IR	Oral immediate release tablet

Trospium	Oral tablet
Darifenacin	Oral tablet
Propiverine	Oral tablet, capsules
Flavoxate	Oral Tablet

IR, immediate release; ER, extended release

Table 6.7 Feasibility assessment conducted on 29th July 2016 using the CPRD database to determine number of patients with neurogenic bladder between 2004-2015.

Diagnosis	No. of pts with a diagnosis (coded)	No. of pts with ≥ 1 prescription of an OAB drug	No. of pts with ≥ 1 prescription of an OAB drug and/or diagnosis of OAB
Neurogenic bladder	967	Not searched	654
Stroke	159,628	48,612	54,135
Multiple sclerosis	12,859	5,593	5,846
Spinal cord injuries	1,556	519	547
Parkinson's disease	24,678	9,469	10,433

pts, patients; OAB, overactive bladder

The full list of Read codes and prodcodes used to identify both definitive and probable NGB patients can be found in Appendix 12 and 13.

6.4.7 Inclusion and Exclusion Criteria

Inclusion Criteria

To be included in this study, a patient must have been:

1) Diagnosed with NGB (1.a) or probable NGB (1.b or 1.c), in order to capture the broad NGB population:

a. At least one diagnosis by Read code/medcode of either Neurogenic bladder OR Neuropathic bladder within the study period (January 1st, 2004 to December 31st, 2016).

OR

b. Have a diagnosis by Read code/medcode of least one of the following conditions: PD, MS, SCI or STK within the selection period (2004-2016) AND at least one prescription of an OAB drug AND/OR one diagnosis of OAB within the study period (January 1st, 2004 to December 31st, 2016).

OR

c. Have a diagnosis by Read code/medcode of SB within the whole follow-up period (from start to end of enrolment in CPRD) AND at least one prescription of an OAB drug AND/OR one diagnosis of OAB within the study period (January 1st, 2004 to December 31st, 2016). A longer enrolment period was employed in this neurological condition because SB is a congenital disorder, therefore patients are likely to have been diagnosed earlier on in their enrolment to the CPRD.

2) Be ≥19 years at index date to ensure all data in the analysis (including within the look-back period) was collected when the patient was aged 18 or over.

3) Have ≥12 months of continuous enrolment in the CPRD GOLD database prior to the index date, without prescription of an OAB drug or diagnosis of NGB or OAB to ensure new patient status. The pre-index period is also used to determine co-morbidity score. As SB is a congenital condition, it is not possible to discern the date of first diagnosis within the study period. Therefore, the purpose of the 12 months pre-index period in SB patients serves only to determine the co-morbidity score.

4) Have ≥12 months of continuous enrolment in the CPRD GOLD database post OAB/NGB diagnosis or OAB drug prescription to determine drug utilisation patterns and HRU estimates.

5) Have patient acceptable data at UTS practice (CPRD quality criteria)

Exclusion criteria

Patients are excluded from the study if they:

1) Have a diagnosis of dementia (due to company restrictions in analysing this patient group) (Appendix 14)

2) Have idiopathic OAB (i.e. they do not have an accompanying neurological condition diagnosis or a diagnosis of NGB)

After application of inclusion and exclusion criteria to the source cohort, a patient file was produced which listed the patient identification number (patid) for all suitable patients. This file was used to extract the relevant data for this study.

6.4.8 Patient Selection Flow Diagram

Visual aids are often useful when there are multiple ways by which patients could be included into a study.

Patients could have been included into the present study in the following ways:

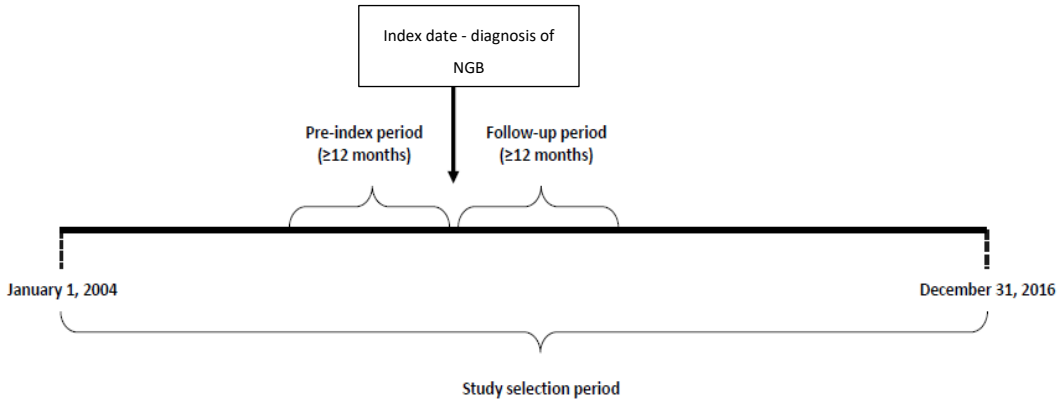


Figure 6.1 Patients with definitive neurogenic bladder

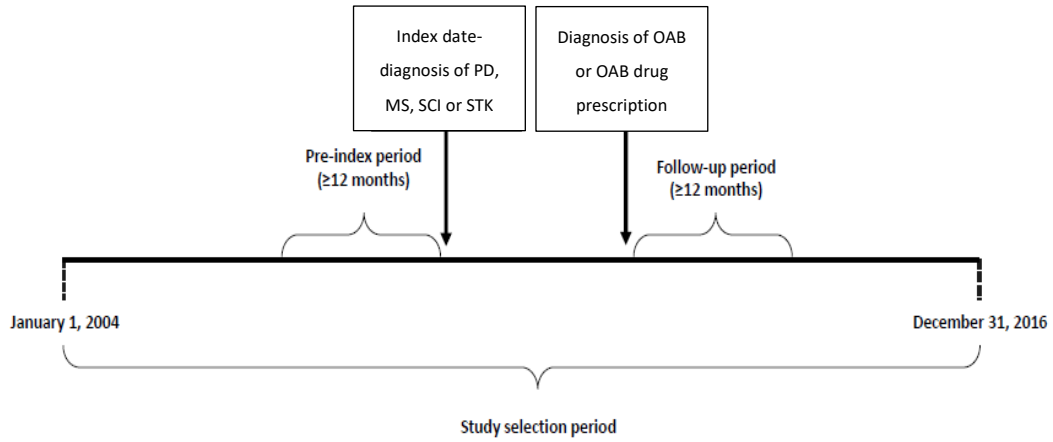


Figure 6.2 Patients with probable neurogenic bladder (PD, MS, SCI or Stroke)

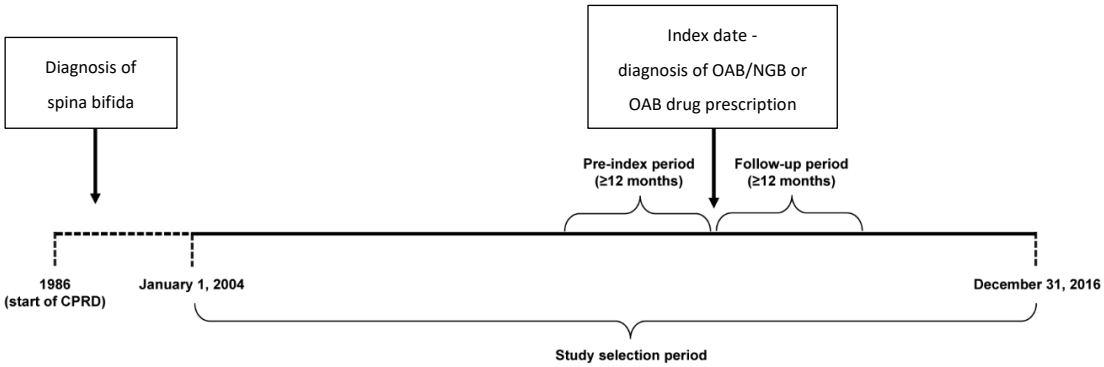


Figure 6.3 Patients with probable neurogenic bladder (spina bifida)

6.4.9 Index Date

For patients with an NGB diagnosis, the index date is defined as the first date of NGB diagnosis within the selection period (January 1st, 2004 to December 31st, 2016). For patients with PD, MS, STK or SCI the first diagnosis date of the underlying neurological

condition within the selection period will be considered as the index date. For patients with SB, the index date will be the first OAB drug prescription or first OAB/NGB diagnosis date, (whichever comes first) within the selection period.

6.4.10 Study Sub-Cohorts

NGB patients face unique challenges according to their underlying neurological condition and thus should be managed accordingly (Apostolidis et al., 2017). Moreover, by identifying which groups are more resource intensive, those more likely to be in need of services and treatments can be identified. Taking this into account, six sub-groups of patients were identified, and outcomes were described separately according to NGB diagnosis or underlying neurological condition.

Table 6.8 Study sub-cohorts

Subgroup	Description
Definitive NGB sub-cohort	Patients who meet the study inclusion/exclusion criteria with at least one diagnosis of NGB (within the selection period) and no NGB/OAB diagnosis or OAB drug prescription before the index date.
PD sub-cohort (probable NGB)	Patients who meet the study inclusion/exclusion criteria, with at least one diagnosis of PD (within the selection period) and no NGB/OAB diagnosis or OAB drug prescription before index date to ensure the underlying condition precedes NGB/OAB diagnosis or treatment.
MS sub-cohort (probable NGB)	Patients who meet the study inclusion/exclusion criteria with at least one diagnosis of MS (within the selection period) and no NGB/OAB diagnosis or OAB drug prescription before index date to ensure the underlying condition precedes NGB/OAB diagnosis or treatment.

STK Sub-cohort (probable NGB)	Patients who meet the study inclusion/exclusion criteria with at least one diagnosis of STK (within the selection period) and no NGB/OAB diagnosis or OAB drug prescription before index date to ensure the underlying condition precedes NGB/OAB diagnosis or treatment.
SCI Sub-cohort (probable NGB)	Patients who meet the study inclusion/exclusion criteria with at least one diagnosis of SCI (within the selection period) and no NGB/OAB diagnosis or OAB drug prescription before index date to ensure the underlying condition precedes NGB/OAB diagnosis or treatment.
SB Sub-cohort (probable NGB)	Patients who meet the study inclusion/exclusion criteria with at least one diagnosis of SB.

NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida.
Definitive NGB refers to those patients with a Read coded diagnosis of NGB. 'Probable' indicates that the cohort of patients were identified via proxy means.

There are prominent health differences between the young and old, and between sexes, which can augment treatment patterns and the level of HRU (Keene and Li, 2005; Regitz-Zagrosek, 2012). Further subgroup analysis was employed to stratify the results by age groups (19 years – 65 years and over 65 years) and by sex.

6.4.11 Hospital Episode Statistics Linkage Process

A full HES record was requested for all candidate patients, where available, to enable accurate characterisation of secondary care resource use. The broadest possible patient definition was used to compile a list of NGB patient IDs (patids) (i.e. the definition used in the sensitivity analysis (Section 6.3.15.1)). The unique patid was used to link these records with text files available in the CPRD customer website that specify individuals with HES eligibility (binary flag for patient eligibility). This filtered the CPRD patids that met the inclusion/exclusion criteria for this study. This resulting list of patids was sent to CPRD, who

then provided the linkage data (HES APC & Outpatient), which was loaded onto the analysis platform.

6.4.12 Analysis of Outcomes

Table 6.9 lists the various endpoints that were sought in this study and the definitions, where applicable. All of the variables are described in more detail in the sections below.

Table 6.9 Primary and secondary endpoints of the epidemiological study using the CPRD database

Endpoint	Variable	Definition
Primary endpoints		
Patient demographics	Age at index date Sex	
Comorbidities	Number of distinct BNF headers within the 12-month pre-index period	Defined by the number of distinct BNF headers within 12-months before the index date
	Number of QoF comorbidities within the 12-month pre-index period	Defined by the number of QoF comorbidities as defined by the NHS business rules within 12-months before the index date
Diagnosis of NGB or underlying neurological condition	Diagnosis of NGB or OAB preceded by diagnosis of underlying neurological condition (PD, MS, SCI, STK or SB)	
	Duration between diagnosis of NGB/underlying condition and OAB diagnosis/OAB drug prescription	Calculated as the difference between the date of OAB diagnosis/OAB drug prescription (whichever comes first), and the date of NGB/underlying condition (whichever comes first)
Complications	Complications over 12-month follow-up period, i.e., UTI, incontinence, sepsis/septicaemia, urinary retention, obstructive	

	uropathy, renal failure (acute and other), hydronephrosis	
Drug utilisation at index date	ACB score	Sum of ACB scores for all anticholinergic medicines prescribed at time of the first OAB/NGB diagnosis or OAB drug prescription
	Polypharmacy	Defined by the number of distinct BNF headers within 30 days before and after index date, and the number of distinct substance names within 30 days before and after index date
Drug utilisation during the 12-month follow-up period	OAB drug prescribed at index date	Defined by the bladder muscarinic or mirabegron that was prescribed at index date
	Number of OAB prescriptions	
	Cumulative number of days' supply of OAB drugs	Sum of days' supply of all prescriptions occurring over the 12-month post-index period
	Total quantity of OAB drug (mg)	Sum of all doses prescribed over the 12-month post-index period
	Number of patients with concomitant use of two or more OAB drugs (combination use)	Patients were considered to having a combination of OAB drugs if at least two drugs overlapped for more than 30 days
	Number of patients with intermittent catheter and indwelling catheter accompanying OAB drug use	
	Number of patients with prescriptions for α-adrenergic antagonist or 5-ARIs	
	Number of patients with prescriptions for antibiotics for UTI	
Secondary endpoints		
Healthcare resource use	Occurrence (yes/no) and number of outpatient referrals (CPRD)	

during the 12-month follow up period	Occurrence (yes/no) and number of outpatient referrals (urologists, and gynaecologists) (CPRD)	
	Number of all-cause GP consultations (CPRD)	
	Number of pads used (CPRD)	
	Urological investigations/tests	Included: urinalysis; culture and assessment of post-void residual urine; cystoscopy; urodynamics; imaging (upper tract, spine)
	Radiology (CPRD)	Radiology procedures used in NGB, ie, mercaptuacetyltriglycine (MAG, renal scan), ultrasound, computed tomography scan
	Number of hospital admissions (urology) (HES)	All admissions associated with: a primary ICD-10 code related to a urological disease; a primary ICD-10 code related to PD, MS, SCI, STK, SB and a secondary ICD-10 code related to a urological disease
	Number of procedures and operations performed (HES)	All events from the HES procedure dataset associated with an OPCS-4 code related to the following surgical interventions: intermittent catheterisation; indwelling catheterisation; injections of botulinum toxin A; sacral nerve stimulation; bladder augmentation; sling procedures; artificial urinary sphincter
Healthcare resource use costs during the 12-month follow-up period	Costs of primary care visits Costs of secondary care referrals Costs of incontinence pad use Costs of diagnostic tests Costs of laboratory tests, i.e., costs of radiology Costs of hospitalisations Costs of procedures and operations performed	Healthcare resource use costs potentially related to NGB were estimated at the patient level by applying to each resource utilisation unit observed during the 12-month follow-up period the associated unit cost from the NHS perspective, and then summing costs by healthcare resource category

5-ARI, 5α-reductase inhibitor; ACB, anticholinergic cognitive burden; BNF, British National Formulary; QoF, Quality Outcomes Framework; CPRD, Clinical Practice Research Datalink; GP, general practitioner; HES, Hospital Episode Statistics; ICD-10, International Classification of Diseases, 10th Revision; MS, Multiple Sclerosis; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; SB, spina bifida; SCI, Spinal Cord injuries; SD, standard deviation; STK, stroke; UTI, urinary tract infection.

6.4.12.1 Patient Demographics

6.4.12.1.1 Duration Between Diagnosis of Underlying Conditions and OAB/NGB Diagnosis/OAB Drug Prescription

The duration between diagnosis of underlying neurological condition and diagnosis of OAB, NGB or prescription of an OAB drug was determined. This was calculated as the difference between the date of OAB diagnosis/OAB drug prescription (whichever comes first), and the date of NGB/underlying condition (whichever comes first).

6.4.12.1.2 Number of Distinct British National Formulary Headers and Substances at Index Date (Polypharmacy)

The concurrent use of multiple medications is defined as polypharmacy. High polypharmacy has been implicated in drug–drug interactions, low adherence to medications and increased rates of adverse events (Rohrer, 2013). In this study, polypharmacy was defined by the number of distinct BNF headers within 30 days before and after index date, and the number of distinct substance names within 30 days before and after index date. Repeat prescriptions of the same drug or different drugs in the same class were only counted once

The BNF is a reference book that lists the medications that are generally prescribed in the UK (including over 70,000 medicines). It is organised in a hierarchical fashion, beginning with the BNF chapter (i.e. the BNF header) which correlates to specific aspects of medical care (French, 2017). The variable –bnfcode- in the therapy file of CPRD represents a chapter in the BNF, including all drugs within the same class. Substances may be included in multiple

BNF headers. An example of how BNF headers and substances appear in the CPRD is shown in Table 6.10.

Table 6.10 Example of BNF headers and substances in the clinical practice research datalink (CPRD) database

BNF Header	Substance
Alpha-adrenoceptor Blocking Drugs/Alpha-blockers (in Urinary Retention)	Indoramin hydrochloride
Alpha-adrenoceptor Blocking Drugs/Alpha-blockers (in Urinary Retention)	Prazosin hydrochloride
Drugs for Urinary Frequency, Enuresis, and Incontinence	Flaxovate Hydrochloride
Urinary Incontinence	Mirabegron
Urinary Incontinence	Darifenacin hydrobromide
Urinary Incontinence	Flaxovate Hydrochloride
Urinary Incontinence	Fesoterodine fumarate

BNF, British National Formulary

6.4.12.1.3 Measurements of Comorbidity Score

Comorbidity refers to the total burden of illness (Gijsen et al., 2001). Chronic conditions can be summarised into a single numerical variable to indicate the level of comorbidity. There is no gold standard for calculation of comorbidity. Two measures were employed to calculate the comorbidity score:

1) The number of unique BNF headers (variable –bnfcode-) in an individual's prescription data was counted from the therapy table to determine their level of comorbidity. The nature of the BNF is described in Section 6.4.12.1.2; although

primarily used as a means to determine polypharmacy, it has proved a useful proxy measure of comorbidity.

2) A count of the 17 chronic diseases included in the Quality Outcomes Framework (QoF) were counted. The QoF is a pay-for-performance (P4P) scheme that incorporates 17 common chronic diseases in the UK including chronic heart disease, diabetes and certain mental health conditions (Gillam et al., 2012; Forbes, 2016). Recording for data points in these diseases are considerably complete (Section 8.2.1.3). Read codes of the QoF business rules, sought in the therapy table of CPRD can be found in Appendix 15.

In a study measuring the explanatory power of various morbidity measures both the BNF and QoF counts were deemed to have moderate predictive validity for consultation in primary care, with the BNF score being the most powerful of six different measures tested (Brilleman and Salisbury, 2013; Bessou, 2015).

6.4.12.1.4 Complications Over 12-Month Follow up Period

The number of complications specific to NGB were calculated over the 12 months post OAB/NGB diagnosis or OAB drug prescription. The search terms in Table 6.11 were used to identify relevant read codes. The full list of Read codes can be found in Appendix 16.

Table 6.11 Inclusion terms to identify Read codes for complications related to neurogenic bladder

Condition	Inclusion terms
UTI	*urinary*infec*, *UTI*, *cystitis*, *pyelonephritis*, *urethritis*
Incontinence	*urin*incont*, *enuresis*
Sepsis	*sepsis*, *septicaemia*, *bacteremia*, *septic syndrome*

Urinary retention	*urinary reten*
Obstructive uropathy	*obstructive urop*
Renal failure (acute and other)	*renal fail*, *kidn*fail*,
Hydronephrosis	*hydroneph*, *hydroureter*, *hydronephrotic solitary kidney*

*-represents a wild card indicating that any character can take this place.
Words could appear in any order.

6.4.12.2 Drug Utilisation

6.4.12.2.1 Overactive Bladder Drug Prescriptions

This outcome was measured by conducting a simple count of individuals prescribed OAB drugs. OAB drugs are defined as a prescription of any of the drugs listed in Table 6.5 (Full prodcode list can be found in Appendix 13). According to medical experts, these medications are most likely utilised to manage NGB in UK clinical practice (Drake and de Ridder, 2017).

6.4.12.2.2 Total Quantity of Bladder Muscarinic Drug (in mg) (Sum of Daily Dose)

An automated algorithm in the CPRD database derives a numerical daily dose from unstructured text dosage instructions. The derived numerical daily dose values of OAB drugs calculated by this algorithm were utilised in this study along with the dose per tablet. The daily dose is calculated as follows:

dose per tablet x numeric daily dose

The overall consumption of OAB drugs was calculated as the sum of the daily dose over the 12-month post OAB/NGB diagnosis or OAB drug prescription period.

6.4.12.2.3 Cumulative Number of Days' Supply of OAB drugs

This was defined as the sum of days' supply of all prescriptions occurring over the 12-month post-index period. If a prescription date fell within the 12-month post-index period but ended outside it, only days' supply within the follow-up period were considered.

6.4.12.2.4 Number of Combinations of Overactive Bladder Drugs

In this study, combination use is defined as overlapping use of two or more OAB drugs for more than 30 days (i.e. concurrent use for 30 days) (Figure 6.4). The number of patients on any combinations of OAB drugs (Table 6.5) were reported.

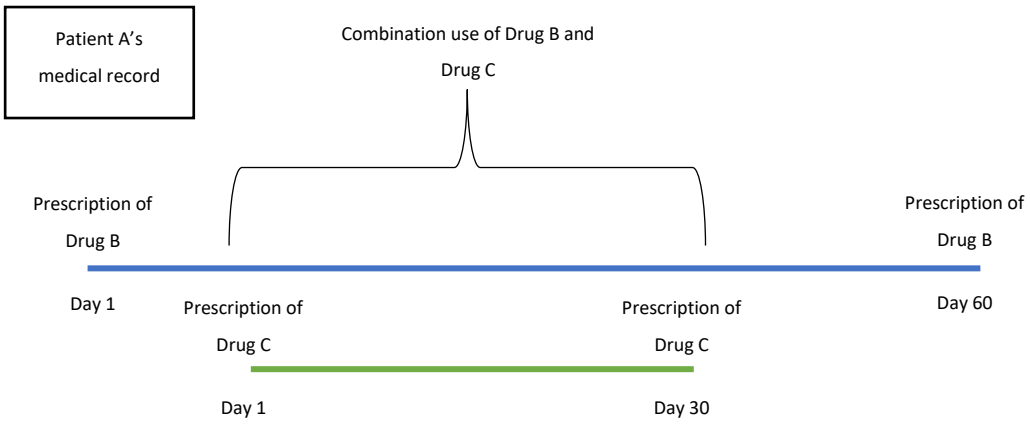


Figure 6.4 Combination use of overactive bladder drugs

6.4.12.2.5 Number of Patients Prescribed α-Adrenergic Antagonist or 5-Alpha-Reductase Inhibitors at Any Dosage

A simple count of individuals that were prescribed α-adrenergic antagonists and 5-Alpha-Reductase Inhibitors (5-ARIs) was conducted (Full prodcode list Appendix 17).

α-adrenergic antagonists are recommended for management of bladder outlet obstruction (BOO) by the EAU and ICI CGs. Identifying patients on these drugs could act as a proxy means to identify individuals that were also suffering from bladder emptying problems. Several small clinical trials have also demonstrated efficacy of α-adrenergic antagonists in NDO. 5-ARIs are primarily used for BOO in benign prostatic hyperplasia (BPH).

6.4.12.2.6 Number of Patients Prescribed Antibiotics for Urinary Tract Infection

There is a high incidence of UTI in NGB. The causes are multifactorial, including urodynamic testing, catheterisation or surgery (Vigil, 2016). Common antibiotics used to manage UTI's are trimethoprim, ciprofloxacin, nitrofurantoin, amoxyicllin, co-amoxiclav, trimethoprim, ampicillin, nitrofurantoin, pivmecillinam hydrochloride, quinolone, cephalexin, fosfomycin, gentamicin, or ofloxacin. The number of patients using any of these antibiotics, at any dosage, were recorded (Full prodcode list, Appendix 18)

6.4.12.2.7 Anticholinergic Burden Score at Date of First Bladder Muscarinic Drug Prescription

Anticholinergic burden is defined as the cumulative effect of one or more drugs with the potential to cause anticholinergic adverse effects (Nishtala et al., 2016). Individuals with certain neurological conditions are at an increased risk of experiencing cognitive dysfunction due to anticholinergic load (Kay, 2008) (Section 2.5.3). Around ten scales exist to calculate the anticholinergic burden and are used varyingly both in clinical practice and in research. There is currently no gold standard for measurement. The scales are constructed via distinct methodologies, ranging from in vitro measures to utilising evidence from literature reviews. In all scales, expert opinion has a large influence in the resulting classifications, which affects their reliability (Villalba-Moreno et al., 2015; Salahudeen et al., 2015).

The ACB scale was used in this analysis, as it is one of the most widely used and validated scales in the literature. It was developed by an interdisciplinary expert team, through a systematic review (SR) of studies measuring anticholinergic activity of medications and the

association with cognitive function in the elderly (Campbell et al., 2013). It uses a three-point rating scale, where 0 means little/no anticholinergic activity and 3 equates to high anticholinergic activity (Table 6.12). To determine an individual's ACB score, the associated potency scores of each bladder muscarinic medication prescribed is added together (Kersten, 2014). The definition used in this study was: the sum of ACB scores for all anticholinergic medicines prescribed at time of the first OAB/NGB diagnosis or OAB drug prescription. The drugs used to calculate the ACB score can be found in Appendix 19.

Table 6.12 Grading criteria of anticholinergic cognitive burden (ACB) scale

Category	Criteria	ACB score
No anticholinergic effects		0
Possible anticholinergic effects	Evidence of *in vitro* anticholinergic activity or affinity for muscarinic receptors but with no clinically relevant negative cognitive effects	1
Definite anticholinergic effects	Evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect	2
Definite anticholinergic effects	Evidence from literature, expert opinion, or prescriber's information that medication may cause delirium	3

6.4.13 Healthcare Resource Utilisation

The concept of Cost-of-Illness (COI) was introduced in Section 2.8. This following section will outline the methods used to conduct this type of study, with particular emphasis on the HRU aspect.

6.4.13.1 Methods of Healthcare Resource Utilisation Studies

6.4.13.1.1 Perspectives and Costs Considered

The perspective adopted in COI analysis dictates the costs considered in the analysis. Perspectives can include the society, healthcare system, government or payers (Costa et al., 2012). Costs can be categorised into two discrete categories: direct and indirect, and within these categories, medical and non-medical costs can be calculated (Tarricone, 2006).

Direct costs relating to medical services and goods include GP visits, diagnostic tests and secondary care services, amongst others. These costs are most commonly sought when taking a healthcare or payer perspective. Direct costs can also be non-medical related, for example the out-of-pocket expense borne by the patient for transportation to the hospital, or community care services, and are usually considered when taking a societal perspective. (Walter, 2006). Indirect costs may also be considered in the analysis. These costs arise as a result of illness but are not related to the direct purchasing of medical services (Yousefi et al., 2014). The commonly counted costs of this nature are labour and productivity losses, which result in a deficit in economic output due to disease related work absenteeism and other caregiver costs (NCCID, 2016). There are a number of different approaches that are used to calculate indirect costs such as the Human Capital Approach (HCA); its variation, the Friction Cost Method (FCM); and the Health State Valuation (HSV), however they are beyond the scope of this research (Garattini et al., 2001). The present study takes on the perspective of the UK NHS and calculates direct medical costs.

6.4.13.1.2 Approach Taken to Healthcare Resource Utilisation Studies

Based on the epidemiological design of the study, there are two different approaches to estimating resource use and subsequent calculation of costs. The incidence-based approach measures averted costs if new cases of the disease are prevented. This study design involves following the patient from date of diagnosis to cure (or death) in order to determine lifetime costs, hence requires a considerable amount of data, which can often prove difficult to obtain (Jo, 2014). The variations in cost that arise at different stages of

disease can be determined from this method, proving a useful advantage when observing changes in disease costs over time and demonstrating the impact of early interventions (Larg and Moss, 2011). Alternatively, the prevalence approach may be adopted, which measures the impact of all patients (including new and recurrent cases), usually over a period of one year, making this study design considerably more practical to conduct in terms of data collection. In contrast to the incidence-based approach, this design presides on the notion that costs should be assigned to the years in which they are borne. It has been posited as the superior choice for the construction of cost-containment policies and to draw an attention from health policy makers to the burden of disease (Tarricone, 2006). For these reasons and because of the availability of data, the prevalence approach was utilised in the present study.

6.4.13.1.3 Costing Methods

As well as the selection of an epidemiological design which governs the time-frame in which resources and costs are collected, a costing method should also be chosen. There are two common methods to examine costs; the top-down approach (gross-costing) or the bottom-up approach (micro-costing) (Songer, 1998).

The top-down approach (otherwise known as population based), measures costs on an aggregate level. Costs related to the use of healthcare services is typically calculated by averaging total health expenditures by the number of individuals with the disease (Songer, 1998). In contrast, the bottom-up approach estimates the frequency of separate health resources used by the individual. The resources are then multiplied by the unit costs to derive a final cost calculation of resources consumed (Tarricone, 2006). Using unit costs ascertains the value, reflecting the opportunity cost of the resources consumed. In some instances, there may be uncertainty around which unit costs should be employed because of variation between hospitals or payers. In this study, the perspective of the UK NHS was employed, where the unit costs are averaged on a national scale, and the official data is made freely accessible to researchers.

In comparison to the top-down approach, the bottom-up approach to costing can be time-consuming to apply, as granular data is necessary to create a comprehensive picture of the resources consumed (Jo, 2014). In addition, the bottom-up approach relies on extrapolation of results from a sample to the population, therefore, it is imperative that the sample is unbiased and truly representative of the population at large. The present study uses the CPRD database and unit costs from the PSSRU and NHS schedule reference costs which are representative of the UK population. One disadvantage of extrapolation is the potential for double counting of costs, whereas the top-down approach avoids this risk through the use of aggregated data (Hodgson, 1994). There are also a number of inherent disadvantages to the top-down approach, in particular the inability to calculate costs on a longitudinal scale, which limits applicability in the present study. Furthermore, because costs are calculated at an aggregate level, the ability to provide cost estimates stratified by disease subgroups or patient characteristics is limited (Larg and Moss, 2011).

The bottom-up approach is generally considered the superior method of costing, by virtue of its reliable and flexible nature, and thus was employed in the present study. Determining the level of resources consumed consists of a simple counting method of variables outlined in the sections below, which was then multiplied by unit costs to derive total per patient costs.

6.4.13.2 Healthcare Resource Utilisation Variables

6.4.13.2.1 Number of Outpatient General Practitioner Consultations

Face-to-face and telephone GP consultations were identified from the consultation table using the -constype- variable. The consultations counted are shown in Table 6.13. More than one consulting record per day was counted as separate consultations. For example, if a patient visited their GP in the surgery and then later on in the day received a telephone consultation, this counted as two separated consultations.

Table 6.13 General Practitioner consultation types

Code (constype)	Role	Consultation categories
9	Surgery consultation	Surgery consultation
22	Third party consultation	Surgery consultation
1	Clinic	Clinic
10	Telephone call from a patient	Telephone consultation
21	Telephone call to a patient	Telephone consultation
11	Acute visit	Home visit/surgery consultation
8	Out of hours, non-practice	Out of hours
27	Home visit	Home visit
3	Follow-up/routine visit	Home visit/surgery consultation
7	Out of hours, practice	Out of hours
2	Night visit, Deputising service	Out of hours
30	Nursing home visit	Home visit
55	Telephone consultation	Telephone consultation
6	Night visit, practice	Out of hours
31	Residential home visit	Home visit
4	Night visit, local rota	Out of hours
34	Walk-in centre	Surgery consultation
36	Co-op surgery consultation	Surgery consultation
37	Co-op home visit	Home visit
32	Twilight visit	Out of hours
40	Community clinic	Clinic
28	Hotel visit	Home visit

6.4.13.2.2 Urodynamic and Radiological Tests

The NICE and ICI CGs recommend that urodynamic tests are carried out in individuals that are at high risk of renal damage. In contrast, the EAU CGs recommend that urodynamic tests are carried out for all NGB patients. In order to determine how many individuals undergo urodynamic testing, medcodes for a number of different tests were sought and the number of patients with any of these codes over the 12-month follow up period were counted. Urological investigations/tests include: urinalysis, culture and assessment of post-void residual urine, cystoscopy, urodynamics, imaging (upper tract, spine). All events from the test tables associated with a medcode related to urological investigations/tests were selected. The codes were identified by means of the CPRD medical dictionary as test events with a medcode including specific key words related to urological tests (Table 6.14). Full code list can be found in Appendix 20.

Table 6.14 Inclusion terms for urodynamic and radiological tests to retrieve relevant medcodes

Variable	Inclusion terms
Urodynamic and Radiological Tests	*urinalys*, *cystoscop*, *urodynam*, *urin*tract*, *spine*, *uroflowmetr*, *cystometr*, *electromyogr *, *ultrason*, *comput*tomograph*.

6.4.13.2.3 Number of Visits to a Specialist

The number of visits a patient made to the urologist or gynaecologist can give an indication of severity of urological symptoms and an understanding of the common practices in referrals amongst physicians. The frequency of visits over the 12-month follow-up period

was counted from the CPRD GOLD and determined by using the NHS speciality (–nhsspec-variable) in the referral table (Full code list, Appendix 21).

6.4.13.2.4 Number of Incontinence Pads

Pads are often used as a precaution against urinary incontinence, in conjunction with other management strategies (Dorsher and McIntosh, 2012). All events from the Therapy file associated with a product code (-prodcode- variable) related to pad prescriptions were chosen. The codes were selected by means of the CPRD product dictionary as prescriptions events with a BNF header including the following specific key word: '*pad*'. Each code (and related product name) was reviewed to avoid misclassification. The average number of pads used per person over the 12-month follow up period was calculated (Full code list, Appendix 22).

6.4.13.2.5 Number of Procedures and Operations Performed

The number of pre-specified procedures and operations performed over the 12-month follow up period were counted. These included all events from the HES procedure dataset associated with an OPCS-4 code related to the following interventions: intermittent catheterisation; indwelling catheterisation; injections of Onabotulinum-A; sacral nerve stimulation; bladder augmentation; sling procedures; artificial urinary sphincter (AUS) (Full code list, Appendix 23).

6.4.13.2.6 Number of Hospitalisations and Duration of Hospitalisation

The number of times an individual was hospitalised due to NGB related events over the 12-month follow up period was counted using data from the HES. A hospitalisation counted as a primary ICD-10 code related to a urological disease or a primary ICD-10 code related to PD, MS, SCI, STK, SB and a secondary ICD-10 code related to a urological disease (Full code list, Appendix 24).

The duration of hospital stays was defined as the difference between the admission and discharge dates ("admidate", "discharged") for admissions taking place within 12 months

following the NGB/OAB date. If a hospital admission was overlapping with the 12-month follow-up period (e.g. a patient admitted within the 12-month period and discharged after), only the days of overlap between the admission and the 12-month period were considered. The sum of all admissions durations was calculated.

6.4.14 Statistical Methods

6.4.14.1 Sample Size Justification

Although sample size calculations are not necessary for a descriptive study, determination of the minimum sample size can provide information on the level of precision required to provide estimates of summary statistics such as the mean (Berkowitz, 2007). Chochran's formula was used to calculate the minimum sample size in this study (Cochran, 1977):

$$\mathrm{n}_0 = \frac{z^2 pq}{e^2}$$

Where:

e = desired level of precision

p = (estimated) proportion of the population which has NGB

q = 1 – p.

A recent meta-analysis found the prevalence of urinary incontinence (UI) was 50.9% in patients with MS, 52.3% with SCI, 33.1% with PD and 23.6% with STK (Ruffion et al., 2013). Assuming a 95% confidence level, a precision of +/- 5% and an infinite population (conservative assumption), the minimum sample size for patients with neurogenic bladder would be 384 patients with MS or SCI, 341 patients with PD, 278 patients with STK (Table 6.15). Based on these minimum sample size calculations, expected numbers from the feasibility analysis (Table 6.6) were deemed sufficiently large enough to provide a representative sample.

Table 6.15 Minimum sample size calculations

	Prevalence among the underlying condition (Ruffion et al., 2013)	Confidence level	Precision	Sample size (assuming an infinite population)
MS	50.90%	0.95	+/- 5%	384
SCI	52.30%	0.95	+/- 5%	384
PD	33.10%	0.95	+/- 5%	341
Stroke	23.60%	0.95	+/- 5%	278

MS, multiple sclerosis; SCI, spinal cord injuries; PD, Parkinson's disease.

6.4.14.2 Data Analyses

The aim of this study was to describe the uncharacterised UK NGB patient population therefore only descriptive statistics were used.

Aggregate summary statistics were reported. N, mean, median, standard deviation, minimum, maximum, 25th percentile and 75th percentile was calculated for continuous variables and frequency tables were presented for categorical variables. The calculation of proportions did not include the missing/invalid category.

6.4.14.3 Calculation of Healthcare Costs

A bottom-up approach to costing was employed (Section 6.3.13.3). Healthcare costs were evaluated at the patient level, by multiplying resource utilisation units observed within 12 months, with associated unit costs, from the perspective of the NHS (Table 6.16). Healthcare costs were calculated by summing costs for all healthcare resources consumed, overall and by type of resource. This study included data over a 12-year period; however, in order to account for inflation and variations in pricing over time, costs were used from one base year only (2016-17), reflecting the most recent period.

Primary care costs in the UK are derived from the Unit Costs of Health and Social Care 2015 from the Personal Social Services Research Unit (PSSRU). The GP visit costs were calculated by multiplying the average minutes of GP time spent during a particular type of consultation (Table 6.16), by the cost per minute (£4). The average number of minutes was derived from the GP workload survey, carried out in 2006/07, which asked GPs from a representative sample of 329 practices across the UK to complete diary sheets for one week in September or December of 2006 (The Information Centre, 2007). The time for home visits included the time spent at the patient's home only (i.e. excluding travel costs).

The cost of secondary care is calculated according to national tariff prices, based on the national average unit costs available in the National Schedule of Reference Costs. Patient activity is described according to groupings referred to as Healthcare Resource Groups (HRG), containing diagnostic codes, treatments and procedures with similar levels of resource utilisation, which are used to attract a tariff (Weir et al., 2017). An algorithm is used to generate an appropriate HRG code by grouping secondary care events such as procedures and operations performed and duration of care into spells (Weir et al., 2017). A file was created containing HRG codes and the corresponding tariff, which was then merged with the HES to assign a cost to each hospitalisation or procedure carried out.

Table 6.16 Unit costs of outpatient primary and specialist consultations

Variable	Unit costs	Source
Primary care (general practitioner)		
Surgery consultation (lasting 9.22 minutes)	£37.00	Curtis et al. 2017
Clinic	£68.80[a]	Curtis et al. 2017; Curtis 2014
Home visit	£45.60[b]	Curtis et al. 2017; Curtis 2014
Telephone consultation	£28.40[c]	Curtis et al. 2017; Curtis 2014
Specialists (outpatient attendance)		
Urologist	£109.40	NHS 2016–17
Gynaecologist	£140.93	NHS 2016–17

Urological tests		
Urodynamic test	£126.00	NHS 2016–17
Cystoscopy	£146.00	NHS 2016–17
Incontinence pads		
One pad	£0.20[d]	Age UK
Radiology		
Ultrasound	£144.00	NHS 2016–17
Computed tomography	£83.00	NHS 2016–17
Procedures and surgical interventions	–[e]	Adapted from NHS 2016–17
Hospital visits	–[e]	Adapted from NHS 2016–17

[a]17.2 minutes @ £4 per minute.

[b]11.4 minutes @ £4 per minute.

[c]7.1 minutes @ £4 per minute.

[d]Lille Healthcare Classic Pad PE Backed Maxi 1250 ml pack of 30 (£5.99 for 30 pads).

[e]For each episode, costs were derived from HRG tariffs published by the NHS (2016/17) as follows:

short episodes (length of stay (LOS) ≤ trimpoint)

cost=T; long episodes (LOS $\geq$ trimpoint)

cost =T + (LOS - D) * E.

Where:

T= combined day case/ordinary elective spell tariff

D= ordinary elective long-stay trimpoint (days)

E= per day long-stay payment (for days exceeding trimpoint) (£)

Trimpoint= excess bed days beyond the standard number of days anticipated for a given HRG

Missing Healthcare Resource Group (HRG) tariffs were collected from the national schedule of reference costs OR if not available, determined from previous years if available and an inflation rate was applied OR, if not available, imputed as £0.1 (Gaughan, 2012).

6.4.15 Sensitivity Analyses

Neurological conditions may be mistaken for milder prodromal symptoms such as sleep disorders or depression. This could mean that the diagnosis of these conditions are made

later than actual occurrence of disease (Butler and Zeman, 2005). In these instances, it is plausible to assume that diagnosis of OAB/NGB or prescription of an OAB drug could occur before the diagnosis of the neurological condition. Therefore, the sensitivity analysis employed in this study consisted of altering the patient definition where the diagnosis of underlying neurological condition or OAB/NGB or OAB drug prescription could appear in any order within the selection period (Butler and Zeman, 2005).

It was hypothesised that this method of case ascertainment could improve the sensitivity of the search. Although, of course a tradeoff with increasing sensitivity is that that specificity decreases, and some patients included into the analysis may not be genuine NGB patients, however expert opinion suggests that the margin of error will not be large (Drake and de Ridder, 2017)

6.5 Chapter Summary

This chapter outlined the methodology for a novel descriptive epidemiological study using the CPRD database, with the aim of characterising many pertinent aspects of the NGB patient journey. The CPRD and HES databases, including the strengths and weaknesses were described. Furthermore, the methods of HRU and costing were presented. Finally, the variables sought in this study which provide a detailed picture of the NGB population from the perspective of the NHS were outlined. The next chapter will present the results from this study.

7) Chapter Seven - Clinical Practice Research Datalink (CPRD) Study – Results

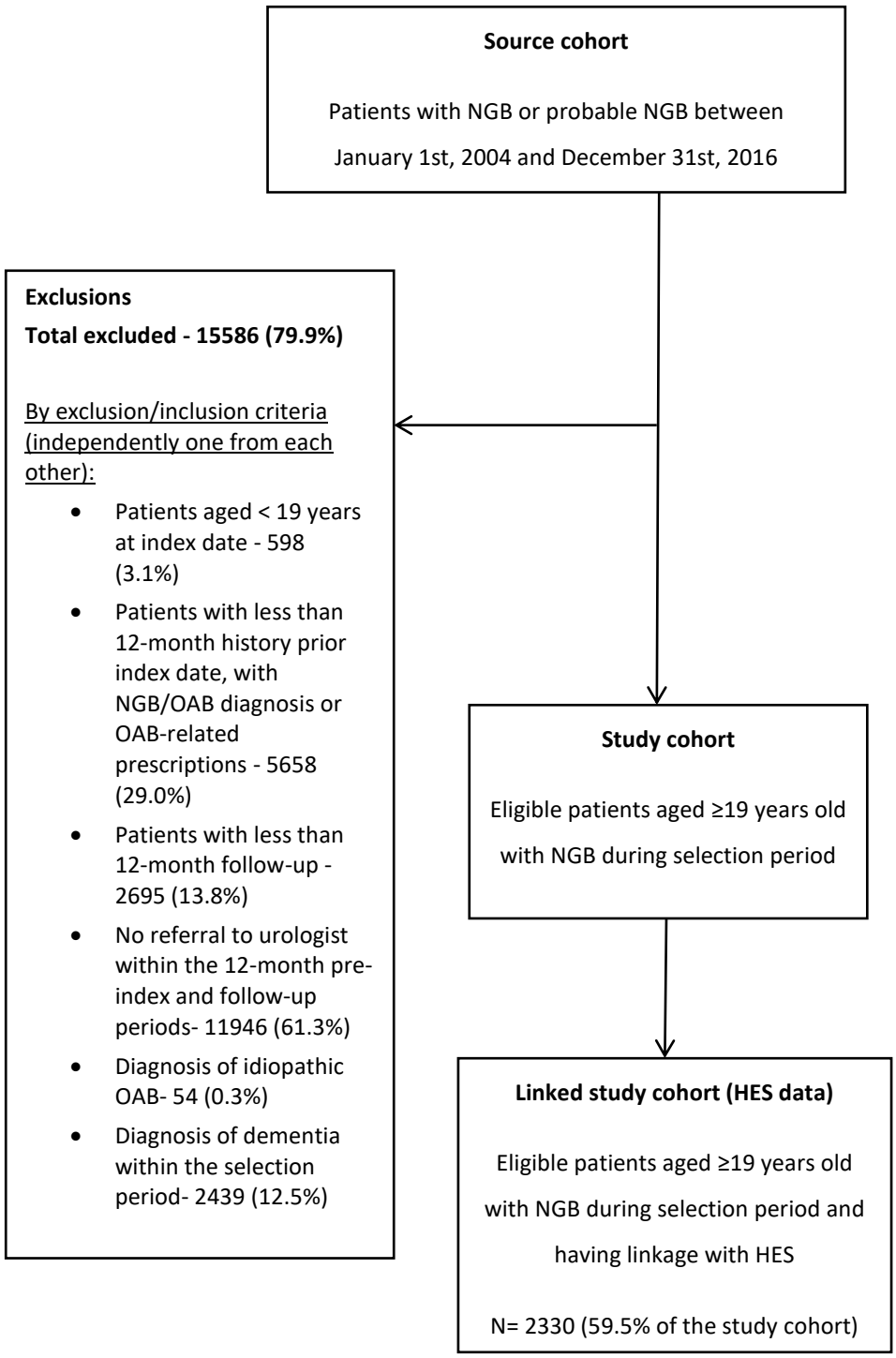
7.1 Introduction

The following section presents the results from the Clinical Practice Research Datalink (CPRD) study into the patient characteristics, drug utilisation patterns and healthcare resource utilisation (HRU) of patients with neurogenic bladder (NGB) in the UK.

7.2 Inclusion into the Study

Patients' inclusion in the study is described in Figure 7.1. Between January 1st, 2004 and December 31st, 2016, 19,499 patients with NGB or probable NGB were identified and included into the study. For patients with Parkinson's disease (PD), multiple sclerosis (MS), spinal cord injuries (SCI) or stroke (STK) the first diagnosis date of the underlying condition was considered as the index date. For patients with spina bifida (SB), it was the first overactive bladder (OAB) drug prescription or first OAB/NGB diagnosis, whichever comes first, within the selection period.

Among the patients included in the source cohort, 29.0% (n=5658) had already received OAB drugs or a diagnosis of NGB or OAB in the year prior to the index date or had less than 12 months history before the index date. These patients were excluded to ensure patients included in the study were newly diagnosed. In addition, 13.8% (n=2695) patients had less than 12 months follow-up after the NGB/OAB diagnosis or OAB prescription date, 3.1% (n=598) were aged less than 19 years, 61.3% (n=11946) were without referral to a urologist, 0.3% (n=54) had idiopathic OAB and 12.5% (n=2439) had dementia, and thus were excluded from the study. In total, 79.9% of the source cohort patients were excluded (n=15,586). The final study cohort was comprised of 3913 patients. Amongst these, 59.5% (n=2330 patients) had available data from the hospital episode statistics (HES) database.



NGB, neurogenic bladder; OAB, overactive bladder; HES, hospital episode statistics

Figure 7.1 Flow chart of neurogenic bladder patient selection and linkage to Hospital Episode Statistics Data

7.3 Study Sub-Cohorts

The distribution of patients by sub-cohort is presented in Table 7.1. The definitive NGB group consisted of 363 patients (9.3% of study cohort) which was smaller than the STK sub-cohort (n=1720, 44.0%), MS sub-cohort (n=1029, 26.3%) and PD sub-cohort (n=713, 18.2%). The SCI sub-cohort and SB sub-cohort accounted for the rest (5.6%) of the population.

Table 7.1 Distribution of patients by sub-cohort of interest

Subgroup*	**(n=3913)**
Definitive NGB	363 (9.3%)
PD cohort	713 (18.2%)
MS cohort	1029 (26.3%)
STK cohort	1720 (43.9%)
SCI cohort	41 (1.0%)
SB cohort	180 (4.6%)

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injury; SB, spina bifida

*The groups are defined inclusively, i.e. patients may be included in more than one group (NGB group and/or underlying neurological condition group).

7.4 Demographics and Clinical Characteristics

7.4.1 Age of Patients at Index Date

Age of the population at index date ranged from 19 and 104 years old with a mean of 61.7 years (SD=16.3) (Table 7.2). The mean age was 65.0 years (SD=15.1) in the male group and 56.8 years (SD=16.8) in the female group (Table 7.3). The PD sub-cohort showed the highest mean age at 70.7 years (SD=9.2), closely followed by the STK sub-cohort (mean=70.3 [SD=11.6]). Patients in the SB sub-cohort were the youngest with a mean age of 36.1 years (SD=11.9) (Table 7.2).

Table 7.2 Age at index date by underlying neurological condition

Characteristics		Definitive NGB n=363	PD Cohort n=713	MS Cohort n=1029	STK Cohort n=1720	SCI Cohort n=41	SB Cohort n=180	All n=3913
Age at index-date	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	48.30 (15.91)	70.67 (9.16)	48.71 (11.84)	70.32 (11.56)	46.63 (14.76)	36.11 (11.93)	61.72 (16.29)
	Median	48	72	49	72	49	34.5	64
	Min-Max	[19.0; 87.0]	[31.0; 92.0]	[19.0; 83.0]	[21.0; 98.0]	[20.0; 68.0]	[19.0; 76.0]	[19.0; 98.0]
	Q1-Q3	[36.0; 60.0]	[65.0; 77.0]	[40.0; 57.0]	[63.5; 79.0]	[34.0; 58.0]	[26.0; 44.0]	[50.0; 75.0]

SD, standard deviation; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

Table 7.3 Age at index date by age and sex subgroups

Characteristics		[19 years – 65 years[n=2038	Over 65 years n=1875	Male n=2334	Female n=1579
Age at index-date	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	49.03 (11.69)	75.51 (6.33)	65.03 (15.09)	56.82 (16.76)
	Median	51	75	68	56
	Min-Max	[19.0; 65.0]	[66.0; 98.0]	[19.0; 98.0]	[19.0; 97.0]
	Q1-Q3	[41.0; 59.0]	[70.0; 80.0]	[57.0; 76.0]	[45.0; 70.0]

SD, standard deviation

7.4.2 Number of Quality Outcomes Framework Chronic Diseases within the Pre-Index Period (Comorbidity)

The Quality Outcomes Framework (QoF) was employed to determine comorbidity. The STK sub-cohort showed the highest level of comorbidity over the 12-month pre-index period with a mean number of QoF chronic diseases of 1.4 (SD=1). Amongst the other sub-cohorts, the level varied from 0.2 (SD=0.5) in the SCI sub-cohort to 0.3 (SD=0.6) in the definitive NGB sub-cohort (Table 7.4). Elderly patients (≥65 years old) showed a higher level of morbidity

than patients aged ≤65 years old with a mean of 1 (SD=0.9) QoF chronic diseases vs 0.5 (SD=0.7). The level of morbidity was also higher in male patients than in female patients: 0.8 (SD=0.9) vs 0.6 (SD=0.8) (Table 7.5).

Table 7.4 Count of chronic diseases from the QOF within the 12-month pre-index period by underlying neurological condition

Characteristics		Definitive NGB n=363	PD Cohort n=713	MS Cohort n=1029	STK Cohort n=1720	SCI Cohort n=41	SB Cohort n=180	All n=3913
QoF count	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	0.29 (0.59)	0.27 (0.60)	0.17 (0.45)	1.37 (0.69)	0.17 (0.50)	0.21 (0.47)	0.73 (0.83)
	Median	[0.0; 3.0]	[0.0; 4.0]	[0.0; 3.0]	[0.0; 5.0]	[0.0; 2.0]	[0.0; 2.0]	[0.0; 5.0]
	Min-Max	0	0	0	1	0	0	1
	Q1-Q3	[0.0; 0.0]	[0.0; 0.0]	[0.0; 0.0]	[1.0; 2.0]	[0.0; 0.0]	[0.0; 0.0]	[0.0; 1.0]

QoF, Quality Outcomes Framework; SD, standard deviation; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

Table 7.5 Count of chronic diseases from the QOF within the 12-month pre-index period by age and sex subgroups

Characteristics		[19 years – 65 years[n =2038	Over 65 years n =1875	Male n =2334	Female n =1579
QoF count	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	0.49 (0.74)	0.99 (0.85)	0.81 (0.85)	0.61 (0.80)
	Median	[0.0; 5.0]	[0.0; 5.0]	[0.0; 5.0]	[0.0; 5.0]
	Min-Max	0	1	1	0
	Q1-Q3	[0.0; 1.0]	[0.0; 1.0]	[0.0; 1.0]	[0.0; 1.0]

QoF, Quality Outcomes Framework; SD, standard deviation

7.4.3 Number of Distinct British National Formulary Headers within the Pre-Index Period (Comorbidity)

The number of distinct British National Formulary (BNF) headers was the second method employed to determine comorbidity. Overall, the mean level of comorbidity was 8.6 (SD=7.6) and ranged from 6.5 (SD=7.1) in the MS subgroup and 11 (SD=8.9) in the SB subgroup. Most patients (n=1511, 39.6%) received drug from 8-19 BNF headers. The SB subgroup showed the largest portion of patients prescribed drugs from 20+ BNF headers (n=28, 15.6%) (Table 7.6).

Comorbidity over the pre-index period was higher in elderly patients (10 [SD=7.3]) than in patients aged less than 65 years old (7.4 [SD=7.7]). Most elderly patients were prescribed drugs from 8-19 BNF headers (n=891 [SD=47.5%]), as were most patients aged between 19-64 (n=620, 30.4%). Comorbidities were slightly higher in females (9.1 [SD=8.3]) than males (8.3 [SD=7.2]) (Table 7.7).

Table 7.6 Comorbidity using the British National Formulary headers by underlying neurological condition

Characteristics		Definitive NGB n=363	PD Cohort n=713	MS Cohort n=1029	STK Cohort n=1720	SCI Cohort n=41	SB Cohort n=180	All n=3913
Number of distinct BNF headers within the 12-month pre-index period	Valid values	363	713	1029	1720	41	180	3913
	Mean (SD)	9.55 (9.06)	9.12 (6.93)	6.50 (7.11)	9.26 (7.58)	7.07 (8.55)	10.97 (8.91)	8.62 (7.64)
	Min-Max	[0.0; 45.0]	[0.0; 44.0]	[0.0; 42.0]	[0.0; 56.0]	[0.0; 35.0]	[0.0; 42.0]	[0.0; 56.0]
	Median	8	8	4	8	3	9	7
	Q1-Q3	[2.0; 15.0]	[4.0; 13.0]	[1.0; 9.0]	[4.0; 13.0]	[0.0; 14.0]	[4.0; 16.0]	[3.0; 13.0]
	0	78 (21.5%)	77 (10.8%)	211 (20.5%)	263 (15.3%)	11 (26.8%)	16 (8.9%)	620 (15.8%)
	1-3	43 (11.8%)	81 (11.4%)	243 (23.6%)	150 (8.7%)	11 (26.8%)	27 (15.0%)	533 (13.6%)
	4-7	53 (14.6%)	187 (26.2%)	236 (22.9%)	382 (22.2%)	4 (9.8%)	35 (19.4%)	881 (22.5%)

	8-19	143 (39.4%)	302 (42.4%)	273 (26.5%)	751 (43.7%)	12 (29.3%)	74 (41.1%)	1511 (38.6%)
	20+	46 (12.7%)	66 (9.3%)	66 (6.4%)	174 (10.1%)	3 (7.3%)	28 (15.6%)	368 (9.4%)

BNF, British National Formulary; SD, standard deviation; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

Table 7.7 Comorbidity using the British National Formulary headers and substances by age and sex subgroups

Characteristics		**[19 years – 65 years[n =2038**	**Over 65 years n=1875**	**Male n=2334**	**Female n=1579**
Number of distinct BNF headers Within the 12-month pre-index period	**Valid values**	2038	1875	2334	1579
	Mean (SD)	7.39 (7.71)	9.96 (7.34)	8.33 (7.16)	9.05 (8.29)
	Min-Max	[0.0 ; 51.0]	[0.0 ; 56.0]	[0.0 ; 46.0]	[0.0 ; 56.0]
	Median	5	9	7	7
	Q1-Q3	[1.0 ; 11.0]	[5.0; 14.0]	[3.0 ; 12.0]	[3.0 ; 13.0]
	0	411 (20.2%)	209 (11.1%)	357 (15.3%)	263 (16.7%)
	1-3	398 (19.5%)	135 (7.2%)	321 (13.8%)	212 (13.4%)
	4-7	444 (21.8%)	437 (23.3%)	555 (23.8%)	326 (20.6%)
	8-19	620 (30.4%)	891 (47.5%)	917 (39.3%)	594 (37.6%)
	20+	165 (8.1%)	203 (10.8%)	184 (7.9%)	184 (11.7%)

SD, standard deviation; BNF, British National Formulary

7.4.4 Number of Distinct British National Formulary Headers at Index Date (Polypharmacy)

The mean number of distinct BNF headers at index date was 5.2 (SD=4.8) with the majority of patients taking drugs from 4 to 7 different BNF categories (n=1175, 30%) or from 8 to 19 (n=997, 26%) (Table 7.8). The level of polypharmacy varied between sub-cohorts: it was the highest in the SB sub-cohort (mean=6.3 [SD=5.9]) and the lowest in the MS sub-cohort (mean=3.7 [SD=4.2]) (Table 7.8). Polypharmacy was lower in patients aged between 19 and

65 years (mean=4.4 [SD=4.8]] than in elderly patients [mean=6.1 (SD=4.6)] and relatively similar in male patients (mean=5.3, [SD=4.7]) and female patients (mean=5.1 [SD=4.9]); the level of polypharmacy was slightly higher in elderly patients than in patients aged less than 65 years old: in the former (elderly), 35% received drugs from 4 to 7 BNF headers at index date, 33% from 8 to 19 BNF headers and 17% from 1 to 3 different BNF headers, and in the second age group (less than 65 years old) it was respectively 26%, 19% and 30%. Distributions were similar in female patients and male patients (Table 7.9).

Results on the mean number of substances prescribed at index date were similar to the results on the mean number of BNF headers in the general cohort and when stratifying by age and sex. When looking at underlying condition sub-cohorts, results were slightly different, the STK sub-cohort showed the highest level of polypharmacy (mean=5.7 [SD=4.6]), closely followed by the PD sub-cohort and the SB sub-cohort (mean=5.6 [SD=4.2]).

Table 7.8 Polypharmacy using the British National Formulary headers and substances by underlying neurological condition

Characteristics		**Definitive NGB n=363**	**PD Cohort n=713**	**MS Cohort n=1029**	**STK Cohort n=1720**	**SCI Cohort n=41**	**SB Cohort n=180**	**All n=3913**
Polypharmacy[1] at index-date (using BNF headers)	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	5.48 (5.68)	5.61 (4.41)	3.71 (4.21)	5.79 (4.75)	4.44 (5.74)	6.35 (5.88)	5.24 (4.78)
	Median	4	5	2	5	1	5	4
	Min-Max	[0.0 ; 30.0]	[0.0 ; 24.0]	[0.0 ; 30.0]	[0.0 ; 25.0]	[0.0 ; 19.0]	[0.0 ; 31.0]	[0.0 ; 31.0]
	Q1-Q3	[1.0 ; 9.0]	[2.0 ; 8.0]	[1.0 ; 5.0]	[2.0 ; 9.0]	[0.0 ; 8.0]	[2.0 ; 9.0]	[1.0 ; 8.0]
	0	89 (24.5%)	84 (11.8%)	251 (24.4%)	335 (19.5%)	18 (43.9%)	19 (10.6%)	754 (19.3%)
	1-3	80 (22.0%)	182 (25.5%)	386 (37.5%)	262 (15.2%)	6 (14.6%)	51 (28.3%)	934 (23.9%)
	4-7	84 (23.1%)	252 (35.3%)	227 (22.1%)	577 (33.5%)	6 (14.6%)	55 (30.6%)	1175 (30.0%)
	8-19	101 (27.8%)	189 (26.5%)	156 (15.2%)	520 (30.2%)	11 (26.8%)	49 (27.2%)	997 (25.5%)

	≥20	9 (2.5%)	6 (0.8%)	9 (0.9%)	26 (1.5%)	0 (0.0%)	6 (3.3%)	53 (1.4%)
Polypharmacy[1] at index-date (using BNF substances)	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	4.62 (4.95)	5.63 (4.22)	3.32 (3.65)	5.71 (4.56)	3.59 (4.82)	5.38 (4.79)	4.99 (4.44)
	Median	3	5	2	5	1	4	4
	Min-Max	[0.0 ; 26.0]	[0.0 ; 22.0]	[0.0 ; 25.0]	[0.0 ; 25.0]	[0.0 ; 18.0]	[0.0 ; 24.0]	[0.0 ; 26.0]
	Q1-Q3	[0.0 ; 7.0]	[3.0 ; 8.0]	[0.0 ; 5.0]	[2.0 ; 9.0]	[0.0 ; 6.0]	[2.0 ; 8.0]	[1.0 ; 8.0]
	0	98 (27.0%)	85 (11.9%)	258 (25.1%)	337 (19.6%)	19 (46.3%)	21 (11.7%)	773 (19.8%)
	1-3	94 (25.9%)	167 (23.4%)	392 (38.1%)	256 (14.9%)	7 (17.1%)	57 (31.7%)	935 (23.9%)
	4-7	84 (23.1%)	257 (36.0%)	251 (24.4%)	582 (33.8%)	8 (19.5%)	55 (30.6%)	1212 (31.0%)
	8-19	83 (22.9%)	202 (28.3%)	123 (12.0%)	532 (30.9%)	7 (17.1%)	44 (24.4%)	968 (24.7%)
	≥20	4 (1.1%)	2 (0.3%)	5 (0.5%)	13 (0.8%)	0 (0.0%)	3 (1.7%)	25 (0.6%)

SD, standard deviation; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

[1]Polypharmacy was defined as the number of distinct BNF headers/ drug substances (including non-NGB/OAB drugs) in the therapy dataset

Table 7.9 Polypharmacy using the British National Formulary headers and substances by age and sex subgroups

Characteristics		**[19 years – 65 years[n =2038**	**Over 65 years n =1875**	**Male n=2334**	**Female n=1579**
Polypharmacy[1] at index-date (using BNF headers)	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	4.42 (4.82)	6.13 (4.59)	5.32 (4.69)	5.11 (4.92)
	Median	3	6	5	4
	Min-Max	[0.0 ; 31.0]	[0.0 ; 25.0]	[0.0 ; 31.0]	[0.0 ; 30.0]
	Q1-Q3	[1.0 ; 6.0]	[3.0 ; 9.0]	[1.0 ; 8.0]	[1.0 ; 8.0]
	0	492 (24.1%)	262 (14.0%)	437 (18.7%)	317 (20.1%)
	1-3	615 (30.2%)	319 (17.0%)	525 (22.5%)	409 (25.9%)

	4-7	519 (25.5%)	656 (35.0%)	734 (31.4%)	441 (27.9%)
	8-19	381 (18.7%)	616 (32.9%)	611 (26.2%)	386 (24.4%)
	≥20	31 (1.5%)	22 (1.2%)	27 (1.2%)	26 (1.6%)
Polypharmacy[1] at index-date (using BNF substances)	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	4.08 (4.35)	5.98 (4.33)	5.10 (4.34)	4.84 (4.58)
	Median	3	6	4	4
	Min-Max	[0.0 ; 26.0]	[0.0 ; 22.0]	[0.0 ; 24.0]	[0.0 ; 26.0]
	Q1-Q3	[0.0 ; 6.0]	[3.0 ; 9.0]	[1.0 ; 8.0]	[1.0 ; 7.0]
	0	510 (25.0%)	263 (14.0%)	448 (19.2%)	325 (20.6%)
	1-3	620 (30.4%)	315 (16.8%)	518 (22.2%)	417 (26.4%)
	4-7	537 (26.3%)	675 (36.0%)	763 (32.7%)	449 (28.4%)
	8-19	354 (17.4%)	614 (32.7%)	595 (25.5%)	373 (23.6%)
	≥20	17 (0.8)	8 (0.4)	10 (0.4)	15 (0.9)

SD, standard deviation; BNF, British National Formulary

[1]Polypharmacy was defined as the number of distinct BNF headers/ drug substances (including non-NGB/OAB drugs) in the therapy dataset

7.4.5 Duration between Diagnosis of Neurogenic Bladder/Underlying Conditions and Overactive Bladder Diagnosis/Overactive Bladder Drug Prescription

Mean duration between diagnosis of NGB/underlying conditions and OAB diagnosis/OAB drug prescription was 1140.1 days (SD =1352.6). The longest duration was in the SB cohort (mean=4149.4 [SD=4161.2]), and the shortest duration was in the SCI cohort (mean=457.8 [SD=519.9]) (Table 7.10). Duration was longer in younger patients (mean=1347.8 [SD=1678.8]) than the elderly (mean=928.9 [SD=858.6]). Males (mean=1134.8 [SD=1312.6]) had a slightly longer duration than females (mean=1147.9 [SD=1410) (Table 7.11).

Table 7.10 Duration between diagnosis of NGB/underlying conditions and OAB diagnosis/OAB drug prescription by underlying neurological condition

Characteristics		Definitive NGB n=363	PD Cohort n=713	MS Cohort n=1029	STK Cohort n=1720	SCI Cohort n=41	SB Cohort n=180	All n=3913
Duration between diagnoses	No. of valid values	135	711	1017	1715	37	135	3678
	Mean (SD)	846.27 (1063.57)	1034.01 (1008.44)	1095.89 (1010.47)	1028.50 (986.38)	457.84 (519.94)	4149.35 (4161.17)	1140.06 (1352.63)
	Min-Max	[1.0 ; 5890.0]	[4.0 ; 12935.0]	[1.0 ; 4364.0]	[1.0 ; 15911.0]	[3.0 ; 2454.0]	[2.0 ; 16025.0]	[1.0 ; 16025.0]
	Median	487	778	787	721	218	2625	748.5
	Q1-Q3	[136.0 ; 1158.0]	[302.0 ; 1506.0]	[250.0 ; 1715.0]	[259.0 ; 1567.0]	[115.0 ; 828.0]	[624.0 ; 6514.0]	[258.0 ; 1647.0]

SD, standard deviation; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

Table 7.11 Duration between diagnosis of NGB/underlying conditions and OAB diagnosis/OAB drug prescription by age and sex subgroups

Characteristics		[19 years – 65 years[n =2038	Over 65 years n =1875	Male n=2334	Female n=1579
Duration between diagnosis of NGB/underlying conditions and OAB diagnosis/OAB drug prescription (days)	No. of valid values	1854	1824	2192	1486
	Mean (SD)	1347.83 (1678.79)	928.87 (858.55)	1134.77 (1312.62)	1147.87 (1410.00)
	Min-Max	[1.0 ; 16025.0]	[2.0 ; 4122.0]	[1.0 ; 15911.0]	[1.0 ; 16025.0]
	Median	875.5	662	748.5	749
	Q1-Q3	[293.0 ; 1876.0]	[235.0 ; 1389.0]	[266.5 ; 1660.5]	[251.0 ; 1597.0]

SD, standard deviation; NGB, neurogenic bladder; OAB, overactive bladder

7.4.6 Complications Attributable to the Source Condition

In the general cohort, 558 patients (14.3%) experienced urinary tract infection (UTI), 557 patients (14.2%) experienced incontinence, and 96 patients (2.5%) experienced urinary retention. Other complications of interest were detected in less than 1% of patients. Incontinence was the most frequent complication in the PD sub-cohort (16.7%) and STK sub-cohort (15.1%), followed by UTI (10.1%, and 13.8%, respectively). In other underlying condition sub-cohorts, the most frequent complication was UTI (definitive NGB sub-cohort: 19.6%, MS sub-cohort: 14.9%, SCI sub-cohort: 34.1%, SB sub-cohort: 19.4%) followed by incontinence (8.5%, 13.7%, 4.9% and 11.7%, respectively) (Table 7.12). Proportions of complications were very similar between the two age groups. Proportions of patients with incontinence or with UTI were almost twice as high in female patients (incontinence: n=315, 19.9%, UTI: n=301, 19.1%) than male patients (incontinence: n=242, 10.4%, UTI: n=257, 11.0%) (Table 7.13).

Table 7.12 Complications within 12 months after the first OAB/NGB diagnosis or OAB prescription date, overall and by underlying conditions sub-cohorts)

Characteristics	Definitive NGB (n =363)	PD cohort (n =713)	MS cohort (n =1029)	STK cohort (n =1720)	SCI cohort (n =41)	SB cohort (n =180)	All (n =3913)
Urinary tract infection	71 (19.6%)	72 (10.1%)	153 (14.9%)	237 (13.8%)	14 (34.1%)	35 (19.4%)	558 (14.3%)
Incontinence	31 (8.5%)	119 (16.7%)	141 (13.7%)	260 (15.1%)	2 (4.9%)	21 (11.7%)	557 (14.2%)
Sepsis/septicaemia	4 (1.1%)	5 (0.7%)	7 (0.7%)	18 (1.0%)	1 (2.4%)	2 (1.1%)	34 (0.9%)
Urinary retention	13 (3.6%)	21 (2.9%)	19 (1.8%)	45 (2.6%)	0 (0.0%)	1 (0.6%)	96 (2.5%)
Obstructive uropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.0%)

Renal failure (acute and other)	13 (3.6%)	5 (0.7%)	2 (0.2%)	7 (0.4%)	0 (0.0%)	5 (2.8%)	27 (0.7%)

NGB, neurogenic bladder; PD, Parkinson's disease; MS, Multiple Sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

Table 7.13 Complications within 12 months after the first OAB/NGB diagnosis or OAB prescription date, by age and sex subgroups

Characteristics	[19 years – 65 years[(n=2038)	Over 65 years (n=1875)	Male (n=1579)	Female (n=2334)
Urinary tract infection	312 (15.3%)	246 (13.1%)	257 (11.0%)	301 (19.1%)
Incontinence	278 (13.6%)	279 (14.9%)	242 (10.4%)	315 (19.9%)
Sepsis/septicaemia	13 (0.6%)	21 (1.1%)	25 (1.1%)	9 (0.6%)
Urinary retention	36 (1.8%)	60 (3.2%)	83 (3.6%)	13 (0.8%)
Obstructive uropathy	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Renal failure (acute and other)	15 (0.7%)	12 (0.6%)	19 (0.8%)	8 (0.5%)

7.5 Drug Utilisation

7.5.1 Prescriptions of Anticholinergics and Anticholinergic Burden Score

Overall, nearly half of the population (1776, 45.4%) were not prescribed any anticholinergic drugs within the 12-month pre-index period and 893 (22.8%) were prescribed only 1 anticholinergic drug. A sizable proportion 366 (9.4%) of patients were prescribed 4 or more anticholinergics (Table 7.14). Distributions were similar across age subgroups and sex subgroups (Table 7.15).

The mean Anticholinergic Cognitive Burden (ACB) score in the general study cohort was 6.6 (SD=5.9). The lowest mean ACB score was observed in the definitive NGB sub-cohort (2.9 [SD=4.5]) and the highest mean ACB score was observed in the STK sub-cohort (7.6 [SD=6.3]) (Table 7.14). The general trend showed that ACB score increased in the post-index period within all subgroups, with the same also being true within the age and sex subgroups. Patients between 19 and 65 years old had a slightly lower mean ACB score (6.3 [SD=5.9]), compared to elderly patients (6.9 [SD=5.7])) and male patients had a slightly lower mean ACB score (6.5 [SD=5.7]), compared to female patients (6.7 [SD=6.1]) (Table 7.15).

Table 7.14 Anticholinergic burden and number of anticholinergics prescribed by underlying neurological condition

Characteristics		**Definitive NGB n=363**	**PD Cohort n=713**	**MS Cohort n=1029**	**STK Cohort n=1720**	**SCI Cohort n=41**	**SB Cohort n=180**	**All n=3913**
ACB score[1]	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	2.85 (4.47)	6.80 (5.94)	6.04 (4.89)	7.62 (6.26)	6.93 (7.06)	4.58 (4.67)	6.59 (5.85)
	Median	[0.0 ; 37.0]	[0.0 ; 57.0]	[0.0 ; 69.0]	[0.0 ; 66.0]	[0.0 ; 37.0]	[0.0 ; 33.0]	[0.0 ; 69.0]
	Min-Max	0	6	5	6	6	3	6
	Q1-Q3	[0.0 ; 5.0]	[3.0 ; 8.0]	[3.0 ; 7.0]	[4.0 ; 9.0]	[3.0 ; 9.0]	[3.0 ; 6.0]	[3.0 ; 8.0]
ACB Score at date d	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	0.65 (1.42)	3.09 (1.12)	3.19 (1.43)	3.22 (1.13)	3.02 (1.56)	2.38 (1.60)	2.98 (1.42)
	Median	[0.0 ; 7.0]	[0.0 ; 11.0]	[0.0 ; 23.0]	[0.0 ; 12.0]	[0.0 ; 6.0]	[0.0 ; 9.0]	[0.0 ; 23.0]
	Min-Max	0	3	3	3	3	3	3
	Q1-Q3	[0.0 ; 0.0]	[3.0 ; 3.0]	[3.0 ; 3.0]	[3.0 ; 3.0]	[3.0 ; 4.0]	[0.0 ; 3.0]	[3.0 ; 3.0]
ACB Score 12 months before d	**No. of valid values**	363	713	1029	1720	41	180	3913

	Mean (SD)	11.17 (20.35)	15.70 (23.28)	12.59 (18.22)	18.54 (26.50)	15.24 (23.86)	12.59 (19.95)	15.67 (23.48)
	Median	2	6	5	10	4	3	7
	Min-Max	[0.0 ; 133.0]	[0.0 ; 265.0]	[0.0 ; 202.0]	[0.0 ; 348.0]	[0.0 ; 100.0]	[0.0 ; 155.0]	[0.0 ; 348.0]
	Q1-Q3	[0.0 ; 14.0]	[3.0 ; 19.0]	[3.0 ; 15.0]	[4.0 ; 22.0]	[3.0 ; 14.0]	[3.0 ; 17.0]	[3.0 ; 19.0]
ACB Score 12 months after d	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	18.22 (27.58)	37.35 (42.88)	34.20 (39.82)	41.70 (46.53)	46.10 (36.26)	24.80 (32.41)	36.68 (43.03)
	Median	6	30	27	31	45	15	27
	Min-Max	[0.0 ; 204.0]	[0.0 ; 471.0]	[0.0 ; 450.0]	[0.0 ; 622.0]	[0.0 ; 180.0]	[0.0 ; 298.0]	[0.0 ; 622.0]
	Q1-Q3	[0.0 ; 26.0]	[14.0 ; 46.0]	[10.0 ; 42.0]	[15.0 ; 53.0]	[18.0 ; 63.0]	[3.5 ; 36.0]	[12.0 ; 46.0]
Number of prescribed anticholinergic drugs within the pre-index period	**Valid values**	363	713	1029	1720	41	180	3913
	0	178 (49.0%)	305 (42.8%)	564 (54.8%)	738 (42.9%)	24 (58.5%)	36 (20.0%)	1776 (45.4%)
	1	68 (18.7%)	172 (24.1%)	223 (21.7%)	384 (22.3%)	6 (14.6%)	63 (35.0%)	893 (22.8%)
	2	49 (13.5%)	116 (16.3%)	133 (12.9%)	263 (15.3%)	4 (9.8%)	34 (18.9%)	580 (14.8%)
	3	22 (6.1%)	47 (6.6%)	59 (5.7%)	154 (9.0%)	3 (7.3%)	22 (12.2%)	298 (7.6%)
	4+	46 (12.7%)	73 (10.2%)	50 (4.9%)	181 (10.5%)	4 (9.8%)	25 (13.9%)	366 (9.4%)

SD, standard deviation; BNF, British National Formulary; NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; ACB, Anticholinergic Cognitive Burden

[1] The ACB score was calculated within 1 month before and after the first OAB/NGB diagnosis or OAB prescription date (date 'd')

For patients with no anticholinergic prescriptions between 1 month before/after date 'd': ACB score =0

Table 7.15 Anticholinergic burden and number of anticholinergics prescribed by age and sex subgroups

Characteristics		[19 years – 65 years[n=2038	Over 65 years n=1875	Male n=2334	Female n=1579
ACB score[1]	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	6.31 (5.94)	6.90 (5.73)	6.51 (5.65)	6.72 (6.14)
	Min-Max	[0.0 ; 69.0]	[0.0 ; 66.0]	[0.0 ; 64.0]	[0.0 ; 69.0]
	Median	5	6	6	6
	Q1-Q3	[3.0 ; 8.0]	[3.0 ; 8.0]	[3.0 ; 8.0]	[3.0 ; 9.0]
ACB Score at date d	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	2.85 (1.60)	3.11 (1.17)	2.95 (1.36)	3.02 (1.51)
	Min-Max	[0.0 ; 23.0]	[0.0 ; 12.0]	[0.0 ; 12.0]	[0.0 ; 23.0]
	Median	3	3	3	3
	Q1-Q3	[3.0 ; 3.0]	[3.0 ; 3.0]	[3.0 ; 3.0]	[3.0 ; 3.0]
ACB Score 12 months before d	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	15.06 (24.22)	16.32 (22.62)	14.91 (22.67)	16.79 (24.58)
	Min-Max	[0.0 ; 309.0]	[0.0 ; 348.0]	[0.0 ; 348.0]	[0.0 ; 309.0]
	Median	5	9	7	6
	Q1-Q3	[3.0 ; 18.0]	[3.0 ; 21.0]	[3.0 ; 18.0]	[3.0 ; 21.0]
ACB Score 12 months after d	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	36.47 (44.03)	36.90 (41.92)	35.70 (41.97)	38.12 (44.53)
	Min-Max	[0.0 ; 471.0]	[0.0 ; 622.0]	[0.0 ; 471.0]	[0.0 ; 622.0]
	Median	27	27	27	28
	Q1-Q3	[9.0 ; 45.0]	[14.0 ; 46.0]	[11.0 ; 45.0]	[12.0 ; 48.0]
Number of patients on anticholinergic drugs within the pre-index period	**Valid values**	2038	1875	2334	1579
	0	1016 (49.9%)	760 (40.5%)	1100 (47.1%)	676 (42.8%)
	1	463 (22.7%)	430 (22.9%)	554 (23.7%)	339 (21.5%)
	2	250 (12.3%)	330 (17.6%)	329 (14.1%)	251 (15.9%)

	3	135 (6.6%)	163 (8.7%)	164 (7.0%)	134 (8.5%)
	4+	174 (8.5)	192 (10.2)	187 (8.0)	179 (11.3)

SD, standard deviation; ACB, Anticholinergic Cognitive Burden

[1] The ACB score was calculated within 1 month before and after the first OAB/NGB diagnosis or OAB prescription date (date 'd')

For patients with no anticholinergic prescriptions between 1 month before/after date 'd': ACB score=0

7.5.2 Overactive Bladder Drug Use

Overall, the mean number of bladder muscarinic prescriptions over 12 months after the first OAB/NGB diagnosis or OAB prescription date was 6.9 (SD=8.2). It was relatively heterogeneous from one underlying condition sub-cohort to another, varying from 1.6 (SD=3.5) in the definitive NGB sub-cohort to 9 (SD=5.6) in the SCI sub-cohort. Most patients were prescribed 1 to 4 bladder muscarinic prescriptions over the 12-month period, except in the SCI sub-cohort (63.4% of patients reported 5 to 14 OAB prescriptions) and in the definitive NGB sub-cohort (70% of patients did not report any OAB prescriptions) (Table 7.16). The mean numbers of OAB prescriptions were very similar between age subgroups; 19 and 65 years old (mean=6.9 [SD=8.1]) and elderly patients (mean=7 [SD=8.3]). The mean numbers of OAB prescriptions were also similar between male patients (mean=6.9 [SD=8.2]) and female patients (mean=7 [SD=8.1]) (Table 7.17).

The average cumulative numbers of days' supply of OAB drugs over 12 months following the first OAB/NGB diagnosis or OAB prescription date was 202.9 days (SD=210.9). It was relatively heterogeneous between the different underlying condition sub-cohorts, varying from 50.5 days in the definitive NGB sub-cohort (SD=112.5) to 273.2 (SD=158.5, median=336 days) in the SCI sub-cohort. In the definitive NGB sub-cohort, majority of individuals received $\geq$30 cumulative days' supply of OAB drugs (74.9%) (Table 7.16). The average cumulative numbers of days' supply of OAB drugs was relatively similar in both age groups and both sex groups: 207.95 days (SD=246.6) in patients between 19 and 65 years old, 197.3 days (SD=163.4) in elderly patients, 200.7 (SD=179.12) in female patients and 206.1 (SD=250.6) in male patients (Table 7.17).

Overall, 312 patients (8.0%) were prescribed at least two OAB drugs concomitantly over the 12 months following the first OAB/NGB diagnosis or OAB prescription date. It varied from 2.8% in the definitive NGB sub-cohort to 10.2% in the MS sub-cohort (Table 7.16). There was a small difference between age subgroups (for patients aged between 19 and 65 years old: 8.1%, for the elderly: 7.8%). Combination use was higher in female patients (10.4%) than in male patients (6.3%) (Table 7.17). Overall, the most frequently prescribed drugs concomitantly were solifenacin, tolterodine and oxybutynin immediate release (IR) (Table 7.18).

Table 7.16 Overactive bladder drug use by underlying neurological condition

Characteristics		**Definitive NGB n=363**	**PD Cohort n=713**	**MS Cohort n=1029**	**STK Cohort n=1720**	**SCI Cohort n=41**	**SB Cohort n=180**	**All n=3913**
Number of OAB prescriptions	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	1.56 (3.47)	7.62 (8.07)	7.10 (7.33)	7.51 (9.07)	9.00 (5.62)	4.99 (6.30)	6.92 (8.20)
	Min-Max	[0.0 ; 21.0]	[0.0 ; 55.0]	[0.0 ; 64.0]	[0.0 ; 104.0]	[0.0 ; 24.0]	[0.0 ; 52.0]	[0.0 ; 104.0]
	Median	0	6	6	5	9	3	5
	Q1-Q3	[0.0 ; 1.0]	[2.0 ; 12.0]	[2.0 ; 11.0]	[1.0 ; 11.0]	[6.0 ; 13.0]	[1.0 ; 8.5]	[1.0 ; 11.0]
	0	255 (70.2%)	11 (1.5%)	35 (3.4%)	29 (1.7%)	4 (9.8%)	44 (24.4%)	307 (7.8%)
	1-4	58 (16.0%)	304 (42.6%)	412 (40.0%)	759 (44.1%)	5 (12.2%)	63 (35.0%)	1571 (40.1%)
	5-9	31 (8.5%)	160 (22.4%)	275 (26.7%)	416 (24.2%)	13 (31.7%)	32 (17.8%)	911 (23.3%)
	10-14	14 (3.9%)	177 (24.8%)	243 (23.6%)	370 (21.5%)	13 (31.7%)	37 (20.6%)	841 (21.5%)
	15-44	5 (1.4%)	51 (7.2%)	52 (5.1%)	117 (6.8%)	6 (14.6%)	3 (1.7%)	231 (5.9%)
	45+	0 (0.0%)	10 (1.4%)	12 (1.2%)	29 (1.7%)	0 (0.0%)	1 (0.6%)	52 (1.3%)
Cumulative numbers of days' supply	**No. of valid values**	363	713	1029	1720	41	180	3913

of OAB drugs	**Mean (SD)**	50.50 (112.48)	221.53 (202.27)	222.21 (188.47)	210.42 (232.57)	273.20 (158.49)	155.04 (155.61)	202.86 (210.90)
	Min-Max	[0.0 ; 637.7]	[0.0 ; 3392.0]	[0.0 ; 3177.0]	[0.0 ; 6956.0]	[0.0 ; 532.0]	[0.0 ; 447.6]	[0.0 ; 6956.0]
	Median	0	206	210	174.5	336	88	168
	Q1-Q3	[0.0 ; 30.0]	[56.0 ; 364.0]	[56.0 ; 364.0]	[56.0 ; 364.0]	[128.0 ; 392.0]	[21.0 ; 333.0]	[30.0 ; 360.0]
	0-29	272 (74.9%)	101 (14.2%)	155 (15.1%)	283 (16.5%)	7 (17.1%)	66 (36.7%)	804 (20.5%)
	30-119	40 (11.0%)	190 (26.6%)	250 (24.3%)	455 (26.5%)	2 (4.9%)	34 (18.9%)	952 (24.3%)
	120-349	32 (8.8%)	201 (28.2%)	318 (30.9%)	515 (29.9%)	15 (36.6%)	44 (24.4%)	1107 (28.3%)
	350-549	18 (5.0%)	211 (29.6%)	292 (28.4%)	445 (25.9%)	17 (41.5%)	36 (20.0%)	1003 (25.6%)
	≥550	1 (0.3%)	10 (1.4%)	14 (1.4%)	22 (1.3%)	0 (0.0%)	0 (0.0%)	47 (1.2%)
OAB combination use (yes/no)	**Yes: n (%)**	10 (2.8%)	58 (8.1%)	105 (10.2%)	130 (7.6%)	2 (4.9%)	11 (6.1%)	312 (8.0%)

SD, standard deviation; NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; OAB, overactive bladder

Table 7.17 Overactive bladder drug use by age and sex subgroups

Characteristics		**[19 years – 65 years[n =2038**	**Over 65 years n =1875**	**Male n=2334**	**Female n=1579**
Number of OAB prescriptions	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	6.87 (8.10)	6.99 (8.31)	6.90 (8.24)	6.96 (8.14)
	Min-Max	[0.0 ; 104.0]	[0.0 ; 102.0]	[0.0 ; 104.0]	[0.0 ; 102.0]
	Median	5	5	5	5
	Q1-Q3	[1.0 ; 11.0]	[1.0 ; 11.0]	[1.0 ; 11.0]	[1.0 ; 11.0]
	0	243 (11.9%)	64 (3.4%)	181 (7.8%)	126 (8.0%)
	1-4	724 (35.5%)	847 (45.2%)	944 (40.4%)	627 (39.7%)
	5-9	483 (23.7%)	428 (22.8%)	540 (23.1%)	371 (23.5%)

	10-14	441 (21.6%)	400 (21.3%)	508 (21.8%)	333 (21.1%)
	15-44	118 (5.8%)	113 (6.0%)	128 (5.5%)	103 (6.5%)
	45+	29 (1.4%)	23 (1.2%)	33 (1.4%)	19 (1.2%)
Cumulative numbers of days' supply of OAB drugs	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	207.95 (246.60)	197.34 (163.37)	200.69 (179.12)	206.08 (250.63)
	Min-Max	[0.0 ; 6956.0]	[0.0 ; 1440.0]	[0.0 ; 3392.0]	[0.0 ; 6956.0]
	Median	170	150	168	168
	Q1-Q3	[30.0 ; 360.0]	[30.0 ; 360.0]	[30.0 ; 364.0]	[30.0 ; 360.0]
	0-29	463 (22.7%)	341 (18.2%)	476 (20.4%)	328 (20.8%)
	30-119	439 (21.5%)	513 (27.4%)	579 (24.8%)	373 (23.6%)
	120-349	568 (27.9%)	539 (28.7%)	641 (27.5%)	466 (29.5%)
	350-549	538 (26.4%)	465 (24.8%)	615 (26.3%)	388 (24.6%)
	≥550	30 (1.5%)	17 (0.9%)	23 (1.0%)	24 (1.5%)
OAB combination use (yes/no)	**Yes: n (%)**	166 (8.1%)	146 (7.8%)	147 (6.3%)	165 (10.4%)

Table 7.18 Combination use overall in neurogenic bladder patients

Substance 1	Substance 2	n (%) *
Solifenacin	Tolterodine	58 (14.7 %)
Oxybutynin IR	Tolterodine	56 (14.2 %)
Oxybutynin IR	Solifenacin	47 (11.9 %)
Oxybutynin ER	Oxybutynin IR	33 (8.4 %)
Tolterodine	Trospium	25 (6.3 %)
Solifenacin	Trospium	20 (5.1 %)
Oxybutynin ER	Tolterodine	19 (4.8 %)

Oxybutynin IR	Trospium	18 (4.6 %)
Oxybutynin ER	Solifenacin	18 (4.6 %)
Fesoterodine	Solifenacin	12 (3.0 %)
Mirabegron	Solifenacin	11 (2.8 %)
Flavoxate	Oxybutynin IR	10 (2.5 %)
Propiverine	Tolterodine	9 (2.3 %)
Fesoterodine	Tolterodine	7 (1.8 %)
Flavoxate	Solifenacin	6 (1.5 %)
Fesoterodine	Trospium	5 (1.3 %)
Fesoterodine	Oxybutynin IR	5 (1.3 %)
Mirabegron	Oxybutynin IR	5 (1.3 %)
Propiverine	Trospium	4 (1.0 %)
Mirabegron	Trospium	3 (0.8 %)
Flavoxate	Tolterodine	3 (0.8 %)
Oxybutynin IR	Propiverine	2 (0.5 %)
Oxybutynin ER	Trospium	2 (0.5 %)
Mirabegron	Tolterodine	2 (0.5 %)
Mirabegron	Oxybutynin ER	2 (0.5 %)
Propiverine	Solifenacin	2 (0.5 %)
Darifenacin	Oxybutynin IR	2 (0.5 %)
Darifenacin	Mirabegron	2 (0.5 %)
Fesoterodine	Oxybutynin ER	1 (0.3 %)
Fesoterodine	Mirabegron	1 (0.3 %)
Flavoxate	Trospium	1 (0.3 %)

Flavoxate	Oxybutynin ER	1 (0.3 %)
Darifenacin	Solifenacin	1 (0.3 %)
Darifenacin	Trospium	1 (0.3 %)

IR, immediate release; ER, extended release

* Total ≥ 312 as some patients have multiple combinations

7.5.3 Other Drug Use

More than 50% of the study population had antibiotics prescriptions for UTI (53.9%), the average number of prescriptions over 12 months follow-up period was 2.91 (SD=7.95). This was similar between the neurological conditions (ranged between 2 and 3 prescriptions on average, over 12 months) (Table 7.19). When comparing male and female patients, the former had less prescriptions 1.7 (3.5) compared to the latter 2.9 (4.6). The numbers were relatively similar between the age subgroups with 2.3 (4.2) prescriptions in the 19-65 years subgroup and 2.1 (3.9) in the over 65 years subgroup (Table 7.20).

α-adrenergic antagonists or 5-Alpha-Reductase Inhibitors (5-ARIs) prescriptions were identified in 25.5% of the overall population. Prescriptions were higher in PD and STK populations compared to the other sub-cohorts (≥4 prescriptions vs. less than 1 prescription on average respectively) (Table 7.19). Prescriptions were higher in the elderly compared to younger patients (4.5 prescriptions vs. 1.5 prescriptions on average over 12 months respectively). Between sexes, the male subgroup had a significantly higher number of prescriptions 4.7 (9.7) compared to females 0.3 (2.4).

Table 7.19 Number of α-adrenergic antagonists, 5-Alpha-Reductase Inhibitors (5-ARIs) and antibiotics prescriptions by underlying neurological condition

Characteristics		Definitive NGB n=363	PD Cohort n=713	MS Cohort n=1029	STK Cohort n=1720	SCI Cohort n=41	SB Cohort n=180	All n=3913
Number of antibiotics prescriptions for UTI	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	2.72 (4.25)	1.70 (3.31)	2.37 (4.24)	2.14 (3.80)	3.46 (4.86)	3.13 (6.22)	2.22 (4.03)
	Min-Max	[0.0 ; 24.0]	[0.0 ; 44.0]	[0.0 ; 36.0]	[0.0 ; 46.0]	[0.0 ; 18.0]	[0.0 ; 59.0]	[0.0 ; 59.0]
	Median	1	0	1	1	1	1	1
	Q1-Q3	[0.0 ; 4.0]	[0.0 ; 2.0]	[0.0 ; 3.0]	[0.0 ; 2.0]	[0.0 ; 7.0]	[0.0 ; 4.0]	[0.0 ; 3.0]
	0	159 (43.8%)	371 (52.0%)	473 (46.0%)	768 (44.7%)	20 (48.8%)	71 (39.4%)	1803 (46.1%)
	1–4	130 (35.8%)	261 (36.6%)	384 (37.3%)	713 (41.5%)	8 (19.5%)	70 (38.9%)	1520 (38.8%)
	5–9	42 (11.6%)	55 (7.7%)	97 (9.4%)	144 (8.4%)	9 (22.0%)	25 (13.9%)	352 (9.0%)
	10–14	23 (6.3%)	22 (3.1%)	49 (4.8%)	54 (3.1%)	2 (4.9%)	9 (5.0%)	155 (4.0%)
	15–19	9 (2.5%)	4 (0.6%)	26 (2.5%)	40 (2.3%)	2 (4.9%)	4 (2.2%)	81 (2.1%)
	≥20	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.6%)	2 (0.1%)
Number of α-blockers or 5-ARI's prescriptions	**No. of valid values**	363	713	1029	1720	41	180	3913
	Mean (SD)	0.84 (2.87)	4.34 (9.81)	0.55 (2.44)	4.27 (9.53)	0.63 (3.75)	0.63 (2.70)	2.91 (7.95)
	Min-Max	[0.0 ; 25.0]	[0.0 ; 106.0]	[0.0 ; 29.0]	[0.0 ; 108.0]	[0.0 ; 24.0]	[0.0 ; 23.0]	[0.0 ; 108.0]
	Median	0	0	0	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 6.0]	[0.0 ; 0.0]	[0.0 ; 6.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 1.0]
	0	321 (88.4%)	448 (62.8%)	958 (93.1%)	1107 (64.4%)	39 (95.1%)	165 (91.7%)	2916 (74.5%)
	1–4	14 (3.9%)	63 (8.8%)	18 (1.7%)	126 (7.3%)	1 (2.4%)	6 (3.3%)	223 (5.7%)
	5–9	16 (4.4%)	76 (10.7%)	26 (2.5%)	177 (10.3%)	0 (0.0%)	4 (2.2%)	296 (7.6%)
	10–14	10 (2.8%)	76 (10.7%)	23 (2.2%)	190 (11.0%)	0 (0.0%)	4 (2.2%)	300 (7.7%)
	15–19	2 (0.6%)	41 (5.8%)	4 (0.4%)	102 (5.9%)	1 (2.4%)	1 (0.6%)	151 (3.9%)

	≥20	0 (0.0%)	9 (1.3%)	0 (0.0%)	18 (1.0%)	0 (0.0%)	0 (0.0%)	27 (0.7%)

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation; UTI, urinary tract infection; 5-ARIs, 5-Alpha-Reductase Inhibitors

Table 7.20 Number of α-adrenergic antagonists, 5-Alpha-Reductase Inhibitors (5-ARIs) and antibiotics prescriptions by age and sex subgroups

Characteristics		**[19 years – 65 years[n =2038**	**Over 65 years n =1875**	**Male n =2334**	**Female n =1579**
Number of antibiotics prescriptions for UTI	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	2.29 (4.17)	2.14 (3.88)	1.74 (3.51)	2.93 (4.62)
	Min-Max	[0.0 ; 59.0]	[0.0 ; 46.0]	[0.0 ; 46.0]	[0.0 ; 59.0]
	Median	1	1	0	1
	Q1-Q3	[0.0 ; 3.0]	[0.0 ; 2.0]	[0.0 ; 2.0]	[0.0 ; 4.0]
	0	954 (46.8%)	849 (45.3%)	1221 (52.3%)	582 (36.9%)
	1–4	753 (36.9%)	767 (40.9%)	855 (36.6%)	665 (42.1%)
	5–9	199 (9.8%)	153 (8.2%)	158 (6.8%)	194 (12.3%)
	10–14	87 (4.3%)	68 (3.6%)	62 (2.7%)	93 (5.9%)
	15–19	44 (2.2%)	37 (2.0%)	37 (1.6%)	44 (2.8%)
	≥20	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Number of α-blockers or 5-ARI's prescriptions	**No. of valid values**	2038	1875	2334	1579
	Mean (SD)	1.45 (5.51)	4.50 (9.69)	4.66 (9.71)	0.32 (2.43)
	Min-Max	[0.0 ; 108.0]	[0.0 ; 107.0]	[0.0 ; 108.0]	[0.0 ; 54.0]
	Median	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 6.0]	[0.0 ; 7.0]	[0.0 ; 0.0]
	0	1743 (85.5%)	1173 (62.6%)	1384 (59.3%)	1532 (97.0%)
	1–4	75 (3.7%)	148 (7.9%)	216 (9.3%)	7 (0.4%)
	5–9	97 (4.8%)	199 (10.6%)	277 (11.9%)	19 (1.2%)

	10–14	87 (4.3%)	213 (11.4%)	283 (12.1%)	17 (1.1%)
	15–19	29 (1.4%)	122 (6.5%)	149 (6.4%)	2 (0.1%)
	≥20	7 (0.3%)	20 (1.1%)	25 (1.1%)	2 (0.1%)

SD, standard deviation; UTI, urinary tract infection; 5-ARIs, 5-Alpha-Reductase Inhibitors

7.5.4 Distribution of Patients by Overactive Bladder drug at the Date of the First Neurogenic Bladder/Overactive Bladder Diagnosis or Overactive Bladder Prescription

Overall, 738 of patients included into the study cohort (18.9%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription. 992 individuals (25.4%) were prescribed with solifenacin, 803 individuals (20.5%) with oxybutynin IR and 723 individuals (18.5%) with tolterodine. In all subgroups solifenacin, tolderodine and oxybutynin were the most prescribed OAB drugs (Table 7.21).

Among the 363 patients that were diagnosed with definitive NGB, the majority of them (n=326, 89.8%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription (due to the way patients are included into the study), 12 patients (3.3%) were prescribed with oxybutynin IR, followed by 10 patients that were prescribed with solifenacin (2.8%).

The PD sub-cohort consisted of 713 patients; 99 of them (13.9%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription. Most patients received solifenacin (n=208, 29.2%), followed by tolterodine (n=143, 20.1%) and oxybutynin IR (n=119, 16.7%) respectively.

Amongst the 1029 patients who were diagnosed with MS, 144 (14.0%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription. The rest were mainly prescribed with oxybutynin IR (n=265, 25.8%), solifenacin23.6%) or tolterodine (n=194, 18.9%).

Amongst the 1720 patients in the STK group, 205 (11.9%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription. Patients were prescribed with solifenacin (n=495, 28.8%), oxybutynin IR (n=380, 22.1%) and tolterodine (n=349, 20.3%), respectively.

In the SCI sub-cohort (n=41), 7 (17.1%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription. 12 patients (29.3%) used oxybutynin ER and 8 patients used solifenacin (19.5%).

Amongst the 180 patients under SB condition, 49 (27.2%) did not receive any OAB treatment at the date of the first NGB/OAB diagnosis or OAB prescription. 41 patients (22.8%) were prescribed with solifenacin, 36 were prescribed with tolterodine (20.0%) and 31 with Oxybutynin IR (17.2%).

Table 7.21 Distribution of patients by overactive bladder (OAB) drug at the date of the first neurogenic bladder/OAB diagnosis or OAB prescription by underlying neurological condition

Drug	Definitive NGB (n=363)	PD Cohort (n=713)	MS Cohort (n=1029)	STK Cohort (n=1720)	SCI Cohort (n=41)	SB Cohort (n=180)	All (n=3913)
No OAB treatment	326 (89.8%)	99 (13.9%)	144 (14.0%)	205 (11.9%)	7 (17.1%)	49 (27.2%)	738 (18.9%)
Darifenacin	0 (0.0%)	8 (1.1%)	2 (0.2%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	14 (0.4%)
Emepronium	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fesoterodine	0 (0.0%)	20 (2.8%)	31 (3.0%)	49 (2.8%)	2 (4.9%)	2 (1.1%)	104 (2.7%)
Flavoxate	0 (0.0%)	12 (1.7%)	11 (1.1%)	17 (1.0%)	0 (0.0%)	3 (1.7%)	43 (1.1%)
Mirabegron	0 (0.0%)	19 (2.7%)	9 (0.9%)	19 (1.1%)	0 (0.0%)	1 (0.6%)	48 (1.2%)
Meladrazine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Oxybutynin ER	3 (0.8%)	33 (4.6%)	78 (7.6%)	96 (5.6%)	12 (29.3%)	14 (7.8%)	233 (6.0%)
Oxybutynin IR	12 (3.3%)	119 (16.7%)	265 (25.8%)	380 (22.1%)	6 (14.6%)	31 (17.2%)	803 (20.5%)
Propiverine	1 (0.3%)	5 (0.7%)	11 (1.1%)	10 (0.6%)	1 (2.4%)	1 (0.6%)	28 (0.7%)
Solifenacin	10 (2.8%)	208 (29.2%)	243 (23.6%)	495 (28.8%)	8 (19.5%)	41 (22.8%)	992 (25.4%)
Terodiline	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tolterodine	7 (1.9%)	143 (20.1%)	194 (18.9%)	349 (20.3%)	4 (9.8%)	36 (20.0%)	723 (18.5%)
Trospium	4 (1.1%)	47 (6.6%)	41 (4.0%)	96 (5.6%)	1 (2.4%)	2 (1.1%)	187 (4.8%)

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injury; SB, spina bifida; IR, immediate release; ER, extended release

7.5.5 Cumulative prescribed quantity of OAB drugs within 12 months after the first NGB/OAB diagnosis or OAB prescription

For most OAB drugs (solifenacin, oxybutynin IR, tolterodine, trospium, fesoterodine, mirabegron and propiverine), the highest mean cumulative OAB drug quantity was observed in the SCI sub-cohort; the lowest mean cumulative OAB drug quantities for solifenacin, mirabegron and propiverine were observed in SB sub-cohort; the lowest mean cumulative OAB drug quantities of oxybutynin IR and fesoterodine were observed in definitive NGB sub-cohort (Table 7.22). Patients aged less than 65 years old showed higher mean cumulative quantities compared to elderly patients when treated with solifenacin, oxybutynin IR, tolterodine, trospium, oxybutynin ER and propiverine. Male patients showed higher mean cumulative quantities than female patients when treated with oxybutynin IR, oxybutynin ER, fesoterodine, mirabegron and darifenacin (Table 7.23).

Table 7.22 Cumulative prescribed quantity (in grams) within 12 months after the first NGB/OAB diagnosis or OAB prescription, overall and by underlying neurological condition

Substances		Definitive NGB N=363	PD Cohort N=713	MS Cohort N=1029	STK Cohort N=1720	SCI Cohort N=41	SB Cohort N=180	All N=3913
Solifenacin Cumulative dose in grams	**No. of valid values**	40	272	341	681	11	55	1377
	Mean (SD)	1.05 (1.21)	1.23 (1.04)	1.40 (1.39)	1.18 (1.15)	2.07 (1.56)	1.00 (0.81)	1.24 (1.19)
	Min-Max	[0.1 ; 4.4]	[0.1 ; 4.5]	[0.1 ; 15.9]	[0.0 ; 7.9]	[0.1 ; 4.3]	[0.1 ; 3.6]	[0.0 ; 15.9]
	Median	0.4	1	1.2	0.8	2	0.8	0.9
	Q1-Q3	[0.2 ; 1.7]	[0.3 ; 2.0]	[0.3 ; 2.0]	[0.3 ; 1.9]	[0.8 ; 4.2]	[0.3 ; 1.7]	[0.3 ; 2.0]
Oxybutynin IR Cumulative dose in grams	**No. of valid values**	31	205	298	491	4	42	1052
	Mean (SD)	0.42 (0.38)	0.73 (0.72)	0.65 (0.58)	0.63 (0.59)	1.19 (0.83)	0.60 (0.57)	0.65 (0.61)
	Min-Max	[0.1 ; 1.7]	[0.0 ; 6.8]	[0.0 ; 2.9]	[0.0 ; 3.1]	[0.1 ; 2.1]	[0.1 ; 1.7]	[0.0 ; 6.8]
	Median	0.3	0.5	0.4	0.3	1.3	0.3	0.4
	Q1-Q3	[0.1 ; 0.6]	[0.1 ; 1.3]	[0.1 ; 1.1]	[0.1 ; 1.1]	[0.6 ; 1.7]	[0.1 ; 1.3]	[0.1 ; 1.2]
Tolterodine Cumulative dose in grams	**No. of valid values**	30	159	332	471	9	39	1024
	Mean (SD)	1.04 (1.13)	0.69 (0.76)	1.03 (1.15)	0.98 (1.28)	1.86 (0.92)	0.95 (1.24)	0.95 (1.16)
	Min-Max	[0.0 ; 3.6]	[0.0 ; 3.6]	[0.0 ; 6.7]	[0.0 ; 10.0]	[0.4 ; 3.1]	[0.0 ; 5.9]	[0.0 ; 10.0]
	Median	0.4	0.3	0.6	0.4	2	0.5	0.4
	Q1-Q3	[0.1 ; 2.0]	[0.1 ; 1.1]	[0.2 ; 1.7]	[0.1 ; 1.3]	[1.4 ; 2.6]	[0.2 ; 1.4]	[0.1 ; 1.4]
Trospium Cumulative dose in grams	**No. of valid values**	8	59	111	134	14	18	340
	Mean (SD)	1.94 (3.05)	1.27 (1.26)	1.11 (1.18)	1.94 (6.18)	2.27 (1.48)	2.24 (2.52)	1.57 (4.04)
	Min-Max	[0.2 ; 9.2]	[0.1 ; 4.2]	[0.1 ; 7.2]	[0.1 ; 69.6]	[0.3 ; 5.1]	[0.2 ; 9.2]	[0.1 ; 69.6]
	Median	0.8	0.8	0.8	0.7	1.7	1.3	0.8
	Q1-Q3	[0.4 ; 1.8]	[0.3 ; 1.9]	[0.2 ; 1.8]	[0.2 ; 2.0]	[1.1 ; 3.3]	[0.6 ; 3.1]	[0.2 ; 2.0]

Oxybutynin ER Cumulative dose in grams	**No. of valid values**	12	82	83	149	5	4	326
	Mean (SD)	7.21 (6.15)	7.03 (7.93)	7.44 (6.96)	7.39 (7.46)	4.77 (5.99)	12.74 (7.39)	7.30 (7.41)
	Min-Max	[0.3 ; 15.7]	[0.0 ; 31.2]	[0.6 ; 24.8]	[0.0 ; 38.4]	[1.1 ; 15.1]	[1.7 ; 16.8]	[0.0 ; 38.4]
	Median	6.3	3.4	4.6	3.6	1.7	16.2	3.6
	Q1-Q3	[1.2 ; 13.5]	[1.2 ; 9.4]	[1.2 ; 13.4]	[1.7 ; 11.2]	[1.1 ; 4.8]	[8.7 ; 16.8]	[1.2 ; 12.0]
Fesoterodine Cumulative dose in grams	**No. of valid values**	5	36	48	81	2	5	177
	Mean (SD)	0.65 (0.62)	0.99 (0.87)	0.75 (0.83)	0.79 (0.77)	2.18 (0.71)	0.68 (0.94)	0.83 (0.81)
	Min-Max	[0.1 ; 1.7]	[0.1 ; 3.7]	[0.1 ; 3.1]	[0.1 ; 3.2]	[1.7 ; 2.7]	[0.2 ; 2.4]	[0.1 ; 3.7]
	Median	0.6	0.7	0.4	0.4	2.2	0.2	0.6
	Q1-Q3	[0.2 ; 0.7]	[0.3 ; 1.5]	[0.1 ; 1.1]	[0.2 ; 1.2]	[1.7 ; 2.7]	[0.2 ; 0.4]	[0.2 ; 1.3]
Mirabegron Cumulative dose in grams	**No. of valid values**	3	33	24	51	1	3	114
	Mean (SD)	3.25 (1.89)	10.71 (8.47)	7.02 (6.49)	7.32 (6.81)	14.85 (--)	1.97 (0.90)	8.11 (7.32)
	Min-Max	[1.5 ; 5.3]	[0.8 ; 25.5]	[1.5 ; 22.5]	[0.8 ; 25.2]	[14.9 ; 14.9]	[1.4 ; 3.0]	[0.8 ; 25.5]
	Median	3	9	4.5	5.1	14.9	1.5	4.5
	Q1-Q3	[1.5 ; 5.3]	[3.0 ; 19.5]	[2.6 ; 10.5]	[1.5 ; 12.0]	[14.9 ; 14.9]	[1.4 ; 3.0]	[1.5 ; 15.0]
Flavoxate Cumulative dose in grams	**No. of valid values**	1	17	16	30	0 (0.0%)	3	67
	Mean (SD)	216.00 (0)	65.88 (77.10)	101.25 (107.25)	72.35 (85.39)	-	72.00 (112.24)	79.74 (90.06)
	Min-Max	[216.0 ; 216.0]	[11.2 ; 252.0]	[16.8 ; 352.8]	[5.6 ; 270.0]	-	[6.0 ; 201.6]	[5.6 ; 352.8]
	Median	216	33.6	45	23.6	-	8.4	33.6
	Q1-Q3	[216.0 ; 216.0]	[18.0 ; 90.0]	[17.4 ; 180.0]	[18.0 ; 117.6]	-	[6.0 ; 201.6]	[18.0 ; 117.6]
Propiverine Cumulative dose in grams	**No. of valid values**	2	8	26	17	2	1	54
	Mean (SD)	4.64 (5.37)	2.02 (1.61)	5.71 (5.89)	3.22 (3.53)	10.50 (10.10)	0.84 (--)	4.47 (5.12)
	Min-Max	[0.8 ; 8.4]	[0.8 ; 5.9]	[0.4 ; 16.8]	[0.4 ; 11.2]	[3.4 ; 17.6]	[0.8 ; 0.8]	[0.4 ; 17.6]
	Median	4.6	1.7	2.9	1.7	10.5	0.8	1.7

	Q1-Q3	[0.8 ; 8.4]	[1.3 ; 1.8]	[0.8 ; 10.9]	[0.8 ; 4.4]	[3.4 ; 17.6]	[0.8 ; 0.8]	[0.8 ; 6.7]
Darifenacin Cumulative dose in grams	**No. of valid values**	1	8	3	10	0 (0.0%)	0 (0.0%)	22
	Mean (SD)	0.42 (0)	2.09 (2.30)	0.28 (0.12)	0.85 (1.07)	-	-	1.20 (1.67)
	Min-Max	[0.4 ; 0.4]	[0.2 ; 5.9]	[0.2 ; 0.4]	[0.1 ; 2.9]	-	-	[0.1 ; 5.9]
	Median	0.4	0.8	0.2	0.4	-	-	0.5
	Q1-Q3	[0.4 ; 0.4]	[0.4 ; 4.1]	[0.2 ; 0.4]	[0.2 ; 0.6]	-	-	[0.2 ; 1.1]

SD, standard deviation; NGB, neurogenic bladder; PD, Parkinson's disease; MS, Multiple Sclerosis, STK, stroke; SCI, spinal cord injuries; SB, spina bifida; IR, immediate release; ER, extended release, SD, standard deviation

Table 7.23 Cumulative prescribed quantity (in grams) within 12 months after the first NGB/OAB diagnosis or OAB prescription, by age and sex subgroups

Substances		**[19 years – 65 years[n=2038**	**Over 65 years n=1875**	**Male n=2334**	**Female n=1579**
Solifenacin Cumulative dose in grams	**No. of valid values**	698	679	830	547
	Mean (SD)	1.35 (1.28)	1.12 (1.08)	1.23 (1.13)	1.26 (1.27)
	Min-Max	[0.0 ; 15.9]	[0.0 ; 7.9]	[0.0 ; 7.9]	[0.1 ; 15.9]
	Median	1.1	0.8	0.8	0.9
	Q1-Q3	[0.3 ; 2.0]	[0.3 ; 1.8]	[0.3 ; 2.0]	[0.3 ; 2.0]
Oxybutynin IR Cumulative dose in grams	**No. of valid values**	503	549	590	462
	Mean (SD)	0.68 (0.65)	0.63 (0.57)	0.70 (0.64)	0.60 (0.57)
	Min-Max	[0.0 ; 6.8]	[0.0 ; 3.1]	[0.0 ; 6.8]	[0.0 ; 3.1]
	Median	0.4	0.4	0.4	0.3
	Q1-Q3	[0.1 ; 1.2]	[0.1 ; 1.1]	[0.1 ; 1.3]	[0.1 ; 1.0]
Tolterodine Cumulative dose in grams	**No. of valid values**	538	486	575	449
	Mean (SD)	1.10 (1.27)	0.79 (1.01)	0.94 (1.10)	0.97 (1.24)
	Min-Max	[0.0 ; 10.0]	[0.0 ; 6.7]	[0.0 ; 6.9]	[0.0 ; 10.0]
	Median	0.6	0.3	0.4	0.4
	Q1-Q3	[0.2 ; 1.7]	[0.1 ; 1.1]	[0.2 ; 1.4]	[0.1 ; 1.4]
Trospium Cumulative dose in grams	**No. of valid values**	190	150	191	149
	Mean (SD)	1.77 (5.18)	1.31 (1.70)	1.48 (1.72)	1.68 (5.79)
	Min-Max	[0.1 ; 69.6]	[0.1 ; 14.4]	[0.1 ; 14.4]	[0.1 ; 69.6]
	Median	0.9	0.7	1	0.7

	Q1-Q3	[0.3 ; 2.0]	[0.2 ; 1.8]	[0.3 ; 2.1]	[0.2 ; 1.8]
Oxybutynin ER Cumulative dose in grams	**No. of valid values**	145	181	200	126
	Mean (SD)	7.71 (7.41)	6.97 (7.42)	7.48 (7.53)	7.00 (7.24)
	Min-Max	[0.3 ; 31.2]	[0.0 ; 38.4]	[0.0 ; 38.4]	[0.0 ; 31.2]
	Median	4.8	3.6	3.6	3.6
	Q1-Q3	[1.2 ; 14.4]	[1.7 ; 10.1]	[1.2 ; 13.4]	[1.2 ; 11.5]
Fesoterodine Cumulative dose in grams	**No. of valid values**	101	76	108	69
	Mean (SD)	0.83 (0.87)	0.83 (0.74)	0.86 (0.79)	0.78 (0.86)
	Min-Max	[0.1 ; 3.7]	[0.1 ; 3.2]	[0.1 ; 3.7]	[0.1 ; 3.2]
	Median	0.4	0.6	0.7	0.4
	Q1-Q3	[0.2 ; 1.2]	[0.2 ; 1.3]	[0.2 ; 1.4]	[0.2 ; 1.0]
Mirabegron Cumulative dose in grams	**No. of valid values**	62	52	73	41
	Mean (SD)	6.76 (6.32)	9.72 (8.13)	8.57 (7.32)	7.29 (7.35)
	Min-Max	[1.4 ; 25.2]	[0.8 ; 25.5]	[0.8 ; 25.5]	[0.8 ; 25.2]
	Median	3.4	6	6	3
	Q1-Q3	[1.5 ; 10.5]	[1.7 ; 18.2]	[1.5 ; 15.0]	[1.5 ; 13.5]
Flavoxate Cumulative dose in grams	**No. of valid values**	27	40	48	19
	Mean (SD)	79.70 (97.46)	79.76 (85.99)	71.73 (90.95)	99.96 (86.85)
	Min-Max	[5.6 ; 352.8]	[6.0 ; 270.0]	[5.6 ; 352.8]	[6.0 ; 260.4]
	Median	18	34.8	18	108
	Q1-Q3	[16.8 ; 117.6]	[18.0 ; 125.4]	[18.0 ; 89.4]	[18.0 ; 162.0]
Propiverine Cumulative dose in grams	**No. of valid values**	33	21	22	32
	Mean (SD)	5.37 (5.93)	3.04 (3.10)	4.45 (5.49)	4.48 (4.93)
	Min-Max	[0.4 ; 17.6]	[0.4 ; 11.2]	[0.4 ; 17.6]	[0.4 ; 16.8]
	Median	1.9	1.7	1.4	1.7
	Q1-Q3	[0.8 ; 10.2]	[0.8 ; 4.4]	[0.8 ; 5.9]	[0.8 ; 7.6]
Darifenacin Cumulative dose in grams	**No. of valid values**	12	10	13	9
	Mean (SD)	1.19 (2.04)	1.22 (1.17)	1.58 (1.99)	0.65 (0.88)
	Min-Max	[0.1 ; 5.9]	[0.2 ; 2.9]	[0.1 ; 5.9]	[0.2 ; 2.9]
	Median	0.3	0.6	0.6	0.2
	Q1-Q3	[0.2 ; 0.6]	[0.2 ; 2.7]	[0.2 ; 2.7]	[0.2 ; 0.6]

IR, immediate release; ER, extended release, SD, standard deviation

7.6 Resource Utilisation and Costs

7.6.1 Specialist Visits

Almost 50% of the patients had a urologist and/or gynaecologist visit over 12 months after the first OAB/NGB diagnosis or OAB prescription date (46.7%) (Table 7.24). When stratified by age groups, the proportion of visits was almost the same (47.4% in the elderly vs 46.1% for those under 65 years old) (Table 7.25). More men visited the specialist (49.1%) compared to women (43.2%). The overall average number of visits was 2.6 (SD=1.65, median=2) visits during the 12-month period (similar in all the neurological condition subgroups) and ranged from 1 visit to 15 visits (STK population) (Table 7.24). The average total cost associated with specialist visits was £252.53 (SD=£186.42, median=£218.8), and was comparable between, underlying conditions subgroups (Table 7.24). Costs were also comparable between age and sex subgroups (Table 7.25).

Table 7.24 Number of specialist visits and costs by underlying neurological condition subgroups

		Definitive NGB (n =363)	**PD cohort (n=713)**	**MS cohort (n=1029)**	**STK cohort (n=1720)**	**SCI cohort (n=41)**	**SB cohort (n=180)**	**All (n=3913)**
Specialist visits – all (Urologist/gynaecologist)	**≥ 1 visit n (%)**	184 (50.7%)	342 (48.0%)	396 (38.5%)	859 (49.9%)	23 (56.1%)	92 (51.1%)	1828 (46.7%)
	Mean (SD)	2.42 (1.64)	2.11 (1.42)	2.09 (1.41)	2.38 (1.83)	2.09 (1.24)	1.98 (1.41)	2.26 (1.65)
	Min-Max	[1.0 ; 10.0]	[1.0 ; 12.0]	[1.0 ; 9.0]	[1.0 ; 15.0]	[1.0 ; 5.0]	[1.0 ; 7.0]	[1.0 ; 15.0]
	Median	2	2	2	2	2	1	2

	Q1-Q3	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 2.0]	[1.0 ; 3.0]
Specialist visits (Urologist)	**≥1 visit n (%)**	174 (47.9%)	328 (46.0%)	367 (35.7%)	820 (47.7%)	20 (48.8%)	85 (47.2%)	1729 (44.2%)
	Mean (SD)	2.28 (1.69)	2.01 (1.45)	1.88 (1.40)	2.19 (1.79)	1.87 (1.42)	1.72 (1.30)	2.07 (1.63)
	Min-Max	[0.0 ; 10.0]	[0.0 ; 12.0]	[0.0 ; 9.0]	[0.0 ; 15.0]	[0.0 ; 5.0]	[0.0 ; 6.0]	[0.0 ; 15.0]
	Median	2	2	1	2	2	1	2
	Q1-Q3	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 2.0]	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 2.0]	[1.0 ; 3.0]
Specialist visits (gynaecologist)	**≥ 1 visit n (%)**	18 (5.0%)	20 (2.8%)	50 (4.9%)	79 (4.6%)	5 (12.2%)	9 (5.0%)	175 (4.5%)
	Mean (SD)	0.15 (0.51)	0.11 (0.53)	0.21 (0.65)	0.19 (0.75)	0.22 (0.42)	0.26 (1.03)	0.18 (0.70)
	Min-Max	[0.0 ; 3.0]	[0.0 ; 6.0]	[0.0 ; 4.0]	[0.0 ; 8.0]	[0.0 ; 1.0]	[0.0 ; 6.0]	[0.0 ; 8.0]
	Median	0	0	0	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
Costs (£) - all (Urologist/gynaecologist)	**Mean (SD)**	269.80 (181.62)	234.69 (158.60)	235.63 (160.24)	266.85 (206.97)	235.17 (132.29)	224.65 (171.40)	252.53 (186.42)
	Min-Max	[109.4 ; 1094.0]	[109.4 ; 1312.8]	[109.4 ; 1079.2]	[109.4 ; 1641.0]	[109.4 ; 547.0]	[109.4 ; 955.0]	[109.4 ; 1641.0]
	Median	218.8	218.8	218.8	218.8	218.8	140.9	218.8

	Q1-Q3	[109.4 ; 328.2]	[109.4 ; 328.2]	[109.4 ; 328.2]	[109.4 ; 328.2]	[109.4 ; 328.2]	[109.4 ; 234.6]	[109.4 ; 328.2]

SD, standard deviation; NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis, STK, stroke; SCI, spinal cord injuries; SB, spina bifida

Table 7.25 Number of specialist visits and costs by age and sex subgroups

		[19 years – 65 years[(n=2038)	**Over 65 years (n=1875)**	**Male (n=2334)**	**Female (n=1579)**
Specialist visits (Urologist/gynaecologist)	**≥ 1 visit n (%)**	940 (46.1%)	888 (47.4%)	1146 (49.1%)	682 (43.2%)
	Mean (SD)	2.23 (1.60)	2.28 (1.70)	2.31 (1.70)	2.17 (1.54)
	Min-Max	[1.0 ; 15.0]	[1.0 ; 12.0]	[1.0 ; 15.0]	[1.0 ; 11.0]
	Median	2	2	2	2
	Q1-Q3	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]
Specialist visits (Urologist)	**≥ 1 visit n (%)**	866 (42.5%)	863 (46.0%)	1144 (49.0%)	585 (37.0%)
	Mean (SD)	2.17 (1.57)	2.21 (1.62)	2.30 (1.70)	1.97 (1.35)
	Min-Max	[1.0 ; 15.0]	[1.0 ; 12.0]	[1.0 ; 15.0]	[1.0 ; 11.0]
	Median	2	2	2	1
	Q1-Q3	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]	[1.0 ; 3.0]
Specialist visits (Gynaecologist)	**≥ 1 visit n (%)**	122 (6.0%)	53 (2.8%)	6 (0.3%)	169 (10.7%)
	Mean (SD)	1.74 (1.13)	2.26 (1.68)	1.17 (0.41)	1.92 (1.35)
	Min-Max	[1.0 ; 6.0]	[1.0 ; 8.0]	[1.0 ; 2.0]	[1.0 ; 8.0]

	Median	1	2	1	1
	Q1-Q3	[1.0 ; 2.0]	[1.0 ; 3.0]	[1.0 ; 1.0]	[1.0 ; 2.0]
Costs (£) - all (Urologist/gynaecologist)	**Mean (SD)**	250.93 (180.23)	254.23 (192.86)	252.69 (186.63)	252.27 (186.22)
	Min-Max	[109.4 ; 1641.0]	[109.4 ; 1312.8]	[109.4 ; 1641.0]	[109.4 ; 1203.4]
	Median	218.8	218.8	218.8	218.8
	Q1-Q3	[109.4 ; 328.2]	[109.4 ; 328.2]	[109.4 ; 328.2]	[109.4 ; 328.2]

SD, standard deviation

7.6.2 Outpatient Physician Office Visits

All study patients had at least one all-cause physician office visit over 12 months after the first OAB/NGB diagnosis or OAB prescription date. The overall average number of visits was 67.7 (SD=42.6, median=59) and ranged from 1 to 402 visits (some patients had more than one visit a day). Patients with STK or SCI had higher average number of physician visits compared to the other underlying conditions cohorts; 76.3 (SD=44, median=67) and 75.49 (SD=54.1, median=70) visits respectively vs. 55.20 (SD=43.8, median=48), 69.67 (SD=39.4, median=62), 57.4 (SD=39.4, median=50) and (49.9 SD=35.07, median=46) visits in NGB, PD, MS and SB cohorts respectively) (Table 7.26).

Older patients (72.9 [SD=41.4], median=65) had higher cumulative number of physician office visits than those under 65 years old (mean=63.01 [SD=43.2], median=54) (Table 7.27). The mean number of visits was similar between males 67.4 (SD=42.3, median=59) and females 68.3 (SD=43.1, median=60).

The overall average total cost associated with outpatient physician office visits was £1448.39 (SD=£967.05, median= 1243.6) (Table 7.26). Costs were highest in the STK subgroup (£1627.33 [SD=£1004.93], median= £1398.1). Costs were lower in the younger

cohort with a cost of £1348.24 over 12 months, (SD=£969.96, median=£1144.9) in comparison to the older subgroup which had a total cost of £1557.20 (SD=£952.28, median= £1366.2).

Table 7.26 Number of outpatient physician office visits by underlying neurological condition subgroups

		Definitive NGB (n =363)	PD cohort (n=713)	MS cohort (n=1029)	STK cohort (n=1720)	SCI cohort (n=41)	SB cohort (n=180)	All (n=3913)
Outpatient physician office visits (all)	**≥ 1 visit n (%)**	363 (100.0 %)	713 (100.0 %)	1029 (100.0 %)	1720 (100.0 %)	41 (100.0 %)	180 (100.0 %)	3913 (100.0 %)
	Mean (SD)	55.20 (43.84)	69.67 (39.35)	57.42 (39.40)	76.29 (43.97)	75.49 (54.07)	49.93 (35.07)	67.74 (42.60)
	Min-Max	[1.0 ; 263.0]	[3.0 ; 295.0]	[1.0 ; 302.0]	[4.0 ; 402.0]	[5.0 ; 291.0]	[1.0 ; 185.0]	[1.0 ; 402.0]
	Median	48	62	50	67	70	46	59
	Q1-Q3	[22.0 ; 76.0]	[42.0 ; 92.0]	[30.0 ; 74.0]	[45.0 ; 98.0]	[38.0 ; 92.0]	[23.5 ; 65.5]	[38.0 ; 89.0]
Outpatient physician office visits (clinical)	**≥ 1 visit n (%)**	283 (78.0 %)	662 (92.8 %)	869 (84.5 %)	1623 (94.4%)	32 (78.0%)	143 (79.4 %)	3510 (89.7 %)
	Mean (SD)	3.66 (4.85)	5.06 (5.84)	3.72 (4.40)	5.83 (5.72)	4.56 (7.24)	3.70 (4.06)	4.90 (5.43)
	Min-Max	[0.0 ; 49.0]	[0.0 ; 92.0]	[0.0 ; 54.0]	[0.0 ; 52.0]	[0.0 ; 44.0]	[0.0 ; 27.0]	[0.0 ; 92.0]
	Median	2	4	3	4	3	3	3

	Q1-Q3	[1.0 ; 5.0]	[2.0 ; 7.0]	[1.0 ; 5.0]	[2.0 ; 8.0]	[1.0 ; 5.0]	[1.0 ; 5.0]	[2.0 ; 7.0]
Outpatient physician office visits (Surgery)	**≥ 1 visit n (%)**	311 (85.7 %)	702 (98.5 %)	1001 (97.3 %)	1680 (97.7%)	39 (95.1%)	165 (91.7 %)	3787 (96.8 %)
	Mean (SD)	16.14 (15.66)	21.54 (14.30)	18.01 (15.33)	22.45 (16.02)	23.07 (17.54)	15.51 (13.24)	20.50 (15.61)
	Min-Max	[0.0 ; 78.0]	[0.0 ; 92.0]	[0.0 ; 144.0]	[0.0 ; 128.0]	[0.0 ; 76.0]	[0.0 ; 80.0]	[0.0 ; 144.0]
	Median	12	19	15	19	20	13	17
	Q1-Q3	[4.0 ; 23.0]	[11.0 ; 29.0]	[8.0 ; 24.0]	[11.0 ; 30.0]	[10.0 ; 33.0]	[6.0 ; 21.0]	[10.0 ; 27.0]
Outpatient physician office visits (Home visit)	**≥ 1 visit n (%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Min-Max	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
	Median	0	0	0	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
Outpatient physician office visits (Out of hours)	**≥ 1 visit n (%)**	350 (96.4 %)	713 (100.0 %)	1024 (99.5 %)	1719 (99.9%)	41 (100.0 %)	175 (97.2 %)	3896 (99.6 %)
	Mean (SD)	28.20 (23.95)	35.28 (21.49)	29.27 (21.47)	39.33 (23.78)	40.05 (31.50)	24.67 (18.32)	34.63 (23.12)
	Min-Max	[0.0 ; 158.0]	[1.0 ; 147.0]	[0.0 ; 211.0]	[0.0 ; 198.0]	[3.0 ; 157.0]	[0.0 ; 111.0]	[0.0 ; 211.0]

	Median	23	30	24	35	34	23	30
	Q1-Q3	[11.0 ; 38.0]	[19.0 ; 46.0]	[15.0 ; 38.0]	[22.0 ; 51.0]	[19.0 ; 46.0]	[11.5 ; 33.5]	[18.0 ; 45.0]
Outpatient physician office visits (Telephone consultation)	**≥ 1 visit n (%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Min-Max	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
	Median	0	0	0	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
Outpatient physician office visits (Home visit/surgery consultation)*	**≥ 1 visit n (%)**	360 (99.2 %)	702 (98.5 %)	985 (95.7 %)	1697 (98.7%)	40 (97.6%)	173 (96.1 %)	3825 (97.8 %)
	Mean (SD)	7.20 (6.35)	7.80 (6.42)	6.42 (6.52)	8.68 (7.24)	7.80 (7.16)	6.05 (5.16)	7.71 (6.83)
	Min-Max	[0.0 ; 51.0]	[0.0 ; 67.0]	[0.0 ; 92.0]	[0.0 ; 62.0]	[0.0 ; 36.0]	[0.0 ; 39.0]	[0.0 ; 92.0]
	Median	6	6	5	7	5	5	6
	Q1-Q3	[3.0 ; 10.0]	[4.0 ; 10.0]	[2.0 ; 8.0]	[4.0 ; 11.0]	[3.0 ; 10.0]	[2.0 ; 9.0]	[3.0 ; 10.0]
Costs (£) outpatient physician office visits (all)	**Mean (SD)**	1180.75 (984.70)	1500.57 (910.55)	1217.72 (880.30)	1627.33 (1004.93)	1523.40 (1157.72)	1104.35 (809.31)	1448.39 (967.05)
	Min-Max	[45.6 ; 6529.8]	[114.4 ;	[37.0 ; 9382.2]	[45.6 ; 10776.0]	[45.6 ; 6512.0]	[37.0 ; 3924.8]	[37.0 ; 10776.0]

			8099.2]					
	Median	937.4	1333.4	1024.6	1398.1	1423	963.2	1243.6
	Q1-Q3	[456.8 ; 1617.2]	[871.6 ; 1936.8]	[617.8 ; 1584.6]	[926.2 ; 2099.9]	[763.2 ; 1953.0]	[514.1 ; 1493.6]	[776.0 ; 1887.4]

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation

* Represents acute visits and follow-up/routine visit sub-categories from Table 6.5

Table 7.27 Number of outpatient physician visits by age and sex subgroups

		[19 years – 65 years[(n=2038)	**Over 65 years (n=1875)**	**Male (n=2334)**	**Female (n=1579)**
Outpatient physician office visits	**≥ 1 visit n (%)**	2038 (100.0%)	1875 (100.0%)	2334 (100.0%)	1579 (100.0%)
	Mean (SD)	63.01 (43.18)	72.89 (41.38)	67.38 (42.28)	68.28 (43.09)
	Min-Max	[1.0 ; 402.0]	[2.0 ; 348.0]	[1.0 ; 402.0]	[1.0 ; 302.0]
	Median	54	65	59	60
	Q1-Q3	[33.0 ; 83.0]	[43.0 ; 94.0]	[37.0 ; 89.0]	[38.0 ; 88.0]
Outpatient physician office visits (Clinical)	**≥ 1 visit n (%)**	1759 (86.3%)	1751 (93.4%)	2088 (89.5%)	1422 (90.1%)
	Mean (SD)	4.26 (4.85)	5.60 (5.91)	4.86 (5.75)	4.96 (4.91)

	Min-Max	[0.0 ; 54.0]	[0.0 ; 92.0]	[0.0 ; 92.0]	[0.0 ; 49.0]
	Median	3	4	3	4
	Q1-Q3	[1.0 ; 6.0]	[2.0 ; 7.0]	[2.0 ; 6.0]	[2.0 ; 7.0]
Outpatient physician office visits (Surgery)	**≥ 1 visit n (%)**	1958 (96.1%)	1829 (97.5%)	2259 (96.8%)	1528 (96.8%)
	Mean (SD)	19.71 (16.01)	21.36 (15.12)	20.37 (15.26)	20.71 (16.11)
	Min-Max	[0.0 ; 144.0]	[0.0 ; 124.0]	[0.0 ; 128.0]	[0.0 ; 144.0]
	Median	16	19	17	17
	Q1-Q3	[8.0 ; 26.0]	[11.0 ; 28.0]	[10.0 ; 27.0]	[9.0 ; 28.0]
Outpatient physician office visits (Home visit)	**≥ 1 visit n (%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Min-Max	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
	Median	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
Outpatient physician office visits (out of hours)	**≥ 1 visit n (%)**	2021 (99.2%)	1875 (100.0%)	2326 (99.7%)	1570 (99.4%)
	Mean (SD)	31.92 (23.22)	37.57 (22.66)	34.58 (23.05)	34.71 (23.24)
	Min-Max	[0.0 ; 211.0]	[2.0 ; 198.0]	[0.0 ; 198.0]	[0.0 ; 211.0]

	Median	27	33	29	30
	Q1-Q3	[16.0 ; 42.0]	[21.0 ; 49.0]	[18.0 ; 45.0]	[19.0 ; 45.0]
Outpatient physician office visits (Telephone consultation)	**≥ 1 visit n (%)**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Min-Max	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
	Median	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]
Outpatient physician office visits (Home visit/surgery consultation)*	**≥ 1 visit n (%)**	1980 (97.2%)	1845 (98.4%)	2279 (97.6%)	1546 (97.9%)
	Mean (SD)	7.12 (6.63)	8.35 (6.97)	7.58 (6.58)	7.91 (7.17)
	Min-Max	[0.0 ; 92.0]	[0.0 ; 62.0]	[0.0 ; 67.0]	[0.0 ; 92.0]
	Median	5	6	6	6
	Q1-Q3	[3.0 ; 10.0]	[4.0 ; 11.0]	[3.0 ; 10.0]	[3.0 ; 10.0]
Costs (£) outpatient physician office visits (all)	**Mean (SD)**	1348.24 (969.96)	1557.20 (952.28)	1434.53 (959.40)	1468.89 (978.20)
	Min-Max	[37.0 ; 10776.0]	[45.6 ; 7423.6]	[37.0 ; 10776.0]	[37.0 ; 9382.2]
	Median	1144.9	1366.2	1240.1	1255.1
	Q1-Q3	[683.6 ; 1789.6]	[900.8 ; 1997.8]	[767.8 ; 1872.6]	[791.6 ; 1924.6]

SD, standard deviation
* Represents acute visits and follow-up/routine visit sub-categories from Table 6.5

7.6.3 Number of Incontinence Pad Prescriptions

Few patients were prescribed with at least one incontinence pad over 12 months after the first OAB/NGB diagnosis or OAB prescription date (14 patients overall, 0.4%). The average number of pads prescribed during a 12-month period was 5.21 pads (SD=6, median=2), and ranged from 1 pad (SD=0, median=1) in the PD cohort to 10 pads in the MS cohort (SD=7, median=10) (Table 7.28).

The overall average total cost associated with pads utilisation was £40.46 over 12 months (SD=£46.99, median=£14). Average total costs were higher in MS cohort compared to the other underlying conditions; £87.60 (SD=£49.24, median=£120), compared to £13.00 (SD=£3.61, median=£13), £8.00 (SD=£2.83, median=£8.00), £10.48 (SD=£8.10, median=£6) and £50.00 (median=£50.00) respectively in the NGB, PD, STK and SCI cohorts (Table 7.26). Total costs were higher among younger patients compared to the elderly (mean=£57.11 [SD=£51.78], median=£50) and (mean=£10.48 [SD=£8.10], median=£6) respectively), and also higher in females compared to males ((mean=£49.13 [SD=£49.83], median=£10), and (mean=£8.67 [SD=£2.31], median=£24) respectively) (Table 7.29).

Table 7.28 Number of incontinence pads prescriptions and costs by underlying neurological condition subgroups

		Definitive NGB (n=363)	**PD cohort (n=713)**	**MS cohort (n=1029)**	**STK cohort (n=1720)**	**SCI cohort (n=41)**	**SB cohort (n=180)**	**All (n=3913)**
Incontinence Pads	**≥ 1 pad n (%)**	2 (0.6%)	2 (0.3%)	5 (0.5%)	5 (0.3%)	1 (2.4%)	0 (0.0%)	14 (0.4%)

	Mean (SD)	1.50 (0.71)	1.00 (0.00)	10.00 (6.96)	3.80 (4.21)	1.00 (--)	-	5.21 (5.95)
	Min-Max	[1.0 ; 2.0]	[1.0 ; 1.0]	[2.0 ; 21.0]	[1.0 ; 11.0]	[1.0 ; 1.0]	-	[1.0 ; 21.0]
	Median	1.5	1	10	2	1	-	2
	Q1-Q3	[1.0 ; 2.0]	[1.0 ; 1.0]	[7.0 ; 10.0]	[1.0 ; 4.0]	[1.0 ; 1.0]	-	[1.0 ; 10.0]
Costs (£)	**Mean (SD)**	13.00 (4.24)	8.00 (2.83)	87.60 (49.24)	10.48 (8.10)	50.00 (--)	-	40.56 (46.99)
	Min-Max	[10.0 ; 16.0]	[6.0 ; 10.0]	[16.0 ; 126.0]	[4.4 ; 24.0]	[50.0 ; 50.0]	-	[4.4 ; 126.0]
	Median	13	8	120	6	50	-	14
	Q1-Q3	[10.0 ; 16.0]	[6.0 ; 10.0]	[56.0 ; 120.0]	[6.0 ; 12.0]	[50.0 ; 50.0]	-	[6.0 ; 56.0]

Table 7.29 Number of incontinence pads prescriptions and costs by underlying age and sex subgroups

		[19 years – 65 years[(n=2038)	**Over 65 years (n=1875)**	**Male (n=2334)**	**Female (n=1579)**
Incontinence Pads	**≥ 1 pad n (%)**	9 (0.4%)	5 (0.3%)	3 (0.1%)	11 (0.7%)
	Mean (SD)	6.00 (6.84)	3.80 (4.21)	1.00 (0.00)	6.36 (6.27)
	Min-Max	[1.0 ; 21.0]	[1.0 ; 11.0]	[1.0 ; 1.0]	[1.0 ; 21.0]
	Median	2	2	1	4
	Q1-Q3	[1.0 ; 10.0]	[1.0 ; 4.0]	[1.0 ; 1.0]	[1.0 ; 10.0]

Costs (£)	**Mean (SD)**	57.11 (51.78)	10.48 (8.10)	8.67 (2.31)	49.13 (49.83)
	Min-Max	[6.0 ; 126.0]	[4.4 ; 24.0]	[4.4 ; 126.0]	[6.0 ; 126.0]
	Median	50	6	10	24
	Q1-Q3	[10.0 ; 120.0]	[6.0 ; 12.0]	[6.0 ; 56.0]	[10.0 ; 120.0]

SD, standard deviation

7.6.4 Number of Urological Tests

Three categories of urological tests were assessed: urodynamics, cystoscopy, and other diagnostic tests (mainly imaging). Overall, 2.5%, 8.8%, and 2.1% of the population had at least 1 test of urodynamics, cystoscopy, and imaging respectively, over a 12-month follow up period (Table 7.30). The average number of urological tests performed was similar between underlying condition cohorts as well as sex and age subgroups (Table 7.31).

The cost associated with urological tests was comparable between the cohorts (generally there was no more than £100 difference). Total average costs were £178.71 (SD=93.88, median=£126), £171.11 (SD=£66.45, median=146), and £100.86 (SD=£82.89, median=£144) respectively for urodynamics, cystoscopy, and imaging tests (Table 7.30).

Table 7.30 Number of urological tests and costs by underlying neurological condition subgroups

		Definitive NGB (n =363)	**PD cohort (n=713)**	**MS cohort (n=1029)**	**STK cohort (n=1720)**	**SCI cohort (n=41)**	**SB cohort (n=180)**	**All (n=3913)**
Urodynamics	**≥1 test n (%)**	9 (2.5%)	11 (1.5%)	27 (2.6%)	51 (3.0%)	0 (0.0%)	3 (1.7%)	98 (2.5%)

	Mean (SD)	1.11 (0.33)	1.82 (0.60)	1.70 (1.07)	1.25 (0.52)	-	1.00 (0.00)	1.42 (0.75)
	Min-Max	[1.0 ; 2.0]	[1.0 ; 3.0]	[1.0 ; 5.0]	[1.0 ; 3.0]	-	[1.0 ; 1.0]	[1.0 ; 5.0]
	Median	1	2	1	1	-	1	1
	Q1-Q3	[1.0 ; 1.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 1.0]	-	[1.0 ; 1.0]	[1.0 ; 2.0]
Urodynamics costs (£)	**Mean (SD)**	140.00 (42.00)	229.09 (75.98)	214.67 (134.51)	158.12 (65.92)	-	126.00 (0.00)	178.71 (93.88)
	Min-Max	[126.0 ; 252.0]	[126.0 ; 378.0]	[126.0 ; 630.0]	[126.0 ; 378.0]	-	[126.0 ; 126.0]	[126.0 ; 630.0]
	Median	126	252	126	126	-	126	126
	Q1-Q3	[126.0 ; 126.0]	[126.0 ; 252.0]	[126.0 ; 252.0]	[126.0 ; 126.0]	-	[126.0 ; 126.0]	[126.0 ; 252.0]
Cytoscopy	**≥1 test n (%)**	55 (15.2%)	74 (10.4%)	58 (5.6%)	147 (8.5%)	4 (9.8%)	22 (12.2%)	343 (8.8%)
	Mean (SD)	1.22 (0.60)	1.14 (0.34)	1.07 (0.26)	1.23 (0.54)	1.00 (0.00)	1.18 (0.50)	1.17 (0.46)
	Min-Max	[1.0 ; 4.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 4.0]	[1.0 ; 1.0]	[1.0 ; 3.0]	[1.0 ; 4.0]
	Median	1	1	1	1	1	1	1
	Q1-Q3	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]
Cytoscopy costs (£)	**Mean (SD)**	177.85 (87.47)	165.73 (50.25)	156.07 (37.32)	179.77 (78.43)	146.00 (0.00)	172.55 (73.16)	171.11 (66.45)
	Min-Max	[146.0 ; 584.0]	[146.0 ; 292.0]	[146.0 ; 292.0]	[146.0 ; 584.0]	[146.0 ; 146.0]	[146.0 ; 438.0]	[146.0 ; 584.0]
	Median	146	146	146	146	146	146	146

	Q1-Q3	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]
Other tests (imaging)	**≥1 test n (%)**	9 (2.5%)	9 (1.3%)	24 (2.3%)	37 (2.2%)	2 (4.9%)	5 (2.8%)	83 (2.1%)
	Mean (SD)	1.00 (0.00)	1.00 (0.00)	1.13 (0.34)	1.11 (0.31)	1.00 (0.00)	1.00 (0.00)	1.08 (0.28)
	Min-Max	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 2.0]
	Median	1	1	1	1	1	1	1
	Q1-Q3	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]
Other tests (imaging) (£)	**Mean (SD)**	73.22 (72.09)	64.00 (75.89)	138.00 (79.20)	87.00 (85.20)	144.00 (0.00)	92.23 (85.03)	100.86 (82.89)
	Min-Max	[0.0 ; 144.0]	[0.0 ; 144.0]	[0.0 ; 288.0]	[0.0 ; 288.0]	[144.0 ; 144.0]	[0.0 ; 173.2]	[0.0 ; 288.0]
	Median	83	0	144	144	144	144	144
	Q1-Q3	[0.0 ; 144.0]	[0.0 ; 144.0]	[144.0 ; 144.0]	[0.0 ; 144.0]	[144.0 ; 144.0]	[0.0 ; 144.0]	[0.0 ; 144.0]

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida, SD, standard deviation

Table 7.31 Number of urological tests and costs by age and sex subgroups

		[19 years – 65 years [(n=2038)	**Over 65 years (n=1875)**	**Male (n2334)**	**Female (n=1579)**
Urodynamics	**≥1 test n (%)**	48 (2.4%)	50 (2.7%)	51 (2.2%)	47 (3.0%)
	Mean (SD)	1.52 (0.90)	1.32 (0.55)	1.18 (0.39)	1.68 (0.93)

	Min-Max	[1.0 ; 5.0]	[1.0 ; 3.0]	[1.0 ; 2.0]	[1.0 ; 5.0]
	Median	1	1	1	1
	Q1-Q3	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 1.0]	[1.0 ; 2.0]
Urodynamics costs (£)	**Mean (SD)**	191.63 (113.26)	166.32 (69.43)	148.24 (48.51)	211.79 (117.81)
	Min-Max	[126.0 ; 630.0]	[126.0 ; 378.0]	[126.0 ; 252.0]	[126.0 ; 630.0]
	Median	126	126	126	126
	Q1-Q3	[126.0 ; 252.0]	[126.0 ; 252.0]	[126.0 ; 126.0]	[126.0 ; 252.0]
Cystoscopy	**≥1 test n (%)**	154 (7.6%)	189 (10.1%)	210 (9.0%)	133 (8.4%)
	Mean (SD)	1.14 (0.43)	1.20 (0.47)	1.21 (0.51)	1.11 (0.33)
	Min-Max	[1.0 ; 3.0]	[1.0 ; 4.0]	[1.0 ; 4.0]	[1.0 ; 3.0]
	Median	1	1	1	1
	Q1-Q3	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]
Cytoscopy costs (£)	**Mean (SD)**	165.91 (62.61)	175.35 (69.30)	177.29 (75.14)	161.37 (48.43)
	Min-Max	[146.0 ; 438.0]	[146.0 ; 584.0]	[146.0 ; 584.0]	[146.0 ; 438.0]
	Median	146	146	146	146
	Q1-Q3	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]	[146.0 ; 146.0]
Other tests (imaging)	**≥1 test n (%)**	49 (2.4%)	34 (1.8%)	45 (1.9%)	38 (2.4%)
	Mean (SD)	1.10 (0.31)	1.06 (0.24)	1.11 (0.32)	1.05 (0.23)
	Min-Max	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]

	Median	1	1	1	1
	Q1-Q3	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]	[1.0 ; 1.0]
Other tests (imaging) costs (£)	**Mean (SD)**	109.78 (84.77)	88.00 (79.58)	86.83 (93.44)	117.47 (65.74)
	Min-Max	[0.0 ; 288.0]	[0.0 ; 288.0]	[0.0 ; 288.0]	[0.0 ; 288.0]
	Median	144	144	83	144
	Q1-Q3	[0.0 ; 144.0]	[0.0 ; 144.0]	[0.0 ; 144.0]	[144.0 ; 144.0]

SD, standard deviation.

7.6.5 Procedures and Operations Performed

Overall, 5.7% of the overall study patients had at least 1 procedure or operation performed during the 12-month follow up period. The proportion of patients having at least 1 procedure or operation performed was higher in SCI and NGB cohorts compared to the other conditions (17.1% and 12.1% respectively) (Table 7.32) but was comparable between age (19-65 years old=5.9% and $\geq$65 years=5.4%) and sex (males=6.2% and females=4.9%) (Table 7.33).

Average total costs associated with procedures or operations over 12 months was £2284.97 (SD=£3919.03, median=£1123) and was higher in the NGB cohort compared to the other conditions (£3407.87 (SD=£7294.86, median=£1513.4)) (Table 7.32). Average costs were higher in the elderly patients compared to those aged under 65 years old (£2678.66 (SD=£5091.57, median=£1417.7) vs. £1966.12 (SD=£2591.79, median=£1067.2)) (Table 7.33).

Table 7.32 Number of procedures and operations performed and costs by underlying neurological condition subgroup

		Definitive NGB (n =363)	PD cohort (n=713)	MS cohort (n=1029)	STK cohort (n=1720)	SCI cohort (n=41)	SB cohort (n=180)	All (n=3913)
Procedures and operations performed	**≥ 1 procedure n (%)**	44 (12.1%)	30 (4.2%)	52 (5.1%)	104 (6.0%)	7 (17.1 %)	2 (1.1%)	223 (5.7%)
	Mean (SD)	1.39 (0.78)	1.57 (0.86)	1.38 (0.57)	1.28 (0.63)	1.29 (0.49)	1.00 (0.00)	1.36 (0.67)
	Min-Max	[1.0 ; 4.0]	[1.0 ; 4.0]	[1.0 ; 3.0]	[1.0 ; 4.0]	[1.0 ; 2.0]	[1.0 ; 1.0]	[1.0 ; 4.0]
	Median	1	1	1	1	1	1	1
	Q1-Q3	[1.0 ; 1.5]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 1.0]	[1.0 ; 2.0]	[1.0 ; 1.0]	[1.0 ; 2.0]
Costs (£)	**Mean (SD)**	3407.87 (7294.86)	2035.25 (1773.86)	1999.37 (2563.90)	2471.99 (5141.95)	788.63 (504.67)	2752.34 (3143.41)	2284.97 (3919.03)
	Min-Max	[228.0 ; 47418.7]	[228.0 ; 6802.0]	[168.0 ; 14934.1]	[220.0 ; 47418.7]	[168.0 ; 1409.9]	[529.6 ; 4975.1]	[168.0 ; 47418.7]
	Median	1513.4	1528.7	1163.4	896.2	693.4	2752.3	1123
	Q1-Q3	[647.5 ; 3404.4]	[564.0 ; 3095.8]	[546.8 ; 2205.5]	[466.5 ; 2990.0]	[369.4 ; 1360.1]	[529.6 ; 4975.1]	[502.4 ; 2673.0]

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation

Table 7.33 Number of procedures and operations performed and costs by age and sex subgroups

		[19 years – 65 years[(n=2038)	Over 65 years (n=1875)	Male (n=2334)	Female (n=1579)
Procedures and operations performed	**≥1 procedure n (%)**	121 (5.9%)	102 (5.4%)	145 (6.2%)	78 (4.9%)
	Mean (SD)	1.32 (0.62)	1.41 (0.72)	1.39 (0.72)	1.32 (0.57)
	Min-Max	[1.0 ; 4.0]	[1.0 ; 4.0]	[1.0 ; 4.0]	[1.0 ; 3.0]
	Median	1	1	1	1
	Q1-Q3	[1.0 ; 1.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]
Costs (£)	**Mean (SD)**	1966.12 (2591.79)	2678.66 (5091.57)	2392.12 (4509.63)	2087.37 (2502.87)
	Min-Max	[168.0 ; 14934.1]	[220.0 ; 47418.7]	[168.0 ; 47418.7]	[168.0 ; 14934.1]
	Median	1067.2	1417.7	1073.6	1129.3
	Q1-Q3	[466.5 ; 2436.0]	[565.3 ; 3240.0]	[466.5 ; 2542.3]	[529.6 ; 2673.0]

SD, standard deviation

7.6.6 Urology Related Hospitalisations and Number of Days Admitted

Overall, 11.0% of the study population had at least one urology related hospitalisation during the 12-month follow up period. The proportion of patients having at least one hospitalisation was higher in the NGB and SCI cohorts compared to the other conditions (20.1% and 19.5% respectively) (Table 7.34) but was comparable between age and sex subgroups (Table 7.35). 1.9% of the population was hospitalised following renal failure.

The average number of days spent in hospital was 12.5 days (SD=26.6, median=3 days). The highest number of days spent in hospital was the NGB cohort (15.5 [SD=32.8], median=2) (Table 7.34). The duration was slightly lower in older patients (12.1 [SD=20.5], median=4) compared to younger patients (12.89 [SD=32.02], median=2), and the results were higher in females (12.9 [SD=28.1], median=3) than in males (11.9 [SD=24.1], median=3) (Table 7.35).

Average total hospitalisation costs over 12 months was £6256.39 (SD=£13472.85, median=£2589.9) and was higher in the NGB cohort compared to the other conditions £8052.07 (SD=£20758.98, median=£1942.5) (Table 7.34). Costs were higher in younger patients (£6879.73 [SD=15604.59], median=£2191.2) compared to older patients (£5859.29 [SD=£11193.30], median=£2952.1) and in males (£6879.73 [SD=£15604.59], median=£2798.2) compared to females (£5283.82 [SD=£9172.44], median=£2257.3).

Table 7.34 Urology related hospitalisations and costs by underlying neurological condition subgroups

		Definitive NGB (n =363)	**PD cohort (n=713)**	**MS cohort (n=1029)**	**STK cohort (n=1720)**	**SCI cohort (n=41)**	**SB cohort (n=180)**	**All (n=3913)**
Hospitalisations	**≥ 1 hospitalisation n (%)**	73 (20.1%)	78 (10.9%)	84 (8.2%)	206 (12.0%)	8 (19.5%)	12 (6.7%)	431 (11.0%)
	Mean (SD)	2.11 (1.95)	1.41 (0.89)	1.74 (1.54)	1.48 (0.87)	1.63 (1.41)	2.25 (2.22)	1.61 (1.27)
	Min-Max	[1.0 ; 11.0]	[1.0 ; 6.0]	[1.0 ; 10.0]	[1.0 ; 5.0]	[1.0 ; 5.0]	[1.0 ; 9.0]	[1.0 ; 11.0]
	Median	1	1	1	1	1	2	1
	Q1-Q3	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 1.5]	[1.0 ; 2.0]	[1.0 ; 2.0]

Hospitalised patients following renal failure	**n (%)**	6 (1.7%)	14 (2.0%)	6 (0.6%)	49 (2.8%)	0 (0.0%)	1 (0.6%)	75 (1.9%)
Number of days admitted	**Mean (SD)**	13.68 (38.39)	9.53 (14.53)	15.49 (32.79)	12.71 (23.51)	7.13 (9.55)	3.33 (6.07)	12.49 (26.61)
	Min-Max	[0.0 ; 223.0]	[0.0 ; 79.0]	[0.0 ; 140.0]	[0.0 ; 172.0]	[0.0 ; 28.0]	[0.0 ; 20.0]	[0.0 ; 223.0]
	Median	1	3	2	4	3.5	1	3
	Q1-Q3	[0.0 ; 8.0]	[0.0 ; 14.0]	[0.0 ; 7.0]	[0.0 ; 15.0]	[1.0 ; 10.0]	[0.0 ; 2.5]	[0.0 ; 13.0]
Hospitalisations costs (£)	**Mean (SD)**	8052.07 (20758.98)	5884.71 (8486.26)	6226.29 (14321.03)	5913.75 (11056.11)	2448.83 (2630.18)	7216.55 (15368.58)	6256.39 (13472.85)
	Min-Max	[264.8 ; 163720.3]	[220.0 ; 50521.2]	[162.0 ; 83316.8]	[162.0 ; 134884.6]	[220.0 ; 8335.2]	[264.8 ; 55306.3]	[162.0 ; 163720.3]
	Median	1942.5	2604.3	1793.6	3146.4	1647.8	2134.4	2589.9
	Q1-Q3	[866.3 ; 6663.7]	[738.9 ; 6791.1]	[564.0 ; 4049.1]	[1004.7 ; 7396.3]	[742.6 ; 3127.3]	[734.8 ; 6505.9]	[738.9 ; 6663.7]

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation

Table 7.35 Urology related hospitalisations and costs by age and sex subgroups

		[19 years – 65 years[(n=2038)	**Over 65 years (n=1875)**	**Male (n=2334)**	**Female (n=1579)**
Hospitalisations	**≥ 1 hospitalisation n (%)**	207 (10.2%)	224 (11.9%)	262 (11.2%)	169 (10.7%)

	Mean (SD)	1.80 (1.56)	1.43 (0.88)	1.62 (1.30)	1.59 (1.22)
	Min-Max	[1.0 ; 11.0]	[1.0 ; 6.0]	[1.0 ; 11.0]	[1.0 ; 10.0]
	Median	1	1	1	1
	Q1-Q3	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]	[1.0 ; 2.0]
Hospitalised following renal failure	**n (%)**	30 (1.5%)	45 (2.4%)	54 (2.3%)	21 (1.3%)
Number of admitted days	**Mean**	12.89 (32.02)	12.13 (20.45)	12.91 (28.14)	11.85 (24.13)
	Min-Max	[0.0 ; 223.0]	[0.0 ; 140.0]	[0.0 ; 223.0]	[0.0 ; 140.0]
	Median	2	4	3	3
	Q1-Q3	[0.0 ; 8.0]	[0.0 ; 15.5]	[0.0 ; 13.0]	[0.0 ; 11.0]
Hospitalisations costs (£)	**Mean (SD)**	6686.57 (15588.16)	5859.29 (11193.30)	6879.73 (15604.59)	5283.82 (9172.44)
	Min-Max	[162.0 ; 163720.3]	[162.0 ; 134884.6]	[162.0 ; 163720.3]	[162.0 ; 80324.5]
	Median	2191.2	2952.1	2798.2	2257.3
	Q1-Q3	[647.5 ; 6837.9]	[933.0 ; 6245.0]	[724.4 ; 6791.1]	[794.4 ; 6151.4]

* Represents acute visits and follow-up/routine visit sub-categories from Table 6.5
SD, standard deviation

7.6.7 Overall costs

The overall costs over 12 months was £2395.03 (SD=£5412.9, median=£1458.2). Costs were highest in the NGB cohort £3378.92 (SD=£10676.34, median=£1308), and lowest in the SB cohort £1756.61 (SD=£4346.80, median=£1182) (Table 7.36). Costs were higher in males £2488.28 (SD=6200.39, median=1458.2) than in females £2257.21 (SD=£3971.53, median= £1461.8) and comparable between the 19-65 years subgroup (£2268.61 [SD=£5804.00],

median=£1340) and the ≥65 years subgroup (£2532.48 [SD=£4950.70], median=£1578.1) (Table 7.37).

Table 7.36 Total costs (£) within 12 months after the first OAB/NGB diagnosis or OAB prescription date by underlying conditions subgroups

		Definitive NGB (n=363)	PD cohort (n=713)	MS cohort (n=1029)	STK cohort (n=1720)	SCI cohort (n=41)	SB cohort (n=180)	All (n=3913)
Total costs	**Mean (SD)**	3378.92 (10676.34)	2355.86 (3849.67)	1923.18 (5033.87)	2624.23 (4944.17)	2290.28 (2025.19)	1756.61 (4346.80)	2395.03 (5412.98)
	Min-Max	[45.6 ; 166644.4]	[160.0 ; 59695.7]	[37.0 ; 94393.2]	[45.6 ; 137793.8]	[119.6 ; 10171.4]	[37.0 ; 57354.3]	[37.0 ; 166644.4]
	Median	1308	1546.2	1180.1	1666.6	1858.2	1182	1458.2
	Q1-Q3	[651.4 ; 2524.7]	[986.0 ; 2346.2]	[697.9 ; 1910.5]	[1057.4 ; 2645.8]	[949.0 ; 2703.3]	[684.5 ; 1842.7]	[896.1 ; 2360.9]

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation

Table 7.37 Total costs (£) within 12 months after the first OAB/NGB diagnosis or OAB prescription date by age and sex subgroups

		[19 years – 65 years[(N=2038)	Over 65 years (N=1875)	Male (N=2334)	Female (N=1579)
Total	**Mean (SD)**	2268.61 (5804.00)	2532.48 (4950.70)	2257.21 (3971.53)	2488.28 (6200.39)

costs	**Min-Max**	[37.0 ; 166644.4]	[45.6 ; 137793.8]	[37.0 ; 90610.2]	[37.0 ; 166644.4]
	Median	1340	1578.1	1461.8	1455.8
	Q1-Q3	[790.8 ; 2205.0]	[1023.0 ; 2485.6]	[889.6 ; 2376.1]	[900.0 ; 2357.6]

SD, standard deviation

7.7 Sensitivity Analyses

In this section, results of sensitivity analysis are presented, where patients were included into the study via a broader definition of NGB (Section 6.4.15).

7.7.1 Patient Inclusion and Sub-Cohorts

Comparisons between patient inclusion in the study as well as sub-cohorts between the base case (BC) and the sensitivity analysis (SA) are provided in Table 7.38 and Table 7.39. Overall, 4930 patients were included in the SA, patient inclusion proportions in the study was similar to the BC.

Table 7.38 Patient inclusion into the study- base case vs sensitivity analysis

Selection criteria	**Included (BC)**	**Included (SA)**
1) Source cohort: NGB/probable NGB between 01/01/2004 and 31/12/2016	19499	24373
2) Be ≥19 years at index date	18901	23776
3) 12-month pre-index period, without NGB/OAB/Rx	13841	16963
4) 12-month follow-up period, post NGB/OAB/Rx	16804	21315
5) Referral to urologist within the 12-month pre-index/follow-up period	7553	9220

6) Idiopathic OAB	19445	24319
7) Diagnosis of dementia within the selection period	17060	21153
Final selection	3913	4930

NGB, neurogenic bladder; OAB, overactive bladder; Rx, prescription; BC, base case; SA, sensitivity analysis

The proportion of sub-cohorts was similar between the BC and SA, with a slightly higher proportion of definitive NGB and SB cohort in the BC analysis.

Table 7.39 Sub-cohorts – base case vs sensitivity analysis

Subgroup	**Study cohort – BC (n=3913)**	**Study cohort –SA (n=4930)**
Definitive NGB	363 (9.3%)	365 (7.4%)
PD cohort	713 (18.2%)	927 (18.8%)
MS cohort	1029 (26.3%)	1175 (23.8%)
STK cohort	1720 (44.0%)	2370 (48.1%)
SCI cohort	41 (1.0%)	48 (1.0%)
SB cohort	180 (4.6%)	181 (3.7%)

BC, base case; SA, sensitivity analysis NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida

7.7.2 Patient Characteristics

Patient characteristics for the SA for study cohorts and subgroups are summarised in Table 7.40 and Table 7.41.

Patient demographic and clinical characteristics in the SA were similar to the BC population characteristics:

- Overall, the average age was 64.3 years (SD=16.4) which was similar to the BC (61.7 years (SD=16.3) and the distribution amongst neurological disease sub-cohorts and age and sex subgroups also proved to be similar.
- Count of chronic diseases from the QOF within the 12-month pre-index period was 0.78 in SA compared to 0.73 in the BC.
- Comorbidity described by BNF headers was also similar (9.6 in the SA vs 8.6 in the BC).
- Mean polypharmacy was 5.8 in the SA compared to in the BC 5.4.
- Average ACB score in the SA population was 6.41 (5.52), compared to 6.59 (5.85) for the BC, which is a comparable result.
- As in the BC, the majority of patients did not have anticholinergic drugs prescription in the 12-month pre-index period (73.3% vs. 72.4 in the BC analysis).

Table 7.40 Population demographic and clinical characteristics, overall and by study sub-cohorts – sensitivity analyses

Characteristics		**Definitive NGB n=365**	**PD Cohort n=927**	**MS Cohort n=1029**	**STK Cohort n=1175**	**SCI Cohort n=48**	**SB Cohort n=181**	**All n=4930**
Age at index-date	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	48.35 (15.88)	72.21 (9.45)	50.05 (12.46)	72.02 (11.74)	48.27 (15.68)	36.19 (11.94)	64.28 (16.37)
	Median	[19.0 ; 87.0]	[31.0 ; 96.0]	[19.0 ; 90.0]	[20.0 ; 98.0]	[20.0 ; 91.0]	[19.0 ; 76.0]	[19.0 ; 98.0]
	Min-Max	48	73	50	74	49	35	67
	Q1-Q3	[37.0 ; 60.0]	[67.0 ; 79.0]	[41.0 ; 58.0]	[65.0 ; 81.0]	[34.5 ; 58.5]	[26.0 ; 44.0]	[53.0 ; 77.0]
Count of chronic	**No. of valid values**	365	927	1175	2370	48	181	4930

diseases from the QOF within the 12-month pre-index period	**Mean (SD)**	0.29 (0.59)	0.27 (0.59)	0.17 (0.46)	1.38 (0.73)	0.25 (0.56)	0.21 (0.47)	0.78 (0.86)
	Median	[0.0 ; 3.0]	[0.0 ; 4.0]	[0.0 ; 3.0]	[0.0 ; 6.0]	[0.0 ; 2.0]	[0.0 ; 2.0]	[0.0 ; 6.0]
	Min-Max	0	0	0	1	0	0	1
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[1.0 ; 2.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 1.0]
Number of distinct BNF headers Within the 12-month pre-index period (Comorbidity)	**Valid values**	365	927	1175	2370	48	181	4930
	0	78 (21.4%)	80 (8.6%)	220 (18.7%)	272 (11.5%)	11 (22.9%)	16 (8.8%)	641 (13.0%)
	1-3	43 (11.8%)	91 (9.8%)	254 (21.6%)	177 (7.5%)	11 (22.9%)	27 (14.9%)	581 (11.8%)
	4-7	53 (14.5%)	222 (23.9%)	255 (21.7%)	497 (21.0%)	6 (12.5%)	35 (19.3%)	1052 (21.3%)
	8-19	144 (39.5%)	420 (45.3%)	334 (28.4%)	1096 (46.2%)	14 (29.2%)	75 (41.4%)	2037 (41.3%)
	20 +	47 (12.9%)	114 (12.3%)	112 (9.5%)	328 (13.8%)	6 (12.5%)	28 (15.5%)	619 (12.6%)
	Mean (Sd)	9.57 (9.06)	10.36 (7.78)	7.63 (8.28)	10.64 (8.13)	8.83 (10.12)	10.97 (8.89)	9.85 (8.30)
	Min-Max	[0.0 ; 45.0]	[0.0 ; 54.0]	[0.0 ; 45.0]	[0.0 ; 73.0]	[0.0 ; 41.0]	[0.0 ; 42.0]	[0.0 ; 73.0]
	Median	8	9	5	10	5	9	8
	Q1-Q3	[2.0 ; 14.0]	[5.0 ; 15.0]	[2.0 ; 11.0]	[5.0 ; 15.0]	[1.0 ; 15.5]	[4.0 ; 16.0]	[4.0 ; 14.0]
Polypharmacy[1] at index-date (Using BNF headers)	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	5.49 (5.68)	6.20 (4.79)	4.29 (4.76)	6.34 (4.89)	5.33 (6.21)	6.34 (5.87)	5.80 (5.01)
	Median	[0.0 ; 30.0]	[0.0 ; 29.0]	[0.0 ; 30.0]	[0.0 ; 37.0]	[0.0 ; 21.0]	[0.0 ; 31.0]	[0.0 ; 37.0]
	Min-Max	4	5	3	6	2.5	5	5
	Q1-Q3	[1.0 ; 9.0]	[3.0 ; 9.0]	[1.0 ; 6.0]	[3.0 ; 9.0]	[0.0 ; 9.0]	[2.0 ; 9.0]	[2.0 ; 9.0]
Polypharmacy[1] at index-date (Using BNF headers)	**Valid values**	365	927	1175	2370	48	181	4930
	0	89 (24.4%)	93 (10.0%)	267 (22.7%)	386 (16.3%)	18 (37.5%)	19 (10.5%)	830 (16.8%)
	1-3	81 (22.2%)	213 (23.0%)	409 (34.8%)	344 (14.5%)	7 (14.6%)	51 (28.2%)	1071 (21.7%)
	4-7	85 (23.3%)	329 (35.5%)	258 (22.0%)	775 (32.7%)	7 (14.6%)	56 (30.9%)	1482 (30.1%)
	8-19	101 (27.7%)	278 (30.0%)	223 (19.0%)	834 (35.2%)	15 (31.3%)	49 (27.1%)	1471 (29.8%)
	≥20	9 (2.5%)	14 (1.5%)	18 (1.5%)	31 (1.3%)	1 (2.1%)	6 (3.3%)	76 (1.5%)

Polypharmacy[1] at index-date (Using substances)	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	4.64 (4.94)	6.13 (4.53)	3.76 (4.02)	6.17 (4.64)	4.33 (5.34)	5.38 (4.78)	5.49 (4.62)
	Median	[0.0 ; 26.0]	[0.0 ; 25.0]	[0.0 ; 25.0]	[0.0 ; 28.0]	[0.0 ; 18.0]	[0.0 ; 24.0]	[0.0 ; 28.0]
	Min-Max	3	5	3	6	2	4	5
	Q1-Q3	[0.0 ; 7.0]	[3.0 ; 9.0]	[1.0 ; 6.0]	[3.0 ; 9.0]	[0.0 ; 7.0]	[2.0 ; 8.0]	[2.0 ; 8.0]
Polypharmacy[1] at index-date (Using substances)	**Valid values**	365	927	1175	2370	48	181	4930
	0	98 (26.8%)	94 (10.1%)	275 (23.4%)	390 (16.5%)	19 (39.6%)	21 (11.6%)	852 (17.3%)
	1-3	94 (25.8%)	200 (21.6%)	418 (35.6%)	347 (14.6%)	9 (18.8%)	57 (31.5%)	1087 (22.0%)
	4-7	85 (23.3%)	336 (36.2%)	294 (25.0%)	782 (33.0%)	10 (20.8%)	56 (30.9%)	1536 (31.2%)
	8-19	84 (23.0%)	288 (31.1%)	183 (15.6%)	834 (35.2%)	10 (20.8%)	44 (24.3%)	1419 (28.8%)
	≥20	4 (1.1%)	9 (1.0%)	5 (0.4%)	17 (0.7%)	0 (0.0%)	3 (1.7%)	36 (0.7%)
ACB score[2]	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	2.88 (4.51)	6.62 (5.56)	5.99 (4.80)	7.07 (5.77)	6.71 (6.74)	4.57 (4.65)	6.41 (5.52)
	Median	[0.0 ; 37.0]	[0.0 ; 57.0]	[0.0 ; 69.0]	[0.0 ; 66.0]	[0.0 ; 37.0]	[0.0 ; 33.0]	[0.0 ; 69.0]
	Min-Max	0	6	5	6	5	3	6
	Q1-Q3	[0.0 ; 5.0]	[3.0 ; 8.0]	[3.0 ; 7.0]	[3.0 ; 9.0]	[3.0 ; 9.0]	[3.0 ; 6.0]	[3.0 ; 8.0]
Number of patients on anticholinergic drugs within the 12-month pre-index period	**No. of valid values**	365	927	1175	2370	48	181	4930
	0	272 (74.5%)	568 (61.3%)	775 (66.0%)	2014 (85.0%)	37 (77.1%)	45 (24.9%)	3616 (73.3%)
	1	45 (12.3%)	163 (17.6%)	177 (15.1%)	139 (5.9%)	6 (12.5%)	62 (34.3%)	574 (11.6%)
	2	17 (4.7%)	87 (9.4%)	100 (8.5%)	64 (2.7%)	3 (6.3%)	28 (15.5%)	290 (5.9%)
	3	11 (3.0%)	42 (4.5%)	45 (3.8%)	30 (1.3%)	1 (2.1%)	19 (10.5%)	143 (2.9%)
	4+	20 (5.5%)	67 (7.2%)	78 (6.6%)	123 (5.2%)	1 (2.1%)	27 (14.9%)	307 (6.2%)

NGB, neurogenic bladder; PD, Parkinson's disease; MS, Multiple Sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation; ACB, Anticholinergic Cognitive Burden; BNF, British

National Formulary; QoF, Quality Outcomes Framework

[1]Polypharmacy was defined as the number of distinct BNF headers/ drug substances (including non-NGB/OAB drugs) in the therapy dataset

[2]The ACB score was calculated within 1 month before and after the first OAB/NGB diagnosis or OAB prescription date (date 'd'). For patients with no anticholinergic prescriptions between 1 month before/after date 'd': ACB score=0

Table 7.41 Population demographic and clinical characteristics, age and sex subgroups – sensitivity analyses

Characteristics		**[19 years – 65 years[n=2038**	**Over 65 years n=1875**	**Male n=2334**	**Female n=1579**
Age at index-date	**No. of valid values**	2249	2681	2980	1950
	Mean (SD)	49.56 (11.57)	76.62 (6.81)	67.30 (14.95)	59.65 (17.34)
	Median	[19.0 ; 65.0]	[66.0 ; 98.0]	[19.0 ; 98.0]	[19.0 ; 97.0]
	Min-Max	52	76	70	60
	Q1-Q3	[42.0 ; 59.0]	[71.0 ; 82.0]	[59.0 ; 78.0]	[47.0 ; 74.0]
Count of chronic diseases from the QOF Within the 12-month pre-index period	**No. of valid values**	2249	2681	2980	1950
	Mean (SD)	0.50 (0.75)	1.01 (0.88)	0.85 (0.87)	0.68 (0.83)
	Median	[0.0 ; 5.0]	[0.0 ; 6.0]	[0.0 ; 6.0]	[0.0 ; 5.0]
	Min-Max	0	1	1	0
	Q1-Q3	[0.0 ; 1.0]	[0.0 ; 1.0]	[0.0 ; 1.0]	[0.0 ; 1.0]
Number of distinct BNF headers Within the 12-month pre-index period	**Valid values**	2249	2681	2980	1950
	0	422 (18.8%)	219 (8.2%)	371 (12.4%)	270 (13.8%)
	1-3	414 (18.4%)	167 (6.2%)	354 (11.9%)	227 (11.6%)
	4-7	480 (21.3%)	572 (21.3%)	677 (22.7%)	375 (19.2%)
	8-19	722 (32.1%)	1315 (49.0%)	1256 (42.1%)	781 (40.1%)
	20 +	211 (9.4%)	408 (15.2%)	322 (10.8%)	297 (15.2%)
	Mean (Sd)	7.39 (7.71)	9.96 (7.34)	8.33 (7.16)	9.05 (8.29)
	Min-Max	[0.0 ; 51.0]	[0.0 ; 56.0]	[0.0 ; 46.0]	[0.0 ; 56.0]
	Median	5	9	7	7
	Q1-Q3	[1.0 ; 11.0]	[5.0 ; 14.0]	[3.0 ; 12.0]	[3.0 ; 13.0]
Polypharmacy[1] at index-date	**No. of valid values**	2249	2681	2980	1950

(Using BNF headers)	**Mean (SD)**	4.73 (5.03)	6.69 (4.81)	5.83 (4.90)	5.75 (5.18)
	Median	[0.0 ; 37.0]	[0.0 ; 29.0]	[0.0 ; 37.0]	[0.0 ; 30.0]
	Min-Max	3	6	5	5
	Q1-Q3	[1.0 ; 7.0]	[3.0 ; 10.0]	[2.0 ; 9.0]	[1.0 ; 9.0]
Polypharmacy[1] at index-date (Using BNF headers)	**Valid values**	2249	2681	2980	1950
	0	513 (22.8%)	317 (11.8%)	486 (16.3%)	344 (17.6%)
	1-3	649 (28.9%)	422 (15.7%)	621 (20.8%)	450 (23.1%)
	4-7	578 (25.7%)	904 (33.7%)	942 (31.6%)	540 (27.7%)
	8-19	469 (20.9%)	1002 (37.4%)	893 (30.0%)	578 (29.6%)
	≥20	40 (1.8%)	36 (1.3%)	38 (1.3%)	38 (1.9%)
Polypharmacy[1] at index-date (Using substances)	**No. of valid values**	2249	2681	2980	1950
	Mean (SD)	4.35 (4.50)	6.45 (4.51)	5.54 (4.49)	5.42 (4.81)
	Median	[0.0 ; 28.0]	[0.0 ; 25.0]	[0.0 ; 28.0]	[0.0 ; 26.0]
	Min-Max	3	6	5	5
	Q1-Q3	[1.0 ; 7.0]	[3.0 ; 9.0]	[2.0 ; 8.0]	[1.0 ; 8.0]
Polypharmacy[1] at index-date (Using substances)	**Valid values**	2249	2681	2980	1950
	0	533 (23.7%)	319 (11.9%)	497 (16.7%)	355 (18.2%)
	1-3	655 (29.1%)	432 (16.1%)	626 (21.0%)	461 (23.6%)
	4-7	605 (26.9%)	931 (34.7%)	975 (32.7%)	561 (28.8%)
	8-19	437 (19.4%)	982 (36.6%)	865 (29.0%)	554 (28.4%)
	≥20	19 (0.8%)	17 (0.6%)	17 (0.6%)	19 (1.0%)
ACB score[2]	**No. of valid values**	2249	2681	2980	1950
	Mean (SD)	6.20 (5.79)	6.58 (5.27)	6.29 (5.29)	6.59 (5.85)
	Median	[0.0 ; 69.0]	[0.0 ; 66.0]	[0.0 ; 64.0]	[0.0 ; 69.0]
	Min-Max	5	6	6	6
	Q1-Q3	[3.0 ; 8.0]	[3.0 ; 8.0]	[3.0 ; 8.0]	[3.0 ; 8.0]
Number of patients on anticholinergic drugs within the 12-month pre-index period	**No. of valid values**	2249	2681	2980	1950
	0	1545 (68.7%)	2071 (77.2%)	2246 (75.4%)	1370 (70.3%)
	1	321 (14.3%)	253 (9.4%)	334 (11.2%)	240 (12.3%)
	2	163 (7.2%)	127 (4.7%)	149 (5.0%)	141 (7.2%)

	3	84 (3.7%)	59 (2.2%)	81 (2.7%)	62 (3.2%)
	4+	136 (6.0%)	171 (6.4%)	170 (5.7%)	137 (7.0%)

SD, standard deviation, ACB, Anticholinergic Cognitive Burden; BNF, British National Formulary; QoF, Quality Outcomes Framework

[1]Polypharmacy was defined as the number of distinct BNF headers/ drug substances (including non-NGB/OAB drugs) in the therapy dataset

[2]The ACB score was calculated within 1 month before and after the first OAB/NGB diagnosis or OAB prescription date (date 'd'). For patients with no anticholinergic prescriptions between 1 month before/after date 'd': ACB score=0

7.7.3 Drug Utilisation

The results for the SA drug utilisation are presented in Table 7.42 and 7.43. the results are similar to the BC findings.

- The number of OAB prescriptions in the SA were 6.3 which is comparable to the BC where it was 6.9.
- The cumulative days' supply in the SA was 187.91, which is slightly less than the BC result, where the days' supply was 202.9.
- Combination use was slightly lower in the SA (7.6%) compared to the BC (8%)
- The average number of UTI and 5-ARI or α-blockers prescriptions were very similar in the SA (2.2 and 2.6 respectively) compared to the BC (2.2 and 2.9 respectively).

Table 7.42 Drug utilisation within 12 months after the first OAB/NGB diagnosis or OAB prescription date, overall and by underlying conditions sub-cohorts – Sensitivity analysis

Characteristics		**Definitive NGB n=365**	**PD Cohort n=927**	**MS Cohort n=1175**	**STK Cohort n=2370**	**SCI Cohort n=48**	**SB Cohort n=181**	**All n=4930**
Number of OAB	**No. of valid values**	365	927	1175	2370	48	181	4930

prescriptions	**Mean (SD)**	1.61 (3.54)	6.88 (7.55)	6.87 (7.13)	6.44 (8.24)	8.10 (5.90)	4.98 (6.28)	6.32 (7.69)
	Min-Max	[0.0 ; 21.0]	[0.0 ; 55.0]	[0.0 ; 64.0]	[0.0 ; 104.0]	[0.0 ; 24.0]	[0.0 ; 52.0]	[0.0 ; 104.0]
	Median	0	5	6	4	8.5	3	4
	Q1-Q3	[0.0 ; 1.0]	[1.0 ; 11.0]	[2.0 ; 10.0]	[1.0 ; 9.0]	[1.0 ; 13.0]	[1.0 ; 8.0]	[1.0 ; 10.0]
Number of OAB prescriptions	**Valid values**	365	927	1175	2370	48	181	4930
	0	255 (69.9%)	14 (1.5%)	46 (3.9%)	46 (1.9%)	5 (10.4%)	44 (24.3%)	339 (6.9%)
	1-4	58 (15.9%)	442 (47.7%)	484 (41.2%)	1217 (51.4%)	10 (20.8%)	64 (35.4%)	2244 (45.5%)
	5-9	32 (8.8%)	200 (21.6%)	306 (26.0%)	529 (22.3%)	13 (27.1%)	32 (17.7%)	1095 (22.2%)
	10-14	14 (3.8%)	207 (22.3%)	269 (22.9%)	419 (17.7%)	14 (29.2%)	37 (20.4%)	947 (19.2%)
	15-44	6 (1.6%)	54 (5.8%)	58 (4.9%)	129 (5.4%)	6 (12.5%)	3 (1.7%)	252 (5.1%)
	45+	0 (0.0%)	10 (1.1%)	12 (1.0%)	30 (1.3%)	0 (0.0%)	1 (0.6%)	53 (1.1%)
Cumulative numbers of days' supply of OAB drugs	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	51.84 (113.99)	203.39 (193.12)	216.51 (186.20)	184.62 (212.85)	245.77 (168.12)	155.11 (155.18)	187.91 (200.09)
	Min-Max	[0.0 ; 637.7]	[0.0 ; 3392.0]	[0.0 ; 3177.0]	[0.0 ; 6956.0]	[0.0 ; 532.0]	[0.0 ; 447.6]	[0.0 ; 6956.0]
	Median	0	168	196	120	312	90	121.3
	Q1-Q3	[0.0 ; 30.0]	[42.0 ; 360.0]	[56.0 ; 364.0]	[30.0 ; 336.0]	[43.0 ; 392.0]	[28.0 ; 330.0]	[30.0 ; 336.0]
Cumulative numbers of	**Valid values**	365	927	1175	2370	48	181	4930

days' supply of OAB drugs	**0-29**	272 (74.5%)	148 (16.0%)	189 (16.1%)	459 (19.4%)	9 (18.8%)	66 (36.5%)	1063 (21.6%)
	30-119	40 (11.0%)	275 (29.7%)	290 (24.7%)	725 (30.6%)	6 (12.5%)	34 (18.8%)	1351 (27.4%)
	120-349	33 (9.0%)	253 (27.3%)	359 (30.6%)	656 (27.7%)	15 (31.3%)	45 (24.9%)	1341 (27.2%)
	350-549	19 (5.2%)	238 (25.7%)	320 (27.2%)	505 (21.3%)	18 (37.5%)	36 (19.9%)	1119 (22.7%)
	≥550	1 (0.3%)	13 (1.4%)	17 (1.4%)	25 (1.1%)	0 (0.0%)	0 (0.0%)	56 (1.1%)
OAB combination use (yes/no)	**Yes: n (%)**	12 (3.3%)	71 (7.7%)	122 (10.4%)	161 (6.8%)	2 (4.2%)	11 (6.1%)	373 (7.6%)
Number of antibiotics prescriptions for UTI	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	2.70 (4.24)	1.67 (3.28)	2.33 (4.17)	2.10 (3.84)	3.04 (4.61)	3.13 (6.20)	2.15 (3.97)
	Min-Max	[0.0 ; 24.0]	[0.0 ; 44.0]	[0.0 ; 36.0]	[0.0 ; 46.0]	[0.0 ; 18.0]	[0.0 ; 59.0]	[0.0 ; 59.0]
	Median	1	0	1	1	0	1	1
	Q1-Q3	[0.0 ; 4.0]	[0.0 ; 2.0]	[0.0 ; 3.0]	[0.0 ; 2.0]	[0.0 ; 6.0]	[0.0 ; 4.0]	[0.0 ; 2.0]
Number of α-blockers or 5-ARI's prescriptions	**No. of valid values**	365	927	1175	2370	48	181	4930
	Mean (SD)	0.84 (2.86)	4.10 (9.33)	0.57 (2.48)	3.67 (8.51)	0.54 (3.47)	0.63 (2.69)	2.75 (7.47)
	Min-Max	[0.0 ; 25.0]	[0.0 ; 106.0]	[0.0 ; 29.0]	[0.0 ; 108.0]	[0.0 ; 24.0]	[0.0 ; 23.0]	[0.0 ; 108.0]
	Median	0	0	0	0	0	0	0
	Q1-Q3	[0.0 ; 0.0]	[0.0 ; 6.0]	[0.0 ; 0.0]	[0.0 ; 5.0]	[0.0 ; 0.0]	[0.0 ; 0.0]	[0.0 ; 1.0]

NGB, neurogenic bladder; PD, Parkinson's disease; MS, multiple sclerosis; STK, stroke; SCI, spinal cord injuries; SB, spina bifida; SD, standard deviation; OAB, overactive bladder; UTI, urinary tract infection; 5-ARI, 5α-reductase inhibitors

7.8 Chapter Summary

Results from an epidemiological study, designed to characterise the NGB patient population using data from the CPRD database were presented in this chapter. The results, which were purely descriptive, provided a concise overview on many pertinent aspects of NGB.

The age of patients was varied and there were slightly more individuals aged between 19-65, as well as more men (59.6%). The mean comorbidity was 8.6 BNF headers over 12 months. The average polypharmacy was described by an average of 5.2 BNF headers per patient and the average ACB score was 6.6. Solifenacin, oxybutynin and tolterodrine were the most prescribed drugs at index date. Around 54% of the population were prescribed antibiotics for UTI, as well as 25.5% of patients prescribed 5-ARI's or α-adrenergic antagonists. The most frequent form of HRU was outpatient physician visits (mean 67.4 visits a year), and the highest cost was for hospitalisations (mean=£6256.39 [SD=£13472.85], median=£2589.9). The next chapter will discuss these results in more detail, contextualising these findings with evidence from the literature.

8) Chapter Eight – Clinical Practice Research Datalink Study – Discussion

8.1 Introduction

The previous chapter presented the results from a descriptive, retrospective study, with the aim of characterising patients with neurogenic bladder (NGB), their drug utilisation patterns and the economic burden of their condition using data from the Clinical Practice Research Datalink (CPRD) database in the UK. This chapter will discuss the results, providing interpretation in the context of other relevant literature as well as comparing the results to the recommendations in the prominent clinical guidelines (CGs) for NGB, namely those from the National Institute for Health and Care Excellence (NICE), the European Association of Urology (EAU) and the International Consultation on Incontinence (ICI). Due to the lack of comparison data in NGB, estimates from the overactive bladder (OAB) population are occasionally used to contextualise the findings, although it should always be kept in mind that these are two distinct disease areas.

8.2 Sub-Optimal Diagnosis/Coding of Neurogenic Bladder

Diagnosis error is defined as 'the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient' (Institute of Medicine [IOM], 2015: 4). The first and perhaps one of the most critical findings from the CPRD study is the exceptionally high rates of potential diagnosis error (type a) in NGB. Between 1st January 2004 and 31st December 2015, only 967 patients with a Read coded diagnosis of NGB were identified (Section 6.3.6).

In light of the high prevalence of NGB documented in the literature (Section 2.2.3), it seemed improbable that 967 patients were truly representative of the UK NGB population, especially considering the wide twelve-year search window that was employed in this study. For example, in the UK, 126,893 individuals were diagnosed with Parkinson's disease (PD) in 2009 and estimates suggest that 27-63.9% of this population experience bladder dysfunction (Parkinson's UK, 2009; Ruffion et al., 2013). By conducting a very crude estimate, at the least there were 34,261 individuals with NGB secondary to PD in 2009, and

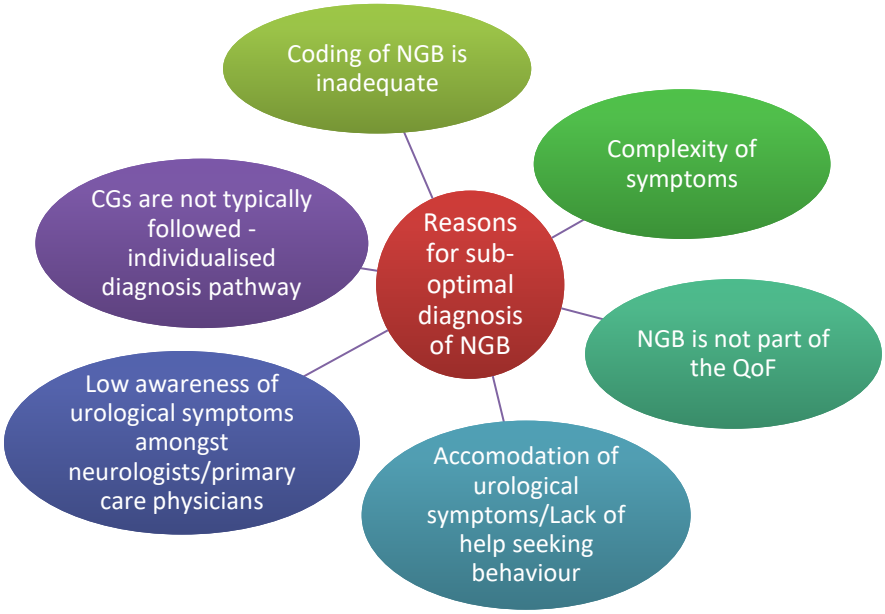
this is just one segment of the broader NGB population. Moreover, a study using the General Practice Research Database (GPRD) database also identified a low frequency of NGB patients (69 patients between the years of 1987 to 2004), further compounding the suspicion that there could be an intrinsic problem in the diagnosis of NGB in the UK (Odeyemi et al., 2006).

A lack of clear diagnosis adds ambiguity to patient characterisation, treatment pathways and complicates future research endevours. Therefore, it is not infeasible to suggest that inadequate diagnosis in NGB could be associated to the high rates of polypharmacy, anticholinergic burden and healthcare resource utilisation (HRU) rates observed in the study, as most patients were identified via a proxy measure, thus may not be managed through the correct care pathways. A correct diagnosis is essential for patients to access appropriate services and the right medical treatments, which subsequently improves their chances of optimal health outcomes as well as reducing healthcare costs.

Diagnosis error is a common occurrence but woefully understudied, partly because there are few valid and reliable techniques that can enable identification of delayed or missed diagnosis (Balogh, 2015). Sub-optimal diagnosis has been identified in multiple chronic disease areas, including in lung cancer, ovarian and cervical cancer, type 2 diabetes mellitus, meningitis and ischaemic heart disease via methods such as retrospective analysis of lab tests, measuring disease progression versus time of diagnosis and clinician surveys (Drivsholm and Olivarius, 2006; Esmail, 2004; Mitchell, 2009; Balogh, 2015). Identifying the potential reasons and failures that led to the low diagnosis rates helps to pave the way for system improvements, as well as providing essential learning information for those accountable in the diagnostic process (Balogh, 2015). Two possible rationalisations for low NGB diagnosis rates are explored in more detail within the following sections, these are: (1) the coding of NGB is inadequate, and (2) diagnosis of NGB is insufficient in UK clinical practice.

8.2.1 Methods

Two methods were used to interpret the rates of NGB diagnosis uncovered from the feasibility analysis and ascertain possible rationalisations. Firstly, two urological experts were invited to participate in short interviews where they were asked to contextualise the NGB patient counts, using their experiential knowledge of working in clinical practice. Secondly, the information provided by the experts was supplemented with evidence from the literature. Further possible information relating to NGB diagnosis pathways was also sought from the literature in order to ascertain other possible reasons that lead to diagnosis error. The themes emerging from the literature and the expert interviews are displayed in Figure 8.1. A central theme emerged regarding a lack of concern and/or understanding of urological dysfunction amongst non-urologist healthcare professionals (HCPs).



QoF, Quality Outcomes Framework; NGB, neurogenic bladder; CGs, clinical guidelines

Figure 8.1 Reasons for sub-optimal diagnosis of neurogenic bladder patients in the UK

8.2.1.1 Coding of Neurogenic Bladder Diagnosis is Inadequate

The Read code system is a medical terminology used in UK clinical practice. There are a multitude of different reasons for missing codes in a patient's record, and the absence of a Read code should not always be interpreted as absence of the disease itself (Section 6.2.1.1.2). There are three separate Read codes relating to NGB that were identified in this study: neurogenic bladder, neuropathic bladder and neuromuscular bladder. No patients were found to have a Read code of neuromuscular bladder, which may be because newer terms have replaced its use (Section 6.3.6).

Disparate medical terminologies can make communicating and aggregating clinical information in a meaningful way across different levels of the healthcare sector challenging (Castle-Clarke, 2015). The Read code system was developed from the view of the general practitioner (GP), which has made implementation into secondary care difficult (Meek, 2015). This is because work activities and organisational structures tend to differ between the care settings, and consequently specialists and consultants typically have differing views to primary care HCPs on the nature of healthcare. Some opinion goes so far as to suggest that 'Read Codes have failed time after time in secondary care' (Meek, 2015: online). As a result of this ineffectuality, even if a specialist such as urologist or gynaecologist has diagnosed a patient with NGB, the information may not be Read coded. As opposed to Read codes in primary care, a distinct coding system named the International Statistical Classification of Diseases and Related Health Problem 10th revision (ICD-10) is applied within UK secondary care.

8.2.1.2 Low Awareness of Urological Symptoms amongst Non-Urologists and Lack of Referrals to Urologists

The extensive second organ effects that characterise neurological conditions renders a simple one-to-one physician-patient relationship insufficient for optimal care. In order to improve the overall Quality of Life (QoL) of multiple sclerosis (MS) and PD patients, NICE recommend their needs are met through a multidisciplinary team of HCPs, including GPs,

speech and language therapists, dieticians, neurologists, and psychologists (NICE, 2014a; NICE, 2018d). The composition of the care team depends on the patient's symptomology, disease severity and progression, as well as their social and psychological wellbeing.

Their superior expertise in bladder dysfunction positions urologists as pre-eminent in the diagnosis and management of NGB, however, they are only included in the multidisciplinary team, based on their perceived necessity. For example, if urological symptoms are not severe, conservative management techniques such as the administration of OAB drugs and introducing patients to catheterisation is easily performed in primary care. Although resources are saved by confining management to primary care, this practice runs the risk of NGB patients remaining undiagnosed, because the awareness of urological symptoms amongst GPs is notoriously low. A report into continence care in the UK found that physicians do not routinely query 'at risk' individuals about their continence issues (Wagg, 2010). Some of the common reasons for this include a fear of being unable to match patient expectations, lack of understanding of urological symptoms, lack of confidence in treating OAB symptoms, and embarrassment in discussing OAB (Smith et al., 2011). All of these factors mean GPs are less likely to conduct the appropriate data gathering necessary to make a timely and accurate diagnosis of any type of bladder dysfunction, let alone NGB, which is considerably more complex. This also indicates that they are more susceptible to making cognitive errors in diagnosis (Balogh, 2015).

Assigning a diagnosis is rarely a straightforward task, often proving challenging, especially in primary care. This particularly holds true in NGB, where symptomology can differ vastly between patients, making it difficult to uniformly apply diagnostic recommendations from CGs (Apostolidis et al., 2017). The temporal nature of NGB also complicates the process because symptoms tend to present later than occurrence of neurological disease, making assigning of causation difficult (Apostolidis et al., 2017). Moreover, there is a large degree of symptom overlap with idiopathic OAB, which can make distinguishing these conditions difficult for the untrained professional, thus patients could be incorrectly diagnosed with OAB rather than NGB. Given the diffuse and often severer nature of NGB, it is important

that the distinction between these conditions is made (Tapia et al., 2013). Further than this, the recommendations for diagnostic practices in the CGs may also be an influencing factor in diagnosis error. The NICE CGs differ from the EAU and ICI CGs in that they only recommend urodynamic investigations in individuals at high risk of renal complications, rather than in all possible NGB cases (NICE, 2012; Apostolidis et al., 2017; Bloc et al., 2017). Although urodynamic investigations are not imperative for diagnosis, the highly specific patient population advocated for testing by NICE may limit diagnosis rates and characterisation of a patient's particular manifestation of NGB. The low rates of urodynamic tests are reflected in the CPRD study (2.5%).

Diagnosis tends to be a team-based and iterative process, which increases the chances of error (Balogh 2015). NICE highlight that there is inadequate correspondence to patients regarding care providers and specialist services, which means patients are less likely to be routed to the correct care pathways (Gallacher et al., 2014; NICE, 2012). This issue is exacerbated by the fragmented healthcare service, where many HCPs are involved in the care of an NGB patient, leading to ambiguity over responsibilities and a potential disregard of CGs and policies (Barth et al., 2016). In most areas of the UK, neurological specialist nurses play an instrumental role in streamlining care from multiple care-providers to create an individualised management pathway for patients with neurological disorders (Bhidayasiri et al., 2016; MacMahon, 1999). However, in the current climate of austerity, the number of nurse specialists working within the community are progressively declining, therefore patients may have to rely on their GP, who, as established have limited awareness of urological symptoms and thus are less likely to be able to diagnose NGB or refer patients to a urologist (Christodoulou, 2012).

In the present CPRD study, 61.3% of the original source cohort did not receive a referral to a urologist (Section 7.2). The Urology Trade Association (UTA) obtained figures from national healthcare service (NHS) England, which revealed that between 2014-2016, there was a decrease in the number of individuals with bladder dysfunction that were referred to a specialist. The UTA postulates that this dip in referrals does not necessarily mean that

less patients were experiencing incontinence issues during these years. They suggest that adequate referrals have not been taking place, and district and practice staff, who lack the necessary skills and training to deal with incontinence issues, may have been managing these patients instead (Ford, 2017). There is unlikely to be any quick solutions to this issue because sub-optimal referrals are observed across innumerable conditions including transient ischaemic attacks and several forms of cancer, indicating this may be a cultural issue necessitating dedicated interventions across the spectra of disease (Foot, 2010).

8.2.1.3 Applicability of Current Neurogenic Bladder Clinical Guidelines

The ICI and EAU CGs scored 53% and 64% respectively in the applicability domain of the AGREE II instrument (Section 3.6.5.6.2). The low scores indicate that these CGs are less likely to be routinely applied for diagnosing patients in clinical practice, owing to a lack of attention the developers devoted to overcoming barriers to implementation. According to the AGREE II appraisal, the NICE CGs were highly applicable (90%), however, given the lack of uptake data, whether this is translated into their actual use in clinical practice is unknown (which is also true for the EAU and ICI) (Section 3.6.5.6.2).

One of the most limiting factors in NGB CG development was the exclusion of a wide variety of stakeholders, in particular of neurologists (all CGs) and GPs (EAU and ICI) (Section 3.6.5.3). This can propagate a lack of application in clinical practice by these HCPs due to the sense their views and opinions have not been incorporated into the recommendations.

8.2.1.4 The Quality Outcomes Framework

The Quality Outcomes Framework (QoF) was set up in the UK in 2004 as a pay-for-performance (P4P) scheme, linking financial incentives to the quality of care, measured against a set of clinical activity indicators (Doran et al., 2008; Quint, 2014). The scheme focused on ten key chronic conditions predominantly managed in primary care that cause significant morbidity and mortality (Gillam et al., 2012; Forbes, 2016). Completeness for many of the data points in these conditions improved in the years subsequent to the introduction of the QoF (Quint, 2014).

The QoF does not include common neurological conditions such as PD, MS or spinal cord injuries (SCI), nor does it include NGB. It is therefore apt to assume that the reporting of these conditions is not to the same standard as those covered by the scheme. A study by Doran et al (2011) found that improvements related to the QoF came at the cost of small deleterious effects to conditions not incentivised under the scheme. If neurological conditions or NGB were included into the QoF, due to the increased incentive for recording, there could be an increase in diagnoses/coding.

8.2.1.5 Perception of Bladder Symptoms by Patients

Patients with neurological disorders experience life-altering symptoms such as loss of mobility, problems with coordination, memory loss and severe pain (Guy, 2017). In contrast to their incapacitating symptoms, patients may not view their urological dysfunction as severe (i.e. an accommodation of symptoms occurs), which can result in a lack of help seeking behaviour (Tapia et al., 2013; Balogh, 2015). Other reasons for avoiding HCP contact include; embarrassment around OAB, lack of faith in treatments and self-management of symptoms (Diokno et al., 2006). A study in idiopathic OAB revealed only 25% of patients visited their doctor for bladder problems (Tubaro, 2004). Ultimately, if patients are not forthcoming with their symptoms, they cannot receive a diagnosis and hence, appropriate treatment.

8.2.2 Implications of Low Diagnosis Rates and How This Trend can be Improved

For optimal patient management in NGB, closing the current diagnosis lacuna is essential. Deprived of a diagnosis, patients will face an up-hill battle in gaining access to services and appropriate medications. This increases the chances of unpredicted situations, secondary conditions and hospitalisations, which places an additional strain on the NHS, an institution that is already over-stretched and under-funded (Vize, 2011). The issue of health inequity also arises, as those most affected will be in areas of the UK experiencing severe underfunding and cuts in specialist nurses, the key facilitators of the NGB care pathway.

There is a gradual migration underway in UK clinical practice from the use of Read codes to the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), with the aim of full replacement by April 2020 (Meek, 2015; Spencer, 2016). SNOMED CT can be cross-mapped to other international standards and classifications, thus it has been described as the 'most comprehensive and precise' clinical terminology in the world (SNOMED, 2018: online). It is envisioned that implementation of SNOMED CT in UK clinical practice will improve the channel of communication between primary and secondary care (Spencer, 2016). It will be of value to assess whether the diagnosis of NGB, and indeed other conditions perceived to be underdiagnosed improves after full implementation is complete.

This analysis revealed that a lack of awareness amongst GPs could be a modulating factor in low rates of NGB diagnosis. Cognitive task and work analysis through in-depth interviews with GPs as well as other important HCPs such as neurologists would be useful in ascertaining the cognitive skill necessary for diagnosis. As cognitive error is closely linked to diagnosis error this method is likely to highlight the specific sources of diagnosis error and thus where interventions will have the most impact (Balogh, 2015).

An intervention that has proved useful in other disease areas are national awareness campaigns to enhance the visibility of disease. In NGB specifically targeting non-urologist HCPs, patients and carers would be especially impactful. In particular, campaigns highlighting the fact that urological symptoms emanating from neurological conditions are very common would be instrumental in changing perceptions and attitudes amongst these stakeholders. Lessons can be learnt from the multiple successful campaigns carried out in the field of idiopathic OAB. One example is the campaign launched by the American Urological Association (AUA), entitled 'It's Time to Talk About OAB', which aimed to alleviate the stigma surrounding talking to a physician about OAB symptoms, and equip patients with a better understanding of their condition. The campaign consisted of a website featuring patient education materials and a 'Voices of OAB' contest, where patients shared testimonials of the way the disease impacts their daily life (AUA, 2012). It

is also important to consider that NGB can often be non-specific in presentation, thus distinguishing it from idiopathic OAB can be challenging for GPs and in some cases for specialists. Campaigns targeted towards GPs and neurologists should focus on the distinct manifestations of these conditions and the different ways these two patient groups should be managed. Another possible solution to improve awareness is to involve neurologists and GPs in NGB CG development. This fosters an increased sense of ownership over the CGs and can encourage active participation of those working in clinical practice in the care and referral of NGB patients to urological specialist care services, ultimately increasing the chances of receiving an accurate diagnosis and subsequently receiving appropriate clinical care.

The QoF has proved to be a successful intervention in improving the referral rates of patients with transient ischaemic attacks (Wright et al., 2006). This indicates that incentivised targets have a direct effect on behaviour in clinical practice. As an alternative to incentivising increased diagnosis within primary care, the NHS could offer financial incentives to GPs for referrals to a urologist. Health economic analysis into the cost-effectiveness of encouraging referrals over management in primary care would be necessary to ensure the efficacy of introducing such a measure. Some evidence suggests that financial incentives alone are not enough to change deep rooted cultural and technical barriers, thus this type of intervention should be introduced alongside other measures (Foot, 2010).

The applicability of the EAU and ICI CGs are low, and the real-life application rates of the NICE CGs for NGB in clinical practice are unknown, which could have implications for the application of diagnostic recommendations in clinical practice. Amongst the possible measures that could be introduced to enhance applicability and thus implementation and dissemination are Clinical Decision Support Systems (CDSS), which represent a sophisticated computational means by which CGs can be integrated into clinical practice (O'Sullivan et al., 2014). CDSS should be capitalised upon to assist GPs with any diagnostic uncertainty that exists around NGB. Some recent systematic reviews (SRs) have

demonstrated promising results; however, some conflicting reviews conclude there is a lack of data demonstrating benefit for patient outcomes (Hemens et al., 2011; Fillmore et al., 2013). Moreover, there are several challenges that have impeded successful implementation on a broad scale across healthcare systems, this includes the necessity of large volumes of high-quality data and the limitations of information technology (IT) infrastructure (O'Sullivan et al., 2014). Ultimately however, the use of IT and artificial intelligence alone is not sufficient, not only because there is uncertainty around the use of CDSS but because relationship-centred care such as the doctor-patient relationship as well as inter-professional relationships between HCPs remain the cornerstone of good-quality care (Goold and Lipkin, 1999; Aguirre-Duarte, 2015). Nurturing better doctor-patient relationships will allow patients feel comfortable sharing their symptoms with their doctor, and for doctors to attune to their patients' requirements and expectations (Ha and Longnecker, 2010). Additionally, because at present much of patient management is confined to primary care, strengthening the channels of communication between doctors and specialists is fundamental in facilitating information exchange and creating learning opportunities for GPs so to enhance their ability to detect and diagnose NGB.

8.2.3 Limitations

This is by no means an exhaustive analysis of the potential reasons for low NGB diagnosis rates in the UK population, and additional research into the way NGB patients are managed in UK clinical care and the resultant patient outcomes is necessary to further contextualise the low diagnosis rates. For example, the possible clinical shortcomings in current diagnostic practices were not explored. Another limitation is that some of this discussion resides on the assumption that urologists are consistently able to differentiate and diagnose NGB adequately, however there is no objective evidence for this, and it is possible the capabilities amongst urologists will vary.

Furthermore, the determinants of referrals should be deciphered through other means. The CPRD database could be used to conduct correlation studies against rates of diagnosis and factors such as socio-economics, sex, and comorbidity (Benjamin and Austin, 2003;

Zielinski et al., 2013). Simulated patients described by case vignettes could also be used to measure variation in clinicians' approaches to diagnosis and treatment (Peabody et al., 2000; Bachmann et al., 2008). In this study, the insight of urologists was used to understand diagnosis error in NGB, an alternative and perhaps more apt method would have been to administer surveys or conduct interviews with GPs as a means by which to understand the way cognitive error can lead to diagnosis error (Balogh, 2015).

8.2.4 Conclusions

Diagnosis and referrals directly impact the patient experience and are important cost drivers in the healthcare system. Improving the diagnosis rates of NGB in the UK will allow appropriate provision of care and services to patients, as well as guiding apposite management choices. Measures such as improving the interoperability between primary and secondary care databases, educational campaigns, financial incentives, CDSS, and fostering better relationships between important stakeholders can help improve the diagnosis rates. Ultimately, this will enhance health outcomes and facilitate efficient resource allocation for NGB patients. Further research into the possible reasons of low diagnosis rates and exploration of the region-level differences that may exist is important to gain further insight into this phenomenon and encourage initiatives to reverse this trend.

8.3 Demographics and duration between diagnosis of the Neurogenic Bladder Population in the UK

Most patients included into this study were male (59.6%). As expected, in the heterogenous disease area of NGB, the age of individuals varied substantially. The mean age of the overall study population was 61.7 (SD=16.3) years. NGB is distinct from idiopathic OAB in that prevalence does not necessarily increase with age; it is instead related to the onset and progression of neurological symptoms (Ginsberg, 2013). Spina bifida is a congenital condition and an alternative selection method was used to identify these patients, therefore the cohort was younger than the other subgroups (mean=36.1 [SD=11.9]). The average age of onset of PD is 60, and similarly stroke patients also tend to be older (Ostwald

et al., 2006). Conversely, the average age of patients with conditions like MS and SCI is much lower (Lunde et al., 2017; McCaughey et al., 2016). Given this variability, one would perhaps expect the mean age of this study population to rest in the middle age, however it is somewhat higher than expected. The mean age of NGB patients identified in the SR (Chapter 5) was much younger at 42.8.

In this study, the mean number of days between the diagnosis of any neurological condition and OAB or OAB drug prescription was 1140.1. This number was inflated by the spina bifida (SB) cohort (mean=4149.4), where the inclusion criteria allowed the diagnosis of SB to occur from any time within the start of follow-up within CPRD to the time of OAB diagnosis. The mean duration in the PD cohort was 1034 (days), which is much lower than another study which demonstrated the time between PD diagnosis and onset of urinary incontinence (UI) was 144 months (12 years) (although lower urinary tract dysfunction (LUTD) was cited as starting a lot earlier) (Rana et al., 2014). The mean duration in the MS cohort was recorded as 1095.9, which again is a lot shorter than estimates in the literature, which valuate the onset of urinary symptoms as 6-8 years after MS diagnosis (Aharony et al., 2017). The duration between diagnoses was shortest in the SCI cohort (mean=457.8). This is longer than would typically be expected in traumatic SCI where OAB symptoms tend to occur a few days to months after injury (Schurch, 2015). Limitations intrinsic to the collection of data for this variable are discussed in Section 8.8.2.

8.3.1 Comorbidity and Polypharmacy in Neurogenic Bladder Patients

A high level of comorbidity and polypharmacy was observed in this study, indicating there is great clinical complexity within NGB, making patient management more challenging and contributing towards a larger healthcare burden. Patients with high polypharmacy and comorbidity tend to exhibit poorer health outcomes leading to increased medical encounters, adverse events (AEs) and HRU (Tolentino, 2017). Specifically, in this patient group, comorbidity and polypharmacy has the ability to influence the underlying neurological condition and exacerbate urological symptoms (Stawicki et al., 2015).

Corresponding cost are also high, therefore, from a payer perspective, effectively managing comorbidity and reducing polypharmacy is essential.

In the present study, the QoF count did not demonstrate an accurate depiction of comorbidity (Section 7.6.5). Conversely, the British National Formulary (BNF) headers proved a much more reliable proxy indicator, revealing a significant level of comorbidity in NGB patients (average of 8.6 comorbidities per individual). NGB patients can experience a wide range of comorbidities that may be directly related to their neurological condition (for example, depression) (Siegert and Abernethy, 2005; Marsh, 2013), due to urological dysfunction (for example, urinary tract infection (UTI)) (Poisson et al., 2010) or can exist completely independently of the primary and secondary conditions (for example, a chronic heart condition).

Comorbidities were highest in the SB cohort (10.97). This result was unexpected as comorbidities tend to increase with age and SB was the youngest cohort (mean age=36.1) (Divo et al., 2014). In accordance with this logic, PD, as the oldest subgroup (mean age=70.7), should have had the highest rate of comorbidities, however the mean number of BNF headers over the 12-month period was lower than in SB (9.1). Nonetheless, given that the rate of comorbidities was close in range, this difference could be considered not significant. Furthermore, SB patients do still tend to experience a wide range of comorbidities including issues with digestion, vision, sex, mood, obesity and depression (Centre for Disease Control, 2017). MS patients had the lowest rate of comorbidities (6.5) in this study. The condition is related to a wide range of co-morbidities, the most common being depression, anxiety, hypertension, hyperlipidemia, and chronic lung disease (Marrie and Horwitz, 2010).

Comorbidities have a negative impact throughout the spectrum of neurological disease, thus it is critical their management is optimised. Due to masking of symptoms, comorbidities have been found to cause a diagnostic delay between the onset of MS symptomology and diagnosis, potentially impeding the timely provision of essential services and resources (Marrie and Horwitz, 2010). They also have the ability to alter the

phenotype and disease progression in PD, affect health-related quality of life (HRQoL) in SB (Bakanienė and Prasauskienė, 2018) and increase chances of hospitalisation in PD and stroke patients (Martignoni et al., 2004; Johansen et al., 2006).

Polypharmacy in the overall NGB population was also considerable. Patients were receiving on average 5.6 medications concomitantly. The extent of polypharmacy may in part be due to the complexity of the underlying neurological disease, which necessitates various medications for symptom control. For example, in PD, a combination of three or more medications are required to control motor symptoms alone, supplementary to other medications for numerous other secondary symptoms such as mood disorders and psychosis (McLean et al., 2017).

When used efficiently, medicines are a cost-effective solution to managing patients. Inappropriate and excessive prescriptions of drugs however lead to unpredicted drug-disease and drug-drug interactions. For example, patients with progressive neurological conditions such as PD and MS may experience worsening of pre-existing delirium and baseline cognitive impairment (Kuzuhara, 2001; Thelen et al., 2014). Polypharmacy can also negatively impact the rehabilitation of stroke patients, causing poorer functional outcomes and increased medical complications (Kose et al., 2016). Moreover, polypharmacy has the ability to impact urinary function. One common example is the use of corticosteroids, which are utilised to increase the speed of recovery from a relapse in MS (Myhr and Mellgren, 2009). These drugs can cause electrolyte imbalances, fluid retention and nocturnal or postural draining. Furthermore, their immunosuppressive effects increase the likelihood of UTI (Denys et al., 2006). In turn, when UTI is not managed adequately, the progression of MS also deteriorates (Mahadeva et al., 2014).

At present, the care provided to neurological patients is typically centred in neurological disease specific clinics, guided by CGs that are purely focused on a single disease. This care model can lead to a dangerous cascade of events because using multiple CGs for each single disease a patient is diagnosed with can become a driver of polypharmacy (Austad et al.,

2016). Drug-drug interactions arising as a result of polypharmacy then further contribute to comorbid conditions and the number of drugs prescribed (Marengoni and Onder, 2015).

Key therapeutic topics by NICE are designed to 'summarise the evidence-base on topics identified to support medicines' (NICE, 2018a: online). Stand-alone key therapeutic topic about multimorbidity and polypharmacy are currently available for use in clinical practice (NICE, 2017). Although these documents are useful, inclusion of the most important and likely drug-drug interactions and comorbidities within the NGB-specific CGs are arguably more beneficial to avoid harm to this particular patient population. For example, focusing on issues such as the common but potentially harmful co-administration of cholinesterase inhibitors and anticholinergic drugs, and the significance and likelihood of anticholinergic burden in PD patients (because patients main form of medication to manage both PD and urological symptoms are anticholinergics). NICE recognise the current situation of only considering one disease in isolation is not effective and are looking into ways their guidance can be updated to better reflect patient complexity (Duerden, 2013).

Further than this, the current care pathway of patients with neurological conditions is fragmented, with evident communication deficiency between care providers (Section 8.2.1.2). Increased collaboration between HCPs is vital to in order to streamline management and decrease the risk of duplication of care. The changes to CGs described above in concurrence with improved communication should enhance recognition of potential issues in patient management and encourage clinicians to conduct comprehensive assessments of comorbidities and structured medication reviews at relevant intervals so that comorbidity and polypharmacy can be sufficiently managed (Blenkinsopp et al., 2012).

8.4 Complications Related to Neurogenic Bladder

UTI was one of the most frequent complications in the present study, with 14% of individuals experiencing at least one episode. Indwelling catheterisation (IndUC) is a particular risk factor for UTI but is often necessary in NGB patients because they are more

likely to have limited manual dexterity (Manack et al., 2011). Section 2.4 and 2.8.4.1 explicate the clinical and economic burden of UTI in some detail.

Although 14% of patients had a Read coded diagnosis of UTI, 53.9% of the study population were prescribed UTI-specific antibiotics, indicating that the actual prevalence may have been considerably higher. Another similar study using a US claims database reported 33% of NGB patients with UTI (Manack et al., 2011). A much higher percentage was reported in a study of NGB patients presenting to the emergency department (ED) (87.6%) (Sood et al., 2017). Given that these patients presented in the ED, the higher instance of UTI could be due to the likely severer nature of their disease.

The average number of antibiotic prescriptions over the 12-month follow-up period was similar between the neurological disease subgroups and ranged between two and three prescriptions over 12 months. In a self-administered survey conducted in five countries (Germany, Switzerland, Poland, Russia and Italy), women with history of UTI reported a similar number of mean prescriptions, ranging from 2.17 (Poland) to 3.36 (Germany) per person, per year (Wagenlehner et al., 2018). Antibiotic overuse can lead to resistance amongst bacteria, which has devastating consequences for wider societal health and the economy (Section 2.4 and 2.8.4.1) (Fatima and Mussaed, 2018). The NHS currently prioritises a policy of infection prevention and control in order to minimise this risk. This includes measures such as aseptic technique and limiting the use of IndUC whilst encouraging IC use (Mantle, 2015). The widespread use of antibiotics in this study could indicate that reviewing the application of these policies may be necessary, and that further interventions and additional resources may be necessary to control UTI rates in NGB and subsequently lessen the threat of antimicrobial resistance (AMR). This includes education, antimicrobial stewardship, and extra due diligence in monitoring patients practicing catheterisation (Cheung et al., 2017; Bartoletti et al., 2016). Furthermore, NGB HCPs adherence to UTI good practice guidelines may also be an important area of further research.

Fourteen percent of patients were diagnosed with incontinence; however, this cannot be used as a proxy to neurogenic detrusor overactivity (NDO). It is likely that a larger

proportion of the population suffered from incontinence but as it is not a commonly coded term, the true prevalence cannot be determined. Incontinence has a negative impact on both patient health, QoL and economic outcomes (Section 2.7 and Section 2.8.4.1).

A similar spectrum of complications that were sought in this study were also documented in a large US claims database study of patients with NGB, albeit at much higher frequencies (Manack et al., 2011). For example, urinary retention and sepsis/septicaemia were reported in 14% and 4% of patients in the US study respectively, compared with 2% and 1% in this study. As key design features, including duration of follow-up, were similar between studies, the reason for the marked disparity between reporting rates is unknown, although could be linked to the differences in healthcare systems (USA vs UK). In particular the low rates of urinary retention in our study are surprising given this is a common complication in NGB (Sayed, 2008).

8.5 Drug utilisation in Neurogenic Bladder

8.5.1 Anticholinergic Burden Score and the Use of Bladder Muscarinics in Neurogenic Bladder

The detrimental impact of high anticholinergic burden, in particular the potential harm it can cause in patients with neurological conditions was discussed in Section 2.5. The average Anticholinergic Cognitive Burden (ACB) score in this study was exceptionally high (6.5). Most strikingly, the score was high for the progressive neurological conditions MS (6) and PD (6.8). Considering that a score of 3 or more can cause delirium (Table 6.12), these scores are concerning. Moreover, the ACB score in the post-index period (36.7) was much higher than in the pre-index period (15.7), indicating that the addition of a bladder muscarinic significantly increases exposure. However, as cumulative score was not taken into account, these results should be interpreted with caution (Section 8.8.4). This study also releveled that one in five patients were prescribed oxybutynin, which is considered one of the more toxic bladder muscarinics (Section 2.5.2). Undoubtedly, the ACB score is not only increased by use of bladder muscarinics, for example, anti-Parkinson's drugs are a common arbiter of

anticholinergic burden elevation in patients with PD (Richardson et al., 2018). These findings suggest that NGB patients are at particular risk for experiencing adverse effects related to anticholinergic medications.

The efficacy of bladder muscarinics has often proved comparable, however little work has been done to differentiate them on the basis of important variances in their potency (Section 2.5) (Buser et al., 2012). The current NGB CGs do not recommend one bladder muscarinic over the other. Furthermore, the most commonly used tools to measure anticholinergic burden, the ACB scale and the Beer's criteria, regard all bladder muscarinics as equally potent (American Geriatrics Society, 2015). Newer scales such as the anticholinergic effect on cognition (AEC) scale help to better discern these differences, however it is yet to be validated and has not been extensively applied in research or clinical practice (Section 6.4.12.2.7).

Due to the perceived similarity of bladder muscarinics, many Health Technology Assessment (HTA)/reimbursement agencies in Europe still recommend the use of generic drugs as first line treatment choice. This decision is normally based on drug acquisition cost alone, as generic medicines can help conserve resources whilst typically avoiding compromising standards of care (SOC) (Godman, 2012). Therefore, as oxybutynin is one of the oldest and cheapest bladder muscarinics, it tends to be the most frequently prescribed. It is also one of the only bladder muscarinics (along with trospium) that has a licensed indication for NGB, and typically, other medicines are not supplied where licensed alternatives exist (Dodds-Smith, 2017). However, in this study, tolterodine and solifenacin were frequently prescribed, despite having no licensed indication. Additionally, the prescription of trospium in the study was scarce, despite having a licensed indication and potentially causing less central nervous system (CNS) side effects than other bladder muscarinics (Chughtai et al., 2008) (Section 2.5.2). This indicates that physicians tend to act on their personal preferences and are more likely to adhere to established norms when prescribing bladder muscarinics.

It is important to eradicate the common school of thought that all bladder muscarinics are identical, and effort should be made to differentiate bladder muscarinics by taking into consideration their varying pharmacokinetic characteristics and potential harm to patients (Cornu, 2012). Specifically, due to the growing concern related to anticholinergic burden in those with neurological conditions and the associated risk of mild cognitive impairment (MCI) and dementia, payers and clinicians alike should be cognisant that there are alternative options available for this vulnerable population. The economic burden of dementia has been well characterised, and current figures indicate the total cost to the UK economy is around £26.3 billion a year. The condition is also related to a higher rate of hospitalisations (Phelan et al., 2012) and visits to the GP (Ydstebø et al., 2015). Thus, from a payer perspective avoiding anticholinergic burden in NGB patients, not only improves outcomes but also saves on the downstream costs of managing MCI and dementia. A study conducted in New Zealand demonstrated a reduction in the ACB score of a group of 691 at-risk individuals by implementing a form of medication review (He and Ball, 2013). Careful review of all prescribed medications conducted at regular intervals is an essential practice to ensure rates of polypharmacy and anticholinergic burden are minimised, and thus should be encouraged in the NGB CGs.

The β3-adrenoceptor agonist, mirabegron is able to bypass the cognitive effects of bladder muscarinics. It is currently second line treatment for OAB, however unlike most of the NGB treatment pathway that mirrors the one for OAB, mirabegron is not a licensed or recommended treatment option for NGB patients. Scarce data has been published on its use in this population (Cameron, 2016), and consequently the drug is not recommended by any of the prominent NGB CGs (Chapter 4). This could constitute a reason for the low numbers of mirabegron prescriptions in this study (1.2%). The low prescriptions for mirabegron will also likely reflect that the drug was introduced in the UK towards the end of the study selection period.

Comparative effectiveness research (CER) is essential to identify to achieve optimal clinical utility as well as relative value in an economic sense (Chang and Winkelmayer, 2012). The

process involves comparing two or more interventions in an environment that is representative of the real world, essentially, carefully balancing of the side effect profile with proven efficacy and cost. Sophisticated measures of economic analyses assist payers in making their reimbursement decisions as well as inform the recommendations made in CGs (Chapter 2). A recent cost-effectiveness analysis (CEA) conducted in OAB patients deemed mirabegron 50mg to be cost-effective when compared to the most widely used bladder muscarinics in the UK. The base-case incremental cost-effectiveness ratios (difference in cost between two possible interventions, divided by the difference in their effect) ranged from £367 (vs. solifenacin 10 mg) to £15,593 (vs. oxybutynin IR 10 mg) per Quality-Adjusted-Life-Year (QALY) gained (Nazir et al., 2015). This study clearly demonstrates the cost-effectiveness of mirabegron, however given the complexity of NGB in comparison to OAB; it would be unwise for payers to apply economic data across these diseases, thus specific CER in NGB is necessary to quantify the value of healthcare interventions in NGB, and subsequently improve uptake of important alternatives.

8.5.2 Combination Use of Overactive Bladder Drugs

A combination of bladder muscarinic drugs is recommended in the current EAU CGs. The EAU and ICI CGs also suggest that combination therapy between mirabegron and a bladder muscarinic could be a viable management strategy in the future, provided further research into the efficacy and safety is conducted (Section 4.6.2). Research in the idiopathic OAB population suggests this is an efficacious practice, and can provide comparable efficacy to bladder muscarinics alone, whilst reducing intolerable AEs (Abrams et al., 2015).

This study observed a low instance of combination use (8%), suggesting that this practice is not well established in clinical practice. Manack et al (2011) reported a very similar level of combination use (8.7%) amongst NGB patients. Some patients in this study and the study by Manack et (2011) reported more than two bladder muscarinics being prescribed, demonstrating deviation from the NGB CGs. Furthermore, the most common combinations were included solifenacin, tolterodine, and oxybutynin, whereas the ICI CGs state that research only exists for oxybutynin, tolterodine and trospium. Section 7.6.6 describes the

possible limitations surrounding the lack of sensitivity analyses; a higher rate of combination use may have been observed if an alternative definition was employed.

8.5.3 Use of α-Adrenergic Antagonists and 5-Alpha Reductase Inhibitors

Approximately one-quarter of patients had prescriptions for α-adrenergic antagonists or 5-alpha reductase inhibitors (5-ARIs), which are traditionally utilised for benign prostatic hyperplasia (BPH) in males (Vaughan, 2003; Lepor, 2007). A small number of these prescriptions were for women (n=47, 0.32%), α-adrenergic antagonists and 5-ARIs could also be used to treat voiding dysfunction unrelated to BPH, which makes them a plausible choice for women with specific types of voiding dysfunction (Nitti, 2005).

α-adrenergic antagonists for bladder outlet resistance in NGB are recommended by the ICI and EAU but not by NICE (Section 4.6.2). Presumably because despite multiple accounts on the use of α-adrenergic antagonists in the management of NGB, evidence primarily comes from small, uncontrolled trials (Nitti, 2005; McCrery and Appell, 2006). The SR described in Chapter 5 found that α-adrenergic antagonists were administered to SCI patients with marked bladder outlet obstruction (BOO), as well as being the most prevalent drugs amongst SCI patients with NDO in another study. Expert opinion suggests that α-adrenergic antagonists are probably rarely used in NGB, where BPH is not a concomitant presence, and are only administered as a last-report option (Drake and de Ridder, 2017).

8.5.4 Cumulative Number of Days Supply of Overactive Bladder Drugs

The average cumulative number of days' supply of OAB drugs (including mirabegron) was 202.86 days. This is exactly the same number of days that Mannack et al (2011) derived from their research in a US population (although their calculation included bladder muscarinics only) (Manack et al., 2011). The rates of discontinuation were not sought in this study, but previous research suggests that less than one third of patients remain continuous on their medication (Manack et al., 2011). If patients properly adhered to their medications, the median time for therapeutic response in idiopathic OAB is around three months but may be longer in NGB given the severity of the condition (Hsiao et al., 2015).

8.6 Healthcare Resource Utilisation in Neurogenic Bladder and Associated Costs

The healthcare burden of NGB was significant in many aspects. The most noteworthy observation was the high number of GP visits, where patients visited or made contact with their GP an average of 68 times over a 12-month period. Patients with stroke or SCI visited their GP more often (76.3 and 75.5, respectively) than other cohorts (range, 49.9 to 69.7). The high frequency of visits was likely due to the inclusion of all-cause visits and because multiple visits to the GP in a day were recorded. A similar number of primary care visits was reported in a UK study of patients with idiopathic OAB (70.3 visits over 12 months) (Odeyemi, 2006). Mannack and colleagues in the US observed a much lower frequency of visits in patients with NGB (16.1 visits over 12 months) (Manack et al., 2011). This discrepancy could be due to differing definitions of what accounted for a 'visit' and the different economic structures of the UK and US healthcare systems. Furthermore, whether visits were all-cause or NGB related was not delineated in the study by Manack et al (2011), and multiple visits on same day were counted only once. The estimated overall mean cost of GP consultations was £1,448 (median=£1243.6) per individual, proving much costlier than idiopathic OAB. One large-scale study determined GP visits in idiopathic OAB to cost €281 (£245.27) per patient, per year in the UK (Irwin et al., 2009).

Although all patients included into this study were referred to a urologist or gynaecologist (inclusion criteria), around half of the cohort were recorded making at least one visit to a specialist over the 12-month follow up period. This could mean that despite being referred, patients did not end up visiting a specialist. Two of the most common reasons cited for patients (with various diseases) not following up with specialist appointments include a lack of time or resolution of symptoms (Forrest et al., 2007). Another possible rationalisation for this phenomenon could be issues with coding, that fail to adequately represent the number of patients visiting their specialist after referral (Forrest et al., 2007). Notwithstanding these potential issues, the frequency of specialist visits could still be considered high, which is to be expected, as the symptoms of NGB are often too severe to

be solely managed in primary care. Mannack et al (2011) showed a similar trend, albeit at a slightly lower frequency, with 39% of patients with NGB visiting a urologist within one year.

Patients in the present study made a mean number of 2.3 visits per year to the specialist. This represented a notable cost component, with a mean cost of £253 (median=£218.8) per individual. In a self-reported survey of OAB patients, individuals reported 0.4 to 1.1 visits to the urologist and 0.1 to 0.9 visits to the urogynaecologists/gynaecologists (incumbent upon incontinence severity level), over a six-month period (Jimenez-Cidre et al., 2014). This indicates that severer cases of idiopathic OAB have a similar rate of specialist visits as NGB patients observed in this study. Most visits in this study (90.8%) were to a urologist rather than a gynaecologist, this is important to highlight, because visits to the gynaecologist may not necessarily be because of NGB and could instead be related to other issues in women's sexual and reproductive health (Shaw and Faúndes, 2006).

Only 14 patients (0.4%) in the study cohort were prescribed incontinence pads with a low mean annual cost of £40.56 (median=£14) per individual. This is at odds with the reporting rate for UI (14%) in this study. A study using 2010 UK costs determined the yearly cost of incontinence pads in OAB patients to be slightly higher at $72.97 (£56.23) (Irwin et al., 2009). Incontinence pads typically represent an ongoing out-of-pocket expense for patients in the UK, thus would not typically appear on electronic healthcare records (EHRs), providing a possible explanation for the low instance of use in this study. To determine eligibility for prescription pads in the UK, the local NHS organisations assess the severity of incontinence by asking patients keeping a bladder diary for three days, a process that can be time-consuming and difficult for those with disabilities. This could ultimately impede access to pads, thus introducing inequalities (NHS, 2015a). If a private care database was used for this research, a higher frequency of pad use would have probably been observed. Interestingly, in an economic model, focusing on five of European countries, 63% of the annual per patient cost of idiopathic OAB management constituted of incontinence pads

(Reeves et al., 2006). This is explained by the fact that Italy and Sweden were included in this analysis, where incontinence pads are reimbursable.

Overall, 2.5% of the study cohort had more than one urodynamic test (£179, median=£126), 8.8% underwent cystoscopy (£171, median=£146), and 2.1% had urology-related imaging (£101, median=£144). There are two possible rationalisations for the low instance of urodynamic testing. Firstly, NICE do not recommend urodynamic investigations in patients with a low risk of renal complications, who are being adequately managed with conservative techniques (NICE, 2012). Therefore, if these CGs are being applied in clinical practice, it is unlikely that many patients included into this study underwent urodynamic testing. The most common time urodynamic testing is carried out is to determine optimal management or before surgery in stress urinary incontinence (SUI) (Agro et al., 2017). The rate of urodynamics was higher (6.1%) in a study amongst idiopathic UI patients in the UK and Ireland. Imaging was also carried out at a higher rate (4.9%), however, cystoscopy was carried out at a much lower rate (1.8%) than the present study (Papanicolaou et al., 2005).

The two main cost drivers of this study were surgical interventions or procedures and hospitalisations. Surgical procedures are most commonly considered a last-resort option if conservative measures fail. At least one procedure or surgical intervention was performed in 5.7% of the study cohort at a mean cost of £2,285 (median=£1123) per individual. Hospitalisations cost £6,256 (median=£2590) per individual and overall, 11.0% of the study cohort were hospitalised (urology related) at least once, for an average duration of 12.5 days during the 12-month follow-up period. Furthermore, 17.4% (75 of 431) of hospitalised patients were admitted following renal failure. The average length of stay was higher than the overall average inpatient stay in the UK, which is 7 days (NHSConfederation, 2017). Hospital admissions were more common in the definitive NGB and SCI cohorts (20.1% and 19.5%, respectively) compared to other cohorts (range=6.7 to 12.0%) but were similar between age and sex subgroups. NGB patients have previously shown to have a higher than average stay at hospital in comparison to other urological patients, consequently putting them at increased risk for contracting nosocomial UTI's, and thus

increased associated costs (Sauerwein, 2002). A long length of stay (LOS) has also been implicated in an increased risk of falls and fractures, episodes of delirium and loss of muscle strength (NHS Improvement, 2018). It is however important to consider that short inpatient stay does not necessarily equate to better outcomes, for example if adequate rehabilitative provisions are not in place, shortened inpatient stays could precipitate further functional decline (Vliet et al., 2017).

The mean total overall costs for NGB patients was £2395.03 (median=£1458.2). The highest cost was in the NGB cohort £3378.92 (median=£1308). A systematic review found that costs of idiopathic OAB across five Western countries was €269 to €706 per patient per year, proving much lower than NGB (Reeves et al., 2006). The considerably high rates of polypharmacy, comorbidity, anticholinergic burden and complications are all factors related to the growth of HRU. From an economic perspective, targeting these aspects through interventions such as medication review, modifications to the NGB CGs, improved cross-communication between HCPs as well as between doctors and patients, is essential to lower the burden. Furthermore, investing more resources to improve the currently sub-optimal diagnosis and referral rates in NGB could also help to reduce the overall costs.

8.7 Strengths of the Study

8.7.1 Patient Selection Process

As is common in database analyses, it was necessary to employ a proxy measure (neurological condition diagnosis + OAB diagnosis/OAB drug prescription) to identify probable NGB patients. Although there is no certainty that these patients definitely have NGB, this method of selection was validated by experts and deemed to be the most specific way to identify additional subjects. A similar approach to patient inclusion was taken by an epidemiological study in the USA (Manack et al., 2011). The use of this proxy measure increased the sample size.

Furthermore, the sensitivity analyses, which involved including patients with any order of diagnoses (OAB diagnosis/drug prescription could come before diagnosis of neurological

condition) proved an excellent way to confirm the selection process, affirming the notion that altering the selection process in this way had no significant impact on results, as patient demographics, drug utilisation patterns were very similar between the base case and sensitivity analysis.

8.7.2 Use of Sub-Cohorts

Another strength of this study was the separation of results by individual neurological condition. Considering all neurological conditions that cause NGB as singular, and transferring evidence from one condition to another is often inappropriate because they are incredibly heterogenous in nature. By incorporating sub-cohorts into the study design, it was possible to understand important factors such as the differences in general patient characteristics, determining which conditions had the highest ACB score and which cost the most to the healthcare system. The results were also split by age and sex. When considering sex, the NICE CGs make some sex-specific recommendations, reinforcing that it is an important factor to consider when making management decisions. Age is also an important influencing factor, for example in this study, older patients had a higher frequency of outpatient physician visits, which could warrant further inquiry and interventions in this specific population.

8.7.3 Use of Electronic Healthcare Records

EHRs present an unprecedented opportunity to detect and analyse real world clinical manifestations and subsequently inform health practice. However, far too often, non-interoperable databases severely limit potential insight that could be derived (De Moor et al., 2015). Fortunately, in this study, there existed an opportunity to link a subset of NGB patients that were included from the CPRD database to the Hospital Episode Statistics (HES) data. Valuable insight of a much larger portion of the patient journey was derived with the collection of several different outcomes related to HRU that would not have been possible without database linkage.

Using EHRs to determine treatment patterns is also useful in circumventing the issue of recall bias. Recall bias is a classic form of information bias, referring to systematic error as a result of inaccuracies or incompleteness of recollections by study participants of past events. Although recall bias typically focuses on differences between subjects in one group compared to the other, the inaccurate reporting of past events can also impact descriptive studies (Althubaiti, 2016). With EHRs, the exact time a patient was prescribed their medications can be specified without having to rely on the patients' memory as an aid, thus improving the internal validity of the study (Casey et al., 2016).

Another important strength of this study, through virtue of the longitudinal nature of the data, was the ability to measure time dependent measures, in particular the cumulative dose of OAB drug.

8.8 Limitations/Biases of the Study

Bias relates to the systematic error that is introduced in the collection or analysis of data and is an important consideration when weighing the accuracy of results (Malone et al., 2014). Several intrinsic biases and limitations with the study design were identified, which are discussed in further detail below. The general limitations associated with HRU studies were discussed in Section 2.8.2.

8.8.1 Limitations in Patient Selection Process

As mentioned previously in this chapter, the 967 Read coded NGB patients that were identified from the CPRD database in a preliminary count do not provide a representative picture of NGB patients in the UK (Section 8.1). A proxy measure was employed to identify further NGB patients, which is both a strength and limitation of this study, as whilst it was deemed a reliable method by experts, there remains uncertainty regarding the NGB status of these individuals, due to the lack of definitive diagnosis. Suboptimal diagnoses/coding of conditions in UK clinical practice may extend further than NGB, evidenced by the discrepancy between the numbers of patients with a UTI diagnosis versus those with a prescription of antibiotics.

Another limitation pertaining to cohort definition was around the Read codes used to identify SCI and SB patients, which could have been improved. In order to capture the largest pool of SCI patients, additional search terms should have been employed to identify relevant Read codes. This includes search terms: triplegia, tetraplegia and paraplegia, which represent distinct injuries in SCI. Similarly, when searching for patients with SB, codes for meningocele and myelomeningocele should have been included. In SCI, the projected number of patients from the sample size calculation was 384, signifying that the 41 patients included into this study was not enough to reach reliable conclusions. These improvements were identified after execution of the study and since then, access to the analysis platform was lost thus these rectifications to patient cohort definition could not be implemented.

8.8.2 Limitations in Calculating Time Between Diagnosis of Neurological Condition and Overactive Bladder

When considering the probable NGB cohort, only patients diagnosed with both a neurological condition and OAB/OAB drug prescription within the 12-year study period were included. It is well established that urological symptoms tend to worsen with increasing severity of the underlying disease (Jost, 2013). Slow neurological disease progression would result in the time between diagnosis of neurological condition and occurrence of OAB symptoms for many NGB patients to be longer than the 12-year period employed in this study, thus excluding a large number of potential subjects. Furthermore, the neurological diagnosis date that was used to calculate this duration is the most recent diagnosis before the OAB diagnosis/prescription. Patients could have been diagnosed prior to this date, and if the first date was utilised, longer durations would be observed.

It is also important to consider that the way diagnoses are recorded in CPRD biases this variable. Patients can be transferred in and out of CPRD practices which means they may have been diagnosed with a neurological condition in secondary care (not captured in the data of this study) therefore underestimating the duration.

8.8.3 Limitations of Prescription Data

Accurate drug taking behaviour is difficult to ascertain, and EHR data such as the CPRD database does not provide information around whether the prescribed medications were actually picked up by the patient and adhered to. Conversely, claims data shows every fill/refill of a prescription, contains information about the actual drug that was dispensed, the amount that was dispensed, and the number of days the prescription lasted for (Wilson, 2012). This type of data is available in countries that have insurance-based healthcare systems, and thus could not have been utilised for characterising the UK NGB population (van Heuckelum et al., 2017).

Patients may opt for complementary and alternative medicine (CAM) to manage their underlying neurological condition or their urological dysfunction if they (or in some cases their doctor) feel conventional therapies are not sufficient enough to control symptoms (Haughn, 2010). Over-the-counter (OTC) medications such as CAM are not included in the CPRD database; therefore, polypharmacy was likely underestimated in this study.

8.8.4 Limitations of Anticholinergic Cognitive Burden Scale

The ACB scale takes into account the age-related pathophysiological changes that occur in the brain to determine the impact of prescribing anticholinergic medications to elderly patients (Campbell et al., 2016). The scale has not been designed with the purpose of application to younger individuals, potentially threatens the reliability of the ACB score results in the present study, which included patients under the age of 65. Moreover, the structural brain changes that accompany neurological disease are often different to that which occur in the aged brain. Changes also differ across the various neurological conditions as a result of the distinct severity and progression rates (Hindle, 2010). The ACB scale is not designed to take into account these specificities of neurological conditions, thus the reliability of use in this patient population is questionable.

Bladder muscarinics vary in their ability to interact with the M_1 and M_2 receptors in the brain, owing to differing pharmacological properties such as degree of lipophilicity and

molecular size, which modulate the ability to move across the blood-brain-barrier (BBB) (Section 2.5). Although the developers of the ACB scale claim that these properties are taken into account, it is clear that this is not the case, instead all bladder muscarinics are categorised as highly potent (ACB score 3). This constitutes a major limitation of this scale. A positive modification to the study design would be to employ a sensitivity analysis, utilising an alternative scale to calculate the anticholinergic burden and determine whether this would have any impact on the results. The AEC scale was developed by two reviewers who identified the main drug classes and medicines commonly used amongst older people in the UK. Electronic searches were performed to determine which drugs were associated with cognitive functioning, and which had known anticholinergic activity. For those drugs with reported anticholinergic activity, the reviewers independently assigned scores of 0, 1, 2, or 3 based on the bladder muscarinic potency, specificity to receptor subtypes, BBB penetration ability, and reports of associated cognitive impairment. Any discrepancy was mediated by a third reviewer. A total of 60 drugs were found to have some anticholinergic activity. The AEC scale is superior to many other scales as it takes into account the differing pharmacological properties of anticholinergics. In contrast to the ACB scale, it differentiates between the bladder muscarinics; for example, oxybutynin is scored a '3' and darifenacin is scored a '1', accurately reflecting their differing abilities to cause cognitive impairment (Bishara et al., 2017).

Increased duration of use and higher doses can result in a greater anticholinergic burden and augment risk of cognitive impairment. The calculation of anticholinergic burden in this study does not take these factors into account, thus the burden may have been over or underestimated. Measures such as the total standardised daily dose (TSDD), which standardises conversion of doses of different anticholinergic medications into a single exposure measure (Gray et al., 2015), or the mean total daily ACB score, which creates a weighted average ACB score for each patient, could have been employed to strengthen the calculation.

Common OTC drugs such as cough and allergy medications possess anticholinergic properties; however, this data is not collected in the CPRD database, and therefore was not included in the ACB score (Gray et al., 2015). Subsequently, there is a good chance that the ACB score calculated in this study for NGB patients is an underestimation.

8.8.5 Limitations in using the Quality Outcomes Framework for Measuring Comorbidity

Using the QoF to measure comorbidity offers benefits in data completeness because data recording is linked to GP rewards. Despite this, the QoF score did not prove to be a reliable indicator of comorbidity in this study, as patients across all subgroups were deemed to have 0-1 comorbidities, which does not seem likely given the numerous comorbidities mentioned in the literature that are associated with neurological conditions.

Frequent comorbidities such as renal disease and psychological disturbances are not included in the QoF hence the true prevalence of comorbidity remains uncharacterised (Salisbury et al., 2011). In addition to this, the one-year follow up employed in this study may have not been long enough to pick up many of the long-term conditions listed in the QoF.

8.8.6 Limitation in Sensitivity Analyses of Combination Use

Combination use was defined as two or more overlapping prescriptions for an OAB drug within a 30-day period. There is no agreement on what constitutes combination use, thus there are a number of definitions that could have been employed. Sensitivity analyses by using alternative definitions of combination use would have been useful to understand whether rates changed according to definition.

Some possible sensitivity analyses that could have been employed include:

- Those prescribed a second OAB drug within the intended prescription interval of the first

- Where the second OAB drug is prescribed within 1.5x the intended prescription interval of the first drug
- Where both OAB drugs were prescribed on the same day
- Where the second OAB drug is prescribed within six months of the intended prescription interval of the first
- Both drugs continue to be prescribed for ≥90 days from combination index date, to distinguish between combination patients and switchers.

8.8.7 Limitations in Filling Data Gaps

Although progress has indubitably been made towards collecting and reporting many previously undescribed variables relating to the NGB population, data gaps remain. For example, further detail on drug taking behaviour such as sequencing and switching, measurements on the usage of cholinesterase inhibitors and a deeper delve into antibiotic use and associated outcomes all could have enriched the results. In addition, resource use and cost data could have been enhanced by taking a wider societal perspective, i.e. understanding the costs borne by the patient, their carer or society. Reporting this data would have offered a more complete picture of the NGB population and provide further direction for hypothesis driven research.

Of course, it is impossible to include all potential variables of interest; however, given these limitations and considering the broad number of variables that could have been collected and described, the results from this study should be considered as only part of the picture on drug utilisation behaviour, and the minimum likely financial costs to the UK healthcare system of the NGB population.

8.9 Generalisability

It is important that study results are generalisable because they are often used to justify practices and draw conclusions for all patients in wider society (Kukull and Ganguli, 2012). This study used data from the CPRD database, which is the largest EHR in the UK, therefore patients included into the database are considered representative of the population at

large (Section 6.2.1.1.1). Given that the selection process is well-designed (albeit with some unavoidable limitations), the sample cohort can be considered representative of the UK NGB population, however it is important to consider that employing too many criteria can threaten the external validity. In this study, patients with missing data for age and sex, those with inadequate follow up, without a referral to a urologist and those with a diagnosis of dementia were excluded. This may have introduced selection bias, which shrinks the study population and limits the generalisability of results to the wider NGB population.

The treatment patterns observed this study would most likely not be generalisable to other countries. The NHS is the sole administrator of healthcare policies and provider of medical care in the UK. Accordingly, drug choices are overwhelmingly influenced by NICE, who stipulate which drugs must be made available to patients through compulsory placement of positively recommended drugs on the formulary (Hill, 2013). In countries without a government-funded healthcare system, healthcare providers have a lot more autonomy in the choice of prescribing, with insurers making many important formulary decisions (Regnier, 2014). Additionally, all UK practising physicians are expected to consider the NICE CGs. In other countries, drug choices in NGB might be influenced more so by the EAU, ICI, or local/disease specific CGs.

8.10 Conclusions

The findings from this study suggest that NGB may be under-recognised among primary care providers, which has led to a low rate of diagnosis in the UK. It is important that efforts are focused on improving this trend through measures such as increased interoperability between primary and secondary care databases, educational campaigns, financial incentives, CDSS and fostering of better relationships between important stakeholders. An improvement in diagnosis rates will be instrumental to the accurate characterisation of patients that will further enhance effective individual treatment pathways and resource allocation.

This study also demonstrated that the burden of illness, healthcare needs and associated costs in this patient population were considerable. Patients had a high rate of polypharmacy, anticholinergic burden, UTI, incontinence and visited their GP and specialists frequently. The total mean per-patient costs for HRU was £2,395. All of these factors indicate that management may be sub-optimal in the UK NGB population, and highlight the need for interventions to improve the treatment landscape. This includes measures such as better infection control measures to lessen the impact of UTI and increased CER for the selection of optimal treatments that can provide the most benefit and avoid harm in the NGB population. Furthermore, modifications to the NGB CGs to include information on polypharmacy, comorbidity and anticholinergic burden are essential to strengthen awareness and knowledge amongst key stakeholders. Hypothesis driven research is crucial to understanding the drivers of HRU, specifically determining the association of NGB and HRU and further investigate the association of anticholinergic burden and cognitive dysfunction in patients with neurological disorders.

8.11 Chapter Summary

The SR conducted in Chapter Five revealed a lack of drug utilisation research (DUR) in NGB. Furthermore, the literature review in Section 2.8.3 established a lack of HRU evidence in this disease area. The CPRD study presented in this thesis fill a very important gap in our understanding of these important topics in a UK population. This study should help payers and policy makers shift their focus onto these pertinent aspects of NGB management when making reimbursement and policy decisions and encourage modifications in the current NGB CGs.

The next chapter will discuss the results from the CPRD study in conjunction with the rest of the research presented in this thesis to formulate overall conclusions, implications for clinical practice and recommendations for further research.

9) Chapter Nine – Summary, Recommendations, Further Research and Conclusions

9.1 Introduction

The overall aim of this research was to raise an awareness and greater understanding of the neurogenic bladder (NGB) population, as well as providing recommendations on how to improve the management of this important patient group. The final chapter presents a summary of findings from the research presented in this thesis and explores the potential implications for both theory and practice. Considerations for further, more advanced research in this field are also explored.

9.2 Outcomes Related to Research Aims

The outcomes and findings in relation to the overall aims of this research that were presented in Chapter One, are presented below:

Primary aims:

1) Enhance the understanding of the current treatment landscape in NGB
2) Enhance the understanding of the current burden of disease in NGB

Outcomes:

1) The quality of the NGB clinical guidelines (CGs) developed by the National Institute for Health and Care Excellence (NICE), European Association of Urology (EAU) and International Consultation on Incontinence (ICI) was assessed using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument. The study revealed that amongst many areas of improvement, one of the most important was in the applicability and incorporation of comparative effectiveness research (CER), which is crucial to ensure uptake in clinical practice.
2) A comparison of treatment recommendations between the NGB CGs was conducted. When considering the results in conjunction with the AGREE II study, it

is clear that the CGs place differing emphasis on costs and expert opinion, which translated in notably different recommendations. It is imperative that the evidence base on which the recommendations were made is strengthened in order to guide more robust and consistent recommendations in future publications.

3) A UK-wide retrospective observational study was conducted using the Clinical Practice Research Datalink (CPRD) database. The study uncovered that the rate of diagnosis error in NGB is high. This has implications for accurate patient characterisation, optimal treatment pathways and resource allocation.
4) The CPRD study revealed that drug-prescribing patterns are consistent with the symptoms and complications of NGB, however interventions are necessary to manage the high levels of comorbidity, polypharmacy, anticholinergic burden and healthcare resource utilisation (HRU).

9.3 Recommendations

The following recommendations pertain to ways in which the management of NGB patients can be improved in light of the findings from the CG assessment and the CPRD study. A particular focus is placed on possible alterations to CGs and their development, which are one of the cornerstones of patient management (Hoesing, 2016).

9.3.1 Improve Management of Polypharmacy and Comorbidity Neurogenic Bladder

Results from the CPRD study revealed a high level of comorbidity and polypharmacy in NGB patients, which poses a major clinical and economic burden (Section 8.2.1 and Section 8.4.1). The CG quality appraisal highlighted that the NGB CGs eschew all information regarding polypharmacy; generally failing to make clear when or how to stop drugs (Section 4.4.2). They also do not include information on how to manage patients with comorbid conditions. Reducing the rates of polypharmacy and managing comorbidities in NGB patients is more challenging without the inclusion of supporting information and guidance in the standard CGs.

Furthermore, it is also important to consider that CGs for a single disease are notoriously difficult to implement in patients with multiple morbidities and the cumulative impact of applying treatment recommendations from various CGs can result in unnecessarily complex drug regimen (Austad et al., 2016). This situation is only exacerbated in NGB because patients may be managed in specific neurological care centres, and communication between the different levels of care often proves sub-optimal.

There are many important aspects of polypharmacy and comorbidity that are specific to NGB patients, such as the risk of anticholinergic burden in PD patients, the problematic concurrent use of cholinesterase inhibitors and anticholinergics, and exacerbation of urological symptoms by MS medications. Inclusion of this information in NGB CGs are essential for the optimisation of care. Moreover, increased communication and collaboration between the multidisciplinary team managing these patients is imperative to ensure appropriate practices are followed and to avoid the duplication of care.

9.3.2 Improve Diagnosis Rates of Neurogenic Bladder

The high rate of diagnosis error in NGB evidenced by the CPRD study has implications for patient characterisation and thus the proper planning and provision of healthcare and services. Inadequate diagnosis is also related to treatment insufficiency, which can lead to increased rates of anticholinergic burden, polypharmacy and HRU, all of which were prominent in the CPRD study.

There are a number of ways in which this trend can be modified, including improving the interoperability between primary and secondary care so that diagnostic information is fed back effectively, educational campaigns targeted towards both HCPs and patients to improve the awareness and understanding of NGB, financial incentives for diagnosis and/or referrals, and fostering better relationships between important stakeholders across healthcare settings.

Deficits in applicability of NGB CGs were also touted as a potential reason for low NGB diagnoses rates. The CGs are less likely to be routinely applied for diagnosing patients in

clinical practice owing to a lack of attention devoted towards overcoming barriers to implementation and a paucity of cost-effectiveness analyses (CEA). Improving the applicability should come through measures such as educational training of HCPs, increased incorporation of comparative effectiveness research (CER), better assessment of local barriers to implementation, CDSS, better monitoring of uptake and raising the profile and understanding of NGB. The CPRD study presented in this thesis paves the way for raising awareness of NGB.

9.3.3 Improving Efficiency of Care in Neurogenic Bladder

The CPRD study highlighted a number of resource-intensive components of the NGB patient journey; this included the high frequency of general practitioner (GP) and specialist visits, the substantial associated costs and a high level of complications. This information demonstrates the scale and scope of the burden and should guide the attention of policy makers towards recognising NGB as a health priority and supporting new policies and interventions in this disease area.

More than half of NGB patients were prescribed antibiotics for urinary tract infection (UTI), which is concerning given the significant costs related to managing UTI as well as the threat of antimicrobial resistance (AMR). Policy makers should focus on prevention of catheter associated UTI (CAUTI), through enhancing awareness of basic infection control measures and introducing targeted interventions (Trautner et al., 2005).

In order to improve efficiencies in NGB, CER should be incorporated into all CG recommendations. The CPRD study in this thesis provides fundamental data that could be used to inform economic models. Through a consideration of local budgets and the promotion of cost-effective treatments, treatment pathways can be enhanced, costs and resources saved and variation in care reduced. In particular, because of the associated risk of dementia, it is essential to objectively assess the benefits and harms of using alternatives to bladder muscarinics in NGB.

Although the incorporation of health economics is essential, there are some barriers that must first be overcome. Due to their broad country remits and lack of resources, CER is not feasible in the EAU and ICI CGs. Although the national scope makes economic analysis possible in the NICE CGs, complete de novo analysis is not realistic given the infeasibility of acquiring resources for such a monumental task. Increased collaboration between these institutions could encourage better integration of health economics in the CGs.

Moreover, there may be resistance to adopting cost-effective recommendations because of clinicians' distrust of health economics (Wailoo et al., 2004; Gupta et al., 2017). One example of this is the potential resistance to the NICE recommendation which suggests conducting bladder augmentation before Onabotulinum-A in patients likely to benefit from treatment for more than 10 years because surgical intervention is potentially curative, possibly resulting in a net cost savings. Clinicians should be educated on the importance of health economics to ensure that once CER is integrated into recommendations, they are genuinely applied in practice.

9.4 Further Research

9.4.1 Enhance the Research Efforts in Neurogenic Bladder Through Modification of the Evidence-Based-Medicine Hierarchy

All NGB CGs were created with the utmost methodological rigour (Section 3.6.5.4) however, in the absence of high-quality research, the developers had no choice but to rely upon expert opinion for the formation of certain recommendations (Chapter 4). Research efforts need to be amplified in order to strengthen the recommendations and thus encourage evidence-based care in clinical practice.

Real-World Evidence (RWE) is essential in filling the evidence gap that currently exists in NGB. Given that CGs are designed for application in real-world clinical practice, the notion that RWE is inherently less valuable than randomised controlled trials (RCTs) seems illogical (Kim et al., 2018). External validity should be emphasised and held up in greater steed because observational studies ensure that recommendations can be applied to different

persons, settings and times, which is especially important in this heterogenous patient population (Fernandez et al., 2015). Moreover, RCTs are largely infeasible to conduct in NGB populations due to difficult patient populations and the apparent self-evident nature of interventions (Buckley and Grant, 2009).

Descriptive epidemiology such as the research presented in this thesis is an important preliminary step to generate hypotheses in under-researched disease areas such as NGB; however, the causes of any trends observed and discussed are purely speculative. Analytic studies are paramount for the evaluation of factors associated with observed trends. Accordingly, pharmacoepidemiological studies utilising electronic healthcare records (EHRs), pragmatic trials and disease registries at centres managing a diverse range of neurological conditions should be prioritised in bridging the gap between efficiency and real-world effectiveness. This will strengthen the recommendations in NGB CGs, encourage increased CER and lead to tangible improvements in the management of patients and lowering of the excessive HRU burden (Ford and Norrie, 2016). In order for RWE to be readily accepted, the linear model of evidence-based medicine (EBM) needs to be revolutionised so that it takes into account the complexity of knowledge and the ability of different study designs to complement each other (Fernandez et al., 2015).

9.4.2 Epidemiological Research in Other Countries

This research consisted of an epidemiological study which provided insight into the UK NGB population and a quality assessment of the CGs that are most typically utilised in the UK and Europe. Although the evidence could be beneficial in other countries for purposes of improved awareness of the disease, the findings are primarily relevant for the UK, because patient populations, healthcare systems and clinical practice norms differ between countries.

The research should incentivise additional epidemiological studies to characterise the NGB patient population in other countries, as the first step in reducing the burden of disease worldwide. This will be particularly useful in developing nations where resources are

significantly stretched and consequently, urological care is of lower quality (Przydacz et al., 2017). It will also aid in cross-comparison between countries, allowing insight into the possible disparities that exist in treatment patterns and quality of care. It is however important to consider that limited access to high quality data from real world data (RWD) and poor IT infrastructure may impair the ability to apply RWE in these countries (Luna et al., 2014).

9.4.3 Qualitative Research

The research in this thesis provided valuable insight into the NGB population through critical analysis of the most prominent CGs and observational research using EHR data. The evidence generated does however fall short of truly understanding the patient experience. The healthcare environment is becoming increasingly patient centric in nature, with patient insight sought at multiples points of the healthcare journey, including during CG development, from health technology assessment (HTA)/payers during reimbursement discussions, from regulators, and in the improvement of services (du Plessis et al., 2017). This insight helps prescribers and policy makers understand patient needs when selecting and advocating optimal management techniques (Fraser et al., 2006). Furthermore, through more progressive models of EBM, qualitative research could help to improve the recommendations in CGs to adopt a more patient-centric approach.

Despite the shift in environment, there has been very little progress in the way of understanding NGB from the perspective of patients (Patel et al., 2016). The CPRD provide a research service which allows the recruitment of patients into interventional studies, presenting a unique opportunity for the same or a similar cohort that was enrolled in the present CPRD retrospective study to be also be followed up prospectively. Patient Reported Outcomes (PROs), measure several subjective and objective dimensions of health through the perspective of the patient (Bonniaud et al., 2008; Megari, 2013) and can be completed electronically in the CPRD research services platform, thus saving the typical hassle and burden of administering paper-based or iPad versions (Valentine, 2018). Patients can also be asked to participate in interviews pertaining to their condition. Qualitative research such

as patient interviews are an excellent way to broaden the evidence base, as QoL measures often prove insufficient to capture the complexity of the patient experience. Interviews can be semi-structured, where open ended questions are posed to the patient in a bid to explore their experiences and viewpoints. Alternatively, interviews may be in-depth, where there is the opportunity to uncover issues or concerns that may not have even been considered by the researchers (Pope et al., 2002). Meta-synthesis, the process of qualitative meta-analysis is still scarcely conducted, which could make understanding these prospective results difficult in the context of other research in this area (Levitt, 2018).

The CPRD interventional research service can also be utilised to administer clinician surveys. Clinicians play a central role in the care of NGB patients and possess unique insight on several key aspects of the patient journey. Surveys are excellent way to access this information and achieve a better understanding of their personal practices and opinions (Chen et al., 2016). As a continuation from the epidemiological CPRD study presented in this thesis, doctors could be probed on the rationale for their prescribing decisions including the reasons for their use of certain combinations of drugs, the prescription of 5-ARI's and α-adrenergic antagonists in women, querying their knowledge on the dangers of anticholinergic burden in NGB, as well as understanding their general attitudes and knowledge of NGB.

The cognitive errors that lead to diagnosis error can also be explored through surveys. One of the potential rationalisations for low NGB diagnosis rates was the lack of referrals by HCPs to a urologist (60% of the original NGB source cohort were not referred to a urologist). It is however important to remember that this, and the other reasons detailed in Section 8.2 remain purely speculative. Through the physician surveys, the rationale for not regularly referring patients to a urologist could be uncovered. More nuanced questions can be also be asked, such as whether patients with certain neurological conditions are referred faster.

9.4.4 Research into Anticholinergic Burden in Patients with Neurological Conditions

There is a pronounced lack of attention given to anticholinergic burden in the three prominent NGB CGs, leaving clinicians without easily accessible guidance on the safe use of these drugs in this patient population. This may provide, at least in part, some explanation for the high ACB score, coupled with the high frequency of oxybutynin use observed in the CPRD study. Moreover, payers do not seem to differentiate between the different bladder muscarinics, despite important differences in pharmacokinetic profiles, translating in differing abilities to cause cognitive deficit.

To date, little research has been conducted to determine the risk anticholinergics pose to patients with neurological disorders. The evidence that does exist suggests their use can be problematic because they can precipitate cognitive dysfunction and increase morbidity (Crispo et al., 2016; Cruce et al., 2012). There are several possible alternatives which can avoid the associated cognitive adverse events related to bladder muscarinics. One option is the β3-adrenoceptor agonist, mirabegron, which is the only other oral pharmacotherapy available on the market for symptoms of OAB. Management methods such as behavioural techniques are encouraged in the NGB CGs despite the objective lack of evidence supporting their use (Section 4.4.1). The evidence base for mirabegron is also small, however it is not advocated in the same way. It was approved by NICE in 2013 for OAB, considerably later than many other treatments, which could indicate a lack of prescribing experience amongst clinicians, and consequently a reluctance to advocate it (Chapple et al., 2017; MIMS, 2013). The low frequency of use in real world practice is evidenced in the CPRD study (1.2% of overall OAB drug use).

Practitioners will inevitably begin to accumulate more experience of using mirabegron in NGB over the coming years. This needs to be accompanied by an increased drive towards CER, considering the various alternatives strategies to bladder muscarinics. This research is imperative to bolster the recommendations for mirabegron and other safer alternatives (including less potent bladder muscarinics) in the NGB CGs. Furthermore, to remedy the

dearth in evidence and quantify the extent of harm to patients, longitudinal real-world studies, monitoring cognitive function in patients with neurological conditions receiving anticholinergics are of great interest. This may be what is needed to influence prescribers and payers to improve the NGB treatment pathway and subsequently avoid the downstream costs of managing MCI and dementia associated with bladder muscarinics.

9.5 Conclusions

This thesis presents entirely novel research into the area of NGB, filling a crucial knowledge gap that currently exists in this disease area and highlighting this disease area as a health priority.

The comprehensive CG quality appraisal and comparison provides a wealth of information on both the advantages and disadvantages of the current NGB CGs, providing insight into how well-equipped practitioners are to manage patients. The assessment revealed that the evidence base on which recommendations are constructed is weak. The CPRD study is the first stepping stone into improving the understanding of the real-world population. A culture-shift on the notion of RCTs as the highest form of evidence is necessary for any additional epidemiological research to be readily accepted and integrated into recommendations. Increased collaboration between NICE, EAU and ICI are essential for the creation of harmonious recommendations and improving the economic applicability across countries.

The UK-wide epidemiological study significantly enhanced the understanding of the UK NGB population. The results demonstrated that the polypharmacy, anticholinergic burden and rate of comorbidities were high, and the healthcare burden was significant. The study also illuminated the issue of diagnosis error in NGB. By introducing modifications in CG development many of these issues could be improved and/or managed more effectively. Furthermore, it is evident that increased awareness of NGB amongst neurologists, payers, patients and GPs is imperative to further raise the profile of this disease and encourage improvements in health policy and management

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Appendices

Appendix 1: Journal article published in Neurourology and Urodynamics

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ORIGINAL BASIC SCIENCE ARTICLE

WILEY Neurourology Urodynamics ICS SUFU

Drug utilization patterns and healthcare resource use and costs in patients with neurogenic bladder in the United Kingdom: A retrospective primary care database study

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Abstract

Aim: To characterize patients with neurogenic bladder (NGB), their treatment patterns, healthcare resource utilization, and associated costs based on records from a primary care database in the United Kingdom.

Methods: This was a retrospective, descriptive, observational study of anonymized data from the Clinical Practice Research Datalink and Hospital Episode Statistics databases (selection period, 1 January 2004 to 31 December 2016). Adults with a definitive or probable diagnosis of NGB and ≥1 referral to a urologist were included.

Results: The study cohort included 3913 patients with definitive (n = 363) or probable (n = 3550) NGB. Patients had a mean of 8.6 (standard deviation [SD], 7.6) comorbidities, and mean Anticholinergic Cognitive Burden Scale score of 6.6 (SD, 5.9). During 12 months' follow-up, urinary tract infection (UTI) and urinary incontinence were the most common complications. Most patients (92.2%) received ≥1 prescription for an antimuscarinic agent or mirabegron, and 53.9% of patients received prescriptions for UTI-specific antibiotics. The mean number of visits to a general practitioner for any cause was 67.7 (SD, 42.6) per individual. Almost half (46.7%) of the study cohort visited a specialist during the 12-month follow-up period, and 11.0% had ≥1 hospital admission. Total mean per patient costs for healthcare resource utilization was £2395.

Conclusions: The burden of illness, healthcare resource needs, and associated costs among patients with NGB are considerable. Drug prescribing patterns are consistent with the symptoms and complications of NGB, although increased awareness of drugs with anticholinergic activity among prescribers may help to reduce the cumulative anticholinergic burden in this vulnerable population.

KEYWORDS
cholinergic antagonists, comorbidity, healthcare costs, healthcare resources, neurogenic, retrospective studies, urinary bladder

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1 | INTRODUCTION

Neurogenic bladder (NGB) is a general term used to describe lower urinary tract dysfunction secondary to neurological disease or central nervous system (CNS) injury.[1] It is thought to affect more than 90% of patients with spina bifida and spinal cord injury, 50% to 80% of patients with multiple sclerosis,[2] 37 to 72% of patients with Parkinson's disease, and 15% of patients with stroke.[3]

NGB has many clinical presentations, and the exact type of urinary tract dysfunction depends on the site, extent, and evolution of the neurological lesion.[4] Urinary symptoms include frequency, urgency, and urinary incontinence. Patients may also be at risk of urinary tract infection (UTI), bladder outlet obstruction, and more serious long-term sequelae of urosepsis and renal failure.[3] For patients with neurological disease, lower urinary tract dysfunction may be one of the worst aspects of their condition,[4] and symptoms are known to have a marked negative effect on quality of life.[5–7]

The goals of treatment for NGB are to restore lower urinary tract function, achieve or maintain urinary continence, protect against renal failure, improve quality of life,[8] and minimize the risk of complications, such as UTI.[9] Management strategies include noninvasive conservative treatments, catheters, and surgery, as well as pharmacological therapies.[4,8,10] The main pharmacological treatments are antimuscarinic agents for neurogenic detrusor overactivity (NDO) and antibiotics for UTIs.[4,8]

There is little information on how patients with NGB are managed in clinical practice,[1] and no studies have been done in the United Kingdom (UK). The primary objective of this study was to characterize patients with NGB in terms of demographics, comorbidities, and complications, and to evaluate their adopted treatment patterns in terms of drug utilization. The study also assessed healthcare resource utilization and associated costs in these patients during a 12-month follow-up period, based on records from a primary care database in the UK. These study objectives were also explored separately according to the underlying neurological condition, as this may influence symptom presentation and severity.

2 | PATIENTS AND METHODS

2.1 | Study design and data sources

This was a retrospective, descriptive, observational study performed using anonymized data from the Clinical Practice Research Datalink (CPRD) GOLD and Hospital Episode Statistics (HES) databases. CPRD is a longitudinal primary care research database that collates medical records from 674 general practices across the UK, and is representative of the national population in terms of age, sex, and ethnicity.[11] It contains information on patient demographics, prescriptions, medical history, diagnostic testing, and secondary care referrals. HES collates data on inpatient, outpatient, and accident and emergency admissions from National Health Service (NHS) hospitals in England; approximately 58% of practices within the CPRD network have consented to a linkage scheme enabling patient-level data to be linked to other databases including HES.[11]

The study was conducted in compliance with requirements for ensuring the rights of participants in non-interventional studies.[12]

2.2 | Study population

The study selection period was from 1 January 2004 to 31 December 2016. Adults aged ≥19 years with a definitive or probable diagnosis of NGB were included. A definitive diagnosis required ≥1 diagnosis of NGB or neuropathic bladder within the study selection period. A probable diagnosis required a diagnosis of Parkinson's disease, multiple sclerosis, spinal cord injury, or stroke within the study selection period; or a diagnosis of spina bifida within the entire CPRD database, in addition to a subsequent diagnosis of overactive bladder (OAB) and/or ≥1 prescription for an OAB medication. Patients were also required to have ≥12 months of continuous enrollment in the CPRD database before the index date (defined as the date of diagnosis of the neurological condition or, for patients with spina bifida, the date of OAB diagnosis or OAB drug prescription, whichever came first), and 12 months continuous enrollment after diagnosis of OAB or OAB drug prescription (Figure S1). All patients were required to have ≥1 referral to a urologist within 12 months before or 12 months after the index date. Patients with idiopathic OAB, a diagnosis of dementia, or those missing data for age or sex were excluded. Only patients deemed acceptable for research by the CPRD, and for whom the study period occurred during an uninterrupted period where the practice was deemed "up to standard,"[11] were included.

2.3 | Study objectives and endpoints

Full details and definitions of study endpoints are provided in Table S1. For the primary objectives, comorbidities were assessed using a proxy measure, that is, the number of drug classes prescribed according to British National Formulary (BNF) headers.[13] Complications considered were UTIs, urinary incontinence, sepsis/septicemia,

urinary retention, obstructive uropathy, renal failure, and hydronephrosis. Drug utilization at index date was described by prescriptions for oral OAB drugs, prescriptions for drugs with anticholinergic activity, Anticholinergic Cognitive Burden (ACB) Scale score calculated within 1 month before and after first OAB/NGB diagnosis or OAB drug prescription date (see Appendix for details),[14,15] and polypharmacy, that is, the number of substances prescribed according to BNF headers. Drug utilization during the 12-month follow-up period included prescriptions for oral OAB drugs, OAB drug combinations (ie, prescriptions overlapping for >30 days), α-adrenergic antagonists or 5α-reductase inhibitors, and UTI-specific antibiotics.

Secondary objectives were to describe healthcare resource utilization and related costs during the 12-month follow-up period. Resource use was defined as all-cause general practitioner (GP) consultations, urological investigations (urodynamics, cystoscopy, imaging), specialist visits (urologist and gynecologist), prescriptions for incontinence pads, procedures/surgical interventions (urology), and hospital visits (urology). Costs were estimated by multiplying each occurrence of resource use by unit costs derived from NHS tariffs or other UK-specific sources[16–18] (Table S2).

2.4 | Data analyses

Statistical analyses were descriptive only. Analyses were performed in the overall study cohort and stratified by underlying neurological condition (Parkinson's disease, multiple sclerosis, spinal cord injury, stroke, and spina bifida), age (19-65 vs >65 years), and sex (female vs male). A sensitivity analysis of the primary objective was performed using an alternative definition of patients with probable NGB, that is, the diagnosis of neurological condition and OAB diagnosis/OAB drug prescription could be in any order. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

2.5 | Ethical approval

Approval for the study protocol was obtained from the CPRD Independent Scientific Advisory Committee [protocol: 17_207RMn].

3 | RESULTS

3.1 | Study population

Between 1 January 2004 and 31 December 2016, 19 499 patients with definitive or probable NGB were identified (Figure 1). After applying the predefined eligibility criteria, 15 586 (79.9%) patients were excluded, most commonly because they were not referred to a urologist (n = 11 946, 61.3%) or because the preindex period was <12 months (n = 5658, 29.0%). The remaining 3913 (20.1%) patients constituted the study cohort, of whom 363 (9.3%) patients had definitive NGB and 3550 (90.7%) patients had probable NGB. Patients with probable NGB were stratified into the following cohorts based on their underlying neurological condition (note: groups were not mutually exclusive): stroke (n = 1720); multiple sclerosis (n = 1029); Parkinson's disease (n = 713); spina bifida (n = 180); and spinal cord injury (n = 41). Approximately 50% of the study cohort (n = 2330 patients) had data linked to the HES database.

The study cohort had a mean age of 61.7 (standard deviation [SD], 16.3) years, and 59.6% were men (Table 1). Comorbidities, assessed by the number of different drug classes prescribed, were common (mean 8.6 [SD, 7.6]), and occurred more frequently among older than younger patients (mean 10.0 [SD, 7.3] vs 7.4 [SD, 7.7]) (Table S3).

3.2 | Drug utilization

Two-thousand one-hundred and thirty-seven (54.6%) patients received ≥1 prescription for drugs with anticholinergic activity before the index period (Table 1). The drugs with at least partial anticholinergic activity were not solely the OAB-therapeutic antimuscarinics. Those most commonly prescribed were solifenacin (8.5%), warfarin (weakly anticholinergic, 7.9%), furosemide (weakly anticholinergic, 7.6%), amitriptyline (7.2%), oxybutynin (7.1%), codeine/paracetamol (weakly anticholinergic, 6.9%), and tolterodine (6.0%) Table S4). The mean ACB score, a measure of cumulative anticholinergic burden, was 6.6 (SD, 5.9) in the study cohort, and ranged from 2.9 (definite NGB cohort) to 7.6 (stroke cohort) (Table 1), but was similar between age and sex subgroups (Table S3).

At index date, 3175 (81.1%) patients were receiving an oral antimuscarinic agent or mirabegron. The most commonly prescribed agents were solifenacin (n = 992, 25.4%), oxybutynin immediate-release (n = 803, 20.5%), tolterodine (n = 723, 18.5%), and oxybutynin extended-release (n = 233, 6.0%) (Table 1). Other agents (including mirabegron) were each prescribed to <5% of patients.

3.3 | During 12-month follow-up

Most of the study cohort (92.2%) received ≥ 1 prescription for an oral antimuscarinic agent or mirabegron over the 12-month follow-up period (Table 2); the mean number of prescriptions per individual was 6.9 (SD, 8.2). A notable exception was the definitive NGB cohort, where only 29.8% of patients received ≥ 1 prescription for these agents

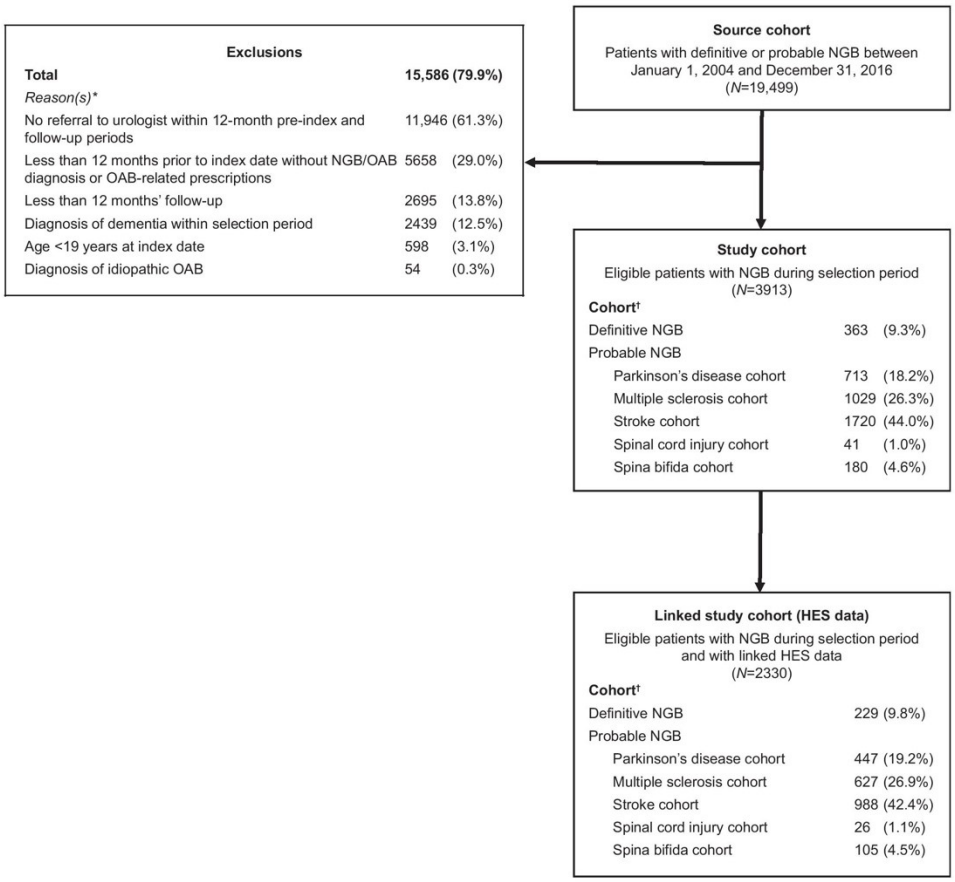

FIGURE 1 Patient selection flowchart. HES, Hospital Episodes Statistics; NGB, neurogenic bladder; OAB, overactive bladder. *Patients may have been excluded for more than one reason. †Patients may have been eligible for more than one cohort

and had an average of 1.6 (SD, 3.5) prescriptions per individual. The mean cumulative number of days' supply of OAB drugs was 203 (SD, 211) per individual in the study cohort. Overall, 312 (8.0%) patients were prescribed a combination of OAB drugs; the most common combinations included solifenacin, tolterodine, and oxybutynin (Table S5). Approximately half the cohort (53.9%) had prescriptions for antibiotics to treat UTIs, and 997 (25.5%) patients had prescriptions for α-adrenergic antagonists or 5α-reductase inhibitors (Table 2). Drug utilization patterns were similar between age and sex subgroups, except for α-adrenergic antagonists/5α-reductase inhibitors were prescribed more often in men (40.7% vs women, 3.0%) and older patients (37.4% vs younger, 14.5%) (Table S6).

3.4 | Complications

During the 12-month follow-up period, 558 (14.3%) patients had UTIs and 557 (14.2%) patients experienced urinary incontinence (Table 3). Other complications were each recorded in <3% of patients. UTIs and urinary incontinence were the most commonly reported complications regardless of underlying neurological condition (Table 3), age, or sex (Table S7).

3.5 | Healthcare resource use and costs

Healthcare resource use and costs during the 12-month follow-up period are presented in Table 4, and by age and sex in Table S8. All patients had ≥1 GP consultation for any cause, with a mean of 67.7 (SD, 42.6) visits per

TABLE 1 Demographic, clinical characteristics, and drug utilization before or at index date (overall study cohort and by underlying neurological condition)

Variable		Definitive NGB (N = 363)	Probable NGB					All (N = 3913)
			PD cohort (N = 713)	MS cohort (N = 1029)	STK cohort (N = 1720)	SCI cohort (N = 41)	SB cohort (N = 180)	
Age at index date, y	Mean (SD)	48.3 (15.9)	70.7 (9.2)	48.7 (11.8)	70.3 (11.6)	46.6 (14.8)	36.1 (11.9)	61.7 (16.3)
Sex, n (%)	Male	199 (54.8)	535 (75.0)	357 (34.7)	1188 (69.1)	31 (75.6)	90 (50.0)	2334 (59.6)
	Female	164 (45.2)	178 (25.0)	672 (65.3)	532 (30.9)	10 (24.4)	90 (50.0)	1579 (40.4)
Time from diagnosis of NGB/ underlying conditions and OAB diagnosis/drug prescription, days	No. of valid values Mean (SD)	135 846 (1064)	711 1034 (1008)	1017 1096 (1010)	1715 1029 (986)	37 458 (520)	135 4149 (4161)	3678 1140 (1353)
Comorbidities within the 12-mo pre-index period, (using BNF headers/codes)	Mean (SD)	9.6 (9.1)	9.1 (6.9)	6.5 (7.1)	9.3 (7.6)	7.1 (8.6)	11.0 (8.9)	8.6 (7.6)
Polypharmacy at index date (using substances)	Mean (SD)	4.6 (5.0)	5.6 (4.2)	3.3 (3.7)	5.7 (4.6)	3.6 (4.8)	5.4 (4.8)	5.0 (4.4)
ACB score[a]	Mean (SD)	2.9 (4.5)	6.8 (5.9)	6.0 (4.9)	7.6 (6.3)	6.9 (7.1)	4.6 (4.7)	6.6 (5.9)
Prescriptions for anticholinergic drugs within the 12-mo preindex period,[b] n (%)	Any 1 2 3 ≥4	185 (51.0) 68 (18.7) 49 (13.5) 22 (6.1) 46 (12.7)	408 (57.2) 172 (24.1) 116 (16.3) 47 (6.6) 73 (10.2)	465 (45.2) 223 (21.7) 133 (12.9) 59 (5.7) 50 (4.9)	982 (57.1) 384 (22.3) 263 (15.3) 154 (9.0) 181 (10.5)	17 (41.5) 6 (14.6) 4 (9.8) 3 (7.3) 4 (9.8)	144 (80.0) 63 (35.0) 34 (18.9) 22 (12.2) 25 (13.9)	2137 (54.6) 893 (22.8) 580 (14.8) 298 (7.6) 366 (9.4)
OAB drug at index date, *n* (%)	Yes	37 (10.2)	614 (86.1)	885 (86.0)	1515 (88.1)	34 (82.9)	131 (72.8)	3175 (81.1)
	Darifenacin	0	8 (1.1)	2 (0.2)	4 (0.2)	0	0	14 (0.4)
	Fesoterodine	0	20 (2.8)	31 (3.0)	49 (2.8)	2 (4.9)	2 (1.1)	104 (2.7)
	Flavoxate	0	12 (1.7)	11 (1.1)	17 (1.0)	0	3 (1.7)	43 (1.1)
	Mirabegron	0	19 (2.7)	9 (0.9)	19 (1.1)	0	1 (0.6)	48 (1.2)
	Oxybutynin ER	3 (0.8)	33 (4.6)	78 (7.6)	96 (5.6)	12 (29.3)	14 (7.8)	233 (6.0)
	Oxybutynin IR	12 (3.3)	119 (16.7)	265 (25.8)	380 (22.1)	6 (14.6)	31 (17.2)	803 (20.5)
	Propiverine Solifenacin	1 (0.3) 10 (2.8)	5 (0.7) 208 (29.2)	11 (1.1) 243 (23.6)	10 (0.6) 495 (28.8)	1 (2.4) 8 (19.5)	1 (0.6) 41 (22.8)	28 (0.7) 992 (25.4)
	Tolterodine	7 (1.9)	143 (20.1)	194 (18.9)	349 (20.3)	4 (9.8)	36 (20.0)	723 (18.5)
	Trospium	4 (1.1)	47 (6.6)	41 (4.0)	96 (5.6)	1 (2.4)	2 (1.1)	187 (4.8)

Abbreviations: ACB, anticholinergic cognitive burden; BNF, British National Formulary; ER, extended release; IR, immediate release; MS, multiple sclerosis; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; SB, spina bifida; SCI, spinal cord injury; SD, standard deviation; STK, stroke.

[a]Prescribed medications with anticholinergic activity and negative cognitive effects were identified from Aging Brain Care[15] and categorized according to the following scale: no anticholinergic activity (0) to definite/high anticholinergic activity (3).[14] ACB score is the total score for all drugs prescribed to an individual patient. ACB score was calculated within 1 mo before and after the first OAB/NGB diagnosis or OAB drug prescription date. Note: over-the-counter medications were not included.

[b]Identified from Aging Brain Care.[15]

TABLE 2 Drug utilization during the 12-mo follow-up period (overall study cohort and by underlying neurological condition)

Variable		Definitive NGB (N = 363)	Probable NGB					All (N = 3913)
			PD cohort (N = 713)	MS cohort (N = 1029)	STK cohort (N = 1720)	SCI cohort (N = 41)	SB cohort (N = 180)	
Number of oral OAB drug prescriptions	Mean (SD)	1.6 (3.5)	7.6 (8.1)	7.1 (7.3)	7.5 (9.1)	9.0 (5.6)	5.0 (6.3)	6.9 (8.2)
Number of oral OAB drug prescriptions, n (%)	0	255 (70.2)	11 (1.5)	35 (3.4)	29 (1.7)	4 (9.8)	44 (24.4)	307 (7.8)
	1-4	58 (16.0)	304 (42.6)	412 (40.0)	759 (44.1)	5 (12.2)	63 (35.0)	1571 (40.1)
	5-9	31 (8.5)	160 (22.4)	275 (26.7)	416 (24.2)	13 (31.7)	32 (17.8)	911 (23.3)
	10-14	14 (3.9)	177 (24.8)	243 (23.6)	370 (21.5)	13 (31.7)	37 (20.6)	841 (21.5)
	15-44	5 (1.4)	51 (7.2)	52 (5.1)	117 (6.8)	6 (14.6)	3 (1.7)	231 (5.9)
	≥45	0	10 (1.4)	12 (1.2)	29 (1.7)	0	1 (0.6)	52 (1.3)
Cumulative number of days' supply of oral OAB drugs	Mean (SD)	50.5 (112.5)	221.5 (202.3)	222.2 (188.5)	210.4 (232.6)	273.2 (158.5)	155.0 (155.6)	202.9 (210.9)
Cumulative number of days' supply of oral OAB drugs, n (%)	0-29	272 (74.9)	101 (14.2)	155 (15.1)	283 (16.5)	7 (17.1)	66 (36.7)	804 (20.5)
	30-119	40 (11.0)	190 (26.6)	250 (24.3)	455 (26.5)	2 (4.9)	34 (18.9)	952 (24.3)
	120-349	32 (8.8)	201 (28.2)	318 (30.9)	515 (29.9)	15 (36.6)	44 (24.4)	1107 (28.3)
	350-549	18 (5.0)	211 (29.6)	292 (28.4)	445 (25.9)	17 (41.5)	36 (20.0)	1003 (25.6)
	≥550	1 (0.3)	10 (1.4)	14 (1.4)	22 (1.3)	0	0	47 (1.2)
Oral OAB drug combination use, n (%)	Yes	10 (2.8)	58 (8.1)	105 (10.2)	130 (7.6)	2 (4.9)	11 (6.1)	312 (8.0)
Number of prescriptions for antibiotics for UTI[a]	Mean (SD)	2.7 (4.3)	1.7 (3.3)	2.4 (4.2)	2.1 (3.8)	3.5 (4.9)	3.1 (6.2)	2.2 (4.0)
Number of prescriptions for antibiotics for UTI[a], n (%)	0	159 (43.8)	371 (52.0)	473 (46.0)	768 (44.7)	20 (48.8)	71 (39.4)	1803 (46.1)
	1-4	130 (35.8)	261 (36.6)	384 (37.3)	713 (41.5)	8 (19.5)	70 (38.9)	1520 (38.8)
	5-9	42 (11.6)	55 (7.7)	97 (9.4)	144 (8.4)	9 (22.0)	25 (13.9)	352 (9.0)
	10-14	23 (6.3)	22 (3.1)	49 (4.8)	54 (3.1)	2 (4.9)	9 (5.0)	155 (4.0)
	15-19	9 (2.5)	4 (0.6)	26 (2.5)	40 (2.3)	2 (4.9)	4 (2.2)	81 (2.1)
	≥20	0	0	0	1 (0.1)	0	1 (0.6)	2 (0.1)
Number of α-adrenergic antagonists or 5-ARI prescriptions[b]	Mean (SD)	0.8 (2.9)	4.3 (9.8)	0.6 (2.4)	4.3 (9.5)	0.6 (3.8)	0.6 (2.7)	2.9 (8.0)
Number of α-adrenergic antagonists or 5-ARI prescriptions,[b] n (%)	0	321 (88.4)	448 (62.8)	958 (93.1)	1107 (64.4)	39 (95.1)	165 (91.7)	2916 (74.5)
	1-4	14 (3.9)	63 (8.8)	18 (1.7)	126 (7.3)	1 (2.4)	6 (3.3)	223 (5.7)
	5-9	16 (4.4)	76 (10.7)	26 (2.5)	177 (10.3)	0	4 (2.2)	296 (7.6)
	10-14	10 (2.8)	76 (10.7)	23 (2.2)	190 (11.0)	0	4 (2.2)	300 (7.7)
	15-19	2 (0.6)	41 (5.8)	4 (0.4)	102 (5.9)	1 (2.4)	1 (0.6)	151 (3.9)
	≥20	0	9 (1.3)	0	18 (1.0)	0	0	27 (0.7)

Abbreviations: 5-ARI, 5α-reductase inhibitors; MS, multiple sclerosis; NGB, neurogenic bladder; OAB, overactive bladder; PD, Parkinson's disease; SB, spina bifida; SCI, spinal cord injury; SD, standard deviation; STK, stroke; UTI, urinary tract infection.

[a]Trimethoprim, ciprofloxacin, nitrofurantoin, amoxicillin, amoxicillin/clavulanic acid at any dosage.

[b]Doxazosin, tamsulosin, alfuzosin, terazosin, finasteride, dutasteride at any dosage.

individual over the 12-month follow-up period. Patients with stroke or spinal cord injury visited their GP more often (76.3 and 75.5, respectively) than other cohorts (range, 49.9-69.7). The estimated overall mean cost of GP consultations was £1448 (SD, £967) per individual. Overall, 2.5% of the study cohort had ≥1 urodynamic test (mean cost, £179 [SD, 94] per individual), 8.8% underwent cystoscopy (£171 [SD, 66] per individual), and 2.1% had urology-related imaging (£101 [SD, 83] per individual). Only 14 (0.4%) patients in the study cohort were prescribed incontinence pads (mean cost, £40 [SD, 47] per individual). Almost half of the study cohort (46.7%) visited a specialist (urologist or gynecologist) over the 12-month follow-up period, with a mean 2.3 (SD, 1.7) visits at a mean cost of £253 (SD, 186) per individual; most visits (90.8%) were to a urologist rather than a gynecologist (Table 4). At least one procedure or surgical intervention was performed in 5.7% of the study cohort at a mean cost of £2285 (SD, £3919) per individual. Overall, 11.0% (n = 431) of the study cohort were hospitalized for

TABLE 3 Complications during the 12-mo follow-up period (overall study cohort and by underlying neurological condition)

Complication,[a] n (%)	Definitive NGB(N = 363)	Probable NGB					All(N = 3913)
		PD cohort (N = 713)	MS cohort (N = 1029)	STK cohort (N = 1720)	SCI cohort (N = 41)	SB cohort (N = 180)	
Urinary tract infection	71 (19.6)	72 (10.1)	153 (14.9)	237 (13.8)	14 (34.1)	35 (19.4)	558 (14.3)
Urinary incontinence	31 (8.5)	119 (16.7)	141 (13.7)	260 (15.1)	2 (4.9)	21 (11.7)	557 (14.2)
Urinary retention	13 (3.6)	21 (2.9)	19 (1.8)	45 (2.6)	0	1 (0.6)	96 (2.5)
Sepsis/septicemia	4 (1.1)	5 (0.7)	7 (0.7)	18 (1.0)	1 (2.4)	2 (1.1)	34 (0.9)
Renal failure (acute or other)	13 (3.6)	5 (0.7)	2 (0.2)	7 (0.4)	0	5 (2.8)	27 (0.7)
Hydronephrosis	6 (1.7)	3 (0.4)	1 (0.1)	3 (0.2)	0	3 (1.7)	14 (0.4)
Obstructive uropathy	0	0	0	0	0	1 (0.6)	1 (0.0)

Abbreviations: MS, multiple sclerosis; NGB, neurogenic bladder; PD, Parkinson's disease; SB, spina bifida; SCI, spinal cord injury; STK, stroke.
[a]Each complication was identified from medical records using prespecified read codes.

a mean of 12.5 days during the 12-month follow-up period; 17.4% (75 of 431) of hospitalized patients were admitted after renal failure. Hospital admissions were more common in the definite NGB and spinal cord injury cohorts (20.1% and 19.5%, respectively) compared to other cohorts (range, 6.7 to 12.0%), but were similar between age and sex subgroups. The mean costs for hospitalization were £6256 (SD, £13,473) per individual.

3.6 | Sensitivity analysis

The primary objectives of the study were reanalyzed using an alternative definition for patients with probable NGB (ie, diagnoses for the underlying neurological condition or OAB diagnosis/OAB drug prescription could be in any order). The results were similar to those of the base-case analysis (data not shown).

4 | DISCUSSION

This study provides detailed descriptive information about patients with NGB and, to our knowledge, is the first study to characterize this patient population in the UK. Over the 13-year study selection period, we identified 363 patients with a definitive diagnosis of NGB and a further 3550 patients with probable NGB based on proxy inclusion criteria. The high number of probable cases suggests that many patients with NGB may not be formally diagnosed in the UK, and is possibly indicative of low awareness of the condition among GPs and neurologists, or limitations in data coding practices. A notable feature of patient selection in our study was the requirement for at least one referral to a urologist, a criterion intended to reduce the risk of including non-NGB patients. This requirement led to the exclusion of many patients (61%) from the original source cohort, suggesting that our final study cohort may be an underestimate of the true size of the NGB population. It also highlights that primary care providers may take responsibility for much of the care of patients with NGB. We recognize also that the requirement for a urologist referral may have removed some patients with a lower burden of illness from our study, and suggest that this should be considered when interpreting the data.

Our findings suggest that patients with NGB have multiple comorbidities and complications. Urinary incontinence and UTIs were common, and more than half (54%) of our study population received prescriptions for UTI-specific antibiotics. Serious complications (renal failure and sepsis) were rare and affected less than 1% of patients each, although observation of these events is likely limited by the short 12-month follow-up period. A similar spectrum of complications was documented in a large US claims database study of patients with NGB (n = 46 271),[1] albeit at much higher frequencies than in our study. For example, UTIs, urinary retention, and sepsis/septicemia were reported in 33%, 14%, and 4% of patients in the US study,[1] respectively, compared with 14%, 2%, and 1% in our study. As key design features, including duration of follow-up, were similar between studies, the reason for the marked disparity between reporting rates is unknown.

The drug utilization patterns documented in our study were consistent with current NGB treatment guidelines.[4,8] Antimuscarinic agents are recommended as first-line pharmacological therapy for NDO,[4,8] and most (92%) patients in our study had ≥1 prescription for an

TABLE 4 Resource use and costs during the 12-mo follow-up period (overall study cohort and by underlying neurological condition)

				Probable NGB					
Resource	**Variable**		**Definitive NGB(N = 363)**	**PD cohort (N = 713)**	**MS cohort (N = 1029)**	**STK cohort (N = 1720)**	**SCI cohort (N = 41)**	**SB cohort (N = 180)**	**All (N = 3913)**
GP consultations (all-cause)[a]	≥1 visit	*n* (%)	363 (100)	713 (100)	1029 (100)	1720 (100)	41 (100)	180 (100)	3913 (100)
	Visits, n	Mean (SD)	55.2 (43.8)	69.7 (39.4)	57.4 (39.4)	76.3 (44.0)	75.5 (54.1)	49.9 (35.1)	67.7 (42.6)
	Cost, £	Mean (SD)	1181 (985)	1501 (911)	1218 (880)	1627 (1005)	1523 (1158)	1104 (809)	1448 (967)
		Median (range)	937 (46-6530)	1333 (114-8099)	1025 (37-9382)	1398 (46-10776)	1423 (46-6512)	963 (37-3925)	1244 (37-10776)
Specialist visits (urologist/ gynecologist)	≥1 visit (overall)	*n* (%)	184 (50.7)	342 (48.0)	396 (38.5)	859 (49.9)	23 (56.1)	92 (51.1)	1828 (46.7)
	Urologist		174 (47.9)	328 (46.0)	367 (35.7)	820 (47.7)	20 (48.8)	85 (47.2)	1729 (44.2)
	Gynecologist		18 (5.0)	20 (2.8)	50 (4.9)	79 (4.6)	5 (12.2)	9 (5.0)	175 (4.5)
	Visits, n (overall)	Mean (SD)	2.4 (1.6)	2.1 (1.4)	2.1 (1.4)	2.4 (1.8)	2.1 (1.2)	2.0 (1.4)	2.3 (1.7)
	Urologist		2.3 (1.7)	2.0 (1.5)	1.9 (1.4)	2.2 (1.8)	1.9 (1.4)	1.7 (1.3)	2.1 (1.6)
	Gynecologist		0.2 (0.5)	0.1 (0.5)	0.2 (0.7)	0.2 (0.8)	0.2 (0.4)	0.3 (1.0)	0.2 (0.7)
	Cost, £ (overall)	Mean (SD)	270 (182)	235 (159)	236 (160)	267 (207)	235 (132)	225 (171)	253 (186)
		Median (range)	219 (109-1094)	219 (109-1313)	219 (109-1079)	219 (109-1641)	219 (109-547)	141 (109-955)	219 (109-1641)
Incontinence pads	≥1 pad	*n* (%)	2 (0.6)	2 (0.3)	5 (0.5)	5 (0.3)	1 (2.4)	0	14 (0.4)
	Prescriptions, n	Mean (SD)	1.5 (0.7)	1.0 (0.0)	10.0 (7.0)	3.8 (4.2)	1.0 (…)	…	5.2 (6.0)
	Cost, £	Mean (SD)	13 (4)	8 (3)	88 (49)	10 (8)	50 (…)	…	40 (47)
		Median (range)	13 (10-16)	8 (6-10)	120 (16-126)	6 (4-24)	50 (50-50)	…	14 (4-126)
Urodynamics	≥1 test	*n* (%)	9 (2.5)	11 (1.5)	27 (2.6)	51 (3.0)	0	3 (1.7)	98 (2.5)
	Tests, n	Mean (SD)	1.1 (0.3)	1.8 (0.6)	1.7 (1.1)	1.3 (0.5)	…	1.0 (0.0)	1.4 (0.8)
	Cost, £	Mean (SD)	140 (42)	229 (76)	215 (135)	158 (66)	…	126 (0)	179 (94)
		Median (range)	126 (126-252)	252 (126-378)	126 (126-630)	126 (126-378)	…	126 (126-126)	126 (126-630)
Cystoscopy	≥1 test	*n* (%)	55 (15.2)	74 (10.4)	58 (5.6)	147 (8.5)	4 (9.8)	22 (12.2)	343 (8.8)
	Tests, n	Mean (SD)	1.2 (0.6)	1.1 (0.3)	1.1 (0.3)	1.2 (0.5)	1.0 (0.0)	1.2 (0.5)	1.2 (0.5)
	Cost, £	Mean (SD)	178 (87)	166 (50)	156 (37)	180 (78)	146 (0)	173 (73)	171 (66)
		Median (range)	146 (146-584)	146 (146-292)	146 (146-292)	146 (146-584)	146 (146-146)	146 (146-438)	146 (146-584)
Imaging[b]	≥1 test	*n* (%)	9 (2.5)	9 (1.3)	24 (2.3)	37 (2.2)	2 (4.9)	5 (2.8)	83 (2.1)
	Tests, n	Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.1 (0.3)	1.1 (0.3)	1.0 (0.0)	1.0 (0.0)	1.1 (0.3)
	Cost, £	Mean (SD)	73 (72)	64 (76)	138 (79)	87 (85)	144 (0)	92 (85)	101 (83)
		Median (range)	83 (0-144)	0 (0-144)	144 (0-288)	144 (0-288)	144 (144-144)	144 (0-173)	144 (0-288)

(Continues)

TABLE 4 (Continued)

Resource	Variable		Definitive NGB(N = 363)	Probable NGB					
				PD cohort (N = 713)	MS cohort (N = 1029)	STK cohort (N = 1720)	SCI cohort (N = 41)	SB cohort (N = 180)	All (N = 3913)
Procedures and surgical interventions (urology)[c,d]	≥1 procedure	*n* (%)	44 (12.1)	30 (4.2)	52 (5.1)	104 (6.0)	7 (17.1)	2 (1.1)	223 (5.7)
	Procedures, n	Mean (SD)	1.4 (0.8)	1.6 (0.9)	1.4 (0.6)	1.3 (0.6)	1.3 (0.5)	1.0 (0.0)	1.4 (0.7)
	Cost, £	Mean (SD)	3408 (7295)	2035 (1774)	1999 (2564)	2472 (5142)	789 (505)	2752 (3143)	2285 (3919)
		Median (range)	1513 (228-47419)	1529 (228-6802)	1163 (168-14934)	896 (220-47419)	693 (168-1410)	2752 (530-4975)	1123 (168-47419)
Hospitalizations (urology)[d,e]	≥1 hospitalization	*n* (%)	73 (20.1)	78 (10.9)	84 (8.2)	206 (12.0)	8 (19.5)	12 (6.7)	431 (11.0)
	Hospitalizations, n	Mean (SD)	2.1 (2.0)	1.4 (0.9)	1.7 (1.5)	1.5 (0.9)	1.6 (1.4)	2.3 (2.2)	1.6 (1.3)
	Admitted days, n	Mean (SD)	13.7 (38.4)	9.5 (14.5)	15.5 (32.8)	12.7 (23.5)	7.1 (9.6)	3.3 (6.1)	12.5 (26.6)
	Cost, £	Mean (SD)	8052 (20759)	5885 (8486)	6226 (14321)	5914 (11056)	2449 (2630)	7217 (15369)	6256 (13473)
		Median (range)	1943 (265-163720)	2604 (220-50521)	1794 (162-83317)	3146 (162-134885)	1648 (220-8335)	2134 (265-55306)	2590 (162-163720)
Total	Cost, £	Mean (SD)	3379 (10676)	2356 (3850)	1923 (5034)	2624 (4944)	2290 (2025)	1757 (4347)	2395 (5413)
		Median (range)	1308 (46-166644)	1546 (160-59696)	1180 (37-94393)	1667 (46-137794)	1858 (120-10171)	1182 (37-57354)	1458 (37-166644)

Abbreviations: GP, general practitioner; MS, multiple sclerosis; NGB, neurogenic bladder; PD, Parkinson's disease; SB, spina bifida; SCI, spinal cord injury; SD, standard deviation; STK, stroke.

[a]Includes surgery and clinical consultations, home visits, out-of-hours visits, and telephone consultations.

[b]Cystography, ultrasound, computed tomography, x-ray, magnetic resonance imaging, and other diagnostic imaging of bladder, spine, genitourinary system, pelvis or abdomen.

[c]Includes intermittent catheterization, indwelling catheterization, botulinum toxin A injections, sacral nerve stimulation, bladder augmentation, sling procedures, and artificial urinary sphincter.

[d]Derived from the Hospital Episode Statistics (HES) database. Patients without linked data available from HES were assumed to have not utilized these resources. Numbers of hospital admissions or procedures and surgical interventions were calculated among patients who had ≥1 resource use item.

[e]Admissions related to a urological disease, or to PD, MS, SCI, STK, SB with a related urological disease. Urological diseases included pyelonephritis, sepsis, hydronephrosis, uropathy, renal failure, chronic kidney disease, calculus, cystitis, neuropathic bladder, urethritis, urinary tract infection, proteinuria, incontinence, and retention.

antimuscarinic agent or mirabegron over the 12-month study period. It is possible that this rate may be elevated by the requirement for an OAB prescription for inclusion into the probable NGB cohort; the prescribing rate was lower (30%) in the definite NGB cohort whose selection was based on NGB diagnosis alone. It is also notable that some of this prescribing were off-label as several of these agents do not have marketing authorization for the treatment for NGB in the UK. Antimuscarinic combinations, also supported by treatment guidelines,[8] were prescribed in 8% of patients. Mirabegron was prescribed infrequently (about 1% of patients), although its use in NGB is not currently supported by treatment guidelines[4,8] and it was introduced in the UK only towards the end of the study selection period. One-quarter of the study cohort also received prescriptions for α-adrenergic antagonists or 5α-reductase inhibitors; α-adrenergic antagonists are recommended for bladder outlet resistance in NGB[4,8] and may have contributed to some of this prescribing.

Neurological patients may be particularly susceptible to the unwanted central actions of some drugs because the integrity of the blood-brain barrier can be disrupted by the disease process.[2,9] The National Institute for Health and Care Excellence (NICE) suggests that the potential for CNS-related side effects with agents known to cross the blood-brain barrier (eg, oxybutynin) should be considered when prescribing an antimuscarinic agent for NGB[10] yet, in our study, oxybutynin was prescribed to approximately 25% of patients. Furthermore, other drugs with anticholinergic activity and the potential for causing negative cognitive effects were commonly prescribed, and the cumulative ACB in our study population at baseline was high (mean ACB score 6.6, where a score ≥3 is considered to be clinically relevant[14]). The implications of overprescribing drugs with anticholinergic effects are well documented; each 1-point increase on the ACB scale is associated with a 13% increase in the risk of cognitive impairment, and an 11% increase in the likelihood of inpatient admission.[19] Increased prescriber awareness of drugs with anticholinergic effects may help to reduce the risk of unwanted CNS events in these patients.

High levels of healthcare resource use were evident in our study population. On average, patients visited or made contact with their general practice 68 times over a 12-month period. Patients also visited a specialist twice on average and had one urology-related hospital admission and one surgical procedure over a 12-month period. An unexpected finding was the very low rate of prescribing for incontinence pads (0.4%), which was at odds with the reporting rate for urinary incontinence (14%) in our study. It seems likely that patients purchased pads as an out-of-pocket expense rather than obtaining them by prescription. After applying unit costs from standard UK sources, the average costs for healthcare resource utilization (excluding drugs) across the overall study cohort was an estimated £2395 per individual over 12 months. To our knowledge, this is first study to provide a comprehensive evaluation of healthcare-related costs in patients with NGB, as previous cost-of-illness studies have focused on emergency department admissions alone.[20,21]

The patient selection criteria adopted in our study (ie, proxy criteria to identify probable cases of NGB [based on diagnosis of a neurological condition plus a diagnosis of OAB/prescription of OAB drug] and requirement for a urologist referral) may introduce selection bias and limit the generalizability of our findings. However, when studying a condition such as NBG with proposed underdiagnoses and low awareness in some clinician groups, the selection process must adopt an appropriate level of specificity and sensitivity. Further, the drug choices reported are likely to have been influenced by NICE and may differ from other countries. The main limitations of our study were its retrospective design and the absence of a control cohort to compare outcomes against. Cost estimates are likely to be conservative as the unit costs and NHS tariffs used in our study did not capture all relevant direct medical costs (eg, theater time), and drug acquisition costs were also not considered.

We suggest that future studies should include a longer follow-up period and include less common neurological conditions associated with NGB (eg, cerebral palsy). Physician surveys, to better understand the rationale for prescribing decisions, as well as studies of cognitive function in patients receiving antimuscarinic agents would also be of interest.

5 | CONCLUSIONS

Our findings suggest that NGB may be underrecognized among primary care providers in the UK. The burden of illness, healthcare needs and associated costs evident in our study population were considerable. Drug prescribing patterns were consistent with the symptoms and complications of NGB, although increased awareness and reduced prescribing of agents with anticholinergic effects may help to improve health outcomes in this vulnerable patient population.

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DISCLOSURE OF INTERESTS

AJ and MA worked full time at Astellas Pharma under a Knowledge Transfer Partnership (KTP) scheme with Manchester Metropolitan University (MMU) when the research was conducted; JN was an employee of Astellas Pharma when the research was conducted; FF reports receiving grants from Astellas during the conduct of the study (project was funded as part of MMU/Astellas KTP), and grants from Astellas outside the submitted work; ES and NC are employees of Astellas Pharma; RA reports receiving grants from Astellas during the conduct of the study, and grants from Astellas outside the submitted work; DdR reports receiving grants from Astellas, Ferring and nonfinancial support from Pierre-Fabre outside the submitted work; MJD reports nonfinancial support from Astellas during the conduct of the study, personal fees from Allergan, Astellas, and grants and personal fees from Ferring outside the submitted work.

DATA AVAILABILITY

Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix 2: Journal article published in AME Medical Journal

Brief Report

Sub-optimal diagnosis of neurogenic bladder among general practitioners in the United Kingdom—evidence from the Clinical Practice Research Datalink

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Abstract: The diagnosis rate for neurogenic bladder (NGB) in the United Kingdom (UK) is surprisingly low. A lack of a clear diagnosis for patients adds ambiguity to their characterisation, treatment pathways and impedes meaningful research. A correct diagnosis means patients are more likely to have access to appropriate services and the right medical treatments, which subsequently improves their chances of optimal health outcomes as well as reducing healthcare costs. Accordingly, the aim of this research was to speculate the reasons for suboptimal diagnosis in NGB and provide recommendations for improvement. Nine hundred and sixty-seven patients were diagnosed with NGB between 2004–2015 in the Clinical Practice Research Datalink (CPRD) database, which in the context of the literature, seems low. Possible reasons include inadequate medical coding, a lack of awareness of urological symptoms amongst non-urologist healthcare professionals (HCPs), failure to follow clinical guidelines in practice, the exclusion of NGB from the Quality Outcomes Framework (QoF) scheme and an accommodation of urological symptoms. For optimal management in NGB, closing the current diagnosis gap is essential. Deprived of a diagnosis, patients will face an uphill battle in gaining access to services and appropriate medications. Measures such as educational campaigns, financial incentives, better use of clinical decision support systems (CDSS) and fostering better relationships between important stakeholders will be instrumental in achieving optimal diagnosis rates. Furthermore, additional hypothesis testing research is essential to ascertain the actual determinants of referrals.

Keywords: Urinary bladder neurogenic; clinical coding; awareness

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Introduction

Disturbance to the normal functioning of the urinary system as a result of central nervous system (CNS) related disorders such as Parkinson's disease (PD), multiple sclerosis (MS), spinal cord injuries (SCI) and stroke is known as neurogenic bladder (NGB) (1). Urological dysfunction manifests in different ways, ranging from retention symptoms to incontinence and sustained bladder pressures, depending on the site of neurological lesion (2). Symptoms and severity are chronic and disabling but tend to depend on the extent of the underlying neurological disease (3).

The multi-faceted and disabling nature of this condition has far-reaching effects. The symptoms of NGB and associated detrimental sequela including chronic urinary tract infection (UTI), urolithiasis and hydronephrosis poses an economic burden across the healthcare sector and has a significant impact on health-related quality of life (HRQoL) (3-5).

A lack of diagnosis (diagnosis error), is defined as '*the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient*' (6). A lack of a clear diagnosis for patients adds ambiguity to their characterisation, treatment pathways and impedes meaningful research. The most detrimental

Table 1 Search conducted in the Clinical Practice Research Datalink (CPRD) to identify neurogenic bladder patients in the United Kingdom

Disease	Keywords	Read terms	Read codes
Neurogenic bladder	Neurogenic	Neurogenic bladder	K16V011
		Neurogenic bladder	F246112
	Neuropathic bladder	Neuropathic bladder	K16V00
		Neuropathic bladder	F246113
		Reflex neuropathic bladder, NEC	K16W.00
		Uninhibited neuropathic bladder, NEC	K16X.00
	Neuromuscular bladder	Other neuromuscular dysfunctions of bladder	Kyu5200
		Neuromuscular dysfunction of bladder, unspecified	Kyu5E00

NEC, not elsewhere classified.

Table 2 Number of patients with neurogenic bladder retrieved from the Clinical Practice Research Datalink (CPRD) database 2004–2015

Year of diagnosis	Neurogenic bladder	Neuropathic bladder	Neurogenic bladder or Neuropathic bladder
2004	35	82	117
2005	32	95	127
2006	38	78	114
2007	29	68	96
2008	29	82	110
2009	28	71	98
2010	34	62	95
2011	41	56	97
2012	27	42	68
2013	28	42	70
2014	14	37	51
2015	10	8	18
Total	327	660	967

outcome of poorly managed NGB is renal dysfunction (7). A correct diagnosis means patients are more likely to have access to appropriate services and the right medical treatments, which subsequently improves their chances of optimal health outcomes and reducing costs. This review investigates the diagnosis rates of NGB in the UK using the Clinical Practice Research Datalink (CPRD) database.

Methods

The Read clinical classification is the standard medical terminology used in primary care practice in the UK. The system consists of alphanumeric codes encompassing all aspects of patient care such as clinical signs, symptoms and observations; laboratory tests; diagnoses; diagnostic and procedures performed (8).

We utilised the CPRD database to determine the number of Read coded NGB patients in the UK between 2004 and 2015 (this was a preliminary feasibility count conducted as part of a larger study, ISAC protocol number 17_027). The CPRD is the largest primary care longitudinal database containing collated anonymised patient data of over 11.3 million patients from 674 practices since 1987 (9). It is therefore largely representative of the UK population.

Keywords relating to NGB were inputted into the CPRD code browser, using the clinical, test and referral dictionaries to identify relevant Read codes. *Table 1* shows the key terms that were used and the resulting Read codes that were retrieved. A medical expert confirmed all key terms and Read codes. The number of patients identified using each Read code was recorded.

Results

A total of 967 patients with a diagnosis of NGB were retrieved from the CPRD database between the 1st January 2004 and 31st December 2014. *Table 2* shows the number of patients with a Read code of NGB or neuropathic bladder. No patients were found with Read codes of neuromuscular

Figure 1 Reasons for sub-optimal diagnosis of neurogenic bladder patients in the United Kingdom. NGB, neurogenic bladder; QoF, Quality Outcomes Framework.

bladder, which is likely due it being replaced by newer terms.

Discussion

Prevalence and incidence rates of NGB are very scarce. The only real large-scale epidemiological study was conducted using a US claims database between 2002–2007. The researchers identified 46,271 patients with NGB, however some subjects were included into the study via a proxy means of identification [overactive bladder (OAB) diagnosis or prescription of an OAB drug plus a diagnosis of a neurological condition] (10).

In the UK, 126,893 individuals were diagnosed with PD in 2009 and estimates suggest that 27–63.9% of this population experience bladder dysfunction (11,12). By conducting a very crude estimate, at the least there were 34,261 individuals with NGB secondary to PD in 2009. This is just one segment of the broader NGB population, because of course there are numerous neurological disorders that can cause NGB. Moreover, a study using the General Practice Research Database (GPRD) also identified a low frequency of NGB patients (69 patients between the years of 1987 to 2004), further compounding the suspicion that there could be an intrinsic problem in the diagnosis of NGB patients in the UK (13). This suggests that the 967 patients NGB patients retrieved from the CPRD is low. *Figure 1* shows some possible speculative reasons for low diagnosis. These reasons are explored in more detail below.

Coding of NGB

There are a multitude of different reasons for missing medical codes, and the absence of a Read code should not always be interpreted as absence of the disease itself (14).

The existence of multiple medical terminologies can make sharing and aggregating clinical information meaningfully across different levels of the healthcare sector challenging. The Read classification has been developed from a general practitioner (GP) perspective, and thus has been notoriously difficult to apply in secondary care (15). This is likely because activities and organisational structures differ between primary and secondary care, and consequently specialists and consultants have differing views to primary care healthcare professionals (HCPs) on the nature of healthcare. Some opinion suggests that 'Read codes have failed time after time in secondary care' (15). As a result of this ineffectuality, even if a urologist has diagnosed a patient with NGB in secondary care, the information may not be Read coded.

NGB and the Quality Outcomes Framework (QoF)

The QoF was set up in 2004 as a pay-for-performance (P4P) scheme, linking financial incentives to the quality of care (16). The scheme focused on ten key chronic conditions managed mainly in primary care including chronic heart disease and diabetes. Completeness for many of the

data points in these conditions improved in the years subsequent to introduction (17).

The QoF does not include common neurological conditions such as PD, MS or SCI, nor does it include NGB. A study found that improvements related to the QoF came at the cost of small deleterious effects to conditions not incentivised under the scheme (16).

Low awareness of urological symptoms amongst non-urologists

The extensive second organ effects in neurological conditions renders a simple one-to-one physician-patient relationship insufficient to manage symptoms. In order to improve the overall QoL of MS and PD patients, The National Institute of Health and Care Excellence (NICE) recommend their needs are met through a multidisciplinary team of HCPs, including GPs, dieticians, neurologists, and psychologists, amongst others (18,19). The composition of the care team depends on the patient's symptomology, disease severity and progression, as well as their social and psychological wellbeing.

Their superior expertise in bladder dysfunction positions urologists as pre-eminent in the diagnosis and management of NGB, however, they are only included in the multidisciplinary team, based on their perceived necessity. For example, if urological symptoms are not severe, conservative management techniques such as the administration of OAB drugs and introducing patients to catheterisation is easily performed in primary care.

Although resources are saved by confining management to primary care, it runs the risk of NGB patients remaining undiagnosed because awareness of urological symptoms amongst GPs is notoriously low. A report into continence care in the UK found that GPs do not routinely query 'at risk' individuals about their continence issues (20). Some of the common reasons include the fear of being unable to match patient expectations, a lack of understanding of urological symptoms and a lack of confidence in treating OAB (21).

Assigning a diagnosis is not a straightforward task, often proving challenging, especially in primary care. This particularly holds true in NGB, where symptomology can differ vastly between patients, making it difficult to uniformly apply diagnostic recommendations from clinical guidelines. Furthermore, there is a large degree of symptom overlap with idiopathic OAB, which can make distinguishing these conditions difficult for the untrained professional. Therefore, patients could be incorrectly diagnosed with OAB rather than NGB. Given the diffuse and often severer nature of NGB, it is important that the distinction between these conditions is made.

In most areas of the UK, neurological specialist nurses play an instrumental role in streamlining care from multiple providers to create an individualised management pathway (22,23). Although multidisciplinary care for neurological patients is crucial, communication amongst HCPs can often prove suboptimal, and is further exacerbated by the fragmented healthcare service (24,25). This ultimately impedes access to urological services, and hence receiving a diagnosis of NGB on time. Such a scenario is particularly likely in the current climate of austerity, where the number of nurse specialists working within the community are declining (26). Patients may therefore have to rely on their GP, who, as established have less awareness of urological symptoms and therefore are less likely to be able to diagnose NGB or refer patients to a urologist.

Another possible rationalisation for low diagnosis rates could pertain to the attending HCPs decision to focus on the primary neurological pathology, since managing it usually improves the symptoms of NGB. Therefore, although symptoms may be adequately managed, patients may not receive a formal diagnosis from a urologist.

Accommodation of urological symptoms

Patients with neurological disorders experience life-altering symptoms such as loss of mobility, problems with coordination, memory loss and severe pain (27). In contrast to their incapacitating symptoms, patients may not view their urological dysfunction as severe (i.e., an accommodation of symptoms occurs), which can result in a lack of help seeking behaviour (3). Other reasons for avoiding HCP contact include; embarrassment around OAB symptoms, lack of faith in treatment and self-management of symptoms (28). If patients do not reveal their symptoms, they cannot receive a diagnosis and consequently, treatment for their condition.

Implications of low diagnosis and potential solutions

For optimal management in NGB, closing the diagnosis gap is essential. Deprived of a diagnosis, patients will face an uphill battle in gaining access to services and appropriate medications. This increases the chances of unpredicted situations, secondary conditions and hospitalisations,

placing an additional strain on the National Healthcare Service (NHS) (29). It is already known that a number of serious sequela complicate the management of NGB, as well as evidence to suggest a substantial cost to the healthcare system (3). The issue of health inequality also arises, as those primarily affected will be in areas of the UK experiencing severe underfunding and cuts in specialist nurses; the key facilitators of the NGB care pathway.

The issue of interoperability between primary and secondary care could be solved through the gradual migration underway in UK clinical practice from Read codes to the Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) (15). It is described as the 'most comprehensive and precise' CT in the world (30). It is envisioned that implementation of SNOMED CT in UK clinical practice will improve the channel of communication between primary and secondary care (15). It will be of value to assess whether the diagnosis of NGB improves after implementation of SNOMED CT is complete.

Considering the high prevalence of bladder symptoms in patients with neurological conditions the permanent inclusion of a urologist in the multidisciplinary team would be a positive move towards improved diagnosis rates in NGB. Furthermore, effort towards enhancing the visibility of disease through national awareness campaigns targeting GPs, patients and carers could further improve the diagnosis rates. In particular, campaigns highlighting that urological symptoms emanating from neurological conditions are very common, would be instrumental in changing perceptions and attitudes amongst these stakeholders.

Lessons can be learnt from the multiple successful campaigns carried out in the field of idiopathic OAB. One example is the campaign launched by the American Urological Association (AUA) entitled 'It's Time to Talk About OAB', which aimed to alleviate the stigma surrounding talking to a physician about OAB symptoms and equip patients with a better understanding of their condition. The campaign consisted of a website featuring patient education materials and a 'Voices of OAB' contest, where patients shared testimonials of life with OAB (31).

Financial incentives can improve reporting and coding, as evidenced by the QoF scheme. The NHS could offer financial incentives to GPs for referrals to a urologist, who are experienced in identifying NGB and differentiating it from idiopathic OAB. Health economic analysis into the cost-effectiveness of encouraging referrals over management in primary care would be necessary to ensure the efficacy of introducing such a measure.

Clinical decision support systems (CDSS) represent a sophisticated computational means by which clinical guidelines can be integrated into clinical practice, assisting GPs with any diagnostic uncertainty surrounding NGB (32). Some recent systematic reviews of trials of CDSS have demonstrated promising results, however some conflicting evidence concludes there is a lack of data demonstrating benefit for patient outcomes (32,33). In any case, the use of information technology (IT) alone is not sufficient. Better relationships amongst stakeholders are imperative to improve the diagnosis and referral rates in NGB; this includes improving doctor-patient relationships, so patients feel comfortable sharing their symptoms with their doctor. Additionally, strengthening the channels of communication between doctors and specialists is fundamental in facilitating information exchange and creating learning opportunities for GPs to enhance their understanding of NGB.

Limitations

This is by no means an exhaustive analysis of the potential reasons for low NGB diagnosis rates. This paper did not explore possible shortcomings in current diagnostic practices. Furthermore, it is important to consider that the reasons presented are purely speculative, and the determinants of referrals should be understood through other means. The CPRD database could be used to conduct correlation studies against factors such as socio-economics, sex, and comorbidity (34,35). Simulated patients described by case vignettes could be used to in future studies to measure variation in clinicians' approaches to diagnosis and treatment (36).

Conclusions

Improving the diagnosis rates of NGB in the UK will allow proper provision of care and services. Measures such as improved interoperability between databases, educational campaigns, financial incentives, CDSS and fostering better relationships between important stakeholders are instrumental. Implementing these measures will enhance patient characterisation, help devise better management strategies, facilitate efficient resource allocation and ultimately improve health outcomes for NGB patients. The authors of this paper suggest hypothesis testing studies to ascertain the actual determinants of referrals.

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None.

Footnote

Conflicts of Interest: A Jaggi worked full-time at Astellas Pharma EU under a Knowledge Transfer Partnership (KTP) with Manchester Metropolitan University (MMU) during the time of the analysis of this study. F Fatoye has no conflicts of interest to declare.

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Appendix 3: Journal article published in Neurourology and Urodynamics

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SOUNDING BOARD

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A critical appraisal of the principal guidelines for neurogenic lower urinary tract dysfunction using the AGREE II instrument

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Aims: The process of identifying research questions, synthesizing and interpreting evidence, and weight given to health economics differs between the clinical guidelines (CGs) for neurogenic lower urinary tract dysfunction (NLUTD). Consequently, the quality also varies which can have implications for clinical practice.

Methods: We used the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument to assess the quality of the National Institute for Health and Care Excellent (NICE), European Association of Urology (EAU), and the International Consultations on Incontinence (ICI) CGs on neurogenic bladder.

Results: The NICE CGs were deemed to be of the highest quality (overall score of 92%). NICE were the only guidelines to systematically incorporate cost-effectiveness research into their recommendations. The EAU CGs received an overall score of 83% and the ICI CGs achieved the lowest overall score (75%). The highest scoring domain among all the CGs was scope purpose (86%) and the lowest scoring domain was applicability (69%). All guidelines were recommended for use (mostly with some modifications).

Conclusions: All CGs had their inherent advantages and disadvantages, though all were still deemed to be of high quality. Incorporating cost-effectiveness research would be near impossible for guidelines with a broad-country remit. Incorporating the AGREE II instrument in the development of CGs and better collaboration between the ICI, NICE, and EAU could improve the quality, and consistency between NLUTD CGs and ultimately improve health outcomes for this important patient group.

KEYWORDS
clinical guidelines, neurogenic lower urinary tract dysfunction

1 | INTRODUCTION

Neurogenic lower urinary tract dysfunction (NLUTD) is a urological dysfunction that occurs as a consequence of neurologic disease. It affects approximately 27-85% of patients with Parkinson's disease (PD), 70-84% with spinal cord injuries (SCI), up to 70% of those with stroke, and

Institution in which work was carried out: Manchester Metropolitan University.

John Heesakkers led the peer-review process as the Associate Editor responsible for the paper.

40-90% of persons with multiple sclerosis (MS).[1–3] Individuals with NLUTD may experience neurogenic detrusor overactivity (NDO), which is characterized by increased frequency of micturition, urinary urgency (if sensation is unaffected by the underlying condition) and urinary incontinence. Alternatively, patients may have problems in voiding, with symptoms including hesitancy, a slow urinary stream, the need to strain, and urinary retention. NLUTD has a substantial impact on patients' health related quality of life (HRQoL) and use of healthcare resources due to bladder symptoms and associated sequela.[4]

The National Academy of Medicine (NAM) (formerly known as the Institute of Medicine (IOM)) was founded in 1970, under the charter of the National Academy of Sciences. The organization comprises of 80 prominent members in the field of medicine and beyond.[5] The NAM define clinical guidelines (CGs) as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[6] CGs are an important tool in establishing evidence-based medicine (EBM) in clinical practice, and adequate implementation can improve patient outcomes, as well as inefficiencies and inequity across care institutions.[7] The three most prominent organizations that produce CGs for the management of NLUTD are the National Institute for Health and Care Excellent (NICE), the European Association of Urology (EAU) and the International Consultations on Incontinence (ICI).[8–10]

The process of identifying research questions, synthesizing and interpreting evidence differs between CGs. These differences are often the result of differing goals, financial resources, and membership of organizations. Consequently, the quality also varies, which can have implications for clinical practice. For example, some developers employ rigorous systematic reviewing techniques whilst other CGs weigh more heavily on expert opinion. Another key differentiating factor is the weight given to health economic evidence. Whereas some CGs include well-integrated economic analysis to determine the most cost-effective management strategies, others focus solely on clinical outcomes.

The Appraisal of Guidelines for Research and Evaluation (AGREE) collaboration defines good quality CGs as "the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice."[11] They developed the AGREE II instrument to critically appraise the transparency and methodological rigor of CG development.[11] The instrument was utilized in the current study to determine the quality of available NLUTD CGs, and identify where potential improvements could be made.

2 | MATERIALS AND METHODS

2.1 | AGREE II instrument

Two appraisers (AJ, ES) independently assessed the quality of the NLUTD CGs using the AGREE II instrument. The instrument consists of 23 items, grouped into six domains: (1) scope and purpose (items 1-3); (2) stakeholder involvement (items 4-6); (3) rigor of development (items 7-14); (4) clarity and presentation (items 15-17); (5) applicability (items 18-21); and (6) editorial independence (items 22-23) (Table 1). Each item is rated on a seven-point Likert scale, where seven correlates to strongly agree. It is important to note that a score of 1 does not necessarily mean that the item criterion was not fulfilled, instead this could represent a lack of relevant information available to the appraiser to assign an appropriate score. The instrument also asks appraisers to make two assessments; on the overall guideline quality, and whether they would recommend the CGs for use.

2.2 | Data analysis

Descriptive statistics were used to summarize the domain and overall scores. A standardized score for the six domains and overall score was calculated by summing the scores of the individual items within each domain to achieve a percentage of the maximum possible score.

The IBM SPSS Statistics version 24 package was used to calculate the agreement between the appraisers using intraclass correlation (ICC), which demonstrates the level of agreement between appraisers. A single measures, two-way random effects model was utilized. The range of ICC is between 0 and 1, where the closer to one a score is the smaller the variation between scores of raters on each item.[12]

3 | RESULTS

3.1 | Clinical guidelines

The three CGs included in this study had notably different intentions of use. In contrast to NICE and the EAU, ICI is not intended to be applied directly in clinical practice. Table 2 describes the characteristics of the CGs.

Scaled domain scores are presented in Table 3. The NICE CGs were deemed to be of the highest quality (overall score of 92%), they scored highest in stakeholder involvement domain (94%), and the lowest scoring domains were clarity of presentation and scope and purpose (86% in both domains). The EAU CGs received an overall score of 83%, the highest scoring domain was clarity of presentation (89%) and the lowest scoring domain was the applicability domain (63%). The ICI CGs achieved the lowest overall score among the CGs (75%). The highest scoring domain in this CG was clarity

40-90% of persons with multiple sclerosis (MS).[1–3] Individuals with NLUTD may experience neurogenic detrusor overactivity (NDO), which is characterized by increased frequency of micturition, urinary urgency (if sensation is unaffected by the underlying condition) and urinary incontinence. Alternatively, patients may have problems in voiding, with symptoms including hesitancy, a slow urinary stream, the need to strain, and urinary retention. NLUTD has a substantial impact on patients' health related quality of life (HRQoL) and use of healthcare resources due to bladder symptoms and associated sequela.[4]

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TABLE 1 Description of the AGREE II instrument

Domain	Questions
One—Scope and purpose (items 1-3)	"is concerned with the overall aim of the guideline, the specific health questions, and the target patient population."
Two—Stakeholder involvement (items 4-6)	"focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users."
Three—rigor of development (items 7-14)	"relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them." An explicit link between evidence and recommendations is essential, as well as ensuring health benefits, side effects and risks have been considered in formulating the recommendations.
Four—clarity of presentation (items 15-17)	"deals with the language, structure, and format of the guideline."
Five—applicability (items 18-21)	"pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline."
Six—editorial Independence (items 22-23)	"is concerned with the formulation of recommendations not being unduly biased with competing interests."
Overall assessment	Asks whether the appraiser would recommend the guideline for use in clinical practice, taking into account the appraisal items.

Adapted from: https://www.agreetrust.org/about-the-agree-enterprise/introduction-to-agree-ii/structure-and-content-of-the-agree-ii/

of presentation (94%) and the lowest scoring domain was applicability (54%). The ICC varied from low to excellent reliability (0.3-1); however, confidence intervals were insignificant in some domains (Table 4).

4 | DISCUSSION

To the best of the authors' knowledge, this is the first study that assesses the quality of the NLUTD guidelines by using the AGREE II scores. Quality varied moderately across the AGREE II domains as well as between the NLUTD CGs. Among all CGs, the highest scoring domain was clarity of presentation and the lowest scoring was applicability. NICE achieved the highest overall score and the ICI achieved the lowest overall score, however all CGs were deemed to be of high quality, and were recommended for use in clinical practice (mostly with some modifications).

The stakeholder representation domain evaluates the extent to which CGs have accurate representation from all relevant intended users, including professional groups and patients. Involving a broad range of stakeholders allows the integration of several unique perspectives on optimal healthcare, aids in the prioritization of important topics, and minimizes bias toward certain treatment options caused by conflicts of interest.[13] NICE scored exceptionally high in the stakeholder involvement domain (94%). The NICE CGs are developed not only by urological experts working in the field but also by a rigorous process of cross-collaboration with specialist and/or general physicians, HEOR specialists, and patient groups. In contrast, the development group for both the EAU and ICI NLUTD CGs are made up almost exclusively of neuro-urological experts; they achieved 78% and 67%, respectively. The EAU is slowly integrating patient perspective into their development process by engaging patient organizations, whereas the ICI acknowledge that increased efforts to incorporate the patient voice into their CGs is necessary. The transparency with which the stakeholders' comments are incorporated into recommendations is an aspect all CGs need to improve upon.

The most vital aspect in the formation of evidence-based recommendations is a comprehensive systematic review of

TABLE 2 Description of neurogenic lower urinary tract dysfunction (NLUTD) clinical guidelines

Guideline title	Institution	Year	Region
Neurologic Urinary and Faecal Incontinence	International Consultations on Incontinence (ICI)	2017	International scope
Clinical Guidelines on Neuro-Urology	European Association of Urology (EAU)	2017	European scope
Urinary Incontinence in Neurological Disease: Management of Lower Urinary Tract Dysfunction in Neurological Disease	National Institute of Health and Care Excellence (NICE)	2012	National scope (United Kingdom)

TABLE 3 Scaled domain percentages for AGREE II domains in the appraisal of neurogenic lower urinary tract dysfunction (NLUTD) guidelines

Guideline	Scope and purpose (%)	Stakeholder involvement (%)	Rigor of development (%)	Clarity of presentation (%)	Applicability (%)	Editorial independence (%)	Overall score (%)	Recommended for use in clinical practice[a]?
ICI	89	67	77	94	54%	79	75	Yes with modifications—2
EAU	83	78	79	89	63%	88	83	Yes with modifications—2
NICE	86	94	89	86	90%	88	92	Yes—1, Yes with modifications—1
Average (95%CI of the mean)	86 (82.6-89.5%)	79.7 (64.3-95.1%)	81.7 (74.4-89%)	89.7 (85.1-94.3%)	69% (47.8-83.2%)	85 (79.1-90.9%)	83.3 (73.7-92.9%)	

ICI, International Consultations on Incontinence; EAU, European Association of Urology; NICE, National Institute for Health and Care Excellence.
[a]1 indicates one appraiser chose this option, 2 indicates both appraisers chose this option.

TABLE 4 Intraclass correlation between two appraisers of neurogenic lower urinary tract dysfunction (NLUTD) guidelines

Domain	ICC (95%CI)	Degree of agreement
Scope and purpose	0.4	Poor
Stakeholder involvement	0.8 (0.4-1)	Good
Rigour of development	0.5	Moderate
Clarity of presentation	0.7 (0.1-0.9)	Moderate
Applicability	1 (0.9-1)	Excellent
Editorial independence	0.3	Poor

95%CI not presented = CI crossed 0, therefore not significant ICC = <0.5 poor reliability, 0.5-<0.75 moderate reliability, 0.75-0.9 good reliability, >0.9 excellent reliability.

available evidence.[14] Recommendations in all three NLUTD CGs occasionally relied on expert opinion. Unfortunately, as the evidence base underlying NLUTD is composed of mainly observational studies, and trials with relatively small patient numbers and perceived weak methodological design, this cannot be avoided. The NICE systematic review process was deemed the most superior by the appraisers, thus achieved the highest score in the rigor of development domain (score 89%). The EAU previously employed a condensed process of evidence review; however, they recently announced a gradual implementation of the Cochrane methodology across their guideline panels. The 2017 version of the NLUTD CGs contained three new systematic reviews using this methodology. All three CGs used a validated grading system to describe the strengths and limitations of the underlying body of evidence.

All CGs scored highly in the clarity of presentation domain, as the recommendations were easily identifiable, specific, and unambiguous. It is important that all management options are presented, so end users can make fully informed clinical decisions. Although the ICI do not promote their CGs to be used directly in clinical practice, in reality they may be interpreted to be used in this way. Instead, the ICI GCs are endorsed as the reference work for the condition of interest, thus they consider an exhaustive number of management strategies compared to the other CGs.[15] This helped achieve the highest score in this domain (94%). The EAU lost points in this domain, as despite providing a thorough discussion on behavioral techniques, no graded recommendations were made for certain forms of management.

It has been demonstrated that improvement in health outcomes is related to adherence to CGs[16]; however, due to multifaceted barriers to implementation, uptake of CGs has remained notoriously low.[17] A 2007 survey sent out to Dutch urologists revealed that the EAU CGs for NLUTD were not systematically employed in clinical practice.[18] The applicability domain measures the steps taken by the developers to improve uptake of the CGs and to what extent the resource

implications of application have been considered. In light of the international scope of the ICI, the CGs achieved a low score for the applicability domain (54%). NICE and EAU have designated implementation teams with the aim of promoting uptake of CGs and overcoming barriers to implementation. They scored 90% and 60%, respectively. Due to their national scope (UK only); it is easier for NICE to introduce strategies at a local level, including promoting a wide range of resources (eg, educational presentations and patient leaflets), and engaging multiple organizations. For the same reason, NICE were able to consider the cost-effectiveness of treatments. Integrating economic evaluation into CGs is imperative given the ever increasing healthcare costs and the introduction of expensive innovative products.[19] The EAU was unique from the other CGs in that it has a designated team named the "Social Media (SoMe) working group," who are responsible for promoting the guidelines on Facebook and Twitter. This is particularly important in an age where SoMe has become a frequent vehicle to disseminate medical information.

The editorial independence domain reviews whether the funding body may have influenced the guideline content, and asks whether potential conflicts of interests (COI) have been adequately recorded and addressed. None of the CGs were pharmaceutical industry funded; however, some development members in all CGs declared financial relationships with industry. The NICE and EAU guidelines have specific policies on how to manage COI, thus scored a higher percentage in this domain (88% in both CGs). Both CGs employ cautionary measures such as excluding development members from voting or in the development of recommendations related to their area of COI.[20,21] A qualitative study into the NICE COI process determined that it was effective and transparent; however, as expected, it relied upon a process of self-reporting, which runs the risk of important omissions being made.[22] Some alternative opinion suggests that financial relationships with industry could provide unique and important expertise into the input of guideline development.[23]

There are some limitations in this study that should be discussed. The AGREE II developers do not provide thresholds for what should be considered "low quality" and "high quality" CGs, thus interpretation of the resulting scores was ultimately a subjective exercise. Although the number of appraisers in this study was in line with the recommendations from the AGREE II collaborators, increasing this number could have improved the inter-rater reliability. One of the authors (MJD) was involved in the development of the ICI CGs, which could have introduced an element of bias; for this reason, MJD was not involved in the appraisal of any of the CGs for the current study. In addition, two authors work in Urology Research and Development based roles for a pharmaceutical company (ES & JN) and all authors based in the UK, which could affect the reliability of conclusions.

5 | CONCLUSIONS

All CGs had their inherent advantages and disadvantages, although all were still deemed to be of high quality. The lower score overall for the ICI guidelines could partly be attributed to the contrasting purpose of development and intention of use as an international guidance document. NICE CGs were deemed to be of the highest quality due to attributes such as the involvement of multiple stakeholders and economic evaluation of treatment options. The EAU has some promising initiatives that will elevate the quality of their CGs in coming years. Incorporating the AGREE II instrument in the development of CGs and better collaboration between the ICI, NICE, and EAU could improve the quality of NLUTD CGs and ultimately improve health outcomes for this important patient group. Institutions will have to overcome barriers such as ensuring the clinical and economic applicability of recommendations to a diverse range of healthcare systems across the globe.

CONFLICTS OF INTEREST

Dr. Siddiqui worked on the submitted work in his personal capacity; however, he works full time in the Medical Affairs Department as Executive Medical Director Urology at Astellas Pharma Europe. Dr. Drake reports non-financial support from Astellas, during the conduct of the study; personal fees and non-financial support from Allergan, grants, personal fees and non-financial support from Ferring, personal fees from Pfizer, personal fees from Hikma, grants, personal fees and non-financial support from Astellas, outside the submitted work. Miss Jaggi reports Works full time at Astellas Pharma EU under a Knowledge Transfer Partnership (KTP) scheme with Manchester Metropolitan University (MMU). Dr. Nazir worked on the submitted work in his personal capacity; however, he works full time as Director in the Health Economics Department at Astellas Pharma Europe. Dr. Giagos and Dr Francis Fatoye have nothing to disclose.

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Appendix 4: Journal article published in Neurourology and Urodynamics

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A comparison of the treatment recommendations for neurogenic lower urinary tract dysfunction in the national institute for health and care excellence, European Association of Urology and international consultations on incontinence guidelines

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Aims: Healthcare guidelines are an important vehicle in establishing up-to-date evidence based medicine (EBM) in clinical practice. Due to varying development processes, clinical guidelines created by different institutions can often contain contrasting recommendations. This can have implications for optimal and standardized patient care across management settings.

Methods: The similarities and differences of treatment recommendations made in the National Institute for Health and Care Excellence (NICE), The European Association of Urology (EAU), and the International Consultation on Continence (ICI) guidelines for neurogenic lower urinary tract dysfunction (NLUTD) were assessed.

Results: The guidelines generally agree on their approach to conservative management, including behavioral therapies, and catheterization techniques. There was discrepancy on the benefit of using an alpha blocker in NLUTD and bladder outlet obstruction (BOO) and administering Botulinum toxin A (Onabotulinum-A) in NLUTD. The highest degree of divergence was seen in recommendations for surgical treatments, where the EAU made gender-specific recommendations, and gave continent urinary diversion higher preference than given in the NICE and ICI guidelines.

Conclusions: In the absence of high-quality clinical evidence, many of the recommendations made across all three guidelines are based on expert opinion. NICE, the EAU and ICI have similarities but they place differing emphasis on costs and expert opinion, which translated in notably different recommendations. It is evident that increased research efforts, possibly in the form of prospective registries, pragmatic trials, and resource utilization studies are necessary to improve the underlying evidence base for NLUTD, and subsequently the strength and concordance of recommendations across guidelines.

KEYWORDS
clinical practice guidelines, neurogenic lower urinary tract dysfunction

Institution in which work was carried out: Manchester Metropolitan University.

Alan Wein led the peer-review process as the Associate Editor responsible for the paper.

1 | BACKGROUND

Disturbance to the normal micturition process emanating from neurological damage or disease is known as neurogenic lower urinary tract dysfunction (NLUTD). The underlying neurological disease differentiates NLUTD from those suffering from idiopathic overactive bladder (OAB). NLUTD encompasses a breadth of neurological etiologies, including stroke, spinal cord injuries (SCI), multiple sclerosis (MS), and Parkinson's disease (PD). Patients that fall under the umbrella term of NLUTD are notably unique in urological symptoms and risk profile due to differences in underlying condition (including stage and severity) and location of neurological lesion.

There are myriad treatment options for the management of NLUTD, supported by a substantial evidence base. The evidence is however dominated by observational studies and clinical studies with weak methodological design. Clinical guidelines aid physicians in making optimal treatment choices through encapsulating the plethora of dynamic scientific research and expert opinion into easy to follow recommendations. The most prominent NLUTD guidelines are produced by the National Institute for Health and Care Excellence (NICE), the European Association of Urology (EAU) and the International Consultation on Continence (ICI).[1–3]

Due to variations in development processes, clinical guidelines by different institutions can often contain contrasting recommendations. This can be confusing for healthcare professionals and patients when devising management strategies, and can affect standardization of care.[4] To assess the concordance of prominent guidelines for NLUTD; we assessed the similarities and differences of treatment recommendations made in the NICE, EAU, and ICI guidelines.

2 | GUIDELINES

We included the three most prominent guidelines for NLUTD from recognized institutions within the UK, Europe, and internationally.

NICE provides evidence-based clinical care guidance for the UK National Health Service (NHS).[5] The guidelines entitled "urinary incontinence related to neurological disease" are applicable to adults and children. The guidelines are updated periodically, and the most recent update was in 2012. NICE uses a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and uses the wording of recommendations to reflect the strength of the recommendation.

The EAU strives to improve urological practice, research, and education across Europe.[6] They provide guidelines on a wide range of urological topics, including for NLUTD. The guidelines are updated annually, with the most recent edition being in 2017. The EAU present levels and grades of recommendations using a modified version of the Oxford Centre for Evidence-based Medicine system (OCEBM 2009).

The International Consultation on Urologic Disease (ICUD) is a non-governmental organization registered with the World Health Organization (WHO). The ICI is a subcommittee of the ICUD, tasked with developing recommendations with worldwide relevance for lower urinary tract dysfunction (LUTD).[7] Their guidelines entitled "neurologic urinary and faecal incontinence" are based on evidence and conclusions drawn at the sixth annual ICI conference. The ICI uses a modified version OCEBM 2011. They provide evidence levels for conclusions drawn from the literature and grades for recommendations.

3 | RESULTS

3.1 | Behavioral interventions

While no graded recommendations are made in the EAU guidelines, behavioral interventions are advocated in both the NICE and ICI guidelines, although recommendations are based on a lack of clinical evidence.

NICE and the ICI broadly agree on their recommendations for individuals with cognitive impairment (Table 1). All three guidelines agree on the use of pelvic floor muscle training (PFMT) in combination with electrical stimulation or biofeedback, however NICE only advocate this technique in SCI or MS, and the EAU recommend it only in MS patients (Table 1). The ICI and EAU endorse expression techniques such as the Credé and Valsalva manoeuvres, only if proven urodynamically safe, however both guidelines also stress that the manoeuvres can be potentially hazardous.

3.2 | Oral pharmacological management

Antimuscarinics are the preferred pharmacological treatment for neurogenic detrusor overactivity (NDO); although NICE make a weaker recommendation for progressive brain conditions (Table 2). All guidelines advise cautionary use of these drugs due to the increased possibility of adverse effects such as cognitive dysfunction, urinary tract infections (UTIs), and constipation. The ICI and NICE guidelines particularly express concern of use in patients with pre-existing cognitive impairment. The EAU suggests employing antimuscarinics in combinations in order to maximize outcomes (Table 2).

The ICI and EAU recommend α-blockers for bladder outlet obstruction (BOO) resistance. Conversely, α-blockers are recommended against in the NICE guidelines for bladder emptying problems, as they are deemed not cost-effective (Table 2).

TABLE 2 Oral pharmacotherapy recommendations for neurogenic lower urinary tract dysfunction in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Oral pharmacotherapy		
NICE	**EAU**	**ICI**
Recommendations which are similar for the three guidelines		
	Use antimuscarinic therapy as the first-line medical treatment for NDO (A)	Antimuscarinic drugs should be recommended for the treatment of NDO (A)
	Prescribe α-blockers to decrease BOO resistance (A)	For decreasing BOO in NGB a-adrenergic antagonists may be used (B/C)
Recommendations differing between the three guidelines		
Offer antimuscarinics to people with spinal cord disease (eg, MS or SCI) and symptoms of OAB	Maximize outcomes for NDO by considering a combination of antimuscarinic agents (B)	
Consider antimuscarinic drug treatment in people with conditions affecting the brain (for example, cerebral palsy, head injury or stroke) and symptoms of OAB	Do not prescribe drug treatment in neurogenic SUI (A)	
Consider antimuscarinic drug treatment in people with urodynamic investigations showing impaired bladder storage	Do not prescribe parasympathomimetics for underactive detrusor (A)	
Do not offer alpha-blockers for bladder emptying problems caused by neurological disease		

OAB, overactive bladder; NDO, neurogenic detrusor overactivity; BOO, bladder outlet obstruction; SCI, spinal cord injuries; MS, multiple sclerosis; NGB, neurogenic bladder.

practice. Adequate management in NLUTD offers benefits to the patient in terms of protection of the upper urinary tract, reduction in the rate of adverse sequelae and promotion of good quality of life (QoL).[9] Additionally, unnecessary costs to the healthcare system can be avoided. Due to varying development processes, clinical guidelines can contain discordant treatment recommendations, which can cause unwarranted variation in care across practices. Despite many similarities, recommendations made in the NICE, EAU, and ICI guidelines also diverged for some therapies.

The guidelines generally agree on their approach to conservative management, including for behavioral therapies and catheterization techniques. The recommendations for behavioral therapy were mostly based on expert opinion. NICE made their recommendations using evidence from the general elderly population, on the basis that no relevant evidence exists for neurological patients.

When considering oral pharmacotherapy, all three guidelines place antimuscarinics as first line for NDO. Level 1 in the ICI evidence states tolterodine, propiverine, trospium, and controlled-release oxybutynin have significantly less side effects compared to immediate release oxybutynin. Due to the lack of evidence differentiating antimuscarinics, NICE recommend balancing side effect profile with cost, rather than advocating the use of one drug over another.

The ICI and NICE recommend further research into the use of newer antimuscarinics in NGB. It is interesting to note that although the ICI guidelines were published 5 years after the NICE guidelines; the same recommendation is made, indicating that little progress has been made in the way of this particular research. Despite highlighting the potential adverse effects of these drugs, none of the guidelines acknowledges the particular concern of use in progressive neurological conditions (eg, PD and MS). Even if notable impairment does not already exist, the blood brain barrier (BBB) can become compromised, increasing the ability of antimuscarinics to bind to the M1 receptors in the brain and cause cognitive side effects.[10,11,8]

The guidelines contain contrasting recommendations on alpha-blockers and Onabotulinum-A. Although some evidence exists demonstrating efficacy of alpha-blockers in NLUTD with BOO, the need for large randomized controlled trials (RCTs) remains.[12] Despite this, alpha-blockers are advocated for use in the EAU and ICI guidelines. Onabotulinum-A is only licensed for NDO in SCI and MS due to the paucity of adequate research in other neurological conditions. The ICI guidelines still recommend Onabotulinum-A in all patients with NDO, regardless of underlying aetiology, thus it is evident that the EAU and NICE guidelines more accurately reflect the evaluated patient population. In

TABLE 3 Minimally invasive treatment recommendations for neurogenic lower urinary tract dysfunction in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Minimally invasive procedures		
NICE	**EAU**	**ICI**
Recommendations which are similar for the three guidelines		
Offer bladder wall injection with BTX-A with spinal cord disease (eg, MS or SCI) and with symptoms of OAB and in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.	Use BTX-A injection in the detrusor to reduce NDO in MS or SCI if antimuscarinic therapy is ineffective (A)	
Offer bladder wall injection with BTX-A to adults with spinal cord disease and with urodynamic investigations showing impaired bladder storage and in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.		
Recommendations differing between the three guidelines		
	Alternative routes of administration (ie, transdermal or intravesical) of antimuscarinic agents may be used (A)	BTX-A should be offered as a treatment option for incontinence associated with NDO (A).
		BTX-A may be considered for DSD in SCI patients (B)
		If pharmacotherapy fails to relax the overactive detrusor, electrical neuromodulation: SNM, anogenital stimulation, pudendal nerve stimulation, dorsal genital nerve stimulation, percutaneous tibial nerve stimulation, magnetic stimulation, and deep brain stimulation) may be optional in patients with neurogenic DO (C/D)

BTX-A, botulinum toxin A; SNM, sacral neuromodulation; SCI, spinal cord injuries; MS, multiple sclerosis; NDO, neurogenic detrusor overactivity.

TABLE 4 Catheter and appliance recommendations for neurogenic lower urinary tract dysfunction in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Catheterization and appliances		
NICE	**EAU**	**ICI**
Recommendations which are similar for the three guidelines		
When discussing treatment options, tell the person that IDUC may be associated with higher risks of renal complications (such as kidney stones and scarring) than other forms of bladder management (such as intermittent self-catheterization)	Use IC, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder. (A)	IC is first choice treatment for inability to empty the bladder adequately and safely in neurogenic voiding dysfunction (A)
	Avoid IDC and SPC whenever possible (A)	Long-term IDC should be the last resort and may be safe only if a careful check-up of urodynamic, renal function, and upper and lower tract imaging are performed (B)
Recommendations differing between the three guidelines		
In people for whom it is appropriate a catheter valve may be used as an alternative to a drainage bag		Short-term IDC during the acute phase of neurological injury is a safe management for neurologic patients (B)
		Regular bladder emptying with low bladder pressures and low post void residual should be confirmed with condom catheters and external appliances (B)

IDC, indwelling catheterization; IDUC, indwelling urethral catheterization; SPC, suprapubic catheterization; IC, intermittent catheterization.

the absence of high quality clinical evidence, recommendations for alpha-blockers and Onabotulinum-A were primarily reliant upon expert opinion.

Disparities were most apparent in surgical treatments. One major difference between the EAU guidelines and the other guidelines were some gender-specific recommendations. Male autologous slings are relatively new interventions, with consequently less data supporting their use than female autologous slings.[13] For this reason, use in males is not advocated in the EAU guidelines. On the other hand, AUS is not recommended in females, as physiological barriers introduce technical difficulties in implantation.[14] All guidelines also differed in recommendations for urinary diversion. Whereas continent cystostomy is advocated in the EAU guidelines, NICE recommend ileal conduit diversion. The ICI do not advocate any one kind of diversion technique, which is perhaps most suitable, as superiority of one type of urinary diversion in terms of functionality and health related quality of life (HRQOL) has not yet been proven.[15] The discrepancy between the NICE and EAU guidelines is again most likely because of differing expert opinion.

Dissimilarities arose as a result of the differing interpretation of the underlying evidence base, varying considerations given to cost, and the weight given to expert opinion. Since the ICI guidelines attempt worldwide relevance, they were most comprehensive. For example, the guidelines provide extensive recommendations for patients with SUI, considering treatments that were not assessed in the NICE or EAU guidelines. An advantage of the NICE guidelines was the well-integrated economic evaluation, which aims to improve national healthcare efficiency in the UK. As a result, certain recommendations diverged from what is recommended by the EAU and ICI, for example, the option to introduce bladder augmentation earlier than Onabotulinum-A in the treatment pathway for a subset of patients. Due to their broad country remit, cost assessment and/or consideration of resource utilization is not possible for the EAU and ICI guidelines. The EAU guidelines were adequately detailed, and considered a broad range of treatments, however they lacked graded recommendations for behavioral management.

In the absence of high-quality clinical evidence, many of the recommendations made across all three guidelines are based on expert opinion. In the EBM hierarchy, expert opinion is assigned the lowest level, as it can be subject to bias. At present, much of the clinical evidence that does exist for NLUTD focuses on SCI and MS, which may not be generalizable to the wider neuro-urological patient population, especially progressive neurological conditions.[16] Filling the research gap is not easy, as conducting RCTs in the vulnerable NLUTD population can be impractical. In order to

TABLE 5 Surgical procedure recommendations for neurogenic lower urinary tract dysfunction in the National Institute of Health and Care Excellence, European Association of Urology, and the International Consultations on Incontinence guidelines

Surgical procedures		
NICE	**EAU**	**ICI**
Recommendations which are similar for the three guidelines		
Consider autologous fascial sling surgery for people with SUI		Autologous slings can be used to treat SUI (B)
Do not routinely use synthetic tapes and slings in people with SUI because of the risk of urethral erosion		Artificial urinary sphincter can be used to treat SUI (A)
Consider surgery to insert an AUS for people with SUI only if an alternative procedure, such as insertion of an autologous fascial sling, is less likely to control incontinence		Due to the limited evidence base, possible sphincter deficiency, perceived risk of complications and potential consequences on future management options, the Committee is unable to recommend routine use of synthetic slings and tapes to treat SUI in neurogenic patients (D)
Recommendations differing between the three guidelines		
Consider augmentation cystoplasty using an intestinal segment for people with non-progressive neurological disorders and complications of impaired bladder storage (eg, hydronephrosis or incontinence)		Any segment of the gastrointestinal tract may be used for bladder augmentation, but the ileum seems to give the best results in terms of ease of use, risk of complications and efficacy (B)
For people with neurogenic lower urinary tract dysfunction who have intractable, major problems with urinary tract management, such as incontinence or renal deterioration consider ileal conduit diversion	Place an autologous urethral sling in female patients with SUI who are able to self-catheterize. (B)	Synthetic tapes could be recommended in older women with stable neurological conditions and SUI due to urethral hypermobility (C)
	Insert an AUS in male patients with SUI (A)	Bulking agents can be used to treat SUI when there is a demand for a minimally invasive treatment (D)
		Bladder neck reconstruction can be used to treat SUI (D)
		Bladder neck closure should be offered to patients who have persistent neurogenic stress incontinence where alternative treatments have either failed or are likely to fail (B)
		Non-continent urinary diversion is the last resort for patients with NGB (A)
		Ileal conduit urinary diversion has the best long-term results for non-continent diversion, if the following pre- and peri-operative precautions are taken (B)
		Where clean IC is not possible, the use of a urethral stent is possible in DSD (B)
		Although surgical sphincterotomy is the accepted reference treatment for neurogenic DSD, analysis of the literature highlights the lack of reliable efficacy and reproducibility criteria for the technique (B)
		In certain situations, dorsal rhizotomies can be undertaken in association with ventral root stimulators (Brindley's technique) or even with continent cystostomy (B)

SUI, stress urinary incontinence; AUS, autologous urinary sling; NDO, neurogenic detrusor overactivity; NGB, neurogenic bladder; DSD, detrusor sphincter dysynergia; IC, intermittent catheterization.

strengthen recommendations, increased research effort should be focused on collecting prospective registries or conducting pragmatic trials at centers managing a diverse range of neurological conditions.

5 | CONCLUSIONS

NICE, the EAU, and ICI guidelines are quite similar, but they do provide differing emphasis on costs and expert opinion,

which translated in notably different recommendations. This is not surprising in the absence of high-quality clinical evidence for NLUTD. It is evident that increased research efforts are necessary to improve the underlying evidence base for NLUTD, and subsequently the strength and concordance of recommendations across guidelines. This will enhance the care that NLUTD receive, and ultimately improve patient outcomes. In addition to this, integrating cost-effectiveness analyses may improve efficiencies.

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Appendix 5: Journal article published in Translational Urology and Andrology

Review Article

Real world treatment patterns in the neurogenic bladder population: a systematic literature review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: A Jaggi; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Myriad treatment modalities are available for neurogenic bladder (NGB) including behavioral therapies, oral pharmacotherapy, catheterization and surgical procedures. Little is known about how NGB patients are managed in the real world, how well patterns relate to clinical guidelines and how strategies may have changed over time. To address this gap, a systematic review (SR) was conducted using MEDLINE and EMBASE [1996–2017]. The inclusion criteria for studies were: (I) published in English; (II) conducted in human subjects; (III) reporting the treatment patterns/use in NGB; (IV) conducted in a real world setting. A narrative synthesis of results was conducted, comparing the results to current treatment guidelines. Percentage of treatment use was summarized using ranges. Eight studies met the inclusion criteria. Although most studies focused on spinal cord injuries (SCI), study designs and settings were heterogeneous. All data was collected before 2007. The most popular form of oral pharmacotherapy was antimuscarinics, used by 12.6–86.7% of patients; 0–100% of patients used catheterization techniques, 2.5–53.1% used reflex voiding (RV), and 0.2–55% underwent surgery. A notable amount of patients switched treatments. This SR revealed that numerous strategies have been used to manage NGB throughout the years and there has been a large variance in their use. Whilst there were some discrepancies, most practices matched recommendations made in current guidelines. Ultimately, this SR showed that there is a large gap of epidemiological studies conducted in the field of NGB and the authors felt that available data was insufficient to build a comprehensive picture of treatment patterns. Epidemiological studies using electronic medical records (EMRs) are necessary to advance our understanding of how treatment patterns have changed, and also build a comprehensive picture of how patients are managed in current practice.

Keywords: Neurogenic bladder (NGB); therapeutics; epidemiology

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Introduction

Micturition involves passive, low pressure filling of the bladder during the urine storage phase whilst voiding requires coordination of detrusor contraction with urinary sphincter relaxation. The process is controlled by a complex neural control system, involving interaction between the sympathetic, parasympathetic and somatic nervous systems (1). Disturbance to the normal micturition process as a result of neurological damage or disease is known as neurogenic bladder (NGB). The term NGB encompasses a breadth of neurological etiologies including spina bifida, stroke, spinal cord injuries (SCI), multiple sclerosis (MS), and Parkinson's disease (PD) (2). Although patients share the same diagnosis of NGB, they are notably unique in

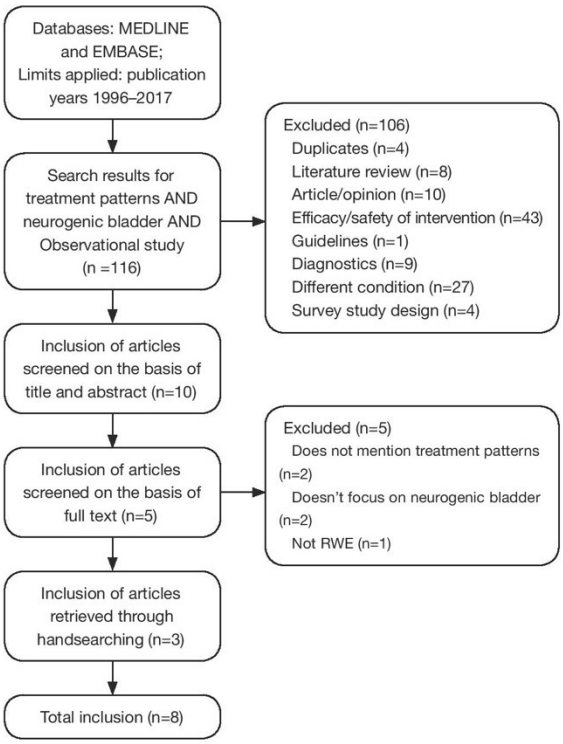

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

urological symptom and risk profile due to the difference in underlying condition (including stage and severity of disease) and location of neurological lesion.

This considerable heterogeneity compounds the availability of a single optimal medical therapy, meaning that treatments are often wide-ranging and individualized to the particular patient (3). Myriad treatment modalities can be employed including behavioral therapies, oral pharmacotherapy, catheterization and surgery. Four key aims outlined by the European Association of Urology (EAU) that are of paramount importance when selecting treatments are protection of the upper urinary tract, improvement of urinary continence, restoration of the lower urinary tract function and improvement of patient quality of life (QoL) (4).

Despite the availability of clinical guidelines, a survey conducted in the Netherlands found that "*18% of urologists used the EAU guidelines on NGB frequently, 35% did so occasionally and 47% did not use them at all*" (5). This systematic review (SR) aims to collate evidence on the management strategies that are employed in the real world and determine whether practices are in concordance with prominent NGB clinical guidelines. This research can act as an important preliminary step in influencing future guideline recommendations to reflect what is working for physicians in the real world. This research also demonstrates how prescribing patterns in NGB may have changed over time. This article aims to describe the treatment patterns and management strategies of NGB in the real word.

Methods

Eligibility criteria

(I) Patients with any neurological condition, e.g., spina bifida, stroke, SCI, MS, PD;
(II) Studies that measure treatment use e.g., percentage use, duration of use, treatment switching, combination use;
(III) Real world studies, including both retrospective or prospective: cohort, case-control, cross-sectional and chart review.

During the pilot search, no studies were retrieved that focused solely on adults therefore the search was expanded to include subjects of any age.

Search strategy

This SR was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (*Figure 1*) (6).

A search was run on 15th February 2017 using a combination of free-text words and medical subject headings in MEDLINE®, and EMBASE® (*Table S1*). Limits were applied for studies published between the years of 1996–2017. Eligibility assessment was conducted in two stages. In the first stage, an independent reviewer (Ashley Jaggi) screened titles and abstracts for alignment with pre-defined inclusion and exclusion criteria (*Table 1*). Ten percent of included papers were cross-examined by a second independent (Francis Fatoye) reviewer. In the second stage, full versions of the included texts, acquiescent with inclusion criteria, were screened by both reviewers. Any disagreements were mediated by discussion.

Data collection and extraction

Information on the study design, patient characteristics,

Table 1 Inclusion and exclusion criteria

Criteria
Inclusion criteria
Published in English
Includes human subjects
Reporting the treatment patterns/use in NGB
Conducted in a real world setting
Exclusion criteria
Non-English publications
In vitro, pre-clinical or animal studies
Randomized controlled trials, SRs, case-report/series, editorials, questionnaires, letters, commentaries, legal cases, newspaper articles or patient education materials

NGB, neurogenic bladder; SRs, systematic reviews.

and treatments in NGB was extracted using a piloted data extraction form.

Summary measures

Treatment patterns were descriptively summarized using narrative review. Percentage of treatment use was summarized using ranges.

Results

A total of 116 publications were yielded. After screening titles and abstracts and removing additional duplicates (ProQuest Dialog® removes most duplicates), 10 articles were retrieved, and the full texts were reviewed. Based on full text review, five papers were excluded for reasons according to the study protocol. A total of eight papers were included for analysis. Three papers were obtained from hand searching (7-14).

Study and patient characteristics

Overall, there were 47,706 patients with NGB, of these, 43.8% were male and the mean age was 42.8. The majority of included patients [46,271] were from two studies. Despite being published at separate times (2009 and 2011), these studies included the same cohort of patients (using the same inclusion criteria and database). Patients included in these studies had mixed underlying neurological conditions including MS, SCI, PD, paralytic syndrome, cerebral palsy and spina bifida. What differentiates the two studies is the 2011 study identified separate sub-cohorts for SCI and MS, including 4,168 and 9,315 patients respectively. Most of the included studies (62.5%) focused on patients with SCI (or included a subgroup), at various levels of neurological injury and varied time since injury. Across the studies, there were a total of 5,182 patients with SCI. One study focused on spina bifida patients, including 421 individuals. The earliest period of data collection began in 1984 and the most recent ended in 2007 (*Table 2*).

Treatment patterns

Oral pharmacotherapy

Five out of the eight included studies included data on the use of oral pharmacotherapy. Three studies included information on antimuscarinic drug use, which spanned between 12.6–86.7%. Results from two studies demonstrated a range of 12.6–39% patients using oxybutynin.

The lowest recorded antimuscarinic drug use was reported by Lemelle *et al.*, where 12.6% of spina bifida patients used oxybutynin regularly. The percentage of patients receiving antimuscarinics was almost double in the study by Chia-Cheng *et al.*, where it was used by 26% of SCI patients with neurogenic detrusor overactivity (NDO). Manack *et al.* [2011] reported much higher percentages, with 71.5% of patients in the NGB cohort, 80.9% in the SCI cohort and 86.7% in the MS cohort using this treatment. A prescription of an antimuscarinic drug (rather than any form of bladder management method), was one way in which a patient could be included into the study by Manack *et al.* [2011], which could explain why percentage use was higher in this study, than other studies in this review. The highest use of oxybutynin of all publications was also recorded in this study (39%), followed by tolerodine (36.9%). El-Masri *et al.* mention that antimuscarinics were administered to those with NDO, but percentage use is not delineated.

El-Masri *et al.* and Chia-Cheng *et al.* reported the use of alpha-blockers; however, neither of the authors communicated the names of drugs. In the study by Chia-Cheng *et al.*, the most prevalent drugs amongst SCI patients with NDO were alpha-blockers, used by 33% of individuals. Alpha-blockers were administered to SCI patients with marked bladder outlet obstruction (BOO) in the study by El-Masri *et al.*, but as with antimuscarinic use, percentage

Table 2 Summary of study and patient characteristics of included studies

Study	Data collection period	Study design	Location	Patient sample characteristics	Neurological condition and severity
Anson [1996]	Not reported	Prospective (longitudinal)	USA	348 individuals, 33% aged over 18, mean age: 36.6, 82% male and 18% female, 80.2% Caucasian	SCI: C0–C4: 19.7%, C5–C8: 36.2%, T1–T11: 29.4%, T12–S5: 14.7%; years since injury: 1–2 years: 26%, 3–5 years: 25.2%, 6–10 years: 29.3%, 11–15 years: 12%, 15+ years: 8%
Chia-Cheng [2012]	2006–2008	Retrospective (cross-sectional)	Taiwan	165 patients, mean age: 54, 64% male and 46% female	Patients with emergency department visits or hospitalizations for SCI
Drake [2005]	1990–1996	Prospective (longitudinal)	UK	196 individuals, aged 15–55, mean age: 57.4, 86% male and 24% female	SCI for at least 20 years; level of injury: paraplegics with complete SCI (Frankel grade A, B, or C): 49%; tetraplegics with complete SCI (Frankel grade A, B, or C): 31.1%; incomplete SCI (Frankel grade E): 18.9%; mean years since injury: 33.26
El-Masri [2012]	From 1984, with follow up ranging between 8 and 21 years	Retrospective (longitudinal)	UK	119 individuals, aged 16–63, mean age: 29, 83.2% males, 16.8% females	SCI: paraplegic (two had S3 sacral lesion): 37.3%; tetraplegic: 27%; Frankel grade A: 34%; Frankel grade B: 4.3%; Frankel grade C: 7.7%; Frankel grade D: 18.4%; mean years since injury: 29
Lemelle [2006]	2003–2004	Retrospective (longitudinal)	France	421 individuals, aged 10–47.5, mean age: 22.1, 140 aged 10–18 and 281 aged over 18; 55% male and 45% female	Spina bifida (myelomeningocele at the neonatal period, which was treated surgically); ability to move: walk with minor aid: 63%; walk with walking appliance: 3%; wheelchair outside + walk at home: 8%; wheelchair most of time: 26%
Manack [2011] & Manack [2009] (NGB cohort only)	April 1, 2002–March 31, 2007	Retrospective (longitudinal)	USA	46,271 individuals in NGB cohort, 9,315 individuals in MS, 4,168 individuals in SCI, aged 0–60+, mean age of NGB cohort was 62.5 years, mean ages in the MS and SCI subcohorts, 53.2 and 61.9 years respectively. 43.6% males and 57.4% females in NGB cohort, 31.3% male and 79.7% female, 41.9% male and 59.1% female in MS and SCI subcohorts respectively	MS, [SCI (including paraplegia, quadriplegia, tetraplegia), spina bifida, Parkinson's disease, cerebral palsy, hemiplegia/ hemiparesis, late effects of stroke, other paralytic syndromes, and neoplasm of the spinal cord]
Weld [2000]	Years not reported; follow up: 18.3 years since injury	Retrospective (longitudinal)	USA	316 individuals, mean age: 38 years, 99% male and 1% females	SCI: injury completeness: complete: 14.2%, incomplete: 85.8%; injury level: suprasacral: 85.1%, sacral: 14.9%; mean years since injury: 18.3 years

C, cervical nerves; T, thoracic nerves; SCI, spinal cord injuries; MS, multiple sclerosis; NGB, neurogenic bladder.

use is not described.

The study by Chia-Cheng *et al.* was the only one to mention use of cholinergics, where it was used by 15% of SCI patients with NDO.

Patterns of use with oral pharmacotherapy

Manack *et al.* [2011] provides information on patterns of oral drug use, which is not available from the other studies. A total of 7,782 continued on an OAB drug, 10,110 discontinued and did not start, and a further 9,030 stopped and restarted. The average length of time on drug was 209.1 days for the MS subcohort and 195.5 days for the SCI cohort.

Catheterization

Urinary catheter use varied substantially. Intermittent catheterization (IC) use was reported in six studies, with a range between 0–84%. Indwelling catheterization (IDC) [both indwelling urethral catheterization (IDUC) and indwelling suprapubic catheterization (SPC)] was reported in four studies, with a range of 0% to 100%.

Chia-Cheng *et al.* reported that catheterization was used by 67% of patients with NDO as a consequence of SCI, however it is unclear whether catheterization refers to IC or IDC

IC

Lemelle *et al.* reported that 71.3% patients with spina bifida were using IC. Anson *et al.* and Weld *et al.* reported much smaller percentages in post-acute phase SCI, with 30.5% and 29.1% respectively.

When considering studies with observations at multiple time points, El-Masri *et al.* reported 27% of SCI patients using assisted IC immediately before admission to the hospital; however, no patients utilized this method upon admission. During hospitalization, 4-hourly IC was the most utilized method, with 84% of patients using it at least once. This is the highest report of IC use from all publications. This markedly declined to 15.1% patients at discharge from hospital. In contrast to El-Masri *et al.*, the use of IC increased by 10.2% in the study by Drake *et al.*; from 3.6% SCI patients in 1990 to 13.8% in 1996.

The difference in IC use between these two studies could be attributable to the varied follow-up. In Drake *et al.*, changes take place over six years whereas follow up in the study by El-Masri *et al.* ranged between 8 and 21 years (mean 17.7).

IDC

Weld *et al.* reported 36.1% post-acute SCI patients that utilized IDUC and 11.4% patients had a SPC fitted. In the study by Anson *et al.*, much lower percentages were reported, with 9.8% that used IDUC and 3.2% that used SPC. The lowest recorded use of SPC use amongst the publications was one spina bifida patient in the study by Lemelle *et al.*

Studies with multiple observations seemed to paint a heterogeneous picture of IDC use. Overall, IDUC use substantially decreased (by 60.6%) in SCI patients, throughout the duration of the study by El-Masri *et al.*, but the general trend was not a linear decline. SPC use decreased at a much lower rate (0.8%) from hospitalization to discharge. In contrast to this, the number of SCI patients utilizing IDUC increased by 1.6% during the study by Drake *et al.*, and SPC use increased by 7.2%.

In the study by El-Masri *et al.*, 69% were managed with IDUC before admission to hospital and this increased to all patients upon admission; 21% of patients utilized this method at least once during hospitalization. After discharge, 8.4% patients remained with IDUC. In the study by Drake *et al.*, 12.2% had IDUC in 1990 and this increased to 13.8% in 1996.

The first recorded use of SPC was in the study by El-Masri *et al.* was during hospitalization, where 5% of patients utilized this method. After discharge, it was used by 4.2% of patients. Only 2% utilized SPC at study entry in the study by Drake *et al.*, but this increased at a much higher rate than IDUC use, with 9.2% of patients utilizing this method at study end.

Reflex voiding (RV)

RV methods can include bladder expression (Credé), straining (Valsalva) and triggered RV (4). In this SR, RV use was reported in four studies, varying from 2.5% to 53.1%.

RV methods are used by 25% of SCI patients in the study by Anson *et al.* and 23% SCI patients in the study by Weld *et al.* Although these percentages are close in range, they cannot be directly compared as Anson *et al.* fail to provide a definition of RV. Weld *et al.* defines spontaneous voiding as "*reflexive voiding with a post-void residual urine of less than 100 cc and a voiding pressure of less than 40 cm*".

In the study by Drake *et al.*, RV was defined as "*leaving a post void residual <10% and with no upper tract dilation, with or without prior sphincterotomy or urethral stent*". Use decreased by 11.8% during the study period, from 53.1% to 41.3%, but it remained the most used method within the study.

El-Masri *et al.* did not specifically define RV. A small number of patients (2.5%) were managed with RV prior to admission and during hospitalization it was used by 16.8% individuals. It was the most common form of bladder management after patients were discharged from the hospital, where it was utilized by 49.8% patients.

In the study by Drake *et al.*, straining methods (defined as either Credé or Valsalva) decreased by 8.2%, from 19.4% to 11.2%. A much lower percentage (2.6%) of patients used expression techniques (Credé) at the end of the study by El-Masri *et al.*

Surgery

Two authors report use of surgery to manage bladder symptoms. Manack *et al.* [2009] reports particularly low numbers of bladder augmentation and interstim therapy (0.2% and 0.4% respectively) in NGB patients. This is in contrast to Lemelle *et al.*, where the majority of spina bifida patients (55%) were surgically treated. Of these patients, 21.3% underwent bladder neck surgery, without bladder augmentation (with or without continent diversion), 36% patients underwent intestinal bladder augmentation (with or without bladder neck procedure) and 28.3% patients underwent intestinal bladder augmentation in addition to Mitrofanoff (with or without bladder neck procedure).

Other management methods

In the study by Lemelle *et al.*, 8.3% of people used pads and 1% of patients used an uriseath.

Combination use

Combinations of oral pharmacotherapy

Manack *et al.* [2011] reported 8.7% of patients on a combination of two or more antimuscarinic drugs; 8.3% were on two drugs, 0.4% were on three drugs and a negligible amount were on four or more drugs. A similar pattern was seen in the MS and SCI subcohorts; 9.5% patients in the MS subcohort were on a combination of two or more antimuscarinics, a further 9% were on two drugs, 0.5% were on three drugs and only two patients were on four or more drugs. When considering the SCI cohort, 9.2% patients were on a combination of two or more antimuscarinics, 8.9% were on two drugs, 0.3% were on three drugs and no patients were on four of more drugs.

A combination of alpha-blockers and antimuscarinics were given to those with detrusor sphincter dyssynergia (DSD) and autonomic dyssynergia in the study by El-Masri *et al.* Percentages of combination use were not reported.

Combination of a therapy with catheterization

Lemelle *et al.* states that 12.6% spina bifida patients regularly utilized IC in combination with oxybutynin. 90% of patients used IC in addition to surgery, including 61% through a continent neoconduit and 39% on abdominal wall.

In the study by Anson *et al.*, 11.5% patients were on a combination of IC and reflex. There is also a report of 3.7% of patients on some combination of treatments between IC, reflex, IDUC, SPC and self-voiding, but actual combinations are not provided.

Combination of surgical procedures and bladder neck injections

Lemelle *et al.* reports 39% of patients undergoing a combination of surgical procedures to achieve reservoir and neck management in spina bifida patients. The most popular combination of procedures is intestinal bladder augmentation + Mitrofanoff principle + neck closure.

Switching

Weld *et al.* mentions that most post-acute SCI patients switched bladder management methods over the course of the study period; with the most prevalent change being from IC to IDUC (percentage is not provided); 14.3% of patients in the study by Drake *et al.*, and one patient in the study by El-Masri *et al.* also made this particular switch of treatments.

As in the study by Weld *et al.*, most patients in the study by Drake *et al.* switched from their original mode of management (62.8%). However, the most prevalent change in this study was straining to IC (28.9%). The most used method in 1990 was RV, and this remained the case in 1996, despite 24% switching to an alternative form of treatment.

El-Masri *et al.* also showed a large proportion of patients (39.5%) that switched treatments during hospitalization. In contrast to both Weld *et al.* and Drake *et al.*, the most prevalent switch was IC to sphincterotomy and IDUC to IC.

Discussion

Selecting optimal treatments and employing appropriate management strategies for NGB patients is integral to improving patients' bladder symptoms and improving QoL. With passing time, clinicians have moved away from techniques associated with higher rates of complications and mortality, thus in recent years, the survival chances of NGB patients have substantially improved (15). This SR revealed that numerous treatments have been used to manage NGB throughout the years and there has been a large variance in their use.

The most popular oral pharmacotherapy in this SR were antimuscarinics, which are cited as first line therapy for NDO in the National Institute for Health and Care Excellence (NICE), EAU and International Consultations on Incontinence (ICI) guidelines (4,16,17). This conclusion should be viewed with some caution, as many studies in this review did not measure the use of oral pharmacotherapy, instead focusing their attention on other methods of bladder management. It is however well known that NDO is frequently observed in SCI (which 62.5% of included studies focused on) and antimuscarinics have acted as the primary mode of treatment for a number of years (18).

In the study by Manack *et al.* [2011], some patients used a combination of two or more antimuscarinics. Based on evidence from a few small clinical trials, the EAU provide a grade B recommendation, asking physicians to consider a combination of antimuscarinic agents (4,19-21). Other available guidelines do not provide graded recommendations on combination antimuscarinic use.

Invasive forms of management such as bladder augmentation are only employed once more conservative measures have been exhausted. A minority of spina bifida patients do not respond well to conservative treatments thus must undergo surgery to improve bladder functionality (22). Conversely, the one study included in this SR, focusing on spina bifida, reported that the majority of patients underwent surgery. This may be due to a high severity of incontinence in this sample, higher incidence of refractory NGB or a less conservative attitude of physicians towards surgery in France between 2003–2004 (the study period).

Many of the studies in this SR have early periods of data collection therefore, it is perhaps comprehensible that some practices deviated from what is currently considered safe and effective. One example of such variance is the use of the Credé and Valsalva manoeuvres in studies that collected data in the 1980's and 1990's (7,11). In current guidelines, these techniques are contraindicated due to complications including epidydymoorchitis and haemorrhoids (4,17,23).

IDC was also widely used (up to 100%) despite the fact that this type of catheterization is associated with an increased risk of urinary tract infection (UTI), and more serious conditions such as bladder cancer (4,16). It is important to remember however, that SCI can result in limited manual dexterity (e.g., in the case of tetraplegia), impeding the ability of intermittent self-catheterization (ICS) (24). The current NICE guidelines recognise that in some instances the choice of management technique is limited by what the patient can manage (16). Furthermore, the latest ICI guidelines suggest that assigning causation of urinary tract damage to IDC may not be accurate, as it is often utilized in patients in whom urinary tract damage has already occurred. Drake sugested that IDC may in fact be protective for the upper urinary tract (25). Although SPC is generally prefered over IDUC, it was used at a much lower rate. This could possibly be because placement of SPC is a more invasive procedure than IDUC (17).

This review had a global geographical scope, thus one may assume that the management methods employed reflect the healthcare system and national guidelines in which the study was conducted. At present, the American Urology Association (AUA) lacks any specific guidelines for the management of NGB. High antimuscarinic use in the two U.S. studies by Manack *et al.* are in line with other internationally available guidelines, where antimuscarinics are first line therapy for patients with NDO (4,16,17). In the study by Chia-Cheng *et al.*, conducted in Taiwan, alpha-blockers were the main method of management for NDO, despite Taiwanese NGB guidelines stating there is strong evidence to support the use of antimuscarinics in NDO (26). Their use may indicate patients had retention symptoms, in conjunction to NDO. Alternatively, several small clinical trials have demonstrated efficacy of alpha-blockers in NDO, which could indicate that clinicians in the real world are making choices in divergence from guideline recommendations (27,28). This notion correlates with results from a survey conducted by Rikken *et al.*, which showed that urologists did not follow guideline recommendations meticulously. Nevertheless, this survey also found that despite not adhering to guidelines, urologists still tended to make choices in accordance with recommendations (5).

Three studies demonstrated notable treatment switching, which could be indicative of the dynamic progression of NGB. Duration of time since injury in SCI can have an impact on bladder compliance that can consequently influence changes in the choice of management strategy (15). Alternatively, treatment switching may demonstrate that a trial and error approach is necessary to establish an optimal treatment regime (29). A number of factors influence the initial choice of management method, including type of NGB, sex, age, hand dexterity and healthcare access (30). In the study by Drake *et al.*, reasons for switching treatments pertained to complications such as functional decline and UTI's (7). Some patients included in this review made their own treatment choices, indicating that individual preference also plays a large role (7,11,12). Current guidelines promote active dialogue between

the physician and patient/their carer. In particular, NICE guidelines make specific recommendations for education of patients and their carers on the advantages and disadvantages of all available options so they are able to make informed management decisions (16,31).

Methodological limitations

The sensitivity of the search strategy could have been increased by including search terms for underlying neurological conditions. Additionally, publication bias and inclusion of mixed study designs could have affected the reliability of results.

Conclusions

Many treatments reported in this review are in line with current guideline recommendations; however, possibly due to the early years of data collection, some divergence was also evident. Due to the small number of studies, varied patient baseline characteristics, and selectiveness in the type of treatments and bladder management methods reported, a representative picture of real world treatment patterns in NGB could not be fully elucidated. Large epidemiological studies using electronic medical records (EMRs) are necessary to advance our understanding in how management strategies have changed over time, understand how patients are managed in current practice, and determine how well patterns relate to clinical guidelines.

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Footnote

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Appendix 6: Individual Neurogenic Bladder Clinical Guidelines AGREE II Appraisal Result

National Institute for Health and Care Excellence - Urinary Incontinence in Neurological Disease: Management of Lower Urinary Tract Dysfunction in Neurological Disease

Section	Item	Appraiser 1	Appraiser 2
Scope and Purpose	1	6	5
Scope and Purpose	2	7	6
Scope and Purpose	3	7	6
Stakeholder Involvement	4	6	6
Stakeholder Involvement	5	7	7
Stakeholder Involvement	6	7	7
Rigour of Development	7	7	6
Rigour of Development	8	7	6
Rigour of Development	9	7	5
Rigour of Development	10	7	5
Rigour of Development	11	7	6
Rigour of Development	12	7	6
Rigour of Development	13	6	6
Rigour of Development	14	7	6
Clarity of Presentation	15	7	6
Clarity of Presentation	16	5	5
Clarity of Presentation	17	7	7
Applicability	18	6	6
Applicability	19	7	7

Applicability	20	7	7
Applicability	21	5	6
Editorial Independence	22	7	5
Editorial Independence	23	7	6
Overall Assessment	OA1	7	6
Overall Assessment	OA2	Yes	Yes, with modifications

European Association of Urology - Clinical Guidelines on Neuro-Urology

Section	Item	Appraiser 1	Appraiser 2
Scope and Purpose	1	7	6
Scope and Purpose	2	5	5
Scope and Purpose	3	7	6
Stakeholder Involvement	4	5	5
Stakeholder Involvement	5	5	6
Stakeholder Involvement	6	7	6
Rigour of Development	7	6	5
Rigour of Development	8	6	6
Rigour of Development	9	7	6
Rigour of Development	10	4	4
Rigour of Development	11	7	6
Rigour of Development	12	6	6
Rigour of Development	13	5	5
Rigour of Development	14	7	6
Clarity of Presentation	15	6	6

Clarity of Presentation	16	6	6
Clarity of Presentation	17	7	7
Applicability	18	5	5
Applicability	19	7	7
Applicability	20	5	5
Applicability	21	2	2
Editorial Independence	22	6	6
Editorial Independence	23	7	6
Overall Assessment	OA1	6	6
Overall Assessment	OA2	Yes, with modifications	Yes, with modifications

International Consultation on Incontinence - Neurologic Urinary and Faecal Incontinence

Section	Item	Appraiser 2	Appraiser 6
Scope and Purpose	1	7	6
Scope and Purpose	2	6	6
Scope and Purpose	3	7	6
Stakeholder Involvement	4	5	5
Stakeholder Involvement	5	4	2
Stakeholder Involvement	6	7	7
Rigour of Development	7	5	6
Rigour of Development	8	7	5
Rigour of Development	9	7	5
Rigour of Development	10	5	5
Rigour of Development	11	7	6

Rigour of Development	12	7	6
Rigour of Development	13	3	3
Rigour of Development	14	7	6
Clarity of Presentation	15	7	6
Clarity of Presentation	16	7	6
Clarity of Presentation	17	7	7
Applicability	18	5	5
Applicability	19	5	5
Applicability	20	5	5
Applicability	21	2	2
Editorial Independence	22	6	4
Editorial Independence	23	7	6
Overall Assessment	OA1	6	5
Overall Assessment	OA2	Yes, with modifications	Yes, with modifications

Appendix 7: Search strategy performed in ProQuest Dialog® to identify real world evidence studies relating to treatment patterns in neurogenic bladder

Set #	Searched for	Results
S5	((S1 AND S2) AND S3) and (pd(19960101-20171231))	116°
S4	(S1 AND S2) AND S3	128°
S3	((treatment pattern*) OR (standard near/2 (treatment OR therapy OR care))) OR MESH.EXACT.EXPLODE("Standard of Care") OR EMB.EXACT.EXPLODE("health care quality") OR EMB.EXACT.EXPLODE("health care utilization")	870350*
S2	((epidemiolog* stud*) OR (case control) OR (cohort NEAR/1 (stud* OR analy*)) OR (observational stud*) OR (longitudinal) OR ((retrospective OR prospective) near/3 (stud* OR analy*)) OR (cross sectional) OR (chart review) OR (medical record review)) OR EMB.EXACT("epidemiology") OR EMB.EXACT.EXPLODE("case control study") OR EMB.EXACT.EXPLODE("prospective study") OR EMB.EXACT.EXPLODE("cross-sectional study") or EMB.EXACT.EXPLODE("cohort analysis") OR EMB.EXACT.EXPLODE("observational study") OR EMB.EXACT.EXPLODE("longitudinal study") OR EMB.EXACT.EXPLODE("retrospective study") or EMB.EXACT.EXPLODE("medical record review") OR MESH.EXACT.EXPLODE("Epidemiologic Studies") OR MESH.EXACT.EXPLODE("Observational Study")	7643028*
S1	ti,ab,if(((bladder OR detrusor) near/3 dyssnergia) OR (neurogenic near/3 detrusor near/3 overactiv*) OR ((neurogenic OR neuropathic) near/3 bladder)) OR EMB.EXACT.EXPLODE("neurogenic bladder") OR MESH.EXACT.EXPLODE("Urinary Bladder, Neurogenic")	20227*

*Duplicates are removed from the search but included in the result count.

° Duplicates are removed from the search and from the result count

Appendix 8: Pilot data extraction form for systematic literature review

Study author and year	Study design	Patient characteristics	Type of NGB (NDO, underactive)	Neurogenic condition	Treatment patterns
Drake et al 2005	Prospective	57.4 years mean age (range 43-81), 171 (86%) male One hundred and ninety six people post injury (YPI) 33		SCI (for at least 20 years)	BMM options differ in respect of prevalence and incidence of complications. At a late stage post injury there remains a high probability of change in BMM.
Drake et al 2005	Prospective	57.4 years mean age (range 43-81), 171 (86%) male One hundred and ninety six people post injury (YPI) 33		SCI (for at least 20 years)	
Drake et al 2005	Prospective	57.4 years mean age (range 43-81), 171 (86%) male One hundred and ninety six people post injury (YPI) 33		SCI (for at least 20 years)	IDUC/SPC IC Strain RV Normal Incomplete (n) 0 7 4 7 19 Para ABC (n) 29 16 11 40 0 Tetra ABC (n) 16 4 7 34 0 Mean age (years) 61.2 (0.03) 58.2 (0.69) 57.3 (0.90) 54.8 (0.0003) 58.2 (0.68) MeanYPI (years) 35.9 (0.007) 35.3 (0.04) 33.2 (0.90) 31.2 (0.0004) 30.7

					(0.06 Gender: M/F 40/5 (0.3) 19/8 (0.35) 13/11 (0.60) 80/1 (0.0001) 18/1 (0.23)
El-Masri et al 2012	Retrospective, longitudinal	Traumatic SCI, Frankel grade A-D, admission within 6 weeks post injury. 99 males and 20 females (5:1), age at time of injury 16-63 (mean 29)	69 paraplegic, 50 tetraplegic.	SCI	All patients used more than one method of management at different times, particularly towards old age.
El-Masri et al 2012	Retrospective, longitudinal	Traumatic SCI, Frankel grade A-D, admission within 6 weeks post injury. 99 males and 20 females (5:1), age at time of injury 16-63 (mean 29)	69 paraplegic, 50 tetraplegic.	SCI	Phase 1- Before admission to MSCI - All patients were initially managed with IndUC. 38 patients (32%) did not have their method of urine drainage documented. Of the remaining 81 patients, 56 (69%) had IndUC, 22 (27%) had ACIC, and in 3 other patients RV and/or bladder expression were used before admission to MSCI. one patient with a C4 frankel injury had an initial IndUC had a sphincterotomy before admission

					in order to achieve RV.
El-Masri et al 2012	Retrospective, longitudinal	Traumatic SCI, Frankel grade A-D, admission within 6 weeks post injury. 99 males and 20 females (5:1), age at time of injury 16-63 (mean 29)	69 paraplegic, 50 tetraplegic.	SCI	Phase 2 - During hospitalisation to MCSI - In those with and without complications, the overwhelming method of bladder management was four hourly intermittent catheterisation
El-Masri et al 2012	Retrospective, longitudinal	Traumatic SCI, Frankel grade A-D, admission within 6 weeks post injury. 99 males and 20 females (5:1), age at time of injury 16-63 (mean 29)	69 paraplegic, 50 tetraplegic.	SCI	Patients without complications at phase 2 No intervention 4 Intermittent catheterisation with or without oral medicinea 41 Intermittent catheterisation+sphincterotomy 5 Intermittent catheterisation-suprapubic catheterization 2 Intermittent catheterisation-sphincterotomy - reflex voiding 1 Intermittent catheterisation-reflex voiding 3 Indwelling urethral catheterisation 3 Indwelling urethral catheterisation-intermittent catheterisation

					9 Indwelling urethral catheterisation-intermittent catheterisation 2 -reflex voiding Reflex voiding 4 Total 74
El-Masri et al 2012	Retrospective, longitudinal	Traumatic SCI, Frankel grade A-D, admission within 6 weeks post injury. 99 males and 20 females (5:1), age at time of injury 16-63 (mean 29)	69 paraplegic, 50 tetraplegic.	SCI	Patients with complications at phase 2 No intervention 1 Intermittent catheterisation with or without oral medicinea 10 Intermittent catheterisation-sphincterotomy 11 Intermittent catheterisation-reflex voiding 4 Intermittent catheterisation-suprapubic catheterisation 2 Intermittent catheterisation-suprapubic catheterisation 1 - sphincterotomy-reflex voiding Intermittent catheterisation - sphincterotomy - reflex voiding 2 Intermittent catheterisation-indwelling urethral catheterisation 1 Intermittent catheterisation-indwelling urethral

					catheterisation -sphincterotomy-reflex voiding 1 Indwelling catheterisation 3 Indwelling catheterisation-intermittent catheterisation 2 Indwelling catheterisation-intermittent catheterisation -sphincterotomy 2 Indwelling catheterisation-intermittent catheterisation -reflex voiding 1 Indwelling catheterisation-suprapubic catheterisation 1 Reflex voiding 1 Reflex voiding-sphincterotomy 2 Total 45
El-Masri et al 2012	Retrospective, longitudinal	Traumatic SCI, Frankel grade A-D, admission within 6 weeks post injury. 99 males and 20 females (5:1), age at time of injury 16-63 (mean 29)	69 paraplegic, 50 tetraplegic.	SCI	Bladder management after discharge from MCSI Phase 3 - Without intervention Complication - 21 No complication - 3 Total - 24 Intermittent catheterization (also sphincterotomy) 4 14 (1) 18 (1) Indwelling catheterisation (also sphincterotomy) 1

					9 (3) 10 (3) Reflex voiding (also sphincterotomy) 19 (3) 40 (24) 59 (27) Expression 1 2 3 Suprapubic catheterisation (also sphincterotomy) 0 5 (3) 5 (3) Total number of patients (also sphincterotomy) 46 (3) 73 (31) 119 (34)
Lemelle et al 2006	Multicentre retrospective cohort of medical charts	421 patients, 230 (55%) male and 191 (45%) female. Mean patient age was 22.1 years (range 10-47.5). 140 aged 10-18 and 281 aged over 18.		Spina bifida	A total of 191 patients (45%) were medically treated for urinary continence management. Mean age was 21.7 years. Clean intermittment catheter performed in 116 (61%), including 69 males and 47 females of whom 53 (46%) used oxybutnin reg. Remaning 35 wore diapers without any method for bladder emptying. Urisheath reg used by 4 patients and 1 had a permanent suprapubic catheter

Lemelle et al 2006	Multicentre retrospective cohort of medical charts	421 patients, 230 (55%) male and 191 (45%) female. Mean patient age was 22.1 years (range 10-47.5). 140 aged 10-18 and 281 aged over 18.		Spina bifida	Of the patients 23 underwent noncontinent urinary diversion, that is a Bricker procedure in 19 and vesicostomy in 4. There were missing data on the surgical procedure in 2 cases. The description of surgical management and urinary continence was relevant in 205 cases. Mean age at first operation for urinary incontinence was 12.8 _ 5.3 years. (range 3 to 29.). Mean followup after initial surgery was 9.25 years. A total of 184 patients (90%) used to perform clean intermittent catheterization through the urethra (112 or 61%) and through a continent neoconduit on the abdominal wall (72 or 39%). Intestinal bladder augmentation was done in 148 cases (72%), including the sigmoid in 95 (64%), the ileum in 47 (32%),

					the stomach in 5 (3%) and the ileumcecum in 1 (1%). Bladder auto-augmentation with detrusorotomy without any other subsequent bladder enlargement was performed in 4 cases (2%). Procedures on the bladder neck were numerous, including mainly bladder neck closure, a urinary AMS800 artificial sphincter (American Medical Systems, Minnetonka, Minnesota), a sling or cinch procedure, a Kropp, PippiSalle or Young-Dees procedure, or biomaterial injection endoscopically or at open surgery.
Manack et al 2009	Retrospective analysis of a claims database	46,271 patients (9.9% of overall OAB patients), 2.9% (1,323) were pediatric 12 years old or younger.		MS, SCI, PD, Paralytic syndrome or CP	33,100 (71.5%) of total 46,271, NOAB patients were on one or more OAB drug during the one year post index period.1 drug (62.8%), 2 drugs (8.3%), 3 drugs (0.4%), 11

					patients on 4 or more drugs.
Manack et al 2009	Retrospective analysis of a claims database	46,271 patients (9.9% of overall OAB patients), 2.9% (1,323) were pediatric 12 years old or younger.		MS, SCI, PD, Paralytic syndrome or CP	Mean number of days on drug therapy on this group was 201.87 (SD 120.59) median - 218
Manack et al 2009	Retrospective analysis of a claims database	46,271 patients (9.9% of overall OAB patients), 2.9% (1,323) were pediatric 12 years old or younger.		MS, SCI, PD, Paralytic syndrome or CP	10,110 NOAB (22% of 46,271) dicontinued OAB oral therapy and did not restart, 7782 (17%) continued, 9,030 (20%) stopped and restarted oral therapy. 1,033 (2%) neither stopped continued not restarted oral therapy. 18,316 (36%) did not initiate oral therapy.
Manack et al 2009	Retrospective analysis of a claims database	46,271 patients (9.9% of overall OAB patients), 2.9% (1,323) were pediatric 12 years old or younger.		MS, SCI, PD, Paralytic syndrome or CP	5 most common meds were oxybutynin (39.0%), tolterodine (36.9%), acetaminophen/hydeocodone biltartate (25.4%), ciproflaxin (21.9%), levoflaxacin (20.9%).

Manack et al 2009	Retrospective analysis of a claims database	46,271 patients (9.9% of overall OAB patients), 2.9% (1,323) were pediatric 12 years old or younger.		MS, SCI, PD, Paralytic syndrome or CP	real world rates of second and third line therapies - vast majority had aumentation cystoplasty (0.2%) and interstim therapy (0.4%)
Anson & Shepard 1996	Data was collected in outpatient clinics when patients retured for routine follow up examinations	348 patients. (Table 1)	36.2% had neurological levels of injury between C4 and C8, C5 (19%), (Table 2).	post-actute SCI	two of the most freq use were IC (n=106, 30.5%) and reflex (n=87.25%). Combination of IC and reflex (n=40, 11.5%), indwelling UC (n=34, 9.8%), suprapubic catheter (n=11, 3.2%). 57 (16.4%) were self voiding and 13 (3.7%) were using some combination of those programmes.
Weld & **Dmochowski** 2000	retrospectively reviewed the medical records, upper tract imaging and video urodynamics of	316 posttraumatic spinal cord injured patients. Mean followup plus or minus standard deviation since injury was 18.3 6 12.4 years. (Table 1)	(Table 1)	posttraumatic spinal cord injured patients	chronic urethral catheterization, clean intermittent catheterization, spontaneous voiding and suprapubic catheterization in 114, 92, 74 and 36, respectively.
Manack et al 2011	Medical and pharmacy	46,271 patients in the Neurogenic	Patients with lower urinary tract dysfunctions related to urinary	NGB	33,100 (71.5%) neurogenic bladder patients were taking one

	claims were retrospectively analyzed from April 1, 2002 to March 31, 2007	bladder cohort, and 9,315 and 4,168 patients in Multiple Sclerosis (MS) and Spinal Cord Injury (SCI) subcohorts. The mean age (SD) of the neurogenic bladder cohort was 62.5 (19.6) years, and the mean ages in the MS and SCI subcohorts were 53.2 (12.0) and 61.9 (20.5) years, respectively (table 1)	incontinence (e.g., hypertonic bladder, detrusor sphincter dyssynergia, bladder paralysis, urinary frequency) due to neurologic disease or injury. MS; SCI (including paraplegia, quadriplegia, tetraplegia); spina bifida; Parkinson's disease; cerebral palsy; and specified paralytic syndromes(hemiplegia/hemiparesis, late effects of stroke, other specified paralytic syndromes, and neoplasm of the spinal cord). Two predefined subcohorts, SCI and MS, were also selected based on an ICD-9-CM diagnosis code during the eligibility period.		or more OAB oral drugs. Oxybutynin (39.0%) and tolterodine (36.9%) were the most frequently used medications.
Manack et al 2011	Medical and pharmacy claims were retrospectively analyzed from April 1, 2002 to March 31, 2007	46,271 patients in the Neurogenic bladder cohort, and 9,315 and 4,168 patients in Multiple Sclerosis (MS) and Spinal Cord Injury (SCI) subcohorts. The mean age (SD) of	Patients with lower urinary tract dysfunctions related to urinary incontinence (e.g., hypertonic bladder, detrusor sphincter dyssynergia, bladder paralysis, urinary frequency) due to neurologic disease or injury. MS; SCI (including paraplegia, quadriplegia, tetraplegia); spina bifida; Parkinson's	NGB	The mean number of days (SD; median) on OAB drug was 201.9 days (120.6; 218). This included 8,075 patients (86.7%) in the MS subcohort and 3,372 patients (80.9%) in the SCI subcohort who were taking ≥1 OAB oral drugs during the 1-year post-index period.

		the neurogenic bladder cohort was 62.5 (19.6) years, and the mean ages in the MS and SCI subcohorts were 53.2 (12.0) and 61.9 (20.5) years, respectively (table 1)	disease; cerebral palsy; and specified paralytic syndromes(hemiplegia/hemiparesis, late effects of stroke, other specified paralytic syndromes, and neoplasm of the spinal cord). Two predefined subcohorts, SCI and MS, were also selected based on an ICD-9-CM diagnosis code during the eligibility period.		
Manack et al 2011	Medical and pharmacy claims were retrospectively analyzed from April 1, 2002 to March 31, 2007	46,271 patients in the Neurogenic bladder cohort, and 9,315 and 4,168 patients in Multiple Sclerosis (MS) and Spinal Cord Injury (SCI) subcohorts. The mean age (SD) of the neurogenic bladder cohort was 62.5 (19.6) years, and the mean ages in the MS and SCI subcohorts were 53.2 (12.0) and	Patients with lower urinary tract dysfunctions related to urinary incontinence (e.g., hypertonic bladder, detrusor sphincter dyssynergia, bladder paralysis, urinary frequency) due to neurologic disease or injury. MS; SCI (including paraplegia, quadriplegia, tetraplegia); spina bifida; Parkinson's disease; cerebral palsy; and specified paralytic syndromes(hemiplegia/hemiparesis, late effects of stroke, other specified paralytic syndromes, and neoplasm of the spinal cord). Two predefined subcohorts, SCI and	NGB	The average length of time (SD; median) on drug was 209.1 days (121.8; 238) for the MS subcohort and 195.5 days (121.5; 206) for the SCI subcohort.

		61.9 (20.5) years, respectively (table 1)	MS, were also selected based on an ICD-9-CM diagnosis code during the eligibility period.		
Manack et al 2011	Medical and pharmacy claims were retrospectively analyzed from April 1, 2002 to March 31, 2007	46,271 patients in the Neurogenic bladder cohort, and 9,315 and 4,168 patients in Multiple Sclerosis (MS) and Spinal Cord Injury (SCI) subcohorts. The mean age (SD) of the neurogenic bladder cohort was 62.5 (19.6) years, and the mean ages in the MS and SCI subcohorts were 53.2 (12.0) and 61.9 (20.5) years,	Patients with lower urinary tract dysfunctions related to urinary incontinence (e.g., hypertonic bladder, detrusor sphincter dyssynergia, bladder paralysis, urinary frequency) due to neurologic disease or injury. MS; SCI (including paraplegia, quadriplegia, tetraplegia); spina bifida; Parkinson's disease; cerebral palsy; and specified paralytic syndromes(hemiplegia/hemiparesis, late effects of stroke, other specified paralytic syndromes, and neoplasm of the spinal cord). Two predefined subcohorts, SCI and MS, were also selected based on	NGB	Most patients were on only one OAB drug (Table II). Eleven patients were receiving ≥4 OAB drugs, and two of those patients belonged to the MS subcohort. No patients were on >3 drugs in the SCI subcohort

		respectively (table 1)	an ICD-9-CM diagnosis code during the eligibility period.		
Manack et al 2011	Medical and pharmacy claims were retrospectively analyzed from April 1, 2002 to March 31, 2007	46,271 patients in the Neurogenic bladder cohort, and 9,315 and 4,168 patients in Multiple Sclerosis (MS) and Spinal Cord Injury (SCI) subcohorts. The mean age (SD) of the neurogenic bladder cohort was 62.5 (19.6) years, and the mean ages in the MS and SCI subcohorts were 53.2 (12.0) and 61.9 (20.5) years, respectively (table 1)	Patients with lower urinary tract dysfunctions related to urinary incontinence (e.g., hypertonic bladder, detrusor sphincter dyssynergia, bladder paralysis, urinary frequency) due to neurologic disease or injury. MS; SCI (including paraplegia, quadriplegia, tetraplegia); spina bifida; Parkinson's disease; cerebral palsy; and specified paralytic syndromes(hemiplegia/hemiparesis, late effects of stroke, other specified paralytic syndromes, and neoplasm of the spinal cord). Two predefined subcohorts, SCI and MS, were also selected based on an ICD-9-CM diagnosis code during the eligibility period.		Most received alpha blockers (33%), antimuscarinic agents (26%) and cholinergic agents (15%). 67% received urinary catheterisations.

Chia-Cheng et al 2012	Cross-sectional	Patients with emergency department visits or hospitalisations for SCI. 941 patients, 165(17.5%) NDO with a mean age of 54, 64% male.	NDO	SCI	Most received alpha blockers (33%), antimuscarinic agents (26%) and cholinergic agents (15%). 67% received urinary catheterisations.

Appendix 9: Strengths and limitations of the CPRD and HES databases

Strengths of the Clinical Practice Research Database GOLD

The aim of this research is to build a comprehensive image of the NGB population in the UK, therefore, it is a logical choice to utilise the largest longitudinal EHR available, that is broadly representative of the UK population. This ensures that the greatest possible number of NGB patients will be captured thus enhancing the generalisability of results.

Contributing GP practices receive guidelines from the CPRD to encourage high quality recording of data. In addition, upon receipt of the data, the CPRD provide feedback and work with the practices to rectify any inconsistences that remain. If the practices are not able to address data quality issues and ultimately fail meet the pre-specified quality criteria, then they are not marked as 'up-to-standard (UTS)' and are no longer included in the dataset (Boston University, N.D). The data is usually considered unacceptable if a surgery has had too large of a gap between uploads, (unless, for example, there is a valid reason like a bank holiday) or if death recording falls below a pre-defined threshold. In addition to UTS quality criteria, individual patients are coded as being 'research acceptable' (acceptable=1 or unacceptable=0), to specify whether their data points are complete and do not contain outliers. Both of these measures enhance data-usability. Only patients with UTS and of research acceptable status were enrolled into this study.

The CPRD contains granular patient level data, and in particular, prescription data is extremely detailed, which allows an accurate and comprehensive description of drug utilisation. Information on drug dose, strength and brand is available. Furthermore, all information is computer generated and recorded simultaneously, reducing the rates of error which typically come with handwritten notes.

Every patient in England and Wales who are registered with the NHS have a unique identifier known as their 'NHS number'. This number is common to multiple datasets in the UK, allowing information on individuals from disparate sources to be linked. The CPRD database can be linked to the hospital episode statistics (HES) database, which allows

longitudinal data capture of the patient journey from primary through to secondary care. This provides more complete information on outcomes such as hospitalisations as well as enrichment of patients' medical and therapeutic histories.

Limitations of the Clinical Practice Research Database GOLD

Despite being the superior choice for this research, there are a number of inherent weaknesses of the CPRD, those most relevant to this study are highlighted in this section.

Although the CPRD is considered broadly representative of the UK population, there are some individuals in the UK who are less likely to not be registered with their GP this includes, prisoners, the homeless, members of the armed forces and asylum seekers. Furthermore, males are less likely to the registered than females due to differences in health-seeking behaviour between the genders (Herrett, 2015).

Another issue is the potential underestimation of disease prevalence as a consequence of the absence of Read codes, which can be misinterpreted as absence of the disease itself. In reality, missing Read codes could reflect inadequate diagnoses, failure of the patient to present to the GP or inconsistencies in coding between primary and secondary care (Herrett, 2015). This concept is explored further in Section 8.2.

The ability to accurately describe drug-taking behaviour from the CPRD is impeded by a few factors. Firstly, despite a wealth of information existing for drugs that are prescribed in clinical practice, information on over-the-counter (OTC) drugs does not appear in the database. Secondly, although a prescription has been issued, it is impossible to know whether patients took their medication as per the prescriber's instructions (i.e. whether they adhered to their medication). Thus, what is observed in the CPRD can be considered only part of the patients' drug taking behaviour.

Strengths of Hospital Episode Statistics Admitted Patient Care and Outpatient

The HES data is assessed for completeness and consistency, with a data quality report published annually. Generally, the completeness of recording admissions is very high. The

diagnostic accuracy in HES has proven adequate (80.3%), as well as the accuracy of procedure coding (84.2%) (Burns et al., 2012). Furthermore, because the GP is the gatekeeper of healthcare, acting as the first point of contact for all non-emergency care by coordinating referrals to specialists, any diagnoses or treatments given in secondary care is fed back to primary care. Information is entered into the electronic patient record to ensure full transparency and facilitation of the appropriate delivery of health care services (Herrett, 2015; La Rocca and Hoholm, 2017).

The data in HES is comprehensive, which posits the database as an excellent resource for research purposes; it includes information on patient and clinical characteristics and administrative information (NHS Digital, 2018). Overall, there are 270 variables available in the core dataset (Herbert, 2017). The universal coverage of HES and possibility to link to patients in the CPRD database provides excellent longitudinal data capture across the patient's entire health journey allowing for the detailed evaluation of factors related to HRU. Furthermore, each episode in the HES can be linked to a Healthcare Resource Group (HRG) code and thus a unit cost, allowing the quantification of burden of disease (Meacock et al., 2015).

Limitations of Hospital Episode Statistics Admitted Patient Care and Outpatient

Although in recent years the coding accuracy in HES has improved, errors in diagnostic, procedure codes and administrative codes are still likely to be present. The instance of errors varies between hospitals, which means there is inconsistency in data quality (Slavin, 2012). Another factor affecting data quality is the payment by results (PbR). This scheme incentivises the accurate coding of data points in order to reimburse hospitals for the care they provide. The scheme was introduced in 2003 and has subsequently expanded to 60% of hospital activity in the UK (Marshall, 2014). Although in itself the scheme has steadily improved the quality of coding of the years, it proves an issue when analysing data over a long period. Consequently, the quality of data points was varied over the period of this study (2004-2016) (Herbert, 2017).

It is important to consider that only a subset of CPRD practices have consented to HES linkage, furthermore HES is only available in the English NHS. This means there was an invariably smaller cohort available to analyse for the secondary objective of this study. This limitation was perhaps less impactful given the descriptive nature of this research.

Appendix 10: Manchester Metropolitan University Ethics Approval

MANCHESTER METROPOLITAN UNIVERSITY
FACULTY OF HEALTH, PSYCHOLOGY AND SOCIAL CARE

M E M O R A N D U M

FACULTY ACADEMIC ETHICS COMMITTEE

Manchester Metropolitan University

To: Ashley Jaggi

From: Prof Carol Haigh

Date: 19/01/2016

Subject: Ethics Checklist 1322

Title: Long Term Outcomes Associated with Oral Neuropathic Pain Medications: Evidence from Real World Data

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Thank you for your Ethics Checklist.

The Faculty Academic Ethics Committee review process has recommended approval of your ethics application. This approval is granted for 42 months for full-time students or staff and 60 months for part-time students. Extensions to the approval period can be requested.

If your research changes you might need to seek ethical approval for the amendments. Please request an amendment form.

We wish you every success with your project.

Prof Carol Haigh and Prof Jois Stansfield
Chair and Deputy Chair
Faculty Academic Ethics Committee

Appendix 11: Independent Scientific Approval Committee (ISAC) protocol number 17_207R

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL		***by e-mail***	
PROTOCOL NO:	17_207		
PROTOCOL TITLE:	Drug Utilisation Patterns and Healthcare Resource Use in Patients With Neurogenic Bladder (NGB): A descriptive study using electronic health records from the UK		
APPLICANT:	Dr. Jameel Nazir, HEOR Director.		
APPROVED ☒	**APPROVED WITH COMMENTS** **(resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJEC** ☐
INSTRUCTIONS: ***Please include your response/s to the Reviewer's feedback below only if you are required to Revise/ Resubmit your protocol.*** ***Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.***			
DATE OF ISAC FEEDBACK:	29/09/2017		
DATE OF APPLICANT FEEDBACK:	25/09/2017		

Appendix 12: Read codes for neurogenic bladder and probable neurogenic bladder patients

Codes for Neurogenic Bladder and Overactive Bladder

Disease	Key words	Read terms	Read codes
Neurogenic bladder	*neurogenic*	Neurogenic bladder	K16V011
		Neurogenic bladder	F246112
	neuropathic bladder	Neuropathic bladder	K16V00
		Neuropathic bladder	F246113
		Reflex neuropathic bladder, not elsewhere classified	K16W.00
		Uninhibited neuropathic bladder, NEC	K16X.00
	*neuromuscular*bladder*	[X]Other neuromuscular dysfunction of bladder	Kyu5200
		[X]Neuromuscular dysfunction of bladder, unspecified	Kyu5E00
		Neuromuscular dysfunction of bladder, unspecified	K16V.00
Overactive Bladder	*overactive*		K16V100
	detrusor	detrusor instability	K165300
		detrusor instability	K16y411
		unstable bladder	K165400
		unstable bladder	K16y412

Codes for Stroke

Read terms	Read codes
Intracerebral haemorrhage	G61..00

Cortical haemorrhage	G610.00
Internal capsule haemorrhage	G611.00
CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11
Stroke due to intracerebral haemorrhage	G61..12
Basal nucleus haemorrhage	G612.00
Cerebellar haemorrhage	G613.00
Pontine haemorrhage	G614.00
Bulbar haemorrhage	G615.00
External capsule haemorrhage	G616.00
Intracerebral haemorrhage; multiple localized	G618.00
Intracerebral haemorrhage in hemisphere; unspecified	G61X.00
Left sided intracerebral haemorrhage; unspecified	G61X000
Right sided intracerebral haemorrhage; unspecified	G61X100
Intracerebral haemorrhage NOS	G61z.00
Cerebral infarct due to thrombosis of precerebral arteries	G63y000
Cerebral infarction due to embolism of precerebral arteries	G63y100
Cerebral arterial occlusion	G64..00
Cerebral thrombosis	G640.00
Cerebral infarction due to thrombosis of cerebral arteries	G640000
Cerebral embolism	G641.00
Cerebral infarction due to embolism of cerebral arteries	G641000
CVA - cerebral artery occlusion	G64..11
Cerebral embolus	G641.11
Infarction - cerebral	G64..12
Stroke due to cerebral arterial occlusion	G64..13

Cerebral infarction NOS	G64z.00
Brainstem infarction	G64z000
Wallenberg syndrome	G64z100
Brainstem infarction NOS	G64z.11
Lateral medullary syndrome	G64z111
Cerebellar infarction	G64z.12
Left sided cerebral infarction	G64z200
Right sided cerebral infarction	G64z300
Infarction of basal ganglia	G64z400
Carotid artery syndrome hemispheric	G653.00
Stroke and cerebrovascular accident unspecified	G66..00
Middle cerebral artery syndrome	G660.00
Anterior cerebral artery syndrome	G661.00
CVA unspecified	G66..11
Stroke unspecified	G66..12
CVA - Cerebrovascular accident unspecified	G66..13
Posterior cerebral artery syndrome	G662.00
Brain stem stroke syndrome	G663.00
Cerebellar stroke syndrome	G664.00
Pure motor lacunar syndrome	G665.00
Pure sensory lacunar syndrome	G666.00
Left sided CVA	G667.00
Right sided CVA	G668.00
Cereb infarct due unsp occlus/stenos precerebr arteries	G6W..00
Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	G6X..00

[X]Other intracerebral haemorrhage	Gyu6200
[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Gyu6300
[X]Other cerebral infarction	Gyu6400
[X]Occlusion and stenosis of other precerebral arteries	Gyu6500
[X]Occlusion and stenosis of other cerebral arteries	Gyu6600
[X]Cereb infarct due unsp occlus/stenos precerebr arteries	Gyu6G00
CVA - cerebrovascular accident in the puerperium	L440.11
Stroke in the puerperium	L440.12
STROKE WITH HYPERTENSION	4360B
CVA (CEREBROVASCULAR ACCIDENT)	4369A
CEREBROVASCULAR ACCIDENT LEFT	4369AL
CEREBROVASCULAR ACCIDENT RIGHT	4369AR
STROKE	4369B
SYNDROME STROKE	4369BN

Codes for spinal cord injuries

Read terms	**Read codes**
Open fracture of sacrum with other spinal cord injury	S117300
Delivery of rehabilitation for spinal cord injury	7P21100
Late effect of spinal cord injury	SC22.00
Frankel grading system for spinal cord injury	ZRBy.00
Spine of spinal cord injury due to birth trauma	Q204.00
Spine of spinal cord injury due to birth trauma NOS	Q204z00
spinal cord injury without spinal bone injury NOS	SJ2z.00

Nerve and spinal cord injuries	SJ…00
Nerve and spinal cord injury NOS	SJz..00
spinal cord injury multiple site without spinal bone injury	SJ2x.00
spinal cord injury without evidence of spinal bone injury	SJ2..00
spinal cord injuries	SJ…13

Codes for multiple sclerosis

Read terms	**Read codes**
Benign multiple sclerosis	F204.00
Generalised multiple sclerosis	F202.00
Multiple sclerosis of the spinal cord	F201.00
Multiple sclerosis of the brain stem	F200.00
Relapsing and remitting multiple sclerosis	F207.00
Multiple sclerosis NOS	F20z.00
Multiple sclerosis	F20..00
Exacerbation of multiple sclerosis	F203.00
Secondary progressive multiple sclerosis	F208.00
Primary progressive multiple sclerosis	F206.00
Disseminated sclerosis	F20..11

Codes for Parkinson’s disease

Read terms	**Read codes**
Paralysis agitans	F120.00
Parkinson's disease	F12..00

Parkinsonism with orthostatic hypotension	F130300
Parkinson's disease NOS	F12z.00
Cerebral degeneration in Parkinson's disease	F11x900

Codes for spina bifida

Read terms	**Read codes**
Spina bifida	P1...00
Spina bifida occulta	PG17.00
FH: Spina bifida	12J2.00
Spina bifida with hydrocephalus, unspecified	P100000
Spina bifida NOS	P1z..00
Repair of spina bifida	7043.00
Spina bifida with hydrocephalus	P10..00
Spina bifida without mention of hydrocephalus	P11..00
Spina bifida with hydrocephalus - open NOS	P102z00
Suspect fetal spina bifida	L250.13
Closed spina bifida with Arnold-Chiari malformation	P101.11
Spina bifida with hydrocephalus NOS	P10z.00
Dandy - Walker syndrome with spina bifida	P10y000
Spina bifida with stenosis of aqueduct of Sylvius	P105.00
Repair of spina bifida NOS	7043z00
Unspecified spina bifida with hydrocephalus	P100.00
Lumbar spina bifida without mention of hydrocephalus	P110300
Sacral spina bifida without hydrocephalus - closed	P118400

Lumbar spina bifida without hydrocephalus - closed	P118300
Lumbar spina bifida with hydrocephalus	P100300
Other specified repair of spina bifida	7043y00
Spina bifida without hydrocephalus - closed	P118.00
Sacral spina bifida without hydrocephalus - open	P117400
Spina bifida without mention of hydrocephalus NOS	P11z.00
Sacral spina bifida with hydrocephalus - open	P102400
Thoracic spina bifida without mention of hydrocephalus	P110200
Spina bifida with hydrocephalus - closed	P103.00
Other specified spina bifida without hydrocephalus	P11y.00
Unspecified spina bifida without hydrocephalus NOS	P110z00
Cervical spina bifida without mention of hydrocephalus	P110100
Insertion of Halber valve for spina bifida	7010111
Thoracic spina bifida with hydrocephalus - open	P102200
Spina bifida with hydrocephalus of late onset	P104.00
Spina bifida without hydrocephalus - open	P117.00
Unspecified spina bifida without hydrocephalus - closed	P118000
Spina bifida without hydrocephalus - open NOS	P117z00
Thoracolumbar spina bifida with hydrocephalus - closed	P103z11
Thoracic spina bifida with hydrocephalus	P100200
Lumbar spina bifida with hydrocephalus - open	P102300
Spina bifida without hydrocephalus, site unspecified	P110000
Sacral spina bifida with hydrocephalus - closed	P103400
Spina bifida without hydrocephalus - closed NOS	P118z00
Cervical spina bifida with hydrocephalus	P100100

Spina bifida with hydrocephalus NOS	P100z00
Lumbar spina bifida with hydrocephalus - closed	P103300
Spina bifida with hydrocephalus - open	P102.00
Other specified spina bifida with hydrocephalus	P10y.00
[X]Unspecified spina bifida with hydrocephalus	Pyu0400
Thoracic spina bifida without hydrocephalus - open	P117200
Lumbar spina bifida without hydrocephalus - open	P117300
Cervical spina bifida without hydrocephalus - closed	P118100

Appendix 13: Product list codes for OAB drugs

Drug class	Substance	Prod code	Product name	Strength	Formulation	Route
AM	Oxybutynin hydrochloride	355	Oxybutynin 2.5mg tablets	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	1304	Oxybutynin 5mg tablets	5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	1339	Ditropan 5mg tablets (Sanofi)	5mg	Tablet	Oral
AM	Flavoxate hydrochloride	1517	Urispas 200mg Tablet (Shire Pharmaceuticals Ltd)	200mg	Tablet	Oral
AM	Flavoxate hydrochloride	2358	Flavoxate 200mg tablets	200mg	Tablet	Oral
AM	Oxybutynin hydrochloride	2524	Ditropan 2.5mg tablets (Sanofi)	2.5mg	Tablet	Oral
AM	Tolterodine tartrate	2529	Tolterodine 1mg tablets	1mg	Tablet	Oral
AM	Tolterodine tartrate	2640	Detrusitol 2mg tablets (Pfizer Ltd)	2mg	Tablet	Oral
AM	Tolterodine tartrate	3283	Tolterodine 2mg tablets	2mg	Tablet	Oral
AM	Propiverine hydrochloride	3284	Propiverine 15mg tablets	15mg	Tablet	Oral
AM	Oxybutynin hydrochloride	3430	Oxybutynin 2.5mg/5ml oral solution	500microgram/1ml	Oral solution	Oral

AM	Terodiline Hydrochloride	3500	Terodiline 12.5mg tablets	12.5mg	Tablets	Oral
AM	Tolterodine tartrate	3922	Detrusitol 1mg tablets (Pfizer Ltd)	1mg	Tablet	Oral
AM	Terodiline Hydrochloride	3991	Micturin 25mg Tablet (Pharmacia Ltd)	25mg	Tablet	Oral
AM	Propiverine hydrochloride	4836	Detrunorm 15mg tablets (AMCo)	15mg	Tablet	Oral
AM	Oxybutynin hydrochloride	5155	Ditropan xl 5mg Tablet (Sanofi-Synthelabo Ltd)	5mg	Modified-release tablet	Oral
AM	Oxybutynin hydrochloride	5399	Oxybutynin 10mg modified-release tablets	10mg	Modified-release tablet	Oral
AM	Oxybutynin hydrochloride	5537	Ditropan xl 10mg Tablet (Sanofi-Synthelabo Ltd)	10mg	Modified-release tablet	Oral
AM	Oxybutynin hydrochloride	5573	Oxybutynin 5mg modified-release tablets	5mg	Modified-release tablet	Oral
AM	Tolterodine tartrate	5595	Detrusitol xl 4mg Capsule (Pharmacia Ltd)	4mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	5641	Tolterodine 4mg modified-release capsules	4mg	Modified-release capsule	Oral
AM	Oxybutynin hydrochloride	5788	Ditropan 2.5mg/5ml elixir (Sanofi)	500microgram/1ml	Oral solution	Oral
AM	Oxybutynin Hydrochloride	5922	Oxybutynin 5mg/5ml oral solution sugar free	5mg/5ml	Solution Sugar-free	Oral
AM	Oxybutynin hydrochloride	6010	Ditropan XL 5mg tablets (Janssen-Cilag Ltd)	5mg	Modified-release tablet	Oral

AM	Trospium chloride	6641	Trospium chloride 20mg tablets	20mg	Tablet	Oral
AM	Solifenacin succinate	6902	Solifenacin 5mg tablets	5mg	Tablet	Oral
AM	Solifenacin succinate	6929	Vesicare 5mg tablets (Astellas Pharma Ltd)	5mg	Tablet	Oral
AM	Solifenacin succinate	7026	Solifenacin 10mg tablets	10mg	Tablet	Oral
AM	Trospium chloride	7234	Regurin 20mg tablets (Speciality European Pharma Ltd)	20mg	Tablet	Oral
AM	Flavoxate Hydrochloride	7670	Urispas 100mg Tablet (Shire Pharmaceuticals Ltd)	100mg	Tablet	Oral
AM	Flavoxate Hydrochloride	7671	Flavoxate 100mg Tablet	100mg	Tablet	Oral
AM	Oxybutynin hydrochloride	7838	Cystrin 3mg tablets (Sanofi)	3mg	Tablet	Oral
AM	Terodiline Hydrochloride	7893	Micturin 12.5mg Tablet (Pharmacia Ltd)	12.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	8090	Oxybutynin 3mg tablets	3mg	Tablet	Oral
AM	Oxybutynin	10143	Oxybutynin 3.9mg/24hours transdermal patches	3.9mg/24hour	Transdermal patch	Transdermal
AM	Solifenacin succinate	10171	Vesicare 10mg tablets (Astellas Pharma Ltd)	10mg	Tablet	Oral
AM	Oxybutynin hydrochloride	10633	Cystrin 5mg tablets (Zentiva)	5mg	Tablet	Oral
AM	Oxybutynin	11790	Kentera 3.9mg/24hours patches (Orion Pharma (UK) Ltd)	3.9mg/24hour	Transdermal patch	Transdermal

AM	Oxybutynin hydrochloride	13012	Ditropan XL 10mg tablets (Janssen-Cilag Ltd)	10mg	Modified-release tablet	Oral
AM	Oxybutynin hydrochloride	14895	Lyrinel XL 5mg tablets (Janssen-Cilag Ltd)	5mg	Modified-release tablet	Oral
AM	Oxybutynin hydrochloride	16016	Lyrinel XL 10mg tablets (Janssen-Cilag Ltd)	10mg	Modified-release tablet	Oral
AM	Oxybutynin hydrochloride	21914	Promictuline 2.5mg Tablet (Ashbourne Pharmaceuticals Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	21993	Promictuline 5mg Tablet (Ashbourne Pharmaceuticals Ltd)	5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	26223	Contimin 2.5mg Tablet (Berk Pharmaceuticals Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	26250	Contimin 5mg Tablet (Berk Pharmaceuticals Ltd)	5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	26718	Urimin 5mg Tablet (Opus Pharmaceuticals Ltd)	5mg	Tablet	Oral
AM	Propiverine hydrochloride	28357	Propiverine 30mg modified-release capsules	30mg	Modified-release capsule	Oral
AM	Propiverine hydrochloride	28669	Detrunorm XL 30mg capsules (AMCo)	30mg	Modified-release capsule	Oral
AM	Oxybutynin hydrochloride	30776	Oxybutynin 5mg tablets (Sterwin Medicines)	5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	31222	Oxybutynin 5mg tablets (Actavis UK Ltd)	5mg	Tablet	Oral

AM	Oxybutynin hydrochloride	34458	Oxybutynin 2.5mg tablets (Actavis UK Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	34529	Oxybutynin 2.5mg tablets (Mylan Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	34530	Oxybutynin 2.5mg tablets (A A H Pharmaceuticals Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	34674	Oxybutynin 2.5mg tablets (Approved Prescription Services Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	34780	Oxybutynin 5mg tablets (A A H Pharmaceuticals Ltd)	5mg	Tablet	Oral
AM	Darifenacin hydrobromide	35121	Darifenacin 7.5mg modified-release tablets	7.5mg	Modified-release tablet	Oral
AM	Darifenacin hydrobromide	35140	Darifenacin 15mg modified-release tablets	15mg	Modified-release tablet	Oral
AM	Oxybutynin Hydrochloride	35791	Oxybutynin 5mg/5ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)	5mg/5ml	Oral Solution	Oral
AM	Darifenacin hydrobromide	35838	Emselex 7.5mg modified-release tablets (Merus Labs Luxco S.a R.L.)	7.5mg	Modified-release tablet	Oral
AM	Darifenacin hydrobromide	36160	Emselex 15mg modified-release tablets (Merus Labs Luxco S.a R.L.)	15mg	Modified-release tablet	Oral
AM	Fesoterodine fumarate	38197	Fesoterodine 4mg modified-release tablets	4mg	Modified-release tablet	Oral
AM	Fesoterodine fumarate	38235	Toviaz 4mg modified-release tablets (Pfizer Ltd)	4mg	Modified-release tablet	Oral

AM	Flavoxate hydrochloride	38252	Urispas 200 tablets (Recordati Pharmaceuticals Ltd)	200mg	Tablet	Oral
AM	Fesoterodine fumarate	38291	Fesoterodine 8mg modified-release tablets	8mg	Modified-release tablet	Oral
AM	Fesoterodine fumarate	38467	Toviaz 8mg modified-release tablets (Pfizer Ltd)	8mg	Modified-release tablet	Oral
AM	Tolterodine tartrate	38816	Detrusitol XL 4mg capsules (Pfizer Ltd)	4mg	Modified-release capsule	Oral
AM	Oxybutynin hydrochloride	40096	Oxybutynin 2.5mg tablets (Strides Shasun (UK) Ltd)	2.5mg	Tablet	Oral
AM	Trospium chloride	40797	Trospium chloride 60mg modified-release capsules	60mg	Modified-release capsule	Oral
AM	Trospium chloride	40962	Regurin XL 60mg capsules (Speciality European Pharma Ltd)	60mg	Modified-release capsule	Oral
AM	Trospium chloride	41429	Flotros 20mg tablets (Galen Ltd)	20mg	Tablet	Oral
AM	Oxybutynin hydrochloride	41580	Oxybutynin 5mg tablets (Teva UK Ltd)	5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	41643	Oxybutynin 2.5mg tablets (Teva UK Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	41649	Oxybutynin 2.5mg tablets (Sterwin Medicines)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	43559	Oxybutynin 2.5mg Tablet (Pharmacia Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	46177	Oxybutynin 2.5mg tablets (Almus Pharmaceuticals Ltd)	2.5mg	Tablet	Oral

AM	Oxybutynin hydrochloride	49365	Oxybutynin 5mg/5ml oral suspension	1mg/1ml	Oral suspension	Oral
AM	Tolterodine tartrate	49414	Detrusitol 1mg tablets (DE Pharmaceuticals)	1mg	Tablet	Oral
AM	Tolterodine tartrate	50126	Detrusitol XL 4mg capsules (Mawdsley-Brooks & Company Ltd)	4mg	Modified-release capsule	Oral
AM	Oxybutynin hydrochloride	50262	Oxybutynin 5mg/5ml oral solution	1mg/1ml	Oral solution	Oral
AM	Fesoterodine fumarate	50596	Toviaz 8mg modified-release tablets (Mawdsley-Brooks & Company Ltd)	8mg	Modified-release tablet	Oral
AM	Tolterodine tartrate	51025	Detrusitol XL 4mg capsules (Necessity Supplies Ltd)	4mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	51868	Detrusitol 1mg tablets (Necessity Supplies Ltd)	1mg	Tablet	Oral
AM	Tolterodine tartrate	51922	Tolterodine 2mg tablets (Actavis UK Ltd)	2mg	Tablet	Oral
AM	Tolterodine tartrate	51929	Tolterodine 1mg tablets (A A H Pharmaceuticals Ltd)	1mg	Tablet	Oral
AM	Trospium chloride	52266	Regurin XL 60mg capsules (Lexon (UK) Ltd)	60mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	52401	Detrusitol XL 4mg capsules (Sigma Pharmaceuticals Plc)	4mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	52421	Detrusitol 1mg tablets (Waymade Healthcare Plc)	1mg	Tablet	Oral
AM	Trospium chloride	52422	Regurin 20mg tablets (DE Pharmaceuticals)	20mg	Tablet	Oral
AM	Trospium chloride	52667	Uraplex 20mg tablets (Speciality European Pharma Ltd)	20mg	Tablet	Oral

AM	Trospium chloride	52753	Trospium chloride 20mg tablets (Teva UK Ltd)	20mg	Tablet	Oral
AM	Oxybutynin hydrochloride	53694	Oxybutynin 2.5mg tablets (Tillomed Laboratories Ltd)	2.5mg	Tablet	Oral
AM	Tolterodine tartrate	53954	Tolterodine 1mg tablets (Pfizer Ltd)	1mg	Tablet	Oral
AM	Oxybutynin hydrochloride	54653	Oxybutynin 5mg tablets (Tillomed Laboratories Ltd)	5mg	Tablet	Oral
AM	Tolterodine tartrate	55108	Mariosea XL 4mg capsules (Teva UK Ltd)	4mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	55688	Efflosomyl XL 4mg capsules (Mylan Ltd)	4mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	55934	Neditol XL 4mg capsules (Aspire Pharma Ltd)	4mg	Modified-release capsule	Oral
AM	Trospium chloride	56517	Regurin XL 60mg capsules (DE Pharmaceuticals)	60mg	Modified-release capsule	Oral
AM	Trospium chloride	59693	Trospium chloride 20mg tablets (A A H Pharmaceuticals Ltd)	20mg	Tablet	Oral
AM	Tolterodine tartrate	60090	Blerone XL 4mg capsules (Zentiva)	4mg	Modified-release capsule	Oral
AM	Tolterodine tartrate	61466	Tolterodine 2mg tablets (Sandoz Ltd)	2mg	Tablet	Oral
AM	Tolterodine tartrate	61956	Preblacon XL 4mg capsules (Actavis UK Ltd)	4mg	Modified-release capsule	Oral
AM	Propiverine hydrochloride	62403	Detrunorm XL 45mg capsules (AMCo)	45mg	Modified-release capsule	Oral

AM	Tolterodine Tartrate	62634	Tolterodine tartrate (roi) 2mg Modified-release capsule	2mg	Modified-release Capsule	NULL
AM	Tolterodine tartrate	63329	Tolterodine 2mg tablets (Teva UK Ltd)	2mg	Tablet	Oral
AM	Propiverine hydrochloride	63828	Propiverine 45mg modified-release capsules	45mg	Modified-release capsule	Oral
AM	Oxybutynin hydrochloride	63984	Oxybutynin 2.5mg/5ml oral solution sugar free	500microgram/1ml	Oral solution	Oral
AM	Tolterodine tartrate	64257	Inconex XL 4mg capsules (Sandoz Ltd)	4mg	Modified-release capsule	Oral
AM	Solifenacin succinate	64473	Vesicare 5mg tablets (DE Pharmaceuticals)	5mg	Tablet	Oral
AM	Trospium chloride	64531	Regurin XL 60mg capsules (Waymade Healthcare Plc)	60mg	Modified-release capsule	Oral
AM	Oxybutynin hydrochloride	64934	Oxybutynin 5mg tablets (Kent Pharmaceuticals Ltd)	5mg	Tablet	Oral
AM	Tolterodine tartrate	64955	Tolterodine 1mg/5ml oral solution	200microgram/1ml	Oral solution	Oral
AM	Oxybutynin hydrochloride	65300	Oxybutynin 2.5mg tablets (Alliance Healthcare (Distribution) Ltd)	2.5mg	Tablet	Oral
AM	Oxybutynin hydrochloride	66668	Oxybutynin 5mg tablets (Almus Pharmaceuticals Ltd)	5mg	Tablet	Oral
AM	Trospium chloride	67932	Trospium chloride 20mg tablets (DE Pharmaceuticals)	20mg	Tablet	Oral
MIRABEGRON	Mirabegron	54923	Mirabegron 50mg modified-release tablets	50mg	Modified-release tablet	Oral

MIRABEGRON	Mirabegron	55131	Mirabegron 25mg modified-release tablets	25mg	Modified-release tablet	Oral
MIRABEGRON	Mirabegron	55152	Betmiga 50mg modified-release tablets (Astellas Pharma Ltd)	50mg	Modified-release tablet	Oral
MIRABEGRON	Mirabegron	55380	Betmiga 25mg modified-release tablets (Astellas Pharma Ltd)	25mg	Modified-release tablet	Oral

Appendix 14: Read codes for dementia (exclusion criteria)

Code	Coding system	Description
3AE..00	Read	Global deterioration scale: assessment of prim deg dementia
66h..00	Read	Dementia monitoring
6AB..00	Read	Dementia annual review
E00..00	Read	Senile and presenile organic psychotic conditions
e000.00	Read	Uncomplicated senile dementia
E000.00	Read	Uncomplicated senile dementia
E001.00	Read	Presenile dementia
E001000	Read	Uncomplicated presenile dementia
E00..11	Read	Senile dementia
E001100	Read	Presenile dementia with delirium
E00..12	Read	Senile/presenile dementia
E001200	Read	Presenile dementia with paranoia
E001300	Read	Presenile dementia with depression
E001z00	Read	Presenile dementia NOS
E002.00	Read	Senile dementia with depressive or paranoid features
E002000	Read	Senile dementia with paranoia
E002100	Read	Senile dementia with depression
E002z00	Read	Senile dementia with depressive or paranoid features NOS
E003.00	Read	Senile dementia with delirium
E004.00	Read	Arteriosclerotic dementia
E004000	Read	Uncomplicated arteriosclerotic dementia
E004100	Read	Arteriosclerotic dementia with delirium

E004.11	Read	Multi infarct dementia
E004200	Read	Arteriosclerotic dementia with paranoia
E004300	Read	Arteriosclerotic dementia with depression
E004z00	Read	Arteriosclerotic dementia NOS
E00y.00	Read	Other senile and presenile organic psychoses
E00y.11	Read	Presbyophrenic psychosis
E00z.00	Read	Senile or presenile psychoses NOS
E012.00	Read	Other alcoholic dementia
E012000	Read	Chronic alcoholic brain syndrome
E012.11	Read	Alcoholic dementia NOS
E041.00	Read	Dementia in conditions EC
Eu00.00	Read	[X]Dementia in Alzheimer's disease
Eu00000	Read	[X]Dementia in Alzheimer's disease with early onset
Eu00011	Read	[X]Presenile dementia;Alzheimer's type
Eu00012	Read	[X]Primary degen dementia; Alzheimer's type; presenile onset
Eu00013	Read	[X]Alzheimer's disease type 2
Eu00100	Read	[X]Dementia in Alzheimer's disease with late onset
Eu00111	Read	[X]Alzheimer's disease type 1
Eu00112	Read	[X]Senile dementia;Alzheimer's type
Eu00113	Read	[X]Primary degen dementia of Alzheimer's type; senile onset
Eu00200	Read	[X]Dementia in Alzheimer's dis; atypical or mixed type
Eu00z00	Read	[X]Dementia in Alzheimer's disease; unspecified
Eu00z11	Read	[X]Alzheimer's dementia unspec
Eu01.00	Read	[X]Vascular dementia
Eu01000	Read	[X]Vascular dementia of acute onset

Eu01100	Read	[X]Multi-infarct dementia
Eu01.11	Read	[X]Arteriosclerotic dementia
Eu01111	Read	[X]Predominantly cortical dementia
Eu01200	Read	[X]Subcortical vascular dementia
Eu01300	Read	[X]Mixed cortical and subcortical vascular dementia
Eu01y00	Read	[X]Other vascular dementia
Eu01z00	Read	[X]Vascular dementia; unspecified
Eu02.00	Read	[X]Dementia in other diseases classified elsewhere
Eu02000	Read	[X]Dementia in Pick's disease
Eu02100	Read	[X]Dementia in Creutzfeldt-Jakob disease
Eu02200	Read	[X]Dementia in Huntington's disease
Eu02300	Read	[X]Dementia in Parkinson's disease
Eu02400	Read	[X]Dementia in human immunodef virus [HIV] disease
Eu02500	Read	[X]Lewy body dementia
Eu02y00	Read	[X]Dementia in other specified diseases classif elsewhere
Eu02z00	Read	[X] Unspecified dementia
Eu02z11	Read	[X] Presenile dementia NOS
Eu02z12	Read	[X] Presenile psychosis NOS
Eu02z13	Read	[X] Primary degenerative dementia NOS
Eu02z14	Read	[X] Senile dementia NOS
Eu02z15	Read	[X] Senile psychosis NOS
Eu02z16	Read	[X] Senile dementia; depressed or paranoid type
Eu04100	Read	[X]Delirium superimposed on dementia
Eu10711	Read	[X]Alcoholic dementia NOS
F110.00	Read	Alzheimer's disease

F110000	Read	Alzheimer's disease with early onset
F110100	Read	Alzheimer's disease with late onset
F111.00	Read	Pick's disease
F112.00	Read	Senile degeneration of brain
F116.00	Read	Lewy body disease
Fyu3000	Read	[X]Other Alzheimer's disease
ZR1K.00	Read	Alzheimer's disease assessment scale
ZR1K.11	Read	ADAS - Alzheimer's disease assessment scale
ZR2X.12	Read	BDRS - Blessed dementia rating scale
ZR3V.00	Read	Clinical dementia rating scale
ZR3V.11	Read	DRS - Clinical dementia rating scale
ZR3V.12	Read	CDR - Clinical dementia rating scale
ZR3V.13	Read	Dementia rating scale
ZS7C500	Read	Language disorder of dementia
2900	OXMIS	SENILE DEMENTIA
2901A	OXMIS	PRESENILE DEMENTIA
2901B	OXMIS	ALZHEIMER'S DISEASE
2901D	OXMIS	JACOB- CREUZFELDT DISEASE WITH DEMENTIA
2919	OXMIS	DEMENTIA ALCOHOLIC
2930	OXMIS	DEMENTIA ARTERIOSCLEROTIC
299 B	OXMIS	DEMENTIA
299 G	OXMIS	DEMENTIA AGGRESSIVE
Y0601JS	OXMIS	DEMENTIA CLINIC ATTENDANCE
Y060 JS	OXMIS	DEMENTIA CLINIC

Appendix 15: QoF Business Rules Read Codes

Condition	Cluster Name	Description	Read V2	CTV3
Asthma	AST_COD	Asthma diagnosis codes	H33* (excluding H333.*);H3120;H3B*;173A*	H33* (excluding H44*;H441*;H440*;X1025*;X1023*;XaKdk*;XaJFG*;Xa1hD*);X1020;Xac33
Atrial Fibrillation	AFIB_COD	Atrial fibrillation codes	G573*	G5730*;G573.*;G5731*
Cancer	CAN_COD	Codes for relevant malignancies	B0*-B32z.;B34*-B6z0. (excluding B677.);Byu*-Byu41;Byu5.-ByuE0;K1323;K01w1;68W24;C184.	XaabR*;B62y.*;X78ef* (excluding B937W*;Byu5A*;Byu43*;Byu4.*;ByuHD*;Byu42*;B5820*;B582z*;B5826*;B5821*;B5825*;B5822*;B5823*;B5824*;Xa0Sh*;XaB49*;X00Z9*;XE1yx*;Xa3eJ*;X78hl*;XM1ML*;X20FX*;X00ZC*;XaFrS*;X78h0*;B331.*;B332z*;B33y.*;B333.*;B334.*;B3320*;B3321*;B3330*;B332.*;B337.*;B330.*;B335.*;B336.*;X78RP*;XaEGW*;XaEGV*;XaCKx*;B33z.*;B33**;Xa0KC*;X78hS*;X00Z6;X78gs;Xa3BF*;Xa0SJ*;XaB46*;XaYiK*;Xa0SY;D41y1*;XE1vh*;C332.*;Xa0l6*;B934.*;Xa0Se*;Xa0Sg*;Xa0Sf*;XaYv2*;X00ZA*;X00Z8*;C3330*;X78ha;X78hm;X78hn;Xa0EY;Xa34C;Xa34D)
Coronary heart disease	CHD_COD	Coronary heart disease codes	G3*-G309.;G30B.-G330z (excluding G310.);G33z.-G3401;G342.-G35X.;G38*-G3z*;Gyu3.* (excluding Gyu31)	XE2uV* (excluding Xa07j*;G341.*;X200B*;X200c;G363.;Gyu31;X200d;X200e);Ua1eH;Xa1dP*;XaYYq;XM0rN

Chronic Kidney Disease	CKD_COD	Chronic kidney disease codes 3-5	1Z12.;1Z13.;1Z14.;1Z15.;1Z16.;1Z1B.-1Z1L.;K053.;K054.;K055.;1Z1T.;1Z1V.;1Z1W.;1Z1X.;1Z1Y.;1Z1Z.;1Z1a.;1Z1b.;1Z1c.;1Z1d.;1Z1e.;1Z1f.	XaLHI*;XaLHJ*;XaLHK*;XacAM*;XacAN*;XacAO*;XacAV*;XacAW*;XacAX*;XacAb*;XacAd*;XacAe*;XacAf*;XacAh*;XacAi*
	CKD1AND2_COD	Chronic kidney disease codes 1-2	1Z10*;1Z11*;1Z17.-1Z1A.;K051*;K052*;1Z1M*;1Z1Q*;1Z1N*;1Z1P*;1Z1R*;1Z1S*	XaLHH*;XaLHG*;Xac9y*;XacA4*;Xac9z*;XacA2*;XacA6*;XacA9*
COPD	COPD_COD	COPD codes	H3*;H31*(excluding H3101;H31y0;H3122);H32*;H36*-H3z* (excluding H3y0.;H3y1.);H5832*;H4640*;H4641*;Hyu30*;Hyu31*	H31*;H32* (excluding XaIQg;H582.);H3* (excluding H3122*);Xaa7C*;Xac33*;H3120*
Dementia	DEM_COD	Codes for Dementia	Eu02*;E00*;Eu01*;E02y1*;E012*;Eu00*;E041*;Eu041*;F110.-F112.;F116*;F118*;F21y2*;A410*;A411*;Eu107*;F11x7*	X002w* (excluding X003E;X003F;X001T);Eu02*;XE1Xt*;E00z*;E02y1*;XE1Xu*;E0120*;Eu041*;F112*;X00Rk*
Depression	DEPR_COD	Depression diagnosis codes	E0013*;E0021*;E112*;E113*;E118*;E11y2*;E11z2*;E130*;E135*;E2003*;E291*;E2B*;E2B1*;Eu204*;Eu251*;Eu32* (excluding Eu32A;Eu32B;Eu329);Eu33*;Eu341*;Eu412*	X00Sb*;X00SO* (excluding 62T1.*;E2B0.;XaCHo;XaX54;XaX53;XaY2C);E0013*;E0021*
Diabetes	DM_COD	Codes for diabetes	C10*;C109J*;C109K*;C10C*;C10D*;C10E*;C10F* (excluding C10F8);C10G*;C10H*;C10M*;C10N*;PKyP*;C10P*;C10Q*	C10*;XaOPu*;XaOPt*;X40J4* (excluding L1805);X40J5* (excluding L1806);X40J6*;X40JA* (excluding XSETI*;C11y0*);X40JG* (excluding

				X40JK);C1010*;C1011*;C1030*;C1031*;XaIrf*;X40JZ*;XSETp*;XM1Xk*;X008t*;Xaagd*;XSETe*
Epilepsy	EPIL_COD	Epilepsy diagnosis codes	F25* (excluding F2501;F2504;F2511;F2516;F256.*;F258.-F25A.;F25y4;F25G.;F25H.);F1321*;SC200*	F25*(excluding X005r*;X005p*;X005q*;X005o*;X005t*;Q480.*;X005s*;XaBM2*;X006G*;Xa0lJ;XaOZG*;X005w*;X006n*)
Heart failure	HF_COD	Heart failure codes	G58*;G1yz1*;662f.-662i.	G58*(excluding G5y4.*)
Hypertension	HYP_COD	Hypertension diagnosis codes	G2*;G20*;G24*-G2z* (excluding G24z1;G2400;G2410;G27*);Gyu2*;Gyu20*	XE0Ub*;XE0Uc*;G24*(excluding 61462;G2400;G2410;G24z1;Gyu21;L1282;Xa0kX);G2*;Xa0Cs*;XSDSb*;G202*;Xa3fQ*;XaZWn*;XaZbz*;XaZWm*;Xab9M*;Xab9L*
Learning disability	LD_COD	Learning Disability codes	E3*;Eu7*;Eu814*;Eu815*;Eu816*;Eu817*;Eu81z*;918e*;Eu818*	E3*;XaQZ4*;XaQZ3*;XaKYb*;XaREt*;XaREu*;Eu81z*;XaaiS*;Xabk1*
Mental Health	MH_COD	Psychosis; schizophrenia + bipolar affective disease codes	E10*;E110*;E111*;E1124*;E1134*;E114.-E117z;E11y* (excluding E11y2);E11z*;E11z0*;E11zz*;E12*;E13*(excluding E135.);E2122*;Eu2*;Eu30*;Eu31*;Eu323*;Eu328*;Eu333*;Eu32A*;Eu329*	X00S6* (excluding Xa9B0*;E14**);X00SL*;X00SM*;X00SJ*;XSGon*;E11z*;E11z0*;E11zz*;XE1ZZ*;XE1Ze*;XaX54*;XaX53*;E130*;E1124*;E1134*;XagU1*
Obesity	BMI30_COD	BMI codes – without an associated BMI value	22K5*;22K7*;22KC*;22KD*;22KE*	22K5*;XaJJH*;XabHx*;XabHy*;XabHz*
	BMIVAL_COD	BMI codes – with an associated BMI value	22K*	22K*;X76CO*

Osteoporosis	OSTEO_COD	Osteoporosis codes	N330* (excluding N3308;N3309);N3312*;N3313*;N3316*;N3318–N331B;N331H–N331M;NyuB0*;NyuB1*;NyuB8*;N3314*;N3315*;N3746*;NyuB2*	Xa0AZ* (excluding X70Au);XE1GA*;N330*;N3300*;N3304*;N330B*;N330z*;X70CK*;N3313*;N3316*;N331B*;XaD4K*;XaD4J*;XaD4I*;NyuB0*;NyuB1*;NyuB8*;XaIIp*;XaC12*;N3307*;N330A*;N3314*;N3315*;N3746;X70Av*;NyuB2*
Peripheral Arterial Disease	PAD_COD	PAD diagnostic codes	G73*;G73z* (excluding G73z1);Gyu74*;G734*;G73y*	Xa0lV*;XE0VP*;G73z*;XE0VR*;Gyu74*;XaZJa*
Palliative Care	PALCARE_COD	Palliative care codes	1Z01*;2JE*;2Jf*;38VY*;38Vb*;38Vd*;38Ve*;38Vf*;38Vg*;38Vh*;38Vi*;8BA2*;8BAP*;8BAS*;8BAT*;8BAe*;8BJ1*;8CM1* (excluding 8CM15);8CM4*;8CME*;8CMj*;8CMk*;8H6A*;8H7L*;8H7g*;8HH7*;8IEE*;9EB5*;9Ng7*;ZV57C*;8CMQ*;9NgD*;9G8*;9c0P*;9c0N*;8CMW3*;9K9*;9367*;9c0L0*;9c0M*;9NNd*;8CMb*;8B2a*;9NNf0*;38QH*;38QK*;8CMg*;2Jg*;9NNq*;9NNr*;9NNs*	1Z01*;XaQg1*;8BA2*;XaIse* (excluding XaIsf);XaIpI*;XaMhi*;XaJv2* (excluding XaZb7);8H6A*;8H7L*;XaAex*;XaIlk*;XaAg6*;XaAT5*;XaEJE*;XaAWN*;XaAPW*;XaRFG*;XaRFF*;9EB5*;ZV57C*;XaXUG*;XaXoP*;XaXoW*;XaYRB*;XaYRD*;XaYRy*;XaYpV*;XaZmb*;XaZcg*;XaZPo*;XaZe1*;XaZLA*;XaZbi*;XaZZe*;XaZPX*;XaZPn*;XaZhw*;XaaIR*;XaaD3*;Xab0s*;Xab1a*;Xab1h*;Xab1f*;Xab1e*;Xab1g*;Xabq2*;XacFk*;XacdB*;XaeCv*;XaeED*;XaeTh*;XaeWb*;XaeWg*;XaeWv*;XaeWw*;XaeWx*;XaeWy*;XaeXv*;XaeYr*;XaeYs*;XaeYt*
Rheumatoid Arthritis	RARTH_COD	Rheumatoid arthritis codes	N040.*;N041.;N042.* (excluding N0420);N047.;N04X.;N04y0;N04y2;Nyu11;Nyu12;Nyu1G;Nyu10;G5yA.;G5y8.	N040.*;XE1DU;X705I;G5y8.
Stroke	TIA_COD	TIA codes	G65*-G654.;G656.-	XE0VK* (excluding F4236;G660.;G661.;G6

			G65zz;ZV12D*;Fyu55*	62.);XaX16*;G65z0*;G65z1*
	OSTR_COD	Non-haemorrhagic stroke codes	G63y0-G63y1;G64**;G665.;G666.;G6760;G6W*;G6X*;Gyu63-Gyu66;Gyu6G	Xa0kZ* (excluding XE1Xs*);G640.* (excluding G663.;G664.);X00D3;G641.;Gyu65;Gyu66
	STRK_COD	Stroke diagnosis codes	G61* (excluding G617*);G63y0*;G63y1*;G64*;G66* (excluding G669*);G6760;G6W*;G6X*;Gyu62*;Gyu66*;Gyu6F*;Gyu6G*	X00D1* (excluding XE1Xs*;F21y2*);G660*;G661*;G662*;Gyu6F*;G641*;Xa6YV*;Gyu62*;Gyu65*;Gyu66*

Appendix 16: Read codes for complications

Read codes for urinary tract infection

Medcode	Readcode	Read term
99759	14D7.00	History of recurrent urinary tract infection
9378	1AG..00	Recurrent urinary tract infections
106661	8CMWE00	On urinary tract infection care pathway
1289	K190.00	Urinary tract infection, site not specified
1572	K190.11	Recurrent urinary tract infection
12570	K190200	Post operative urinary tract infection
10515	K190300	Recurrent urinary tract infection
97002	K190500	Urinary tract infection
150	K190z00	Urinary tract infection, site not specified NOS
107568	SP07Q00	Catheter-associated urinary tract infection

Read codes for sepsis/septicaemia

Medcode	Readcode	Read term
54077	H5y0100	Tracheostomy sepsis
106405	1JN0.00	Suspected sepsis
104141	K190600	Urosepsis
104294	A396.00	Sepsis due to Actinomyces
110225	A3C1z00	Sepsis due to staphylococcus NOS
104492	A3C1000	Sepsis due to Staphylococcus aureus
104260	A3Cz.00	Sepsis NOS
108045	A3C3.11	Sepsis due to Gram negative organisms

105423	A3C0.00	Sepsis due to Streptococcus
37043	Q404z00	Umbilical sepsis NOS
105716	A3C0z00	Streptococcal sepsis, unspecified
110263	A3C1y00	Sepsis due to other specified staphylococcus
104633	A3C2.11	Sepsis due to anaerobes
105075	A3C3.00	Sepsis due to Gram negative bacteria
104577	A3C1.00	Sepsis due to Staphylococcus
104900	A3C0y00	Other streptococcal sepsis
104189	A3C0100	Sepsis due to Streptococcus group B
105102	A3C2.00	Sepsis due to anaerobic bacteria
104028	A3C..00	Sepsis
104150	A3Cy.00	Other specified sepsis
105053	A3C3y00	Sepsis due to other Gram negative organisms
2136	A38z.11	Sepsis
104731	A3C0000	Sepsis due to Streptococcus group A
53182	A38y.00	Other specified septicaemias
101759	Ayu3E00	[X]Other streptococcal septicaemia
12578	A380400	Septicaemia due to enterococcus
49590	A380500	Vancomycin resistant enterococcal septicaemia
31706	A383.00	Septicaemia due to anaerobes
54534	A384400	Serratia septicaemia
16104	A381.00	Staphylococcal septicaemia
15229	A380.00	Streptococcal septicaemia
10978	A380100	Septicaemia due to streptococcus, group B
35232	A384.00	Septicaemia due to other gram negative organisms

42825	A381100	Septicaemia due to coagulase-negative staphylococcus
29950	A380000	Septicaemia due to streptococcus, group A
53762	Ayu3J00	[X]Septicaemia, unspecified
12400	A384300	Pseudomonas septicaemia
72876	A384z00	Other gram negative septicaemia NOS
18809	A021.00	Salmonella septicaemia
72881	Ayu3G00	[X]Septicaemia due to other gram-negative organisms
30102	A381000	Septicaemia due to Staphylococcus aureus
72106	Ayu3H00	[X]Other specified septicaemia
98545	Ayu3F00	[X]Streptococcal septicaemia, unspecified
31517	A384000	Gram negative septicaemia NOS
885	A38..00	Septicaemia
33765	A38z.00	Septicaemia NOS

Read codes for Urinary Retention

Medcode	**Readcode**	**Read term**
6158	R082400	[D]Retention of urine unspecified
5375	1A32.00	Cannot pass urine - retention
5039	R082000	[D]Clot retention of urine
1052	R082.00	[D]Retention of urine
28017	R082300	[D]Chronic retention of urine
3002	R082200	[D]Acute retention of urine

Read codes for Obstructive Uropathy

Medcode	Readcode	Read term
10880	K19C.00	Other obstructive and reflux uropathy
105941	Kyu1300	[X]Obstructive and reflux uropathy, unspecified
107866	Kyu1200	[X]Other obstructive and reflux uropathy
12095	K196.11	Obstructive uropathy, unspecified
12123	K19X.00	Obstructive and reflux uropathy, unspecified

Read codes for renal failure

Medcode	Readcode	Read term
61930	Kyu2.00	[X]Renal failure
35235	K04y.00	Other acute renal failure
108103	K043100	Acute renal failure induced by aminoglycoside
64636	7L1Az00	Compensation for renal failure NOS
11773	7L1A.11	Dialysis for renal failure
59194	7L1By00	Placement ambulatory apparatus- compensate renal failure OS
56760	7L1B.00	Placement ambulatory apparatus compensation renal failure
65089	7L1Cz00	Placement other apparatus- compensate for renal failure NOS
16929	D215.00	Anaemia secondary to renal failure
53940	Kyu2100	[X]Other chronic renal failure
53852	K05..12	End stage renal failure
100205	K0E..00	Acute-on-chronic renal failure
350	K06..00	Renal failure unspecified
107901	7L1Cy00	Placement other apparatus- compensate for renal failure OS
53945	Kyu2000	[X]Other acute renal failure
2266	K04..00	Acute renal failure

512	K05..00	Chronic renal failure
48022	7L1Ay00	Other specified compensation for renal failure
109215	K043300	Acute renal failure induced by cyclosporin A
25582	K04z.00	Acute renal failure NOS
97198	K044.00	Acute renal failure due to urinary obstruction
105739	K04..11	ARF - Acute renal failure
106860	C353600	Renal failure-associated hyperphosphataemia
11554	SP15400	Renal failure as a complication of care
6712	K050.00	End stage renal failure
31549	7L1A.00	Compensation for renal failure
83513	7L1C.00	Placement other apparatus for compensation for renal failure

Read codes for Hyrdonephrosis

Medcode	**Readcode**	**Read term**
8522	K113.11	Hydronephrosis with pelviureteric junction obstruction
27302	K11z.00	Hydronephrosis NOS
98067	Kyu1F00	[X]Hydronephrosis with ureteral stricture NEC
10410	K113.00	Hydronephrosis with ureteropelvic junction obstruction
28159	K11X.00	Hydronephrosis with ureteral stricture NEC
3277	K11..00	Hydronephrosis
72621	Kyu1100	[X]Other and unspecified hydronephrosis
27592	K112.00	Hydronephrosis with renal and ureteral calculous obstruction

Appendix 17: Product list codes for 5-ARI's and alpha-blockers

Drug class	Substance	Prod code	Product name	Strength	Formulation	Route
5ARI	Finasteride	711	Finasteride 1mg tablets	1mg	Tablet	Oral
5ARI	Finasteride	1360	Proscar 5mg tablets (Merck Sharp & Dohme Ltd)	5mg	Tablet	Oral
5ARI	Finasteride	1361	Finasteride 5mg tablets	5mg	Tablet	Oral
5ARI	Finasteride	5993	Propecia 1mg tablets (Merck Sharp & Dohme Ltd)	1mg	Tablet	Oral
5ARI	Dutasteride	6387	Dutasteride 500microgram capsules	500microgram	Capsule	Oral
5ARI	Dutasteride	16128	Avodart 500microgram capsules (GlaxoSmithKline UK Ltd)	500microgram	Capsule	Oral
5ARI	Finasteride	49525	Propecia 1mg tablets (Lexon (UK) Ltd)	1mg	Tablet	Oral
5ARI	Finasteride	52223	Finasteride 5mg tablets (Pfizer Ltd)	5mg	Tablet	Oral
5ARI	Dutasteride	53080	Avodart 500microgram capsules (DE Pharmaceuticals)	500microgram	Capsule	Oral
5ARI	Finasteride	59905	Finasteride 5mg/5ml oral suspension	1mg/1ml	Oral suspension	Oral
5ARI	Finasteride	60337	Finasteride 5mg tablets (A A H	5mg	Tablet	Oral

			Pharmaceuticals Ltd)			
5ARI	Finasteride	63265	Aindeem 1mg tablet (Actavis UK Ltd)	1mg	Tablet	Oral
5ARI	Finasteride	65407	Finasteride 1mg tablets (Accord Healthcare Ltd)	1mg	Tablet	Oral
5ARI	Finasteride	67718	Finasteride 1mg tablets (Ennogen Healthcare Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	119	Doxazosin 1mg tablets	1mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	460	Flomax MR 400microgram capsules (Astellas Pharma Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	493	Doxazosin 2mg tablets	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	582	Doxazosin 4mg modified-release tablets	4mg	Modified-release tablet	Oral
ALPHA	Tamsulosin hydrochloride	634	Tamsulosin 400microgram modified-release capsules	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	755	Cardura XL 4mg tablets (Pfizer Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	1294	Doxazosin 4mg tablets	4mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	2088	Alfuzosin 2.5mg tablets	2.5mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	2120	Alfuzosin 5mg modified-release tablets	5mg	Modified-release tablet	Oral

ALPHA	Terazosin hydrochloride	2346	Hytrin 5mg Tablet (Abbott Laboratories Ltd)	5mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	2347	Hytrin 10mg Tablet (Abbott Laboratories Ltd)	10mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	2348	Hytrin bph 10mg Tablet (Amdipharm Plc)	10mg	Tablet	Oral
ALPHA	Terazosine	3470	Terazosin 1mg tablets	1mg	Tablets	Oral
ALPHA	Terazosine	3923	Terazosin BPH starter pack 7x1mg with 14x2mg with 7x5mg	7 X 1mg + 14 X 2mg + 7 X 5mg	Starter Pack	Oral
ALPHA	Terazosin hydrochloride	3924	Terazosin 5mg tablets	5mg	Tablet	Oral
ALPHA	Doxazosin mesilate	4449	Cardura 1mg tablets (Pfizer Ltd)	1mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	4637	Terazosin 2mg tablets	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	4802	Cardura 2mg tablets (Pfizer Ltd)	2mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	4875	Terazosin 10mg tablets	10mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	5179	Xatral XL 10mg tablets (Sanofi)	10mg	Modified -release tablet	Oral
ALPHA	Terazosin hydrochloride	5337	Hytrin bph 5mg Tablet (Amdipharm Plc)	5mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	5485	Alfuzosin 10mg modified-release tablets	10mg	Modified -release tablet	Oral

ALPHA	Doxazosin mesilate	5496	Doxazosin 8mg modified-release tablets	8mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	5618	Cardura XL 8mg tablets (Pfizer Ltd)	8mg	Modified-release tablet	Oral
ALPHA	Alfuzosin hydrochloride	5624	Xatral 2.5mg tablets (Sanofi)	2.5mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	6008	Omnic 400microgram Modified-release capsule (Paines & Byrne Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Tamsulosin Hydrochloride	7056	Tamsulosin 400microgram modified-release tablets	400micrograms	Modified Release Tablet	Oral
ALPHA	Doxazosin mesilate	7547	Doxadura 2mg tablets (Discovery Pharmaceuticals)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	7549	Doxadura 1mg tablets (Discovery Pharmaceuticals)	1mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	8077	Hytrin 2mg Tablet (Abbott Laboratories Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	8086	Cardura 4mg Tablet (Pfizer Ltd)	4mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	9422	Xatral sr 5mg Tablet (Sanofi-Synthelabo Ltd)	5mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	10088	Doxadura 4mg tablets (Discovery Pharmaceuticals)	4mg	Tablet	Oral
ALPHA	Tamsulosin Hydrochloride	10134	Flomaxtra XL 400microgram tablets (Astellas Pharma Ltd)	400micrograms	Modified Release Tablet	Oral

ALPHA	Tamsulosin hydrochloride	14932	Tabphyn MR 400microgram capsules (Kyowa Kirin Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Terazosin hydrochloride	16201	Hytrin bph 2mg Tablet (Amdipharm Plc)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	19193	Doxazosin 2mg tablets (Teva UK Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	19216	Doxazosin 4mg tablets (IVAX Pharmaceuticals UK Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	20369	Doxazosin 1mg/5ml oral suspension	200microgram /1ml	Oral suspension	Oral
ALPHA	Tamsulosin hydrochloride	24369	Petyme 400microgram MR capsules (Teva UK Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	25487	Cascor 2mg tablets (Ranbaxy (UK) Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	25551	Cascor 4mg tablets (Ranbaxy (UK) Ltd)	4mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	27403	Omnic MR 400microgram capsules (Astellas Pharma Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Tamsulosin hydrochloride	28441	Pamsvax XL 400microgram capsules (Actavis UK Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Tamsulosin hydrochloride	31109	Prosurin XL 400microgram capsules (Mylan Ltd)	400microgram	Modified-release capsule	Oral

ALPHA	Doxazosin mesilate	33094	Doxazosin 2mg tablets (Mylan Ltd)	2mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	34080	Stronazon 400microgram MR capsules (Actavis UK Ltd)	400microgram	Modified -release capsule	Oral
ALPHA	Doxazosin mesilate	34342	Doxazosin 1mg tablets (Teva UK Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	34553	Doxazosin 4mg tablets (Mylan Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	34601	Doxazosin 1mg tablets (Mylan Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	34625	Doxazosin 2mg tablets (A A H Pharmaceuticals Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	34715	Doxazosin 1mg tablets (A A H Pharmaceuticals Ltd)	1mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	35058	Diffundox XL 400microgram capsules (Zentiva)	400microgram	Modified -release capsule	Oral
ALPHA	Doxazosin mesilate	35272	Doxadura XL 4mg tablets (Discovery Pharmaceuticals)	4mg	Modified -release tablet	Oral
ALPHA	Tamsulosin hydrochloride	35312	Bazetham MR 400microgram capsules (Teva UK Ltd)	400microgram	Modified -release capsule	Oral
ALPHA	Tamsulosin hydrochloride	35466	Alphacard MR 400microgram capsules (Ratiopharm UK Ltd)	400microgram	Modified -release capsule	Oral

ALPHA	Doxazosin mesilate	35603	Doxazosin 4mg/5ml oral suspension	800microgram /1ml	Oral suspensi on	Oral
ALPHA	Alfuzosin hydrochloride	35639	Besavar XL 10mg tablets (Zentiva)	10mg	Modified -release tablet	Oral
ALPHA	Tamsulosin hydrochloride	35925	Contiflo XL 400microgram capsules (Ranbaxy (UK) Ltd)	400microgram	Modified -release capsule	Oral
ALPHA	Doxazosin mesilate	36023	Cardozin xl 4mg Tablet (Hillcross Pharmaceuticals Ltd)	4mg	Modified -release tablet	Oral
ALPHA	Tamsulosin hydrochloride	36282	Morvesin XL 400microgram capsules (Sandoz Ltd)	400microgram	Modified -release capsule	Oral
ALPHA	Alfuzosin hydrochloride	36439	Zufal XL 10mg tablets (Teva UK Ltd)	10mg	Modified -release tablet	Oral
ALPHA	Terazosin hydrochloride	36649	Hytrin 2mg tablets (AMCo)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	36740	Slocinx XL 4mg tablets (Zentiva)	4mg	Modified -release tablet	Oral
ALPHA	Terazosin hydrochloride	36780	Hytrin 5mg tablets (AMCo)	5mg	Tablet	Oral
ALPHA	Doxazosin mesilate	37243	Cardozin xl 4mg Tablet (Teva UK Ltd)	4mg	Modified -release tablet	Oral
ALPHA	Terazosin hydrochloride	37428	Hytrin 10mg tablets (AMCo)	10mg	Tablet	Oral
ALPHA	Doxazosin mesilate	38461	Cardozin XL 4mg tablets (Arrow Generics Ltd)	4mg	Modified -release tablet	Oral

ALPHA	Alfuzosin hydrochloride	39373	Fuzatal XL 10mg tablets (Teva UK Ltd)	10mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	40678	Doxazosin 4mg tablets (Teva UK Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	40891	Doxazosin 2mg tablets (IVAX Pharmaceuticals UK Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	41543	Doxazosin 1mg tablets (IVAX Pharmaceuticals UK Ltd)	1mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	42462	Kirtacap mr 400microgram Capsule (Consilient Health Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Alfuzosin hydrochloride	42820	Alfuzosin xl 10mg Tablet (Hillcross Pharmaceuticals Ltd)	10mg	Modified-release tablet	Oral
ALPHA	Tamsulosin hydrochloride	42936	Flomax Relief MR 400microgram capsules (Boehringer Ingelheim Self-Medication Division)	400microgram	Modified-release capsule	Oral
ALPHA	Tamsulosin Hydrochloride/dutasteride	43458	Tamsulosin 400microgram / Dutasteride 500microgram capsules	0.5mg + 0.4mg	Capsules	Oral
ALPHA	Tamsulosin Hydrochloride/dutasteride	43567	Combodart 0.5mg/0.4mg capsules (GlaxoSmithKline UK Ltd)	NULL	Capsules	Oral

ALPHA	Doxazosin mesilate	43695	Colixil XL 4mg tablets (Sandoz Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Alfuzosin hydrochloride	44268	Vasran XL 10mg tablets (Ranbaxy (UK) Ltd)	10mg	Modified-release tablet	Oral
ALPHA	Tamsulosin hydrochloride	44553	Pinexel PR 400microgram capsules (Wockhardt UK Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	45040	Larbex XL 4mg tablets (Teva UK Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	45265	Doxazosin sr 4mg Tablet (Generics (UK) Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	45328	Doxazosin 1mg tablets (Sandoz Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	45342	Doxazosin 4mg tablets (Sandoz Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	45583	Doxazosin 2mg tablets (Dexcel-Pharma Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	46066	Cardozin XL 4mg tablets (Almus Pharmaceuticals Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Tamsulosin hydrochloride	46206	Pamsvax XL 400microgram capsules (Almus Pharmaceuticals Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	46526	Raporsin XL 4mg tablets (Actavis UK Ltd)	4mg	Modified-release tablet	Oral

ALPHA	Alfuzosin hydrochloride	47563	Besavar XL 10mg tablets (Actavis UK Ltd)	10mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	47807	Doxazosin xl 4mg Tablet (Hillcross Pharmaceuticals Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	48150	Doxazosin 1mg tablets (Actavis UK Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	50467	Doxazosin 2mg tablets (Alliance Healthcare (Distribution) Ltd)	2mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	51665	Tamurex 400microgram modified-release capsules (Somex Pharma)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	51685	Doxazosin 4mg tablets (Actavis UK Ltd)	4mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	52055	Tamsulosin 400microgram oral powder sachets	400microgram	Powder	Oral
ALPHA	Tamsulosin hydrochloride	52159	Tamsulosin 400microgram modified-release capsules (Focus Pharmaceuticals Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	53033	Doxzogen XL 4mg tablets (Mylan Ltd)	4mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	53322	Doxazosin 4mg tablets (Bristol Laboratories Ltd)	4mg	Tablet	Oral

ALPHA	Tamsulosin hydrochloride	53964	Tamsulosin 400microgram modified-release capsules (A A H Pharmaceuticals Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Tamsulosin hydrochloride	54497	Galebon 400microgram modified-release capsules (Consilient Health Ltd)	400microgram	Modified-release capsule	Oral
ALPHA	Doxazosin mesilate	54785	Doxazosin 4mg tablets (Medreich Plc)	4mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	55005	Kelanu XL 10mg tablets (Pfizer Ltd)	10mg	Modified-release tablet	Oral
ALPHA	Doxazosin mesilate	55906	Doxazosin 1mg tablets (Dexcel-Pharma Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	55916	Doxazosin 1mg tablets (Alliance Healthcare (Distribution) Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	56145	Doxazosin 2mg tablets (Actavis UK Ltd)	2mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	56793	Alfuzosin 2.5mg tablets (Teva UK Ltd)	2.5mg	Tablet	Oral
ALPHA	Doxazosin mesilate	57074	Doxazosin 2mg tablets (Sigma Pharmaceuticals Plc)	2mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	57145	Terazosin 2mg tablets (A A H Pharmaceuticals Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	57448	Doxazosin 4mg tablets (A A H	4mg	Tablet	Oral

			Pharmaceuticals Ltd)			
ALPHA	Alfuzosin hydrochloride	57549	Xatral 2.5mg tablets (Necessity Supplies Ltd)	2.5mg	Tablet	Oral
ALPHA	Doxazosin mesilate	57784	Doxazosin 2mg/5ml oral suspension	400microgram /1ml	Oral suspensi on	Oral
ALPHA	Doxazosin mesilate	58276	Doxazosin 2mg tablets (Medreich Plc)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	58325	Doxazosin 4mg tablets (Phoenix Healthcare Distribution Ltd)	4mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	58985	Xatral SR 5mg tablets (Sanofi-Synthelabo Ltd)	5mg	Modified -release tablet	Oral
ALPHA	Doxazosin mesilate	59209	Doxazosin 1mg tablets (Kent Pharmaceuticals Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	59862	Doxazosin 4mg tablets (Dexcel-Pharma Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	60200	Doxazosin 4mg tablets (DE Pharmaceuticals)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	60319	Doxazosin 1mg tablets (Bristol Laboratories Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	61066	Doxazosin 2mg tablets (Bristol Laboratories Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	61283	Doxazosin 4mg tablets (Alliance Healthcare (Distribution) Ltd)	4mg	Tablet	Oral

ALPHA	Doxazosin mesilate	62019	Doxazosin 1mg tablets (Almus Pharmaceuticals Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	62158	Doxazosin 4mg tablets (Almus Pharmaceuticals Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	62351	Doxazosin 2mg tablets (Phoenix Healthcare Distribution Ltd)	2mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	62539	Alfuzosin 10mg modified-release tablets (Phoenix Healthcare Distribution Ltd)	10mg	Modified -release tablet	Oral
ALPHA	Tamsulosin hydrochloride	62553	Tamsulosin 400microgram modified-release capsules (Alliance Healthcare (Distribution) Ltd)	400microgram	Modified -release capsule	Oral
ALPHA	Doxazosin mesilate	63158	Doxazosin 2mg tablets (Almus Pharmaceuticals Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	63314	Doxazosin 1mg tablets (Sovereign Medical Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	64233	Doxazosin 1mg tablets (Waymade Healthcare Plc)	1mg	Tablet	Oral
ALPHA	Alfuzosin hydrochloride	64443	Alfuzosin 2.5mg tablets (Sigma Pharmaceuticals Plc)	2.5mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	65124	Tamsulosin 400micrograms/5 ml oral solution	80microgram/ 1ml	Oral solution	Oral

ALPHA	Doxazosin mesilate	65159	Doxazosin 4mg tablets (Waymade Healthcare Plc)	4mg	Tablet	Oral
ALPHA	Terazosin hydrochloride	65442	Terazosin 5mg tablets (Mylan Ltd)	5mg	Tablet	Oral
ALPHA	Doxazosin mesilate	65853	Doxazosin 1mg tablets (Mawdsley-Brooks & Company Ltd)	1mg	Tablet	Oral
ALPHA	Doxazosin mesilate	66065	Doxazosin 2mg tablets (Kent Pharmaceuticals Ltd)	2mg	Tablet	Oral
ALPHA	Doxazosin mesilate	68022	Doxazosin 4mg tablets (Sovereign Medical Ltd)	4mg	Tablet	Oral
ALPHA	Doxazosin mesilate	68161	Doxazosin 4mg tablets (Mawdsley-Brooks & Company Ltd)	4mg	Tablet	Oral
ALPHA	Tamsulosin hydrochloride	68584	Tabphyn MR 400microgram capsules (Genus Pharmaceuticals Ltd)	400microgram	Modified-release capsule	Oral

Appendix 18: Antibiotics for UTI

Prodcode	Product Name	Substance	Stregnth	Formulation
45757	Trimethoprim with sulfamethoxazole 16mg + 80mg/ml Concentrate for solution for infusion	Sulfamethoxazole /Trimethoprim	16mg + 80mg/ml	Concentrate For Solution For Infusion
51510	Trimethoprim 200mg tablets (Bristol Laboratories Ltd)	Trimethoprim	200mg	Tablet
34542	Trimethoprim 100mg tablets (Teva UK Ltd)	Trimethoprim	100mg	Tablet
41967	Co-trimoxazole 240mg/5ml Oral suspension (Hillcross Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
9100	Co-trimoxazole (trimethoprim and sulfamethoxazole) 160mg+800mg	Sulfamethoxazole /Trimethoprim	160mg+800mg	Dispersible Tablet

	dispersible tablets			
57981	Trimethoprim 200mg tablets (Waymade Healthcare Plc)	Trimethoprim	200mg	Tablet
13325	Monotrim 100mg tablets (Abbott Healthcare Products Ltd)	Trimethoprim	100mg	Tablet
31477	Laratrim Liquid (Lagap)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
42517	Co-trimoxazole 40mg+200mg Liquid (Celltech Pharma Europe Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
34252	Trimethoprim 50mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Trimethoprim	10mg/1ml	Oral suspension
7421	Bactrim adult 480mg/5ml Liquid (Roche Products Ltd)	Trimethoprim/Sulfamethoxazole	16mg/1ml + 80mg/1ml	Oral suspension
29907	Comox Tablet (IVAX	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet

	Pharmaceuticals UK Ltd)			
8073	Trimethoprim 300mg Tablet	Trimethoprim	300mg	Tablet
34727	Co-trimoxazole 80mg/400mg tablets (Actavis UK Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
60216	Bactrim 96mg/ml Infusion (Roche Products Ltd)	Sulfamethoxazole /Trimethoprim	96mg/ml	Infusion
53828	Trimethoprim 50mg/5ml oral suspension sugar free (Actavis UK Ltd)	Trimethoprim	10mg/1ml	Oral suspension
43509	Sulfadiazine 500mg tablets (Wockhardt UK Ltd)	Sulfadiazine	500mg	Tablet
34488	Trimethoprim 100mg tablets (Kent Pharmaceuticals Ltd)	Trimethoprim	100mg	Tablet
37	Trimethoprim 200mg tablets	Trimethoprim	200mg	Tablet
34878	Trimethoprim 100mg Tablet (C	Trimethoprim	100mg	Tablet

	P Pharmaceuticals Ltd)			
606	Co-trimoxazole 80mg/400mg tablets	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
53284	Trimethoprim 50mg/5ml oral suspension sugar free (Sigma Pharmaceuticals Plc)	Trimethoprim	10mg/1ml	Oral suspension
52198	Co-trimoxazole 80mg/400mg tablets (Sigma Pharmaceuticals Plc)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
44075	Septrin tablets (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
1604	Septrin paediatric Oral suspension sugar free (Wellcome Medical Division)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
67596	Trimethoprim 100mg tablets (DE Pharmaceuticals)	Trimethoprim	100mg	Tablet

55121	Sulfadiazine 500mg tablets (A A H Pharmaceuticals Ltd)	Sulfadiazine	500mg	Tablet
67613	Co-trimoxazole 80mg+400mg Dispersible tablet (IVAX Pharmaceuticals UK Ltd)	Sulfamethoxazole /Trimethoprim	80mg+400mg	Dispersible Tablet
128	Sulfametopyrazine 2g tablet	Sulfametopyrazine	2g	Tablets
32908	Trimethoprim 200mg tablets (Teva UK Ltd)	Trimethoprim	200mg	Tablet
68225	Trimethoprim 100mg tablets (Crescent Pharma Ltd)	Trimethoprim	100mg	Tablet
1634	Septrin paediatric Dispersible tablet (Wellcome Medical Division)	Sulfamethoxazole /Trimethoprim		Dispersible Tablet
33997	Trimethoprim 200mg tablets (IVAX Pharmaceuticals UK Ltd)	Trimethoprim	200mg	Tablet

25497	Syraprim 100mg Tablet (Wellcome Medical Division)	Trimethoprim	100mg	Tablet
303	Co-trimoxazole 16mg with 80mg/ml concentrate solution for infusion	Sulfamethoxazole /Trimethoprim	16mg + 80mg/ml	Concentrate For Solution For Infusion
41544	Trimethoprim 100mg Tablet (IVAX Pharmaceuticals UK Ltd)	Trimethoprim	100mg	Tablet
10745	Bactrim double strength 160mg+800mg Tablet (Roche Products Ltd)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
29800	Phthalylsulfathiazole 500mg tablet	Phthalylsulfathiazole	500mg	Tablets
56267	Trimethoprim 100mg tablets (Bristol Laboratories Ltd)	Trimethoprim	100mg	Tablet
68726	Co-trimoxazole 80mg/400mg tablets (Sigma	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet

	Pharmaceuticals Plc)			
27921	Laratrim forte Tablet (Lagap)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
33987	Sulfamethoxazole 800mg with trimethoprim 160mg/5ml concentrate solution for infusion	Sulfamethoxazole /Trimethoprim	800mg + 160mg/10ml	Concentrate For Solution For Infusion
25269	Bactrim im 320mg/ml intramuscular injection (Roche Products Ltd)	Sulfamethoxazole /Trimethoprim	320mg/ml	Intramuscular Injection
7616	Trimopan 50mg/5ml Liquid (Berk Pharmaceuticals Ltd)	Trimethoprim	10mg/1ml	Oral suspension
43505	Trimethoprim 200mg Tablet (Numark Management Ltd)	Trimethoprim	200mg	Tablet
3660	Septrin Dispersible tablet (Wellcome Medical Division)	Sulfamethoxazole /Trimethoprim		Dispersible Tablet

54166	Sulfadiazine oral solution	Sulfadiazine		
29351	Trimethoprim 50mg/5ml oral suspension sugar free (Teva UK Ltd)	Trimethoprim	10mg/1ml	Oral suspension
45246	Trimethoprim 100mg tablets (Sandoz Ltd)	Trimethoprim	100mg	Tablet
2460	Septrin Forte 160mg/800mg tablets (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
32906	Trimethoprim 100mg tablets (A A H Pharmaceuticals Ltd)	Trimethoprim	100mg	Tablet
29357	Sulphadimethoxine 500mg tablet	Sulphadimethoxine	500mg	Tablets
14367	Ipral 50mg/5ml Liquid (E R Squibb and Sons Ltd)	Trimethoprim	10mg/1ml	Oral suspension
29532	Trimogal 100mg Tablet (Lagap)	Trimethoprim	100mg	Tablet
24856	Sulphamezathine 333mg/ml	Sulfadimidine	333mg/ml	Injection

	Injection (AstraZeneca UK Ltd)			
21805	Triprimix 200 Tablet (Ashbourne Pharmaceuticals Ltd)	Trimethoprim	200mg	Tablet
28004	Co-trimoxazole (trimethoprim and sulfamethoxazole) 20mg+100mg paediatric tablets	Sulfamethoxazole /Trimethoprim	20mg+100mg	Tablets
131	Septrin for Infusion 80mg/400mg/5ml solution for infusion ampoules (Aspen Pharma Trading Ltd)	Sulfamethoxazole /Trimethoprim	80mg/1ml + 16mg/1ml	Solution for infusion
340	Trimethoprim 100mg tablets	Trimethoprim	100mg	Tablet
68990	Comox forte Tablet (IVAX Pharmaceuticals UK Ltd)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet

33794	Sulfamethoxazole 400mg with trimethoprim 80mg/5ml oral suspension	Sulfamethoxazole /Trimethoprim	400mg + 80mg/5ml	Oral Suspension
20368	Sulfamethoxazole 400mg with trimethoprim 80mg/5ml concentrate solution for infusion	Sulfamethoxazole /Trimethoprim	400mg + 80mg/5ml	Concentrate For Solution For Infusion
67361	Trimethoprim 50mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Trimethoprim	10mg/1ml	Oral suspension
46663	Bactrim paediatric tablets (Roche Products Ltd)	Sulfamethoxazole /Trimethoprim		Tablet
403	Sulfadiazine 500mg tablets	Sulfadiazine	500mg	Tablet
15988	Trimethoprim with sulfamethoxazole 80mg+400mg Tablet	Sulfamethoxazole /Trimethoprim	80mg+400mg	Tablet

65497	Trimethoprim 200mg tablets (Mawdsley-Brooks & Company Ltd)	Trimethoprim	200mg	Tablet
2658	Co-trimoxazole 80mg/400mg/5ml oral suspension	Trimethoprim/Sulfamethoxazole	16mg/1ml + 80mg/1ml	Oral suspension
41991	Co-trimoxazole 80mg+400mg Dispersible tablet (Approved Prescription Services Ltd)	Sulfamethoxazole /Trimethoprim	80mg+400mg	Dispersible Tablet
44241	Fectrim Dispersible tablet (DDSA Pharmaceuticals Ltd)	Sulfamethoxazole /Trimethoprim		Dispersible Tablet
34379	Trimethoprim 200mg tablets (Kent Pharmaceuticals Ltd)	Trimethoprim	200mg	Tablet
34392	Trimethoprim 200mg tablets (Actavis UK Ltd)	Trimethoprim	200mg	Tablet

7420	Bactrim 480mg Tablet (Roche Products Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
43545	Trimethoprim 100mg tablets (Actavis UK Ltd)	Trimethoprim	100mg	Tablet
21037	Uromide Tablet (Consolidated Chemicals (UK) Ltd)	Sulfacarbamide/phenazopyridine Hydrochloride		Tablet
24324	Trimogal 200mg Tablet (Lagap)	Trimethoprim	200mg	Tablet
20126	Trimethoprim with sulfamethoxazole 160mg+800mg Tablet	Sulfamethoxazole /Trimethoprim	160mg+800mg	Tablet
10046	Trimopan 200mg tablets (Teva UK Ltd)	Trimethoprim	200mg	Tablet
58490	Trimethoprim 100mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim	100mg	Tablet
21809	Comixco 80mg+400mg Tablet (Ashbourne	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet

	Pharmaceuticals Ltd)			
10308	Sulfamethoxazole 400mg with trimethoprim 80mg tablet	Sulfamethoxazole /Trimethoprim	400mg + 80mg	Tablets
34455	Trimethoprim 200mg Tablet (C P Pharmaceuticals Ltd)	Trimethoprim	200mg	Tablet
39933	Trimethoprim 200mg tablets (Almus Pharmaceuticals Ltd)	Trimethoprim	200mg	Tablet
52669	Trimethoprim 200mg/5ml oral solution			
10301	Sulfadimidine 500mg/5ml paediatric mixture	Sulfadimidine	500mg/5ml	Mixture
50120	Trimethoprim 200mg tablets (Accord Healthcare Ltd)	Trimethoprim	200mg	Tablet
31227	Trimethoprim 200mg Tablet	Trimethoprim	200mg	Tablet

	(Regent Laboratories Ltd)			
53275	Trimethoprim 50mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Trimethoprim	10mg/1ml	Oral suspension
27048	Syraprim 300mg Tablet (Wellcome Medical Division)	Trimethoprim	300mg	Tablet
31484	Laratrim adult 480mg/5ml Liquid (Lagap)	Trimethoprim/Sulfamethoxazole	16mg/1ml + 80mg/1ml	Oral suspension
17729	Sulfadimidine 500mg tablet	Sulfadimidine	500mg	Tablets
29994	Sulfaguanidine 500mg tablet	Sulfaguanidine	500mg	Tablets
8561	Bactrim paediatric sugar free oral solution	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
53946	Sulfadiazine 500mg tablets (Alliance Healthcare (Distribution) Ltd)	Sulfadiazine	500mg	Tablet
61714	Trimethoprim 50mg/5ml oral suspension sugar	Trimethoprim	10mg/1ml	Oral suspension

	free (Pinewood Healthcare)			
41978	Co-trimoxazole 240mg/5ml Oral suspension (Approved Prescription Services Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
14998	Ipral 200mg Tablet (E R Squibb and Sons Ltd)	Trimethoprim	200mg	Tablet
53276	Trimethoprim 50mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Trimethoprim	10mg/1ml	Oral suspension
30614	Sulfamethoxazole 200mg with trimethoprim 40mg/5ml oral suspension	Sulfamethoxazole /Trimethoprim	200mg + 40mg/5ml	Oral Suspension
31905	Trimethoprim with sulfamethoxazole 80mg + 400mg/5ml Concentrate for	Sulfamethoxazole /Trimethoprim	80mg + 400mg/5ml	Concentrate For Solution For Infusion

	solution for infusion			
60448	Co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules (Alliance Healthcare (Distribution) Ltd)	Sulfamethoxazole /Trimethoprim	80mg/1ml + 16mg/1ml	Solution for infusion
30201	Co-trimoxazole 240mg/5ml Paediatric mixture (Lagap)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
8171	Monotrim 200mg tablets (Abbott Healthcare Products Ltd)	Trimethoprim	200mg	Tablet
67147	Trimethoprim 100mg tablets (Mawdsley-Brooks & Company Ltd)	Trimethoprim	100mg	Tablet
8286	Co-trimoxazole (trimethoprim and sulfamethoxazole) 80mg+400mg dispersible tablets	Sulfamethoxazole /Trimethoprim	80mg+400mg	Dispersible Tablet

51725	Trimethoprim 20mg/5ml oral suspension			
44286	Septrin Paediatric 40mg/200mg/5ml oral suspension (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
135	Septrin Tablet (Wellcome Medical Division)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
68101	Co-trimoxazole 40mg/200mg/5ml oral suspension sugar free (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
38090	Co-trimoxazole 480mg/5ml Adult Mixture (Lagap)	Trimethoprim/Sulfamethoxazole	16mg/1ml + 80mg/1ml	Oral suspension
43262	Co-trimoxazole 240mg/5ml Oral suspension (C P Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
1199	Co-trimoxazole 40mg/200mg/5ml oral suspension sugar free	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension

50797	Trimethoprim 200mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim	200mg	Tablet
298	Sulfadimidine 333mg/ml injection	Sulfadimidine	333mg/ml	Injection
63733	Co-trimoxazole 80mg/400mg tablets (Essential Generics Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
65343	Co-trimoxazole 160mg/800mg tablets (Tillomed Laboratories Ltd)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
27418	Trimethoprim with sulfamethoxazole 40mg + 200mg/5ml Oral suspension	Sulfamethoxazole /Trimethoprim	40mg + 200mg/5ml	Oral Suspension
43537	Trimethoprim 200mg Tablet (Celltech Pharma Europe Ltd)	Trimethoprim	200mg	Tablet
28562	Enteromide 500mg Tablet (Consolidated	Calcium	500mg	Tablet

	Chemicals (UK) Ltd)			
8741	Bactrim Dispersible tablet (Roche Products Ltd)	Sulfamethoxazole /Trimethoprim		Dispersible Tablet
287	Co-trimoxazole (trimethoprim with sulfamethoxazole) 320mg/ml IM injection	Sulfamethoxazole /Trimethoprim	320mg/ml	Im Injection
58282	Co-trimoxazole 80mg/400mg tablets (Waymade Healthcare Plc)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
22991	Chemotrim Liquid (Rosemont Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	8mg/1ml + 40mg/1ml	Oral suspension
1467	Co-trimoxazole 160mg/800mg tablets	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
15081	Ipral 100mg Tablet (E R Squibb and Sons Ltd)	Trimethoprim	100mg	Tablet

68826	Co-trimoxazole 160mg/800mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
59444	Co-trimoxazole 80mg/400mg tablets (Alliance Healthcare (Distribution) Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
68027	Co-trimoxazole 160mg+800mg Tablet (C P Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	160mg + 800mg	Tablet
10318	Sulfamethoxazole 80mg with trimethoprim 16mg/5ml concentrate solution for infusion	Sulfamethoxazole /Trimethoprim	80mg + 16mg/ml	Concentrate For Solution For Infusion
41579	Co-trimoxazole 80mg/400mg tablets (A A H Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
27445	Trimethoprim with sulfamethoxazole 160mg +	Sulfamethoxazole /Trimethoprim	160mg + 800mg/10ml	Concentrate For Solution For Infusion

	800mg/10ml Concentrate for solution for infusion			
109	Septrin Adult 80mg/400mg/5ml oral suspension (Aspen Pharma Trading Ltd)	Trimethoprim/Sulfamethoxazole	16mg/1ml + 80mg/1ml	Oral suspension
20920	Trimethoprim with sulfamethoxazole 80mg + 400mg/5ml Oral suspension	Sulfamethoxazole /Trimethoprim	80mg + 400mg/5ml	Oral Suspension
64028	Trimethoprim 200mg tablets (Crescent Pharma Ltd)	Trimethoprim	200mg	Tablet
27417	Sulphafurazole 500mg tablet	Sulfafurazole Acetyl	500mg	Tablets
57080	Trimethoprim 100mg tablets (Waymade Healthcare Plc)	Trimethoprim	100mg	Tablet
65487	Trimethoprim 200mg tablets (DE Pharmaceuticals)	Trimethoprim	200mg	Tablet

60808	Trimethoprim 50mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Trimethoprim	10mg/1ml	Oral suspension
7962	Kelfizine w 2g Tablet (Pharmacia Ltd)	Sulfametopyrazine	2g	Tablet
27255	Trimethoprim 200mg tablets (A A H Pharmaceuticals Ltd)	Trimethoprim	200mg	Tablet
477	Trimethoprim 50mg/5ml oral suspension sugar free	Trimethoprim	10mg/1ml	Oral suspension
57642	Trimethoprim 20mg/5ml oral solution	Trimethoprim	4mg/1ml	Oral solution
56259	Trimethoprim 100mg tablets (Sigma Pharmaceuticals Plc)	Trimethoprim	100mg	Tablet
57116	Trimethoprim 50mg/5ml oral suspension sugar	Trimethoprim	10mg/1ml	Oral suspension

	free (Waymade Healthcare Plc)			
54914	Co-trimoxazole 80mg/400mg tablets (Kent Pharmaceuticals Ltd)	Trimethoprim/Sulfamethoxazole	80mg + 400mg	Tablet
260	Sulphafurazole 500mg/5ml oral solution	Sulfafurazole Acetyl	500mg/5ml	Syrup
53599	Trimethoprim 200mg tablets (Phoenix Healthcare Distribution Ltd)	Trimethoprim	200mg	Tablet
280	Monotrim 50mg/5ml Liquid (Solvay Healthcare)	Trimethoprim	10mg/1ml	Oral suspension
62630	Trimethoprim 200mg tablets (Ranbaxy (UK) Ltd)	Trimethoprim	200mg	Tablet
53720	Trimethoprim 100mg tablets (Almus Pharmaceuticals Ltd)	Trimethoprim	100mg	Tablet

36622	Monotrim 50mg/5ml oral suspension (Chemidex Pharma Ltd)	Trimethoprim	10mg/1ml	Oral suspension
21640	Trimopan 100mg tablets (Teva UK Ltd)	Trimethoprim	100mg	Tablet
25908	Sulfamethoxazole 800mg with trimethoprim 160mg tablet	Sulfamethoxazole /Trimethoprim	800mg + 160mg	Tablets
16620	Co-trimoxazole 80mg/400mg/5ml solution for infusion ampoules	Sulfamethoxazole /Trimethoprim	80mg/1ml + 16mg/1ml	Solution for infusion
55986	Trimethoprim 200mg/5ml oral suspension	Trimethoprim	40mg/1ml	Oral suspension
20523	Thalazole 500mg Tablet (May and Baker)	Phthalylsulfathiazole	500mg	Tablet
49592	Trimethoprim 100mg tablets (Phoenix Healthcare Distribution Ltd)	Trimethoprim	100mg	Tablet

34633	Trimethoprim 200mg tablets (Sandoz Ltd)	Trimethoprim	200mg	Tablet
15973	Polymyxin B 10,000units/g / Trimethoprim 5mg/g eye ointment	Polymyxin B sulfate/Trimethoprim	10000unit/1gram + 5mg/1gram	Eye ointment
8309	Polytrim eye drops (PLIVA Pharma Ltd)	Polymyxin B sulfate/Trimethoprim	10000unit/1ml + 1mg/1ml	Eye drops
53793	Trimethoprim 50mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Trimethoprim	10mg/1ml	Oral suspension
153	Trimethoprim 100mg/5ml solution for injection ampoules	Trimethoprim	20mg/1ml	Solution for injection
12465	Polytrim ophthalmic ointment (PLIVA Pharma Ltd)	Polymyxin B sulfate/Trimethoprim	10000unit/1gram + 5mg/1gram	Eye ointment
31463	Co-trimoxazole 160mg/800mg/10ml solution for	Sulfamethoxazole/Trimethoprim	80mg/1ml + 16mg/1ml	Solution for infusion

	infusion ampoules			
13306	Monotrim 100mg/5ml solution for injection ampoules (Abbott Healthcare Products Ltd)	Trimethoprim	20mg/1ml	Solution for injection
15972	Polymyxin B 10,000units/ml / Trimethoprim 1mg/ml eye drops	Polymyxin B sulfate/Trimethoprim	10000unit/1ml + 1mg/1ml	Eye drops
54393	Ciprofloxacin 250mg tablets (Arrow Generics Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
49839	Ciproxin 500mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
32388	Ciproxin 200mg/100ml Infusion (Bayer Plc)	Ciprofloxacin Lactate	200mg/100ml	Infusion
51537	Ciprofloxacin 250mg tablets (Alliance	Ciprofloxacin hydrochloride	250mg	Tablet

	Healthcare (Distribution) Ltd)			
14233	Ciprofloxacin 3mg/g eye ointment	Ciprofloxacin hydrochloride	3mg/1gram	Eye ointment
47785	Ciprofloxacin 400mg/200ml infusion bags	Ciprofloxacin lactate	2mg/1ml	Infusion
34494	Ciprofloxacin 500mg tablets (Wockhardt UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
50601	Ciprofloxacin 250mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
43517	Ciprofloxacin 750mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
61302	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
7752	Ciproxin 750mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	750mg	Tablet

54663	Ciproxin Infusion 200mg/100ml solution for infusion bottles (Bayer Plc)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
58246	Ciprofloxacin 400mg/200ml infusion bags (Hospira UK Ltd)	Ciprofloxacin lactate	2mg/1ml	Infusion
53878	Ciprofloxacin 500mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
728	Ciproxin 500mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
58235	Ciprofloxacin 250mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	250mg	Tablet
56789	Ciprofloxacin 500mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
59653	Ciproxin Infusion 400mg/200ml solution for	Ciprofloxacin lactate	2mg/1ml	Solution for infusion

	infusion bottles (Bayer Plc)			
34322	Ciprofloxacin 500mg Tablet (Niche Generics Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
1837	Ciprofloxacin 750mg tablets	Ciprofloxacin hydrochloride	750mg	Tablet
50141	Ciprofloxacin 0.2% eye drops preservative free	Ciprofloxacin hydrochloride	2mg/1ml	Eye drops
34973	Ciprofloxacin 750mg Tablet (Niche Generics Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
66214	Ciprofloxacin 250mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
29343	Ciprofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
45341	Ciprofloxacin 500mg Tablet (Neo Laboratories Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet

66727	Ciprofloxacin 500mg/5ml oral suspension	Ciprofloxacin	100mg/1ml	Oral suspension
63501	Ciprofloxacin 750mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	750mg	Tablet
50055	Ciprofloxacin 500mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	500mg	Tablet
66971	Ciprofloxacin 400mg/200ml solution for infusion vials (A A H Pharmaceuticals Ltd)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
34605	Ciprofloxacin 500mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
45285	Ciprofloxacin 500mg tablets (Teva UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
42174	Ciprofloxacin 500mg tablets (IVAX Pharmaceuticals UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet

5631	Ciloxan 0.3% eye drops (Alcon Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	3mg/1ml	Eye drops
52309	Ciprofloxacin 100mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	100mg	Tablet
56856	Ciprofloxacin 750mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
57960	Ciprofloxacin 500mg tablets (Tillomed Laboratories Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
52099	Ciprofloxacin 750mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
34308	Ciprofloxacin 250mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
52353	Ciproxin 250mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	250mg	Tablet
163	Ciproxin 250mg/5ml oral	Ciprofloxacin	50mg/1ml	Oral suspension

	suspension (Bayer Plc)			
34448	Ciprofloxacin 250mg tablets (Niche Generics Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
57703	Ciprofloxacin 200mg/100ml solution for infusion bottles	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
53519	Ciproxin 250mg tablets (Lexon (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
498	Ciprofloxacin 100mg tablets	Ciprofloxacin hydrochloride	100mg	Tablet
60436	Ciprofloxacin 250mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
61783	Ciprofloxacin 250mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
56381	Ciprofloxacin 250mg tablets (Strides Shasun (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet

65896	Ciproxin 250mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
52177	Ciproxin 500mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
1202	Ciproxin 250mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
34647	Ciprofloxacin 250mg Tablet (Neo Laboratories Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
64814	Ciprofloxacin 400mg/200ml solution for infusion vials (Genus Pharmaceuticals Ltd)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
53641	Ciprofloxacin 500mg tablets (Strides Shasun (UK) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
55917	Ciprofloxacin 500mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	500mg	Tablet

58955	Ciprofloxacin 100mg/50ml solution for infusion vials (A A H Pharmaceuticals Ltd)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
26840	Ciprofloxacin 100mg/50ml solution for infusion bottles	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
59572	Ciprofloxacin 500mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
33215	Ciprofloxacin 200mg/100ml in sodium chloride 0.9% infusion	Ciprofloxacin Lactate	200mg/100ml	Infusion
30707	Ciprofloxacin 500mg tablets (Mylan Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
58021	Ciprofloxacin 100mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet

54302	Ciprofloxacin 250mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
11883	Ciprofloxacin 100mg/50ml solution for infusion vials	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
54555	Ciprofloxacin 100mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	100mg	Tablet
39913	Ciprofloxacin 100mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
38171	Ciprofloxacin 200mg/100ml infusion bags	Ciprofloxacin lactate	2mg/1ml	Infusion
33989	Ciprofloxacin 250mg tablets (Mylan Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
14376	Ciproxin 2mg/ml Infusion (Bayer Plc)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
4091	Ciprofloxacin 250mg/5ml oral suspension	Ciprofloxacin	50mg/1ml	Oral suspension
34655	Ciprofloxacin 250mg tablets	Ciprofloxacin hydrochloride	250mg	Tablet

	(Wockhardt UK Ltd)			
43557	Ciprofloxacin 500mg tablets (PLIVA Pharma Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
29472	Ciprofloxacin 750mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
48031	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
67154	Cilodex ear drops (Alcon Laboratories (UK) Ltd)	Dexamethasone/ Ciprofloxacin hydrochloride	1mg/1ml + 3mg/1ml	Ear drops
34694	Ciprofloxacin 250mg tablets (PLIVA Pharma Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
68409	Ciprofloxacin 750mg tablets (Phoenix Healthcare Distribution Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet

68274	Ciproxin 500mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	500mg	Tablet
281	Ciprofloxacin 250mg tablets	Ciprofloxacin hydrochloride	250mg	Tablet
34478	Ciprofloxacin 250mg tablets (Teva UK Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
64446	Ciprofloxacin 250mg tablets (Tillomed Laboratories Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
49445	Ciprofloxacin 500mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
43814	Ciprofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
61869	Ciproxin 250mg/5ml oral suspension (Waymade Healthcare Plc)	Ciprofloxacin	50mg/1ml	Oral suspension
28544	Ciprofloxaxin 400mg/200ml in	Ciprofloxacin Lactate	400mg/200ml	Infusion

	glucose 5% infusion			
29507	Ciprofloxacin 400mg/200ml in sodium chloride 0.9% infusion	Ciprofloxacin Lactate	400mg/200ml	Infusion
58608	Ciprofloxacin 100mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
42507	Ciprofloxacin 100mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
59937	Ciprofloxacin 750mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
21812	Ciproxin Infusion 100mg/50ml solution for infusion bottles (Bayer Plc)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
43797	Ciprofloxacin 500mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
19512	Ciloxan 3mg/g eye ointment	Ciprofloxacin hydrochloride	3mg/1gram	Eye ointment

	(Alcon Laboratories (UK) Ltd)			
9154	Ciproxin 100mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	100mg	Tablet
54674	Ciprofloxacin 100mg tablets (Phoenix Healthcare Distribution Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
38006	Ciproxin 400mg/200ml Infusion (Bayer Plc)	Ciprofloxacin Lactate	400mg/200ml	Infusion
583	Ciprofloxacin 500mg tablets	Ciprofloxacin hydrochloride	500mg	Tablet
32530	Ciproxin iv flexibag 400mg/200ml Infusion (Bayer Plc)	Ciprofloxacin Lactate	400mg/200ml	Infusion
53088	Ciprofloxacin 500mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
54701	Ciprofloxacin 250mg tablets	Ciprofloxacin hydrochloride	250mg	Tablet

	(Bristol Laboratories Ltd)			
67656	Ciprofloxacin 500mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
52501	Ciprofloxacin 500mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
41561	Ciprofloxacin 250mg tablets (IVAX Pharmaceuticals UK Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
58074	Ciprofloxacin 400mg/200ml solution for infusion bottles	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
52807	Ciproxin 500mg tablets (Mawdsley-Brooks & Company Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
34559	Ciprofloxacin 250mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
58323	Ciprofloxacin 100mg tablets	Ciprofloxacin hydrochloride	100mg	Tablet

	(Alliance Healthcare (Distribution) Ltd)			
66483	Ciprofloxacin 170mg/5ml oral suspension	Ciprofloxacin	34mg/1ml	Oral suspension
10304	Ciprofloxacin 2mg/ml infusion	Ciprofloxacin Lactate	2mg/ml	Infusion
52616	Ciprofloxacin 500mg tablets (Arrow Generics Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
64301	Ciprofloxacin 500mg tablets (Kent Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
528	Ciprofloxacin 0.3% eye drops	Ciprofloxacin hydrochloride	3mg/1ml	Eye drops
29458	Ciprofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
57118	Ciprofloxacin 250mg tablets (Kent Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet

54993	Ciprofloxacin 400mg/200ml solution for infusion vials	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
65115	Ciprofloxacin 0.3% / Dexamethasone 0.1% ear drops	Dexamethasone/ Ciprofloxacin hydrochloride	1mg/1ml + 3mg/1ml	Ear drops
51726	Nitrofurantoin 40mg/5ml oral suspension	Nitrofurantoin	8mg/1ml	Oral suspension
35673	Nitrofurantoin 25mg/5ml oral suspension sugar free (AMCo)	Nitrofurantoin	5mg/1ml	Oral suspension
2023	Furadantin 50mg tablets (AMCo)	Nitrofurantoin	50mg	Tablet
61907	Nitrofurantoin 50mg capsules (Alliance Healthcare (Distribution) Ltd)	Nitrofurantoin	50mg	Capsule
6370	Nitrofurantoin 100mg modified-release capsules	Nitrofurantoin	100mg	Modified-release capsule
53094	Nitrofurantoin 50mg tablets (A A H	Nitrofurantoin	50mg	Tablet

	Pharmaceuticals Ltd)			
54325	Nitrofurantoin 50mg tablets (Phoenix Healthcare Distribution Ltd)	Nitrofurantoin	50mg	Tablet
1825	Macrodantin 50mg capsules (AMCo)	Nitrofurantoin	50mg	Capsule
60713	Nitrofurantoin 100mg capsules (AMCo)	Nitrofurantoin	100mg	Capsule
64389	Nitrofurantoin 30mg/5ml oral solution	Nitrofurantoin	6mg/1ml	Oral solution
67759	Nitrofurantoin 50mg tablets (Mylan Ltd)	Nitrofurantoin	50mg	Tablet
16284	Urantoin 100mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Nitrofurantoin	100mg	Tablet
2198	Nitrofurantoin 25mg/5ml Oral suspension	Nitrofurantoin	25mg/5ml	Oral Suspension

60252	Nitrofurantoin 50mg capsules (AMCo)	Nitrofurantoin	50mg	Capsule
41397	Nitrofurantoin 100mg tablets (Actavis UK Ltd)	Nitrofurantoin	100mg	Tablet
58469	Nitrofurantoin 5mg/5ml oral solution	Nitrofurantoin	1mg/1ml	Oral solution
53638	Nitrofurantoin 100mg tablets (Teva UK Ltd)	Nitrofurantoin	100mg	Tablet
56621	Nitrofurantoin 25mg/5ml oral solution	Nitrofurantoin	5mg/1ml	Oral solution
65207	Nitrofurantoin 24mg/5ml oral suspension	Nitrofurantoin	4.8mg/1ml	Oral suspension
35850	Nitrofurantoin 100mg tablets (A A H Pharmaceuticals Ltd)	Nitrofurantoin	100mg	Tablet
210	Nitrofurantoin 50mg capsules	Nitrofurantoin	50mg	Capsule
57669	Nitrofurantoin 50mg tablets (Genesis	Nitrofurantoin	50mg	Tablet

	Pharmaceuticals Ltd)			
2541	Furadantin 100mg tablets (AMCo)	Nitrofurantoin	100mg	Tablet
466	Nitrofurantoin 100mg capsules	Nitrofurantoin	100mg	Capsule
2036	Macrodantin 100mg capsules (AMCo)	Nitrofurantoin	100mg	Capsule
778	Nitrofurantoin 50mg tablets	Nitrofurantoin	50mg	Tablet
2887	Nitrofurantoin 100mg tablets	Nitrofurantoin	100mg	Tablet
40164	Nitrofurantoin 50mg tablets (Actavis UK Ltd)	Nitrofurantoin	50mg	Tablet
65803	Macrobid 100mg modified-release capsules (Waymade Healthcare Plc)	Nitrofurantoin	100mg	Modified-release capsule
53659	Nitrofurantoin 25mg/5ml oral suspension	Nitrofurantoin	5mg/1ml	Oral suspension
48353	Nitrofurantoin 25mg/5ml oral	Nitrofurantoin	5mg/1ml	Oral suspension

	suspension sugar free			
53171	Nitrofurantoin 50mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Nitrofurantoin	50mg	Tablet
62647	Nitrofurantoin 50mg Tablet (Biorex Laboratories Ltd)	Nitrofurantoin	50mg	Tablet
272	Furadantin 25mg/5ml oral suspension (Mercury Pharma Group Ltd)	Nitrofurantoin	5mg/1ml	Oral suspension
57779	Nitrofurantoin 50mg tablets (Waymade Healthcare Plc)	Nitrofurantoin	50mg	Tablet
61642	Nitrofurantoin 100mg capsules (Alliance Healthcare (Distribution) Ltd)	Nitrofurantoin	100mg	Capsule
67981	Genfura 100mg tablets (Genesis Pharmaceuticals Ltd)	Nitrofurantoin	100mg	Tablet

51959	Nitrofurantoin 50mg tablets (Alliance Healthcare (Distribution) Ltd)	Nitrofurantoin	50mg	Tablet
64690	Nitrofurantoin 100mg/5ml oral solution	Nitrofurantoin	20mg/1ml	Oral solution
65251	Macrodantin 50mg capsules (Waymade Healthcare Plc)	Nitrofurantoin	50mg	Capsule
63588	Nitrofurantoin 50mg capsules (A A H Pharmaceuticals Ltd)	Nitrofurantoin	50mg	Capsule
67762	Nitrofurantoin 100mg tablets (Mylan Ltd)	Nitrofurantoin	100mg	Tablet
7525	Macrobid 100mg modified-release capsules (AMCo)	Nitrofurantoin	100mg	Modified-release capsule
66013	Nitrofurantoin 50mg tablets (Almus Pharmaceuticals Ltd)	Nitrofurantoin	50mg	Tablet

17181	Pivampicillin 175mg sachet	Pivampicillin	175mg	Sachets
28701	Ampicillin 50mg / Cloxacillin 25mg/vial injection	Cloxacillin/Ampicillin	50mg + 25mg/vial	Injection
46175	Ampicillin 125mg/5ml Oral suspension (Hillcross Pharmaceuticals Ltd)	Ampicillin Trihydrate	125mg/5ml	Oral Suspension
8680	Talpen 125mg/5ml Oral solution (Beecham Research Laboratories)	Talampicillin Hydrochloride	125mg/5ml	Oral Solution
308	Magnapen 250mg/250mg capsules (Wockhardt UK Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
951	Flucloxacillin with ampicillin 125mg+125mg Liquid	Ampicillin Trihydrate/Flucloxacillin Magnesium	125mg+125mg	Liquid

2246	Pondocillin 500mg Tablet (LEO Pharma)	Pivampicillin	500mg	Tablet
857	Ampicillin 125mg/5ml oral suspension	Ampicillin	25mg/1ml	Oral suspension
67787	Ampicillin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	Ampicillin	50mg/1ml	Oral suspension
45237	Co-fluampicil 500mg with 500mg injection	Ampicillin Trihydrate/Flucloxacillin Sodium	500mg+500mg	Injection
28919	Ampicillin 250mg / Cloxacillin 250mg/vial injection	Cloxacillin/Ampicillin	250mg + 250mg/vial	Injection
7570	Pivampicillin 500mg tablet	Pivampicillin	500mg	Tablets
31156	Ampitrin 250mg Capsule (OPD Pharm)	Ampicillin	250mg	Capsule
26356	Amfipen 500mg Capsule (Yamanouchi Pharma Ltd)	Ampicillin	500mg	Capsule

54471	Ampicillin 250mg capsules (Kent Pharmaceuticals Ltd)	Ampicillin	250mg	Capsule
34228	Ampicillin 250mg capsules (A A H Pharmaceuticals Ltd)	Ampicillin	250mg	Capsule
25570	Co-fluampicil 250mg/250mg capsules (Sandoz Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
21967	Vidopen 500mg Capsule (Berk Pharmaceuticals Ltd)	Ampicillin	500mg	Capsule
57997	Ampicillin 250mg capsules (Waymade Healthcare Plc)	Ampicillin	250mg	Capsule
204	Penbritin 250mg Capsule (Beecham Research Laboratories)	Ampicillin	250mg	Capsule
4318	Penbritin 250mg/5ml Oral solution (Beecham	Ampicillin	50mg/1ml	Oral suspension

	Research Laboratories)			
31154	Ampitrin 500mg Capsule (OPD Pharm)	Ampicillin	500mg	Capsule
2377	Pondocillin 175mg/5ml Oral suspension sugar free (LEO Pharma)	Pivampicillin	175mg/5ml	Oral Suspension
41744	Ampicillin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Ampicillin	25mg/1ml	Oral suspension
12540	Pivampicillin 250mg with pivmecillinam 200mg tablet	Pivampicillin/Pivmecillinam Hydrochloride	250mg + 200mg	Tablets
13438	Magnapen 1g/vial Injection (C P Pharmaceuticals Ltd)	Ampicillin Trihydrate/Flucloxacillin Sodium	1g/vial	Injection
900	Ampicillin 125mg/5ml sugar free suspension	Ampicillin Trihydrate	125mg/5ml	Suspension Sugar-free
10369	Ampicillin 125mg / Flucloxacillin	Ampicillin Trihydrate/Fluclo	125mg+125mg	Syrup

	125mg oral solution	xacillin Magnesium		
25832	Pivampicillin 125mg with pivmecillinam100 mg tablet	Pivampicillin/Pivmecillinam Hydrochloride	125mg + 100mg	Tablets
31669	Pondocillin 120mg Sachets (LEO Pharma)	Pivampicillin	120mg	Sachets
37485	Penbritin 125mg/5ml syrup (Chemidex Pharma Ltd)	Ampicillin	25mg/1ml	Oral suspension
10603	Penbritin 125mg/5ml Oral solution (Beecham Research Laboratories)	Ampicillin	25mg/1ml	Oral suspension
31471	Vidopen 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Ampicillin	50mg/1ml	Oral suspension
926	Ampicillin 500mg capsules	Ampicillin	500mg	Capsule
18934	Penbritin 125mg/1.25ml Liquid (Beecham	Ampicillin Trihydrate	125mg/1.25ml	Liquid

	Research Laboratories)			
12083	Ampiclox neonatal 90mg/0.6ml Oral suspension (Beecham Research Laboratories)	Cloxacillin/Ampicillin Sodium	90mg/0.6ml	Oral Suspension
41646	Ampicillin 250mg Capsule (Berk Pharmaceuticals Ltd)	Ampicillin	250mg	Capsule
21926	Amfipen 500mg/vial Injection (Yamanouchi Pharma Ltd)	Ampicillin sodium	500mg	Powder for solution for injection
41415	Co-fluampicil 250mg/250mg capsules (Kent Pharmaceuticals Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
21345	Bacampicillin HCl 400mg tablets	Bacampicillin	400mg	Tablets
106	Ampicillin 250mg/5ml oral suspension	Ampicillin	50mg/1ml	Oral suspension

14485	Ampicillin 500mg powder for solution for injection vials	Ampicillin sodium	500mg	Powder for solution for injection
20516	Miraxid Liquid (Rpr / Fisons)	Pivampicillin/Pivmecillinam Hydrochloride		Liquid
15039	Penbritin 500mg Capsule (Beecham Research Laboratories)	Ampicillin	500mg	Capsule
30630	Penbritin 250mg/vial Injection (Beecham Research Laboratories)	Ampicillin Sodium	250mg/vial	Injection
26174	Ampicillin 500mg capsules (A A H Pharmaceuticals Ltd)	Ampicillin	500mg	Capsule
52340	Cloxacillin 30mg with Ampicillin 60mg/0.6ml suspension	Cloxacillin/Ampicillin Sodium		
30764	Co-fluampicil 250mg/250mg capsules (IVAX	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule

	Pharmaceuticals UK Ltd)			
9242	Flucloxacillin with ampicillin 250mg+250mg Capsule	Ampicillin Trihydrate/Flucloxacillin Sodium	250mg+250mg	Capsule
8960	Pondocillin plus Tablet (Edwin Burgess Ltd)	Pivampicillin/Pivmecillinam Hydrochloride		Tablet
16167	Ampicillin 250mg/5ml sugar free suspension	Ampicillin Trihydrate	250mg/5ml	Suspension Sugar-free
58520	Ampicillin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	Ampicillin	250mg	Capsule
34358	Co-fluampicil 250mg/250mg capsules (Mylan Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
20007	Talampicillin 250mg tablets	Talampicillin Hydrochloride	250mg	Tablets
1450	Ampicillin 250mg / Flucloxacillin 250mg capsules	Ampicillin Trihydrate/Flucloxacillin Sodium	250mg+250mg	Capsules
21029	Miraxid 450 Tablet (Rpr / Fisons)	Pivampicillin/Pivmecillinam Hydrochloride		Tablet

34380	Co-fluampicil 250mg/250mg capsules (Actavis UK Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
32760	Ampitrin 125mg/5ml Liquid (OPD Pharm)	Ampicillin	25mg/1ml	Oral suspension
24483	Penbritin 250mg capsules (Chemidex Pharma Ltd)	Ampicillin	250mg	Capsule
13531	Magnapen 500mg powder for solution for injection vials (Wockhardt UK Ltd)	Ampicillin sodium/Flucloxacillin sodium	250mg + 250mg	Powder for solution for injection
10685	Ampicillin 250mg injection	Ampicillin Sodium	250mg	Injection
23485	Flu-amp 500mg Capsule (Generics (UK) Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
38091	Penbritin Forte 250mg/5ml syrup (Chemidex Pharma Ltd)	Ampicillin	50mg/1ml	Oral suspension
16589	Talampicillin 125mg/5ml syrup	Talampicillin Hydrochloride	125mg/5ml	Syrup

12382	Ampiclox 500mg Capsule (Beecham Research Laboratories)	Cloxacillin/Ampicillin	500mg	Capsule
14484	Ampicillin / Cloxacillin 500mg capsules	Cloxacillin/Ampicillin	500mg	Capsules
9473	Co-fluampicil 125mg/125mg/5 ml oral suspension	Flucloxacillin magnesium/Ampicillin trihydrate	25mg/1ml + 25mg/1ml	Oral suspension
54907	Cloxacillin 250mg with Ampicillin 250mg injection	Cloxacillin/Ampicillin Sodium		
8209	Ampicillin 125mg/5ml paediatric oral suspension	Ampicillin Trihydrate	125mg/1.25ml	Suspension
55846	Ampicillin 125mg/5ml Liquid (C P Pharmaceuticals Ltd)	Ampicillin	25mg/1ml	Oral suspension
7531	Penbritin 500mg powder for solution for injection vials	Ampicillin sodium	500mg	Powder for solution for injection

	(Chemidex Pharma Ltd)			
2874	Magnapen syrup (Wockhardt UK Ltd)	Flucloxacillin magnesium/Ampicillin trihydrate	25mg/1ml + 25mg/1ml	Oral suspension
12489	Ambaxin 400mg Tablet (Pharmacia Ltd)	Bacampicillin	400mg	Tablet
10755	Ampiciilin 60mg / Cloxacillin 30mg/0.6ml sugar free oral suspension	Cloxacillin/Ampicillin Sodium	60mg + 30mg/0.6ml	Suspension Sugar-free
10795	Ampiclox 250mg/5ml Oral solution (Beecham Research Laboratories)	Cloxacillin/Ampicillin	250mg/5ml	Oral Solution
115	Ampicillin 250mg capsules	Ampicillin	250mg	Capsule
17161	Miraxid Tablet (Rpr / Fisons)	Pivampicillin/Pivmecillinam Hydrochloride		Tablet
31281	Penbritin 500mg capsules (Chemidex Pharma Ltd)	Ampicillin	500mg	Capsule

21801	Vidopen 250mg Capsule (Berk Pharmaceuticals Ltd)	Ampicillin	250mg	Capsule
20869	Flucloxacillin with ampicillin 250mg+250mg Injection	Ampicillin Trihydrate/Flucloxacillin Sodium	250mg+250mg	Injection
24847	Ampicillin 500mg / Flucloxacillin 500mg injection	Ampicillin Trihydrate/Flucloxacillin Sodium	500mg+500mg	Injection
5454	Co-fluampicil 250mg/250mg capsules	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
11954	Talpen 250mg Tablet (Beecham Research Laboratories)	Talampicillin Hydrochloride	250mg	Tablet
41647	Ampicillin 500mg capsules (Actavis UK Ltd)	Ampicillin	500mg	Capsule
32148	Amfipen forte 250mg/5ml Oral solution (Yamanouchi Pharma Ltd)	Ampicillin	50mg/1ml	Oral suspension
20531	Amfipen 250mg Capsule	Ampicillin	250mg	Capsule

	(Yamanouchi Pharma Ltd)			
10538	Ampiclox neonatal 75mg/vial Injection (Beecham Research Laboratories)	Cloxacillin/Ampicillin	75mg/vial	Injection
26510	Ampicillin 250mg / Flucloxacillin 250mg injection	Ampicillin Trihydrate/Flucloxacillin Sodium	250mg+250mg	Injection
8614	Pivampicillin 175mg/5ml oral solution	Pivampicillin	175mg/5ml	Suspension
19648	Co-fluampicil 250mg/250mg capsules (A A H Pharmaceuticals Ltd)	Flucloxacillin sodium/Ampicillin trihydrate	250mg + 250mg	Capsule
31473	Vidopen 250mg/vial Injection (Berk Pharmaceuticals Ltd)	Ampicillin Sodium	250mg/vial	Injection
23186	Vidopen 125mg/5ml Oral solution (Berk	Ampicillin	25mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
26329	Co-fluampicil 250mg/250mg powder for solution for injection vials	Ampicillin sodium/Flucloxacillin sodium	250mg + 250mg	Powder for solution for injection
22452	Britcin 250mg Capsule (DDSA Pharmaceuticals Ltd)	Ampicillin	250mg	Capsule
32347	Amfipen 125mg/5ml Oral solution (Yamanouchi Pharma Ltd)	Ampicillin	25mg/1ml	Oral suspension
7519	Norfloxacin 400mg tablets	Norfloxacin	400mg	Tablet
32112	Norfloxacin 400mg tablets (Genus Pharmaceuticals Ltd)	Norfloxacin	400mg	Tablet
26586	Noroxin 0.30% Eye drops (MSD Thomas Morson Pharmaceuticals)	Norfloxacin	0.30%	Eye Drops
20187	Norfloxacin 0.3% Eye drops	Norfloxacin	0.30%	Eye Drops

2253	Utinor 400mg tablets (Merck Sharp & Dohme Ltd)	Norfloxacin	400mg	Tablet
26101	Pivmecillinam 100mg/sachet	Pivmecillinam Hydrochloride	100mg/sachet	Suspension
12014	Pivmecillinam 200mg tablets	Pivmecillinam hydrochloride	200mg	Tablet
12540	Pivampicillin 250mg with pivmecillinam 200mg tablet	Pivampicillin/Pivmecillinam Hydrochloride	250mg + 200mg	Tablets
25832	Pivampicillin 125mg with pivmecillinam100 mg tablet	Pivampicillin/Pivmecillinam Hydrochloride	125mg + 100mg	Tablets
20516	Miraxid Liquid (Rpr / Fisons)	Pivampicillin/Pivmecillinam Hydrochloride		Liquid
8960	Pondocillin plus Tablet (Edwin Burgess Ltd)	Pivampicillin/Pivmecillinam Hydrochloride		Tablet
21029	Miraxid 450 Tablet (Rpr / Fisons)	Pivampicillin/Pivmecillinam Hydrochloride		Tablet
12015	Selexid 100mg/sachet	Pivmecillinam Hydrochloride	100mg/sachet	Liquid

	Liquid (Edwin Burgess Ltd)			
9601	Selexid 200mg tablets (LEO Pharma)	Pivmecillinam hydrochloride	200mg	Tablet
17161	Miraxid Tablet (Rpr / Fisons)	Pivampicillin/Pivmecillinam Hydrochloride		Tablet
12277	Cinoxacin 500mg capsules	Cinoxacin	500mg	Capsules
54393	Ciprofloxacin 250mg tablets (Arrow Generics Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
49839	Ciproxin 500mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
32388	Ciproxin 200mg/100ml Infusion (Bayer Plc)	Ciprofloxacin Lactate	200mg/100ml	Infusion
51537	Ciprofloxacin 250mg tablets (Alliance Healthcare (Distribution) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet

47785	Ciprofloxacin 400mg/200ml infusion bags	Ciprofloxacin lactate	2mg/1ml	Infusion
34494	Ciprofloxacin 500mg tablets (Wockhardt UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
50601	Ciprofloxacin 250mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
30877	Tarivid 2mg/ml Infusion (Aventis Pharma)	Ofloxacin Hydrochloride	2mg/ml	Infusion
43517	Ciprofloxacin 750mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
61302	Ciprofloxacin 100mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
7519	Norfloxacin 400mg tablets	Norfloxacin	400mg	Tablet
7752	Ciproxin 750mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	750mg	Tablet

54663	Ciproxin Infusion 200mg/100ml solution for infusion bottles (Bayer Plc)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
58246	Ciprofloxacin 400mg/200ml infusion bags (Hospira UK Ltd)	Ciprofloxacin lactate	2mg/1ml	Infusion
10567	Cinobac 500mg Capsule (Eli Lilly and Company Ltd)	Cinoxacin	500mg	Capsule
17693	Tavanic 250mg tablets (Sanofi)	Levofloxacin hemihydrate	250mg	Tablet
53878	Ciprofloxacin 500mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
728	Ciproxin 500mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
58235	Ciprofloxacin 250mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	250mg	Tablet
56789	Ciprofloxacin 500mg tablets (APC	Ciprofloxacin hydrochloride	500mg	Tablet

	Pharmaceuticals & Chemicals (Europe) Ltd)			
59653	Ciproxin Infusion 400mg/200ml solution for infusion bottles (Bayer Plc)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
34322	Ciprofloxacin 500mg Tablet (Niche Generics Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
1837	Ciprofloxacin 750mg tablets	Ciprofloxacin hydrochloride	750mg	Tablet
34523	Ofloxacin 200mg tablets (Sandoz Ltd)	Ofloxacin	200mg	Tablet
34973	Ciprofloxacin 750mg Tablet (Niche Generics Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
66214	Ciprofloxacin 250mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
29343	Ciprofloxacin 250mg tablets (A A H	Ciprofloxacin hydrochloride	250mg	Tablet

	Pharmaceuticals Ltd)			
10319	Levofloxacin 500mg/100ml Intravenous infusion	Levofloxacin	500mg/100ml	Intravenous Infusion
45341	Ciprofloxacin 500mg Tablet (Neo Laboratories Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
47995	Avelox 400mg/250ml solution for infusion bottles (Bayer Plc)	Moxifloxacin hydrochloride	1.6mg/1ml	Solution for infusion
14389	Comprecin 200mg Tablet (Parke-davis Research Laboratories)	Enoxacin	200mg	Tablet
6206	Tavanic 500mg tablets (Sanofi)	Levofloxacin hemihydrate	500mg	Tablet
66727	Ciprofloxacin 500mg/5ml oral suspension	Ciprofloxacin	100mg/1ml	Oral suspension
56012	Levofloxacin 250mg tablets (Dr Reddy's	Levofloxacin hemihydrate	250mg	Tablet

	Laboratories (UK) Ltd)			
66317	Tarivid 200mg/100ml solution for infusion bottles (Sanofi)	Ofloxacin hydrochloride	2mg/1ml	Solution for infusion
63501	Ciprofloxacin 750mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	750mg	Tablet
34819	Ofloxacin 400mg tablets (Mylan Ltd)	Ofloxacin	400mg	Tablet
32112	Norfloxacin 400mg tablets (Genus Pharmaceuticals Ltd)	Norfloxacin	400mg	Tablet
50055	Ciprofloxacin 500mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	500mg	Tablet
53673	Levofloxacin 500mg/100ml infusion bags			
24373	Tavanic 500mg/100ml solution for	Levofloxacin hemihydrate	5mg/1ml	Solution for infusion

	infusion vials (Sanofi)			
66971	Ciprofloxacin 400mg/200ml solution for infusion vials (A A H Pharmaceuticals Ltd)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
34605	Ciprofloxacin 500mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
55708	Levofloxacin 250mg tablets (Actavis UK Ltd)	Levofloxacin hemihydrate	250mg	Tablet
45285	Ciprofloxacin 500mg tablets (Teva UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
42174	Ciprofloxacin 500mg tablets (IVAX Pharmaceuticals UK Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
52309	Ciprofloxacin 100mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	100mg	Tablet

66211	Levofloxacin 500mg/100ml solution for infusion bottles			
2726	Tarivid 400mg tablets (Sanofi)	Ofloxacin	400mg	Tablet
40252	Ofloxacin 200mg/100ml solution for infusion bottles	Ofloxacin hydrochloride	2mg/1ml	Solution for infusion
56856	Ciprofloxacin 750mg tablets (Ranbaxy (UK) Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
57960	Ciprofloxacin 500mg tablets (Tillomed Laboratories Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
5238	Levofloxacin 500mg tablets	Levofloxacin hemihydrate	500mg	Tablet
52099	Ciprofloxacin 750mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
34308	Ciprofloxacin 250mg tablets (Actavis UK Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet

52353	Ciproxin 250mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	250mg	Tablet
65885	Levofloxacin 500mg tablets (Waymade Healthcare Plc)	Levofloxacin hemihydrate	500mg	Tablet
163	Ciproxin 250mg/5ml oral suspension (Bayer Plc)	Ciprofloxacin	50mg/1ml	Oral suspension
34448	Ciprofloxacin 250mg tablets (Niche Generics Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
57703	Ciprofloxacin 200mg/100ml solution for infusion bottles	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
53519	Ciproxin 250mg tablets (Lexon (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
498	Ciprofloxacin 100mg tablets	Ciprofloxacin hydrochloride	100mg	Tablet
60436	Ciprofloxacin 250mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet

58345	Levofloxacin 250mg tablets (Mylan Ltd)	Levofloxacin hemihydrate	250mg	Tablet
61783	Ciprofloxacin 250mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
56381	Ciprofloxacin 250mg tablets (Strides Shasun (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
48200	Grepafloxacin 400mg Tablet	Grepafloxacin	400mg	Tablet
65896	Ciproxin 250mg tablets (Waymade Healthcare Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
25901	Sparfloxacin 200mg tablet	Sparfloxacin	200mg	Tablets
58940	Levofloxacin 250mg tablets (A A H Pharmaceuticals Ltd)	Levofloxacin hemihydrate	250mg	Tablet
52177	Ciproxin 500mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	500mg	Tablet

34391	Ofloxacin 400mg tablets (Sandoz Ltd)	Ofloxacin	400mg	Tablet
1202	Ciproxin 250mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
25127	Avelox 400mg tablets (Bayer Plc)	Moxifloxacin hydrochloride	400mg	Tablet
34647	Ciprofloxacin 250mg Tablet (Neo Laboratories Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
64814	Ciprofloxacin 400mg/200ml solution for infusion vials (Genus Pharmaceuticals Ltd)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
53641	Ciprofloxacin 500mg tablets (Strides Shasun (UK) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
372	Nalidixic acid 300mg/5ml oral suspension	Nalidixic acid	60mg/1ml	Oral suspension
64991	Levofloxacin 500mg tablets	Levofloxacin hemihydrate	500mg	Tablet

	(Accord Healthcare Ltd)			
55917	Ciprofloxacin 500mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
58955	Ciprofloxacin 100mg/50ml solution for infusion vials (A A H Pharmaceuticals Ltd)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
561	Ofloxacin 200mg tablets	Ofloxacin	200mg	Tablet
26840	Ciprofloxacin 100mg/50ml solution for infusion bottles	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
59572	Ciprofloxacin 500mg tablets (Sigma Pharmaceuticals Plc)	Ciprofloxacin hydrochloride	500mg	Tablet
33707	Ofloxacin 400mg tablets (Teva UK Ltd)	Ofloxacin	400mg	Tablet
33215	Ciprofloxacin 200mg/100ml in	Ciprofloxacin Lactate	200mg/100ml	Infusion

	sodium chloride 0.9% infusion			
6295	Levofloxacin 250mg tablets	Levofloxacin hemihydrate	250mg	Tablet
30707	Ciprofloxacin 500mg tablets (Mylan Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
58021	Ciprofloxacin 100mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
54302	Ciprofloxacin 250mg tablets (Medreich Plc)	Ciprofloxacin hydrochloride	250mg	Tablet
11883	Ciprofloxacin 100mg/50ml solution for infusion vials	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
21147	Uriben 300mg/5ml oral suspension (Rosemont Pharmaceuticals Ltd)	Nalidixic acid	60mg/1ml	Oral suspension
54555	Ciprofloxacin 100mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	100mg	Tablet

39913	Ciprofloxacin 100mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
38171	Ciprofloxacin 200mg/100ml infusion bags	Ciprofloxacin lactate	2mg/1ml	Infusion
33989	Ciprofloxacin 250mg tablets (Mylan Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
14376	Ciproxin 2mg/ml Infusion (Bayer Plc)	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
4091	Ciprofloxacin 250mg/5ml oral suspension	Ciprofloxacin	50mg/1ml	Oral suspension
34655	Ciprofloxacin 250mg tablets (Wockhardt UK Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
9073	Nalidixic acid with sodium citrate 660mg + 3750mg Sachets	Nalidixic Acid/Sodium Citrate	660mg + 3750mg	Sachets
43557	Ciprofloxacin 500mg tablets (PLIVA Pharma Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet

29472	Ciprofloxacin 750mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
45263	Ofloxacin 400mg tablets (A A H Pharmaceuticals Ltd)	Ofloxacin	400mg	Tablet
34694	Ciprofloxacin 250mg tablets (PLIVA Pharma Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
68409	Ciprofloxacin 750mg tablets (Phoenix Healthcare Distribution Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
52945	Ciprofloxacin 200mg/100ml solution for infusion vials			
68274	Ciproxin 500mg tablets (DE Pharmaceuticals)	Ciprofloxacin hydrochloride	500mg	Tablet
281	Ciprofloxacin 250mg tablets	Ciprofloxacin hydrochloride	250mg	Tablet
67572	Levofloxacin 250mg tablets	Levofloxacin hemihydrate	250mg	Tablet

	(Accord Healthcare Ltd)			
34478	Ciprofloxacin 250mg tablets (Teva UK Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
64446	Ciprofloxacin 250mg tablets (Tillomed Laboratories Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
17272	Teflox 300mg Tablet (Abbott Laboratories Ltd)	Temafloxacin	300mg	Tablet
49445	Ciprofloxacin 500mg tablets (Almus Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
43814	Ciprofloxacin 250mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
61869	Ciproxin 250mg/5ml oral suspension (Waymade Healthcare Plc)	Ciprofloxacin	50mg/1ml	Oral suspension
4513	Tarivid 200mg tablets (Sanofi)	Ofloxacin	200mg	Tablet

28544	Ciprofloxaxin 400mg/200ml in glucose 5% infusion	Ciprofloxacin Lactate	400mg/200ml	Infusion
29507	Ciprofloxacin 400mg/200ml in sodium chloride 0.9% infusion	Ciprofloxacin Lactate	400mg/200ml	Infusion
58608	Ciprofloxacin 100mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
60817	Levofloxacin 500mg tablets (Actavis UK Ltd)	Levofloxacin hemihydrate	500mg	Tablet
42507	Ciprofloxacin 100mg tablets (A A H Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
17890	Eradacin 150mg Capsule (Sanofi-Synthelabo Ltd)	Rosoxacin	150mg	Capsule
59937	Ciprofloxacin 750mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	750mg	Tablet
21812	Ciproxin Infusion 100mg/50ml	Ciprofloxacin lactate	2mg/1ml	Solution for infusion

	solution for infusion bottles (Bayer Plc)			
43797	Ciprofloxacin 500mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
9154	Ciproxin 100mg tablets (Bayer Plc)	Ciprofloxacin hydrochloride	100mg	Tablet
17749	Teflox 400mg Tablet (Abbott Laboratories Ltd)	Temafloxacin	400mg	Tablet
56439	Ciprofloxacin 200mg/100ml solution for infusion vials (A A H Pharmaceuticals Ltd)			
54674	Ciprofloxacin 100mg tablets (Phoenix Healthcare Distribution Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
38006	Ciproxin 400mg/200ml Infusion (Bayer Plc)	Ciprofloxacin Lactate	400mg/200ml	Infusion
583	Ciprofloxacin 500mg tablets	Ciprofloxacin hydrochloride	500mg	Tablet

32530	Ciproxin iv flexibag 400mg/200ml Infusion (Bayer Plc)	Ciprofloxacin Lactate	400mg/200ml	Infusion
53088	Ciprofloxacin 500mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
54701	Ciprofloxacin 250mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
67656	Ciprofloxacin 500mg tablets (Bristol Laboratories Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
52501	Ciprofloxacin 500mg tablets (Accord Healthcare Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
23666	Grepafloxacin 600mg Tablet	Grepafloxacin	600mg	Tablet
29280	Ofloxacin 2mg/ml Infusion	Ofloxacin Hydrochloride	2mg/ml	Infusion
41561	Ciprofloxacin 250mg tablets (IVAX	Ciprofloxacin hydrochloride	250mg	Tablet

	Pharmaceuticals UK Ltd)			
34541	Ofloxacin 200mg tablets (Teva UK Ltd)	Ofloxacin	200mg	Tablet
2253	Utinor 400mg tablets (Merck Sharp & Dohme Ltd)	Norfloxacin	400mg	Tablet
566	Ofloxacin 400mg tablets	Ofloxacin	400mg	Tablet
58074	Ciprofloxacin 400mg/200ml solution for infusion bottles	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
35777	Rosoxacin 150mg capsule	Rosoxacin	150mg	Capsules
12428	Enoxacin 200mg tablets	Enoxacin	200mg	Tablets
52807	Ciproxin 500mg tablets (Mawdsley-Brooks & Company Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
34559	Ciprofloxacin 250mg tablets (Sandoz Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet

58323	Ciprofloxacin 100mg tablets (Alliance Healthcare (Distribution) Ltd)	Ciprofloxacin hydrochloride	100mg	Tablet
66483	Ciprofloxacin 170mg/5ml oral suspension	Ciprofloxacin	34mg/1ml	Oral suspension
18661	Temafloxacin 400mg tablets	Temafloxacin	400mg	Tablets
10304	Ciprofloxacin 2mg/ml infusion	Ciprofloxacin Lactate	2mg/ml	Infusion
52616	Ciprofloxacin 500mg tablets (Arrow Generics Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
56075	Levofloxacin 500mg/100ml solution for infusion vials	Levofloxacin hemihydrate	5mg/1ml	Solution for infusion
64301	Ciprofloxacin 500mg tablets (Kent Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	500mg	Tablet
29458	Ciprofloxacin 500mg tablets (A A H	Ciprofloxacin hydrochloride	500mg	Tablet

	Pharmaceuticals Ltd)			
57118	Ciprofloxacin 250mg tablets (Kent Pharmaceuticals Ltd)	Ciprofloxacin hydrochloride	250mg	Tablet
54993	Ciprofloxacin 400mg/200ml solution for infusion vials	Ciprofloxacin lactate	2mg/1ml	Solution for infusion
43123	Moxifloxacin 400mg/250ml solution for infusion bottles	Moxifloxacin hydrochloride	1.6mg/1ml	Solution for infusion
61850	Levofloxacin 500mg tablets (A A H Pharmaceuticals Ltd)	Levofloxacin hemihydrate	500mg	Tablet
6306	Moxifloxacin 400mg tablets	Moxifloxacin hydrochloride	400mg	Tablet
21487	Fosfomycin 3g granules sachets	Fosfomycin Trometamol	3g	Sachets
27986	Monuril 2g Paediatric sachet (Pharmax Ltd)	Fosfomycin	2g	Paediatric Sachet

12379	Monuril 3g Sachets (Pharmax Ltd)	Fosfomycin	3g	Sachets
26113	Fosfomycin 2g Sachets	Fosfomycin	2g	Sachets
46915	Co-amoxiclav 250mg/125mg tablets (Zentiva)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
65056	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
54796	Amoxicillin 250mg capsules (Boston Healthcare Ltd)	Amoxicillin trihydrate	250mg	Capsule
2174	Amoxil 3g oral powder sachets sucrose free (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	3gram	Powder
34679	Amoxicillin 125mg/5ml oral suspension sugar free (Actavis UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
1140	Amoxicillin 3g oral powder	Amoxicillin trihydrate	3gram	Powder

	sachets sugar free			
40243	Amoxicillin 250mg/5ml oral suspension sugar free (Actavis UK Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
829	Co-amoxiclav 250mg/125mg dispersible tablets sugar free	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Dispersible tablet
29337	Amoxicillin 125mg/5ml Oral solution (Neo Laboratories Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
55394	Amoxicillin 500mg capsules (Wockhardt UK Ltd)	Amoxicillin trihydrate	500mg	Capsule
50742	Co-amoxiclav 500mg/125mg tablets (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
28882	Amoxicillin 250mg Capsule (Crosspharma Ltd)	Amoxicillin trihydrate	250mg	Capsule

641	Co-amoxiclav 500mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
68545	Amoxicillin 1g powder for solution for injection vials (A A H Pharmaceuticals Ltd)	Amoxicillin sodium	1gram	Powder for solution for injection
33706	Amoxicillin 500mg capsules (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
17746	Amoxicillin 375mg soluble tablets	Amoxicillin Trihydrate	375mg	Soluble Tablet
53627	Amoxicillin 500mg capsules (Accord Healthcare Ltd)	Amoxicillin trihydrate	500mg	Capsule
24396	Flemoxin 750mg Soluble tablet (Paines & Byrne Ltd)	Amoxicillin Trihydrate	750mg	Soluble Tablet
49321	Augmentin 625mg tablets (Sigma	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet

	Pharmaceuticals Plc)			
59588	Co-amoxiclav 125mg/31mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
54808	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
44154	Co-amoxiclav 500mg/125mg tablets (Zentiva)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
52820	Amoxicillin 500mg capsules (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	500mg	Capsule
42227	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
36054	Amoxicillin 125mg/5ml oral suspension sugar	Amoxicillin trihydrate	25mg/1ml	Oral suspension

	free (Almus Pharmaceuticals Ltd)			
2171	Amoxil 125mg/1.25ml paediatric oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	100mg/1ml	Oral suspension
22438	Amoram 250mg/5ml oral suspension (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
59481	Amoxicillin 250mg capsules (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	250mg	Capsule
58494	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Colorama Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
44854	Amoxicillin 500mg Capsule (Lagap)	Amoxicillin trihydrate	500mg	Capsule

42809	Amoxicillin 250mg Capsule (C P Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
59112	Amoxicillin 125mg/5ml oral suspension sugar free (DE Pharmaceuticals)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
14386	Galenamox 125mg/5ml oral suspension (Galen Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
63911	Amoxicillin 250mg capsules (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
54591	Co-amoxiclav 500mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
17509	Amoxicillin 1g powder for solution for injection vials	Amoxicillin sodium	1gram	Powder for solution for injection

24005	Co-amoxiclav 1000mg/200mg powder for solution for injection vials	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
60134	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
35191	Co-amoxiclav 500mg/100mg powder for solution for injection vials (Teva UK Ltd)	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
38684	Amoxicillin 500mg Capsule (CP Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
585	Amoxicillin 250mg/5ml oral suspension sugar free	Amoxicillin trihydrate	50mg/1ml	Oral suspension
41090	Amoxicillin 250mg/5ml oral suspension (Almus	Amoxicillin trihydrate	50mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
20432	Clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension	Amoxicillin Trihydrate/Potassium Clavulanate	57mg + 400mg/5ml	Suspension Sugar-free
64986	Co-amoxiclav 500mg/100mg powder for solution for injection vials (A A H Pharmaceuticals Ltd)	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
27725	Amoxicillin 250mg/5ml oral suspension (Teva UK Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
25370	Ranclav 375mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
51536	Amoxicillin 250mg capsules (Milpharm Ltd)	Amoxicillin trihydrate	250mg	Capsule
33699	Amoxicillin 250mg/5ml oral suspension sugar free (IVAX	Amoxicillin trihydrate	50mg/1ml	Oral suspension

	Pharmaceuticals UK Ltd)			
63063	Co-amoxiclav 250mg/62mg/5ml oral suspension (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
30783	Co-amoxiclav 250mg/125mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
34885	Amoxicillin 500mg Capsule (DDSA Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
56591	Augmentin-Duo 400/57 oral suspension (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
33840	Amoxicillin 500mg powder for solution for injection vials (Wockhardt UK Ltd)	Amoxicillin sodium	500mg	Powder for solution for injection
31801	Amoxicillin 500mg capsules (Sandoz Ltd)	Amoxicillin trihydrate	500mg	Capsule

30743	Amoxicillin 250mg capsules (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	250mg	Capsule
52666	Augmentin 250/62 SF oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
34232	Amoxicillin 250mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
11613	Amix 250 capsules (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
29356	Co-amoxiclav 500mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
13239	Clavulanic acid 125mg with Amoxicillin 500mg tablets	Amoxicillin Trihydrate/Potassium Clavulanate	125mg+500mg	Tablets

30786	Co-amoxiclav 250mg/125mg tablets (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
54271	Amoxicillin 250mg capsules (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate	250mg	Capsule
37755	Amoxicillin 250mg/5ml Oral suspension (Sandoz Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
54780	Co-amoxiclav 250mg/62mg/5ml oral suspension (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
17121	Clavulanic acid 100mg with amoxicillin 500mg/vial injection	Potassium Clavulanate/Amoxicillin Sodium	100mg + 500mg/vial	Injection
31014	Amoxicillin 125mg/5ml oral suspension sugar free (Mylan Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

5341	Augmentin-Duo 400/57 oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
33110	Amrit 250mg/5ml Liquid (BHR Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
47184	Co-amoxiclav 500mg/100mg powder for solution for injection vials (Wockhardt UK Ltd)	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
29474	Amoxicillin 1000mg with clavulanic acid 100mg/vial injection	Potassium Clavulanate/Amoxicillin Sodium	1g + 200mg/vial	Injection
51194	Augmentin-Duo 400/57 oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
51678	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Almus	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
61207	Amoxicillin 125mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
24819	Amoxil 500mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium	500mg	Powder for solution for injection
439	Amoxicillin with Clavulanic acid dispersible tablets	Amoxicillin Trihydrate/Potassium Clavulanate		Dispersible Tablet
6687	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
62	Amoxicillin 125mg/5ml oral suspension	Amoxicillin trihydrate	25mg/1ml	Oral suspension
13285	Amoxicillin 125mg / Clavulanic acid	Amoxicillin Trihydrate/Potassium Clavulanate	125mg + 31mg/5ml	Oral Suspension

	31mg/5ml oral suspension			
49683	Augmentin 625mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
47640	Amoxicillin 500mg capsules (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
13216	Amoxicillin 500mg / Clavulanic acid 125mg tablets	Amoxicillin Trihydrate/Potassium Clavulanate	500mg+125mg	Tablets
63452	Co-amoxiclav 875mg/125mg tablets (Creo Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	875mg + 125mg	Tablet
25484	Amoxicillin 250mg capsules (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
29353	Co-amoxiclav 500mg/125mg tablets (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet

65958	Amoxicillin 500mg capsules (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	500mg	Capsule
33165	Amoxicillin 250mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
29858	Amoxicillin 125mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
54222	Amoxicillin 250mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
64355	Amoxicillin 125mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
16612	Clavulanic acid 62mg with amoxicillin	Amoxicillin Trihydrate/Potassium Clavulanate	62mg + 250mg/5ml	Suspension Sugar-free

	250mg/5ml sugar free suspension			
33701	Co-amoxiclav 500mg/125mg tablets (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
34638	Amoxicillin 125mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
14396	Galenamox 500mg capsules (Galen Ltd)	Amoxicillin trihydrate	500mg	Capsule
62686	Co-amoxiclav 125mg/31mg/5ml oral suspension (Pharma-z Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
51637	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
55312	Co-amoxiclav 250mg/125mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

15290	Lansoprazole with amoxicillin and clarithromycin 30mg + 500mg + 500mg Triple pack	Amoxicillin Trihydrate/Lansoprazole/Clarithromycin	30mg + 500mg + 500mg	Triple Pack
4582	Amoxicillin 750mg soluble tablets	Amoxicillin Trihydrate	750mg	Soluble Tablet
524	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
54185	Amoxicillin 250mg capsules (Wockhardt UK Ltd)	Amoxicillin trihydrate	250mg	Capsule
42815	Amoxicillin 250mg/5ml Mixture (Celltech Pharma Europe Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
49656	Augmentin 625mg tablets (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
33109	Amrit 125mg/5ml Liquid (BHR	Amoxicillin trihydrate	25mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
15148	Amoxil 500mg Dispersible tablet (SmithKline Beecham Plc)	Amoxicillin Trihydrate	500mg	Dispersible Tablet
17282	Almodan 125mg/5ml syrup (Teva UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
55626	Amoxicillin 125mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
43548	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
509	Augmentin 625mg tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
28874	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (IVAX	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	Pharmaceuticals UK Ltd)			
53942	Amoxicillin 125mg / Clavulanic acid 62.5mg/5ml oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate		
34734	Co-amoxiclav 250mg/125mg tablets (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
45317	Amoxicillin 250mg/5ml Oral solution (Neo Laboratories Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
34775	Amoxicillin 250mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
17711	Amopen 500mg Capsule (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
59042	Amoxicillin 250mg capsules (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	250mg	Capsule

32910	Co-amoxiclav 500mg/125mg tablets (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
59592	Amoxicillin 500mg capsules (Pfizer Ltd)	Amoxicillin trihydrate	500mg	Capsule
23967	Amoxicillin 250mg capsules (Teva UK Ltd)	Amoxicillin trihydrate	250mg	Capsule
58771	Amoxicillin 250mg capsules (DE Pharmaceuticals)	Amoxicillin trihydrate	250mg	Capsule
4010	Amoxil 750mg Sachets (GlaxoSmithKline UK Ltd)	Amoxicillin Trihydrate	750mg	Sachets
12378	Amoram 125mg/5ml oral suspension (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
1746	Amoxicillin 500mg powder for solution for injection vials	Amoxicillin sodium	500mg	Powder for solution for injection
54324	Co-amoxiclav 125mg/31mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	sugar free (Actavis UK Ltd)			
34297	Co-amoxiclav 250mg/125mg tablets (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
3669	Amoxymed 250mg Capsule (Medipharma Ltd)	Amoxicillin trihydrate	250mg	Capsule
54452	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
30705	Co-amoxiclav 500mg/125mg tablets (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
13848	Amoxicillin 125mg sugar free powder	Amoxicillin Trihydrate	125mg	Powder Sugar-free
569	Augmentin 250/62 SF oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension

52122	Amoxicillin 125mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
23740	Amoxicillin 500mg capsules (Mylan Ltd)	Amoxicillin trihydrate	500mg	Capsule
34680	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
34238	Amoxicillin 1g powder for solution for injection vials (Wockhardt UK Ltd)	Amoxicillin sodium	1gram	Powder for solution for injection
58205	Amoxicillin 500mg powder for solution for injection vials (A A H Pharmaceuticals Ltd)	Amoxicillin sodium	500mg	Powder for solution for injection
577	Co-amoxiclav 500mg/100mg powder for	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection

	solution for injection vials			
50279	Augmentin 625mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
49374	Augmentin 375mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
7364	Co-amoxiclav 250mg/62mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
50446	Co-amoxiclav 250mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
24150	Amoxicillin 125mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
28592	Amoxicillin 500mg with clavulanic acid	Potassium Clavulanate/Amoxicillin Sodium	500mg + 100mg/vial	Injection

	100mg/vial injection			
51164	Augmentin 125/31 SF oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
59879	Amoxicillin 500mg capsules (DE Pharmaceuticals)	Amoxicillin trihydrate	500mg	Capsule
42545	Amoxicillin 125mg/5ml oral suspension (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
52771	Amoxicillin 500mg capsules (Bristol Laboratories Ltd)	Amoxicillin trihydrate	500mg	Capsule
55527	Amoxicillin 500mg capsules (Boston Healthcare Ltd)	Amoxicillin trihydrate	500mg	Capsule
485	Amoxicillin 125mg/1.25ml oral suspension paediatric	Amoxicillin trihydrate	100mg/1ml	Oral suspension

18786	Amix 500 capsules (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
26262	Zoxycil 500mg Capsule (Trinity Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
40168	Amoxicillin 3g oral powder sachets sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	3gram	Powder
61407	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Colorama Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
2153	Amoxil 125mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
48038	Amoxicillin 125mg/5ml oral suspension (Kent	Amoxicillin trihydrate	25mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
51623	Co-amoxiclav 250mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
4154	Amoxil fiztab 125mg Tablet (Bencard)	Amoxicillin Trihydrate	125mg	Tablet
22415	Amoram 500mg capsules (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	500mg	Capsule
22016	Almodan 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
46918	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
48683	Augmentin 375mg tablets (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
62332	Co-amoxiclav 875mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	875mg + 125mg	Tablet

58057	Amoxicillin 250mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
37304	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
51382	Amoxicillin 250mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
14407	Galenamox 250mg/5ml oral suspension (Galen Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
49610	Co-amoxiclav 500mg/125mg tablets (Medreich Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
28870	Amoxicillin 125mg/5ml oral suspension (Teva UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

32622	Amoxicillin 125mg/5ml oral suspension (Mylan Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
49065	Amoxicillin 250mg/5ml oral suspension sugar free (Bristol Laboratories Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
32872	Amoxicillin 250mg Capsule (Mepra-Pharm)	Amoxicillin trihydrate	250mg	Capsule
67466	Co-amoxiclav 500mg/125mg tablets (Brown & Burk UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
33383	Amoxicillin 3g oral powder sachets sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	3gram	Powder
49063	Augmentin 375mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
11634	Amix 125 oral suspension (Ashbourne	Amoxicillin trihydrate	25mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
33690	Amoxicillin 125mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
847	Amoxil 500mg capsules (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	500mg	Capsule
21829	Zoxycil 250mg Capsule (Trinity Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
28871	Co-amoxiclav 250mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
65215	Co-amoxiclav 250mg/125mg tablets (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
42732	Amoxicillin 250mg/5ml oral suspension sugar free (Almus	Amoxicillin trihydrate	50mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
57833	Amoxil 500mg capsules (Waymade Healthcare Plc)	Amoxicillin trihydrate	500mg	Capsule
870	Amoxicillin 250mg sugar free chewable tablets	Amoxicillin Trihydrate	250mg	Chewable Tablets Sugar-free
33696	Amoxicillin 125mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
55018	Amoxicillin 250mg/5ml oral suspension (Bristol Laboratories Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
48147	Co-amoxiclav 250mg/125mg tablets (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
2507	Augmentin 375mg dispersible tablets	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Dispersible tablet

	(GlaxoSmithKline UK Ltd)			
40148	Co-amoxiclav 500mg/125mg tablets (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
56578	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
598	Amoxicillin 250mg powder for solution for injection vials	Amoxicillin sodium	250mg	Powder for solution for injection
399	Augmentin 375mg tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
503	Amoxicillin 125mg/5ml oral suspension sugar free	Amoxicillin trihydrate	25mg/1ml	Oral suspension
1391	Amoxicillin 250mg / Clavulanic acid 125mg tablets	Amoxicillin Trihydrate/Potassium Clavulanate	250mg + 125mg	Tablets

34855	Amoxicillin 250mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
43229	Amoxicillin 125mg/5ml Oral suspension (Sandoz Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
31286	Amoxymed 125mg/5ml Oral solution (Medipharma Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
58097	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
53609	Co-amoxiclav 500mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
60034	Co-amoxiclav 250mg/125mg	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

	tablets (DE Pharmaceuticals)			
9925	Clavulanic acid 125mg with Amoxicillin 250mg tablets	Amoxicillin Trihydrate/Potassium Clavulanate	125mg + 250mg	Tablets
7737	Amoxil fiztab 500mg Tablet (Bencard)	Amoxicillin Trihydrate	500mg	Tablet
30745	Amoxicillin 250mg capsules (Mylan Ltd)	Amoxicillin trihydrate	250mg	Capsule
34384	Amoxicillin 125mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
62786	Amoxicillin 250mg powder for solution for injection vials (Wockhardt UK Ltd)	Amoxicillin sodium	250mg	Powder for solution for injection
68408	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (Brown & Burk UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension

65031	Amoxicillin 250mg/5ml oral suspension (Crescent Pharma Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
24203	Respillin 250mg Capsule (OPD Pharm)	Amoxicillin trihydrate	250mg	Capsule
52857	Amoxicillin 125mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
32640	Amoxicillin 250mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
33343	Amoxicillin 250mg capsules (Actavis UK Ltd)	Amoxicillin trihydrate	250mg	Capsule
34857	Amoxicillin 125mg/5ml oral suspension (Actavis UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
34001	Amoxicillin 500mg capsules (Teva UK Ltd)	Amoxicillin trihydrate	500mg	Capsule

42822	Amoxicillin 125mg/5ml Mixture (Celltech Pharma Europe Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
34972	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
19209	Co-amoxiclav 250mg/125mg tablets (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
1722	Amoxicillin 500mg dispersible tablets	Amoxicillin Trihydrate	500mg	Dispersible Tablet
31535	Amoxicillin 250mg/5ml oral suspension sugar free (Mylan Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
40320	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension

59153	Amoxicillin 250mg capsules (Waymade Healthcare Plc)	Amoxicillin trihydrate	250mg	Capsule
2281	Amoxicillin 500mg sugar free chewable tablets	Amoxicillin Trihydrate	500mg	Chewable Tablets Sugar-free
56884	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
33570	Amoxicillin 250mg/5ml Mixture (Crosspharma Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
67694	Co-amoxiclav 250mg/125mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
62597	Augmentin-Duo 400/57 oral suspension (Mawdsley-	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension

	Brooks & Company Ltd)			
7636	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	250mg + 62mg/5ml	Suspension
427	Amoxicillin 250mg/5ml oral suspension	Amoxicillin trihydrate	50mg/1ml	Oral suspension
42485	Clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	62mg + 250mg/5ml	Oral Suspension
61906	Amoxicillin 500mg capsules (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate	500mg	Capsule
35570	Amoxicillin 500mg Capsule (Crosspharma Ltd)	Amoxicillin trihydrate	500mg	Capsule
29697	Amopen 125mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

21963	Almodan 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
17099	Amoxil 1g powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium	1gram	Powder for solution for injection
30528	Amoxicillin 250mg capsules (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
1812	Amoxil 250mg/5ml syrup sucrose free (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
59432	Amoxicillin 250mg capsules (Accord Healthcare Ltd)	Amoxicillin trihydrate	250mg	Capsule
57178	Amoxicillin 3g oral powder sachets sugar free (Mawdsley-	Amoxicillin trihydrate	3gram	Powder

	Brooks & Company Ltd)			
53078	Amoxicillin 125mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
68416	Amoxicillin 500mg capsules (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	500mg	Capsule
50002	Amoxicillin 125mg/5ml oral suspension (Bristol Laboratories Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
34760	Amoxicillin 250mg/5ml oral suspension (Actavis UK Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
1638	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
62377	Co-amoxiclav 500mg/125mg	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet

	tablets (Creo Pharma Ltd)			
61299	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
51436	Amoxil 500mg capsules (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate	500mg	Capsule
33692	Amoxicillin 500mg capsules (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
52207	Augmentin 625mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
28875	Amoxicillin 125mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

52058	Amoxicillin 500mg capsules (Medreich Plc)	Amoxicillin trihydrate	500mg	Capsule
10771	Amoxil 250mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium	250mg	Powder for solution for injection
62102	Amoxicillin 250mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
5662	Amoxicillin 500mg / Clarithromycin 500mg / Lansoprazole 30mg triple pack	Amoxicillin Trihydrate/Lansoprazole/Clarithromycin	500mg + 500mg + 30mg	Triple Pack
58803	Co-amoxiclav 250mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
9343	Amoxicillin 750mg sugar free powder	Amoxicillin Trihydrate	750mg	Powder Sugar-free

33693	Co-amoxiclav 250mg/125mg tablets (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
49048	Augmentin 375mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
41835	Amoxicillin 125mg Powder (IVAX Pharmaceuticals UK Ltd)	Amoxicillin Trihydrate	125mg	Powder
65095	Amoxicillin 250mg/5ml oral suspension sugar free (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
11433	Clarithromycin 500mg with lansoprazole 30mg and amoxicillin 500mg triple pack	Amoxicillin Trihydrate/Lansoprazole/Clarithromycin	500mg + 30mg + 500mg	Triple Pack
415	Augmentin 125/31 SF oral suspension	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	(GlaxoSmithKline UK Ltd)			
66650	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
34042	Amoxicillin 250mg capsules (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	250mg	Capsule
54708	Co-amoxiclav 250mg/62mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
49590	Amoxil 500mg capsules (Lexon (UK) Ltd)	Amoxicillin trihydrate	500mg	Capsule
27714	Amrit 250mg Capsule (BHR Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
33112	Amrit 500mg Capsule (BHR	Amoxicillin trihydrate	500mg	Capsule

	Pharmaceuticals Ltd)			
8906	Amoxicillin 125mg / Clavulanic acid 31mg/5ml oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	125mg + 31mg/5ml	Suspension
34493	Co-amoxiclav 500mg/125mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
22015	Respillin 125mg/5ml Oral solution (OPD Pharm)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
34435	Amoxicillin 250mg Capsule (DDSA Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
18930	Flemoxin 375mg Soluble tablet (Paines & Byrne Ltd)	Amoxicillin Trihydrate	375mg	Soluble Tablet
48	Amoxicillin 500mg capsules	Amoxicillin trihydrate	500mg	Capsule
10200	Co-amoxiclav 125mg/31mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

545	Co-amoxiclav 250mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
59740	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
66905	Co-amoxiclav 1000mg/200mg powder for solution for injection vials (Wockhardt UK Ltd)	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
21775	Clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	31mg + 125mg/5ml	Suspension Sugar-free
59908	Co-amoxiclav 500mg/125mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
55047	Amoxicillin 125mg/5ml oral	Amoxicillin trihydrate	25mg/1ml	Oral suspension

	suspension (Sandoz Ltd)			
65533	Co-amoxiclav 250mg/62mg/5ml oral suspension (CST Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
24093	Clavulanic acid with amoxicillin dispersible tablets	Amoxicillin Trihydrate/Potassium Clavulanate		Dispersible Tablet
21845	Almodan 250mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
54491	Amoxicillin 250mg capsules (Bristol Laboratories Ltd)	Amoxicillin trihydrate	250mg	Capsule
1637	Amoxil fiztab 250mg Tablet (Bencard)	Amoxicillin Trihydrate	250mg	Tablet
62762	Amoxicillin 250mg/5ml oral suspension (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
21799	Almodan 250mg Capsule (Berk	Amoxicillin trihydrate	250mg	Capsule

	Pharmaceuticals Ltd)			
24200	Respillin 500mg Capsule (OPD Pharm)	Amoxicillin trihydrate	500mg	Capsule
54725	Amoxicillin 500mg capsules (Milpharm Ltd)	Amoxicillin trihydrate	500mg	Capsule
62074	Amoxicillin 250mg/5ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
63582	Amoxicillin 125mg/5ml oral suspension (Crescent Pharma Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
53924	Amoxicillin 250mg/5ml oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
50595	Augmentin 125/31 SF oral suspension (Mawdsley-	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	Brooks & Company Ltd)			
15192	Amoxicillin 400mg / Clavulanic acid 57mg/5ml sugar free oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	400mg + 57mg/5ml	Suspension Sugar-free
21844	Amix 250 oral suspension (Ashbourne Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
68476	Amoxil 500mg capsules (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	500mg	Capsule
31661	Amoxicillin 250mg Capsule (Co-Pharma Ltd)	Amoxicillin trihydrate	250mg	Capsule
34234	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
28872	Amoxicillin 125mg/5ml Mixture	Amoxicillin trihydrate	25mg/1ml	Oral suspension

	(Crosspharma Ltd)			
34714	Amoxicillin 250mg Capsule (Neo Laboratories Ltd)	Amoxicillin trihydrate	250mg	Capsule
64794	Amoxicillin 250mg capsules (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate	250mg	Capsule
42240	Amoxicillin 125mg/5ml Oral solution (Co-Pharma Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
31423	Amopen 250mg/5ml Liquid (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
60281	Co-amoxiclav 125mg/31mg/5ml oral suspension (CST Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
41818	Amoxicillin 125mg/5ml Oral solution (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

67771	Co-amoxiclav 1000mg/200mg powder for solution for injection vials (PLIVA Pharma Ltd)	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
64357	Amoxicillin 500mg capsules (Waymade Healthcare Plc)	Amoxicillin trihydrate	500mg	Capsule
3742	Amoxicillin 125mg sugar free chewable tablets	Amoxicillin Trihydrate	125mg	Chewable Tablets Sugar-free
26157	Amoxicillin 500mg capsules (Actavis UK Ltd)	Amoxicillin trihydrate	500mg	Capsule
66062	Amoxicillin 125mg/5ml oral suspension sugar free (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
41734	Amoxicillin 3g Powder (Actavis UK Ltd)	Amoxicillin trihydrate	3gram	Powder
60027	Amoxicillin 250mg/5ml oral suspension sugar	Amoxicillin trihydrate	50mg/1ml	Oral suspension

	free (DE Pharmaceuticals)			
34852	Amoxicillin 500mg capsules (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	500mg	Capsule
133	Amoxil 250mg capsules (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate	250mg	Capsule
24006	Clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	31mg + 125mg/5ml	Oral Suspension
55499	Amoxicillin 250mg/5ml oral suspension (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
45267	Amoxicillin 250mg Capsule (Regent Laboratories Ltd)	Amoxicillin trihydrate	250mg	Capsule
33222	Amoxicillin 250mg Capsule (Lagap)	Amoxicillin trihydrate	250mg	Capsule

19414	Co-amoxiclav 250mg/125mg tablets (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
27681	Ranclav 125mg/31mg/5ml SF oral suspension (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
21827	Almodan 500mg Capsule (Berk Pharmaceuticals Ltd)	Amoxicillin trihydrate	500mg	Capsule
56561	Amoxicillin 125mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
57081	Co-amoxiclav 500mg/125mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
22017	Respillin 125mg/5ml Oral solution (OPD Pharm)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

17852	Augmentin Intravenous 600mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
54732	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
56223	Amoxicillin 250mg/5ml oral suspension (Sandoz Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
53996	Co-amoxiclav 500mg/125mg tablets (Aurobindo Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
60267	Amoxicillin 250mg/5ml oral suspension (DE Pharmaceuticals)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
59391	Amoxicillin 125mg/5ml oral suspension (DE Pharmaceuticals)	Amoxicillin trihydrate	25mg/1ml	Oral suspension

58053	Amoxicillin 250mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
54052	Co-amoxiclav 125mg/31mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
56700	Amoxil 500mg capsules (Necessity Supplies Ltd)	Amoxicillin trihydrate	500mg	Capsule
52685	Amoxicillin 125mg/5ml oral suspension (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
57966	Amoxicillin 250mg capsules (Medreich Plc)	Amoxicillin trihydrate	250mg	Capsule
66747	Co-amoxiclav 250mg/125mg tablets (Brown & Burk UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

244	Augmentin Intravenous 1.2g powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
57886	Amoxil 500mg capsules (Stephar (U.K.) Ltd)	Amoxicillin trihydrate	500mg	Capsule
34912	Amoxicillin 500mg Capsule (Neo Laboratories Ltd)	Amoxicillin trihydrate	500mg	Capsule
28130	Amoxicillin 3g oral powder sachets sugar free (Teva UK Ltd)	Amoxicillin trihydrate	3gram	Powder
14371	Galenamox 250mg capsules (Galen Ltd)	Amoxicillin trihydrate	250mg	Capsule
30498	Amopen 250mg Capsule (Yorkshire Pharmaceuticals Ltd)	Amoxicillin trihydrate	250mg	Capsule
22029	Amiclav 250mg/125mg tablets (Ashbourne	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

	Pharmaceuticals Ltd)			
33689	Amoxicillin 250mg/5ml oral suspension (Mylan Ltd)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
40238	Amoxicillin 250mg/5ml Mixture (Mepra-Pharm)	Amoxicillin trihydrate	50mg/1ml	Oral suspension
9243	Amoram 250mg capsules (LPC Medical (UK) Ltd)	Amoxicillin trihydrate	250mg	Capsule
48006	Amoxicillin 250mg capsules (Sandoz Ltd)	Amoxicillin trihydrate	250mg	Capsule
50341	Co-amoxiclav 500mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
23238	Amoxicillin 125mg/5ml oral suspension (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	25mg/1ml	Oral suspension
62442	Amoxicillin 250mg/5ml oral suspension sugar	Amoxicillin trihydrate	50mg/1ml	Oral suspension

	free (Waymade Healthcare Plc)			
9	Amoxicillin 250mg capsules	Amoxicillin trihydrate	250mg	Capsule
29463	Amoxicillin 500mg capsules (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate	500mg	Capsule
13262	Amoxicillin 250mg / Clavulanic acid 62mg/5ml oral suspension	Amoxicillin Trihydrate/Potassium Clavulanate	250mg + 62mg/5ml	Oral Suspension
46915	Co-amoxiclav 250mg/125mg tablets (Zentiva)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
65056	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
829	Co-amoxiclav 250mg/125mg dispersible tablets sugar free	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Dispersible tablet
50742	Co-amoxiclav 500mg/125mg	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet

	tablets (Actavis UK Ltd)			
641	Co-amoxiclav 500mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
59588	Co-amoxiclav 125mg/31mg/5ml oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
54808	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
44154	Co-amoxiclav 500mg/125mg tablets (Zentiva)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
42227	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
58494	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Colorama	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension

	Pharmaceuticals Ltd)			
54591	Co-amoxiclav 500mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
24005	Co-amoxiclav 1000mg/200mg powder for solution for injection vials	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
60134	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
35191	Co-amoxiclav 500mg/100mg powder for solution for injection vials (Teva UK Ltd)	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
64986	Co-amoxiclav 500mg/100mg powder for solution for injection vials (A A H	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection

	Pharmaceuticals Ltd)			
63063	Co-amoxiclav 250mg/62mg/5ml oral suspension (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
30783	Co-amoxiclav 250mg/125mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
29356	Co-amoxiclav 500mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
30786	Co-amoxiclav 250mg/125mg tablets (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
54780	Co-amoxiclav 250mg/62mg/5ml oral suspension (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
47184	Co-amoxiclav 500mg/100mg powder for solution for injection vials	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection

	(Wockhardt UK Ltd)			
51678	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
6687	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
63452	Co-amoxiclav 875mg/125mg tablets (Creo Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	875mg + 125mg	Tablet
29353	Co-amoxiclav 500mg/125mg tablets (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
33701	Co-amoxiclav 500mg/125mg tablets (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
62686	Co-amoxiclav 125mg/31mg/5ml oral suspension (Pharma-z Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

51637	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
55312	Co-amoxiclav 250mg/125mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
524	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
43548	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
28874	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
34734	Co-amoxiclav 250mg/125mg	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

	tablets (Teva UK Ltd)			
32910	Co-amoxiclav 500mg/125mg tablets (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
54324	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
34297	Co-amoxiclav 250mg/125mg tablets (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
54452	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
30705	Co-amoxiclav 500mg/125mg tablets (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
34680	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	(Ranbaxy (UK) Ltd)			
577	Co-amoxiclav 500mg/100mg powder for solution for injection vials	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
7364	Co-amoxiclav 250mg/62mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
50446	Co-amoxiclav 250mg/125mg tablets (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
61407	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Colorama Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
51623	Co-amoxiclav 250mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

46918	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
62332	Co-amoxiclav 875mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	875mg + 125mg	Tablet
37304	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
49610	Co-amoxiclav 500mg/125mg tablets (Medreich Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
67466	Co-amoxiclav 500mg/125mg tablets (Brown & Burk UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
28871	Co-amoxiclav 250mg/125mg tablets (IVAX Pharmaceuticals UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

65215	Co-amoxiclav 250mg/125mg tablets (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
48147	Co-amoxiclav 250mg/125mg tablets (Almus Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
40148	Co-amoxiclav 500mg/125mg tablets (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
56578	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
58097	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
53609	Co-amoxiclav 500mg/125mg tablets (APC Pharmaceuticals	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet

	& Chemicals (Europe) Ltd)			
60034	Co-amoxiclav 250mg/125mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
68408	Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (Brown & Burk UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
34972	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
19209	Co-amoxiclav 250mg/125mg tablets (Actavis UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
40320	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
56884	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	(Phoenix Healthcare Distribution Ltd)			
67694	Co-amoxiclav 250mg/125mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
1638	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
62377	Co-amoxiclav 500mg/125mg tablets (Creo Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
61299	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
58803	Co-amoxiclav 250mg/125mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

33693	Co-amoxiclav 250mg/125mg tablets (Kent Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
66650	Co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
54708	Co-amoxiclav 250mg/62mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
34493	Co-amoxiclav 500mg/125mg tablets (Ranbaxy (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
10200	Co-amoxiclav 125mg/31mg/5ml oral suspension	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
545	Co-amoxiclav 250mg/125mg tablets	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet

59740	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Phoenix Healthcare Distribution Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
66905	Co-amoxiclav 1000mg/200mg powder for solution for injection vials (Wockhardt UK Ltd)	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
59908	Co-amoxiclav 500mg/125mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
65533	Co-amoxiclav 250mg/62mg/5ml oral suspension (CST Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
34234	Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (Teva UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension
60281	Co-amoxiclav 125mg/31mg/5m	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

	l oral suspension (CST Pharma Ltd)			
67771	Co-amoxiclav 1000mg/200mg powder for solution for injection vials (PLIVA Pharma Ltd)	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection
19414	Co-amoxiclav 250mg/125mg tablets (Sandoz Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
57081	Co-amoxiclav 500mg/125mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
54732	Co-amoxiclav 125mg/31mg/5ml oral suspension (Mylan Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
53996	Co-amoxiclav 500mg/125mg tablets (Aurobindo Pharma Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet

54052	Co-amoxiclav 125mg/31mg/5ml oral suspension (A A H Pharmaceuticals Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
66747	Co-amoxiclav 250mg/125mg tablets (Brown & Burk UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
50341	Co-amoxiclav 500mg/125mg tablets (Alliance Healthcare (Distribution) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
49321	Augmentin 625mg tablets (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
56591	Augmentin-Duo 400/57 oral suspension (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
52666	Augmentin 250/62 SF oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension

5341	Augmentin-Duo 400/57 oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
51194	Augmentin-Duo 400/57 oral suspension (Sigma Pharmaceuticals Plc)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
49683	Augmentin 625mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
49656	Augmentin 625mg tablets (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
509	Augmentin 625mg tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
569	Augmentin 250/62 SF oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	50mg/1ml + 12.5mg/1ml	Oral suspension

50279	Augmentin 625mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
49374	Augmentin 375mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
51164	Augmentin 125/31 SF oral suspension (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
48683	Augmentin 375mg tablets (Lexon (UK) Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
49063	Augmentin 375mg tablets (DE Pharmaceuticals)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
2507	Augmentin 375mg dispersible tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Dispersible tablet

399	Augmentin 375mg tablets (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
62597	Augmentin-Duo 400/57 oral suspension (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	80mg/1ml + 11.4mg/1ml	Oral suspension
52207	Augmentin 625mg tablets (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	500mg + 125mg	Tablet
49048	Augmentin 375mg tablets (Waymade Healthcare Plc)	Amoxicillin trihydrate/Potassium clavulanate	250mg + 125mg	Tablet
415	Augmentin 125/31 SF oral suspension (GlaxoSmithKline UK Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension
50595	Augmentin 125/31 SF oral suspension (Mawdsley-Brooks & Company Ltd)	Amoxicillin trihydrate/Potassium clavulanate	25mg/1ml + 6.25mg/1ml	Oral suspension

17852	Augmentin Intravenous 600mg powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium/Potassium clavulanate	500mg + 100mg	Powder for solution for injection
26658	AUGMENTIN DISPERSIBLE 250/125			
244	Augmentin Intravenous 1.2g powder for solution for injection vials (GlaxoSmithKline UK Ltd)	Amoxicillin sodium/Potassium clavulanate	1000mg + 200mg	Powder for solution for injection

Appendix 19: Anticholinergic burden scale drug list

ACB Score	Drugs
ACB 1	Alimemazine, Alprazolam, Alverine, Aripiprazole, Aesapine, Atenolol, Bupropion, Captopril, Cetrizine, Chlorathildon, Cimetidine, Clidinium, Clorazepate, Codeine, Colchicine, Desloratadine, Diazepam, Digoxin, Dipyridamole, Disopyramide, Fentanyl, Fluvoxamine, Furosemide, Haloperidol, Hydralazine, Hydrocortisone, Iioperidone, Isosorbide, Levocetirizine, Loperamide, Loratadine, Metoprolol, Morphine, Nifedipne, Paliperidone, Prednisone, Quinidine, Ranitdine, Risperidone, Theophylline, Trazodone, Triamterene, Venalfaxine, Warafin
ACB 2	Amantadine, Belladonna, Carbamazepine, Cyclobenaprine, Cyproheptadine, Meperidine, Methotrimeprazine, Molindone, Nefopam, Pimozide, Loxapine, Oxcarbazepine
ACB 3	Amitriptyline, Amoxapine, Atropine, Benztropine, Brompheniramine, Carbinoxamine, Chlorpheniramine, Chlorpromazine, Clemastine, Clomipramine, Clozapine, Darifenacin, Desparime, Dicyclomine, Dicycloverine, Dimenhydrinate, Diphenhydramine, Doxepin, Doxylamine, Fesoterodine, Flovaxate, Hydroxyzine, Hyoscyamine, Imipramine, Meclizine, Methocarbamol, Notriptyline, Olanzapine, Orphenadrine, Oxybutynin, Paroxetine, Perphenazine, Promethazine, Propantheline, Propiverine, Quetiapine, Scoplamine Hyoscine, Solifenacin, Thioridazine, Tolterodine, Triflluoperazine, Trihexyphidyl, Tripramine, Trospium

Appendix 20: OPCS-4 codes for urodynamic tests and imaging

Urodynamic studies

Medcode	Readcode	Read term
2916	317..12	Urodynamic studies
18036	317C.00	Urinary flow rate
3411	7065100	Electromyography
10876	3176	Residual urinary volume
2622	7B2C600	Cystometry
6716	317B.00	Other urodynamic tests
18998	8HR6.00	Refer to Urodynamic studies
64138	7P14300	Urodynamics NEC
25001	R141800	[D]Electromyogram (EMG) abnormal
14451	3117000	EMG - Electromyography normal
55018	7P14100	Uroflowmetry NEC
103500	3177	Uroflowmetry
3632	3173.11	Urodynamic studies normal
12169	3175	Detrusor reflex testing
18018	3173000	Cystometry normal
40731	3174000	Cystometry abnormal
41472	3174.11	Urodynamic studies abnormal
17629	7B2B600	Urethral catheterisation for urodynamics
90890	7B2B700	Urodynamic studies using catheter
103851	3178	Voided urinary volume
103674	3179	Average urinary flow rate

72105	7B2C611	Cystometrogram
103913	317F.00	Urinary flow time
20399	7B45400	Urethral pressure measurement
103615	317E.00	Urinary voiding total flow time
104865	317D.00	Time to maximum urinary flow
105951	317D.11	TQmax - Time to maximum urinary flow rate
43903	561F.00	Fluoroscopy - urinary tract
102094	561G.00	Fluoroscopy - female genital
2916	317..12	Urodynamic studies

Other imaging

Medcode	Read code	Read term
18951	8HQA.00	Referral for DXA scan of hip and spine
59688	7P02400	Magnetic resonance imaging of spine
14377	585E.00	US scan of bladder
69075	7P09.00	Diagnostic imaging of genitourinary system
89458	7P09z00	Diagnostic imaging of genitourinary system NOS
89450	58D8.00	US scan of spine
94660	7P09y00	Other specified diagnostic imaging of genitourinary system
98923	7P0N.00	Other diagnostic imaging of genitourinary system
95679	7P0Ny00	Other specified other diagn imaging of genitourinary system
96882	58DR.00	Ultrasound scan of sacral spine
100620	7P0Nz00	Other diagnostic imaging of genitourinary system NOS
12850	7P06.00	Diagnostic imaging of pelvis

83486	7P06z00	Diagnostic imaging of pelvis NOS
97118	7P05600	Ultrasound scan of inguinal region
12871	7P06100	Ultrasound of pelvis
49116	7P05.00	Diagnostic imaging of abdomen
47119	7P05100	Ultrasound of abdomen
93552	7P09700	Nuclear cystography
89915	7P06y00	Other specified diagnostic imaging of pelvis
56048	7P09400	Ultrasound of bladder
93625	7P05y00	Other specified diagnostic imaging of abdomen
97243	7P06200	Magnetic resonance imaging of pelvis
70547	R135z00	[D]Genitourinary x-ray or scan abnormality NOS
55989	R135.00	[D]Genitourinary x-ray or scan abnormality
696	5856	U-S pelvic scan
103473	585m.00	Ultrasound scan of abdomen and pelvis
14218	567A.00	CAT scan - pelvis
4754	54E..00	Cystography
72665	7B2CC00	Micturating cystography
3726	54E2.00	Cystography normal
27020	54E7.00	Micturating cystography
20285	54E3.00	Cystography abnormal
36254	54EZ.00	Cystography NOS
55118	57...16	Cystographic isotope studies
68785	54E5.00	Percutaneous cystography
60315	54E8.00	Intravenous cystography
44411	54E1.00	Cystography requested

47180	54E4.00	Retrograde cystography
56625	5736	Isotope static cystography
89103	7B2CD00	High intensity focused ultrasound of bladder

Appendix 21: Read codes for specialist visits

Visits to the urologist

Medcode	Read code	Read term
13644	8HVA.00	Private referral to urologist
10895	ZL9GR00	Seen by urologist
2568	8H5B.00	Referred to urologist
104258	ZL9GR00	Seen by urologist
22237	ZL1GS00	Under care of urologist
10313	ZL5GP00	Referral to urologist
26383	ZLD4M00	Discharge by urologist
12038	8H2F.00	Admit urology emergency
98108	9NJp.00	In-house urology discharge
19726	ZLEQL00	Discharge from urology service
16762	8HJF.00	Urology self-referral
51881	9b81.00	Urology
103547	8Hko.00	Referral to community urology service
99551	9NJn.00	In-house urology first appointment
97262	9NJn.00	In-house urology follow-up appointment
6283	9N1I.00	Seen in urology clinic
59482	U623.00	[X]Gastroenterol+urology device assoc with adverse incident
13642	8HTb.00	Referral to male urology clinic
31926	8H3K.00	Non-urgent urology admission
30868	8H4W.00	Referral to urology special interest general practitioner

58609	ZG44.00	Advice on infective conditions in urology
28449	8HMR.00	Listed for Urology admission

Visits to the gynaecologist

Medcode	Readcode	Read term
16776	15...00	Gynaecological history
48342	1J0J.00	Suspected gynaecological cancer
48014	8H4V.00	Referral to gynaecology special interest GP
10663	ZL5D200	Referral to gynaecologist
60028	9NI4.00	Gynaecology outreach clinic
32517	ZLE8200	Discharge from gynaecology service
9966	ZL5D.00	Referral to obstetrician and gynaecologist
99498	9Np4.00	Seen in fast track suspected gynaecological cancer clinic
30253	159Z.00	H/O:gynaecological problem NOS
25242	ZLD2X00	Discharge by obstetrician and gynaecologist
91081	9NJP.00	In-house gynaecology follow-up appointment
10175	159..00	H/O:gynaecological problem NOS
19215	8H3B.00	Non-urgent gynaecol.admission
6606	7E2Az11	Gynaecological examination under anaesthetic
32693	ZLE8.00	Discharge from obstetrics and gynaecology service
71562	8HKO.00	Gynaecological D.V. requested
107526	9NJv.00	In-house gynaecology
18646	ZLD2Y00	Discharge by gynaecologist
11377	7H29211	Gynaecological laparoscopy NEC

88893	9NJN.00	In-house gynaecology first appointment
61394	9b9S.00	Obstetrics and gynaecology
20820	7130700	Subcutaneous mastectomy for gynaecomastia
8353	K311011	Bilateral gynaecomastia
35900	7D...11	Gynaecological operations of lower female genital tract
6508	9N1J.00	Seen in gynaecology clinic
107988	8T0B.00	Referral to paediatric gynaecology service
16673	26B2.00	O/E - gynaecomastia
21340	8HJ6.00	Gynaecological self-referral
10643	ZL9B100	Seen by gynaecologist
95358	9Ni7.00	DNA gynaecology special interest general practitioner clinic
9631	ZL9B.00	Seen by obstetrician and gynaecologist
16796	ZV72300	[V]Gynaecological examination
13647	8HV7.00	Private referral to gynaecologist
102348	26L..00	Gynaecologic examination
64263	8HLO.00	Gynaecological D.V. done
3150	K311000	Gynaecomastia
21718	8L7..00	Gynaecological operation planned
53711	9b9T.00	Gynaecology
26012	ZL1C.00	Under care of obstetrician and gynaecologist
2116	8H58.00	Gynaecological referral
85845	8Hn1.00	Fast track referral for suspected gynaecological cancer
107888	9Nic000	DNA fast track suspected gynaecological cancer clinic
103854	8Hku.00	Referral to community gynaecology service
43123	15Z..00	Gynaecological history NOS

103892	9b9T000	Gynaecological oncology
2128	K311012	Unilateral gynaecomastia
55061	4JRK.00	Gynaecology cytology screening test
94231	9Nk2.00	Seen in urogynaecology clinic
71064	9NJQ.00	In-house gynaecology discharged from care
10172	ZL1C100	Under care of gynaecologist
94652	K311200	Idiopathic gynaecomastia
45816	7E...11	Gynaecological operations on upper female genital tract
37793	4M4..00	FIGO staging of gynaecological malignancy
6109	8H26.00	Admit gynaecological emergency

Appendix 22: Product code list for incontinence pads

Prodcode	Product name	BNF code	BNF header
61097	Spring truss back pad sliding	71490300	Spring Truss Back Pad: Fixed Or Sliding
29738	Long flanged plastic bag with foam pad, compatible with MK4 urinal system 0821 32/38mm (S.G.& P.Payne Ltd)	74130600	Plastic Bag With Foam Pads
31659	Long flanged plastic bag with foam pad, compatible with MK4 urinal system 0822 45mm (S.G.& P.Payne Ltd)	74130600	Plastic Bag With Foam Pads
6273	Tena incontinence pad 60cm x 60cm (Molnlycke Health Care Ltd)	74160000	Incontinence Pads
6308	Tena incontinence pad 40cm x 60cm (Molnlycke Health Care Ltd)	74160000	Incontinence Pads
21021	Attends Cover Dri Plus incontinence pad 60cm x 60cm (Procter & Gamble (Health & Beauty Care) Ltd)	74160000	Incontinence Pads
15806	Attends Cover Dri Super incontinence pad 60cm x 60cm (Procter & Gamble (Health & Beauty Care) Ltd)	74160000	Incontinence Pads
9864	Robinson Plus incontinence pad 40cm x 60cm (Robinson Healthcare)	74160000	Incontinence Pads
19150	Attends Cover Dri Super incontinence pad 60cm x 90cm (Procter & Gamble (Health & Beauty Care) Ltd)	74160000	Incontinence Pads
21174	Ecopad incontinence pad 58cm x 60cm (Warden Dressings Company)	74160000	Incontinence Pads
49019	Dansac Seals 070-30 30mm (Dansac Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)
48298	Dansac Seals 070-20 20mm (Dansac Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)

49053	Dansac Seals 070-40 40mm (Dansac Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)
50943	Adapt oval convex barrier ring 79602 30mm-48mm (Hollister Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)
50838	Adapt oval convex barrier ring 79601 22mm-38mm (Hollister Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)
49221	Dansac Seals 070-50 50mm (Dansac Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)
50356	Adapt oval convex barrier ring 79603 38mm-56mm (Hollister Ltd)	75190000	Skin Protector (wafers,blankets,foam Pads,washers)
28802	Ostomy foam pad WJ275-32-W 76mm diameter, 32mm opening White (Jade-Euro-Med)	75190100	Foam Pad
31861	Ostomy foam pad WJ275-38-K 76mm diameter, 38mm opening White (Jade-Euro-Med)	75190100	Foam Pad
31363	SoftPads skin protector SP101 (SASH)	75190100	Foam Pad
37654	Ostomy foam pad WJ275-25-A 76mm diameter, 25mm opening White (Jade-Euro-Med)	75190100	Foam Pad

Appendix 23: Procedures and operations performed (HES data)

	OPCS-4	Description
SNS (Insertion of neurostimulator electroduces into peripheral nerve)	*In addition to one of the below OPCS-4 codes the following site code would be assigned: Z11.2 Sacral nerve*	
	A70.1	Implantation of neurostimulator into peripheral nerve
	A70.2	Maintenance of neurostimulator in peripheral nerve
	A70.3	Removal of neurostimulator from peripheral nerve
	A70.4	Insertion of neurostimulator electrodes into peripheral nerve
	A70.8	Other specified neurostimulation of peripheral nerve
	A70.9	Unspecified neurostimulation of peripheral nerve
Catheterisation	M30.2	Endoscopic catheterisation of ureter
	M38.2	Cystostomy and insertion of suprapubic tube into bladder
	M47.2	Change of urethral catheter into bladder
	M47.3	Removal of urethral catheter from bladder
	M47.5	Maintenance of urethral catheter in bladder
	M47.8	Other specified urethral catheterisation of bladder
	M47.9	Unspecified urethral catheterisation of bladder
	M49.2	Change of suprapubic tube into bladder
	M49.3	Removal of suprapubic tube from bladder
Other surgical procedures	M51.8	Other specified combined abdominal and vaginal operations to support outlet of female bladder

	M51.9	Unspecified combined abdominal and vaginal operations to support outlet of female bladder
	M52.8	Other specified abdominal operations to support outlet of female bladder
	M52.9	Unspecified abdominal operations to support outlet of female bladder
	M54.8	Other specified open operations on outlet of female bladder
	M54.9	Unspecified open operations on outlet of female bladder
	M57.8	Other specified other vaginal operations to support outlet of female bladder
	M57.9	Unspecified other vaginal operations to support outlet of female bladder
Sphincter AUS	M54.3	Removal of artificial urinary sphincter from outlet of female bladder
	M55.2	Implantation of artificial urinary sphincter into outlet of female bladder
	M60.3	Removal of artificial urinary sphincter from outlet of male bladder
	M64.2	Implantation of artificial urinary sphincter into outlet of male bladder
Sphincterotomy	M66.1	Endoscopic sphincterotomy of external sphincter of male bladder
Urinary diversion	M19.1	Construction of ileal conduit
	M19.2	Creation of urinary diversion to intestine NEC
	M19.4	Cutaneous ureterostomy NEC
	M19.8	Other specified urinary diversion
	M19.9	Unspecified urinary diversion
Surgical procedure for	M361	Caecocystoplasty
	M362	Ileocystoplasty

bladder enlargement	M363	Colocystoplasty
Urodynamics	M474	Urodynamic studies using catheter
	U264	Urodynamics NEC
Botox injection	X85.1 (in conjuction with M43.4)	Torsion dystonias and other involuntary movements drugs Band 1
	M49.5 (in conjuction with M43.4)	Injection of therapeutic substance into bladder wall
	M43.4 (in conjuction with M49.5 or X85.1)	Endoscopic injection of neurolytic substance into nerve of bladder
Bladder Augmentation	M36.1	Caecocystoplasty
	M36.2	Ileocystoplasty
	M36.3	Colocystoplasty
	M36.8	Other specified enlargement of bladder
	M36.9	Unspecified enlargement of bladder
Sling Procedures / Mid-urethral sling	M52.1	Suprapubic sling operation
	M53.3	Introduction of tension-free vaginal tape
	M53.5	Partial removal of tension-free vaginal tape
	M53.6	Introduction of transobturator tape
	M55.6	Insertion of retropubic device for female stress urinary incontinence NEC
Artificial Urinary Sphincter	M55.2	Implantation of artificial urinary sphincter into outlet of female bladder
	M64.2	Implantation of artificial urinary sphincter into outlet of male bladder
MRI Ultrasound Followed by: Y53.7	Q20.6	Focused ultrasound to lesion of uterus
	U08.2	Ultrasound of abdomen

	U09.2	Ultrasound of pelvis
X-ray	U08.3	Plain x-ray of abdomen
CT Scan	U08.1	Computed tomography of abdomen NEC
	U09.1	Computed tomography of pelvis
Bulking agents	M568	Other specified therapeutic endoscopic operations on outlet of female bladder

Appendix 24: ICD-10 codes for hospitalisations

Chapter	Description
A418	Other specified sepsis
A419	Sepsis, unspecified
N110	Nonobstructive reflux-associated chronic pyelonephritis
N111	Chronic obstructive pyelonephritis
N130	Hydronephrosis with ureteropelvic junction obstruction
N131	Hydronephrosis with ureteral stricture, not elsewhere classified
N132	Hydronephrosis with renal and ureteral calculous obstruction
N133	Other and unspecified hydronephrosis
N134	Hydroureter
N136	Pyonephrosis
N137	Vesicoureteral-reflux-associated uropathy
N138	Other obstructive and reflux uropathy
N139	Obstructive and reflux uropathy, unspecified
N170	Acute renal failure with tubular necrosis
N171	Acute renal failure with acute cortical necrosis
N172	Acute renal failure with medullary necrosis
N178	Other acute renal failure
N179	Acute renal failure, unspecified
N181	Chronic kidney disease, stage 1
N182	Chronic kidney disease, stage 2
N183	Chronic kidney disease, stage 3
N184	Chronic kidney disease, stage 4

N185	Chronic kidney disease, stage 5
N189	Chronic kidney disease, unspecified
N19X	Unspecified kidney failure
N200	Calculus of kidney
N201	Calculus of ureter
N202	Calculus of kidney with calculus of ureter
N209	Urinary calculus, unspecified
N210	Calculus in bladder
N211	Calculus in urethra
N218	Other lower urinary tract calculus
N219	Calculus of lower urinary tract, unspecified
N23X	Unspecified renal colic
N300	Acute cystitis
N301	Interstitial cystitis (chronic)
N302	Other chronic cystitis
N308	Other cystitis
N309	Cystitis, unspecified
N310	Uninhibited neuropathic bladder, not elsewhere classified
N311	Reflex neuropathic bladder, not elsewhere classified
N312	Flaccid neuropathic bladder, not elsewhere classified
N318	Other neuromuscular dysfunction of bladder
N319	Neuromuscular dysfunction of bladder, unspecified
N320	Bladder-neck obstruction
N323	Diverticulum of bladder
N324	Rupture of bladder, nontraumatic

N328	Other specified disorders of bladder
N329	Bladder disorder, unspecified
N341	Nonspecific urethritis
N342	Other urethritis
N343	Urethral syndrome, unspecified
N390	Urinary tract infection, site not specified
N391	Persistent proteinuria, unspecified
N392	Orthostatic proteinuria, unspecified
N393	Stress incontinence
N394	Other specified urinary incontinence
N398	Other specified disorders of urinary system
N399	Disorder of urinary system, unspecified
R32X	Unspecified urinary incontinence
R33X	Retention of urine
R34X	Anuria and oliguria
R35X	Polyuria