Assessment of Health-Related Quality of Life and Patient Preferences for Treatments of Overactive Bladder

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Abstract

Overactive bladder (OAB) is a highly prevalent symptomatic condition characterised by urinary symptoms: urgency and urinary frequency, and is often accompanied by incontinence and nocturia. Although it has no impact on mortality, OAB is a debilitating condition and has a significant impact on health-related quality of life (HRQoL). The patient perspective is becoming increasingly important in the assessment of the value of new treatments by Health Technology Assessment (HTA) bodies as it informs the burden of disease, the clinical relevance of the treatment benefit and can be a predictor of the persistence with treatment which is often an important factor in health economic evaluations. Therefore, it is important to ensure that a robust assessment of the patient perspective is included during the HTA process for OAB therapies. The aim of this thesis was to provide an understanding and a critical assessment of HRQoL for treatments of OAB in relation to HTA.

The thesis presented and critically assessed eight peer reviewed publications by the researcher that examined several aspects of patient perspective by applying different methodologies. The studies that were included in this thesis provide a coherent body of evidence that has been used by HTA bodies to assess the value of OAB treatments and has had an influence on reimbursement guidelines for mirabegron, a first in class treatment for overactive bladder.

Patient burden was assessed using concept elicitation interviews allowing a comprehensive evaluation of the quality of life dimensions affected by OAB. The patient preferences influencing patients and physician treatment choices were investigated through two discrete choice experiments conducted in three European countries. The clinical relevance of the treatment benefit on OAB symptoms was examined in three large clinical trials by conducting single and double responder analyses involving a response based on both objectively assessed symptoms and PRO instruments. Finally, the estimation of utility values and a robust economic evaluation that were integral part of the single technology appraisal of mirabegron in the United Kingdom were discussed.

The thesis concluded that performing a robust and comprehensive assessment of the patient perspective is a critical component of the value demonstration in OAB and has been a critical element informing HTA decisions in OAB. Limitations were

discussed and the thesis provides recommendations for future research to further examine the generalisability of this work in other settings

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Table of Contents

List of Figures

List of Tables

Chapter 1: Introduction

1.1 Patient perspective in Overactive Bladder

Overactive bladder (OAB) a common symptomatic disease characterised by urinary urgency, usually accompanied by frequent urinations and incontinence (Abrams et al., 2003). Although not life threatening, OAB symptoms can have a significant impact on patient life as illustrated in details in Chapter 2 of this thesis. It is therefore critical to ensure that the patient perspective is adequately captured and assessed during the Health Technology Assessment (HTA) of new mediations or technologies that treat OAB symptoms.

This chapter will introduce the notion of Health Related Quality of Life (HRQoL), the requirements to use validated Patient Reported Outcome (PRO) instruments, and present the objectives of the thesis.

The researcher has worked on the development of several PRO instruments, including one in Overactive Bladder (*The Bladder Assessment Tool*) (Kelleher C et al. 2018, Chapple et al. 2021) and one for Underactive Bladder (the International Consultation on Incontinence Questionnaire-underactive bladder [*ICIQ-UAB*] (Uren et al. 2019). The latter was developed in collaboration with the FDA.

1.2 Definitions

The Quality of Life (QoL) is a complex, abstract, multidimensional concept that implies an evaluation of the effect of all aspects of life. The Health Related Quality of Life reflects an attempt to restrict the complex concept of QoL to those aspects of life specifically related to the individual health. It is a multidomain concept that represents patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life (FDA, 2009).

1.3 Guidelines for Development of Patient Reported Outcomes – qualitative research

In order to ensure that PROs are developed according to a consistent processes and measure important aspect of patient's QoL in a reliable and reproductible manner, several guidelines and good practice documents on the development of patient reported outcomes or HRQoL measures have been developed in the past 15 years. For example, the European Medicine Agency (EMA) has published a reflection paper describing the key elements to consider while using HRQL measures for the evaluation of medicinal products (EMA 2005). In this document, EMA highlighted the need to use adequately validated instruments, and to apply rigorous statistical methods for the planning and execution of data analyses. It is especially recommended to formulate a priori hypotheses based on prior knowledge such as early phase clinical trials (phase 2) or literature review, to justify the sample size adequately and to assess the clinical relevance of the results, in addition to the statistical significance.

In 2006, the United States Food and Drug Administration (FDA) issued a draft PRO guidance that was replaced by a final guidance in 2009 (FDA, 2009). The PRO guidance is a methodological document that describes the different steps that need to be taken to validate a PRO instrument for use in label claim for medicinal products.

The starting point for the development of a PRO instrument should aim at identifying the patient population to be investigated, the intended application of the instrument and to perform a literature review. Gathering expert input is also recommended from the initial step. Once the literature review has been completed, a hypothesised conceptual framework, identifying the symptoms and HRQoL dimensions of interest and their relations should be drafted.

The second steps consists in adjusting the conceptual framework and drafting the PRO instrument. At this stage, it is critical to ensure robust patient input, by means of open ended concept elicitation interviews (either individual interviews or focus groups) with until concept saturation. Concept saturation is reached at the point when no new relevant information on how patients experience their symptoms or impacts on HRQoL emerge while interviewing additional patients (Kerr et al., 2010). Once the

items of the PRO instrument have been drafted based on input from patient, a series of cognitive debriefing interviews should be conducted to ensure an adequate understanding of the concepts by the patients. Special attention should be given to the choice of response options to avoid potential floor or ceiling effect (when too many patients respond at the response continuum top or bottom) and the choice of recall period. It is important that the chosen recall period is as short as possible to avoid recall bias. It is generally accepted that the recall period should ask patient their experience of symptoms or HRQoL impact ‘at present time’ and should not be longer than the past 24h (FDA, 2018).

1.4 Translation and linguistic validation of Patient Reported Outcomes

Once a PRO is developed in one language, it often requires translation in multiple other languages for use in multi-country clinical trials or in clinical practice. The translation of PROs requires a robust process called ‘linguistic validation’ in order to ensure that the concepts that are intended to be measured are adequately translated in the target languages. The Quality of Life Special Interest group (QoL-SIG)—Translation and Cultural Adaptation group from ISPOR has issued 2 good practice documents (Wild 2005 and Wild 2009) describing the process for PRO linguistic validation. These guidelines have been reassessed in 2018 by the PRO consortium who issued an updated and more precise version of the recommendation for linguistic validation (Eremenco et al., 2018). Based on these latest recommendation, the linguistic validation process consists now of 12 steps :

- The first step is the ‘preparation’, consisting at obtaining the permission to translate from the developer of the questionnaire and the definition of each item constituting the PRO.
- Steps 2 to 4 include of a minimum of two forward translations, a reconciliation of the forward translations, followed by back translation.
- The step 5 consists of a revision of reconciled forward translations, taking into consideration feedback from multiple target countries, and implementation of changes

- Steps 6 and 7 (international harmonization and proofreading) consist of a review of translations in all target languages for consistency, conceptual equivalence and correcting any mistake or grammatical error.
- Steps 8 and 9 consist of obtaining patient input through cognitive debriefing interview with a minimum of 5 patients in each target language
- Steps 10 to 12 consist of final review, reporting and archiving

One significant addition from the recommendations from the PRO consortium is the possibility to develop universal translation for a given language (for instance, 1 identical version for Spanish for Spain and Mexico). This has been introduced to reduce logistical complexity of managing country-specific versions and minimize variability among translations of the same language.

1.5 Guidelines for Development of Patient Reported Outcomes – psychometric evaluation of the measurement properties

Once the qualitative phase and linguistic validation have been conducted as described in section 1.3 and 1.4, the psychometric assessment of the measurement properties can be conducted as illustrated in FDA Wheels and Spoke diagram in Figure 1.6.

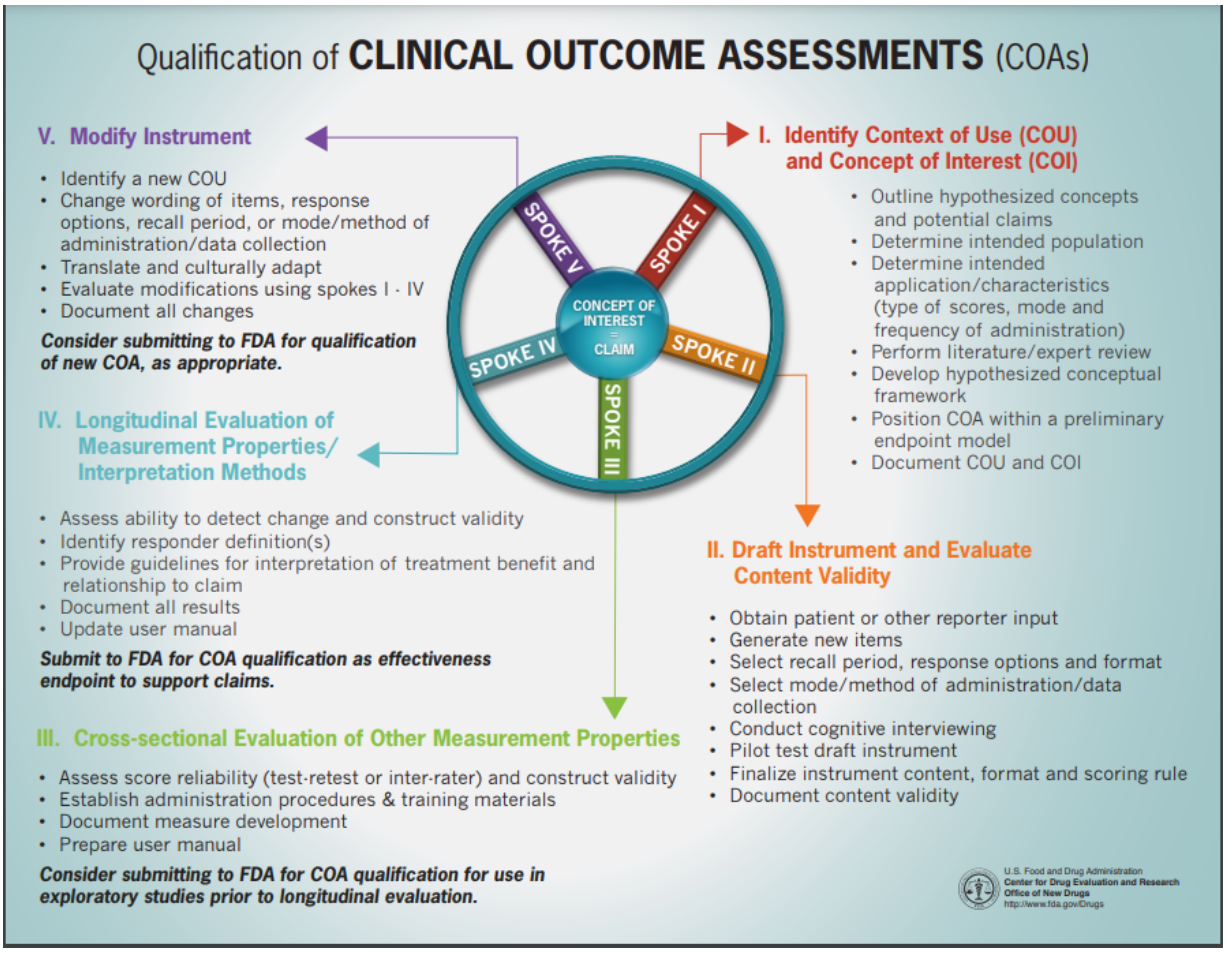


Figure 1.6: Overview of Wheel and Spokes Diagram: Clinical Outcomes Assessment (FDA)

Source: FDA 2015

The psychometric validation of PROs consists of the third and fourth steps (following steps one and two described in section 1.3) by assessing the reliability, validity and responsiveness to change. These are assessed in a cross sectional and longitudinal manner (FDA, 2015).

Classical test theory methods (assuming that every measurement is composed of an individual's true score of the latent variable [i.e., pure measure of the latent variable] as well as measurement error [i.e., random and/or systematic error]) are often used for the psychometric validation of PROs. The reliability is evaluated measuring the ability of PROs to produce consistent, reproducible estimates of the true treatment

effect. In order to assess the reproducibility of the PRO data (test-retest reliability), the PRO is administered at a first time point, and a second time usually 1 or 2 weeks apart to minimize memory effects. Intra-Class Correlation coefficients (ICC) are then calculated, and it is commonly accepted that an ICC of 0.7 or more is indicative of acceptable reproducibility (Terwee et al. 2007). It is important to ensure that the respondents are in a stable health condition between the first and the second assessment to ensure that the PRO is measuring a similar health state severity between the first and second assessment.

The internal consistency reliability tests (Cronbach alpha) aim to determine agreement among responses to different questions for multi-items PROs. A Cronbach's alpha coefficient of 0.7 or more is generally considered to represent an acceptable internal consistency (Terwee et al. 2007).

The PRO validity (besides the content validity based on qualitative research described in section 1.3) should is usually assessed by conducting several types of analyses:

- Inter-item correlations to understand the relationship between items (including strength and direction of the correlations). Of note, if 2 items are perfectly (or near perfectly) correlated, it is likely that both items measure the same concept.
- Correlation between the PRO and other validated PROs measures (discriminant and convergent validity). These correlations should be hypothesised a priori.
- Known group validity to explore if the PRO can differentiate clinically distinct groups (for instance groups with severe, mild to moderate, and no symptoms).
- Distribution of response options for each item: This analysis allows to understand the existence of floor or ceiling effect and therefore identify a potential impact on ability of the PRO instrument to detect changes .

An assessment of missing data should also be made as part of the assessment of the measurement properties. Level of missing data is often informative of the content validity as a high rate of missing data for particular items can indicate a difficulty for

patients to understand the item(s), or indicate that the content of the item(s) may be irrelevant for the patient population.

The ability to detect changes (within person change over time) is an important aspect of the assessment of measurement properties of PRO instruments. PRO scores are expected to change (positively or negatively) when the patient's health state has changed with respect to the concept of interest. Using a responder definition as a definition of within patient change can also be considered but this can lead to potential loss of statistical power or misclassification errors. Responder analyses are generally not recommended by FDA unless the responder definition is related to complete resolution of signs and symptoms (FDA 2019).

Anchor-based methods (using for instance a patient global impression of change [PGIC] or a patient global impression of severity [PGIS]), in addition to empirical cumulative distribution functions and probability density function curves are recommended to estimate what constitutes a clinically meaningful within patient change. Distribution-based methods (effect sizes, standard error of measurement) can be used to complement anchor-based methods.

The researcher has directly worked on the psychometric validation of several PRO instruments (including interactions with FDA and EMA and HTA bodies) as exemplified by the peer-reviewed work from Notte et al, 2012, Matthias et al. 2014 and Chapple et. al 2021 in which the researcher was a key contributor.

It is important to note that there are substantial differences between requirement for PRO validation between regulators such as FDA, and HTA bodies. For instance, in contrast with FDA that may not recommend responder definitions to define what constitutes a clinical meaningful change, HTA bodies find these usually very informative and they often rely on responder analyses based on Minimally Clinical Important Differences (MCID) to estimate the extent of the product added value based on HRQoL. This is exemplified in the recent HTA assessment of Macitentan (Opsumit®, Actelion Pharmaceuticals, pulmonary hypertension) in Germany for which no added benefit considering HRQoL was assessed due to the lack of responder analysis based on an established MCID (Böhme et al 2017).

The fifth and last step consist in modifying the PRO instrument when necessary to accommodate a new patient population, new modality of administration, change the items wording, response option as well as translation and linguistic validation.

Extensive guidelines on PRO development and interpretation have also been issued by the Internal Society for Pharmacoeconomics and Outcomes Research (ISPOR). These good practice documents are consistent with the guidelines from EMA and FDA (EMA 2016, FDA 2009, FDA 2015, FDA 2018, FDA 2019, Patrick et al., 2011a; Patrick et al. 2011b).

1.6 Aims of the thesis:

The overall aim of the thesis is to provide an understanding and a critical assessment of HRQoL for treatments of OAB in relation to Health Technology Assessment based on published research.

To achieve the aim of the thesis, eight articles relevant to Overactive Bladder and selected from more than 40 manuscript published by the researcher in peer-reviewed journals will be included. These manuscripts provide understanding of the patient relevant quality of life concepts for OAB as well as the key validation aspects to develop adequate PRO measures. In addition, novel methods for treatment benefit using subjective and objective measures will be discussed.

1.7 Contribution of the researcher in the articles supporting the thesis

The researcher has 18 years of research experience in health economics and outcomes research, published his first peer-reviewed manuscript in 2007 and has a h-index of 19 (Google Scholar - as of 20th December 2021). Since then, he has co-authored more than 40 peer-reviewed manuscripts in peer-reviewed journals with a total of 1483 citations from other articles, as well as more than 50 poster or oral presentations at international congresses. In the context of the work presented in this thesis, the researcher has participated at several type C meetings with the FDA, scientific advise meetings with the EMA, and scientific advise meeting with HTA bodies (NICE, EUNetHTA etc..) to discuss use of quality of life data in product information and HTA submissions. The researcher is a reviewer for several journals,

including *Advances in Therapy* (Impact Factor 2020: 3.871), *BMC Urology* (Impact Factor 2020: 2.264) or *Neurourology and Urodynamics* (Impact Factor 2022: 2.696) amongst others. In addition, the researcher gives lectures at the European Market Access University Diploma (EMAUD) from the University Aix-Marseille (France).

In accordance to the International Committee of Medical Journal Editors good publication practices (Battisti et al. 2015), the researcher has contributed to all stages of the published work, from concept, to statistical analysis, interpretation of the results, and drafting of the manuscript. Information on the contribution of the researcher for each article has been added to each relevant section in which the article has been discussed. All the studies were initiated and conducted by the researcher in order to generate data to support access and reimbursement for overactive bladder medications in jurisdictions where the products were licensed.

As the researcher is working in the pharmaceutical industry, where publication and/or authorship is not a work requirement, no particular criteria were used to determine the order of the author list except that the recommendation was to give the preference to external authors as first authors.

1.8 Structure of the thesis

The first two chapters provide an introduction to the thesis and background information on the epidemiology, available treatment options, as well as the humanistic and economic burden of OAB.

Chapters three to five will provide a critical appraisal of each of the eight studies included in the thesis, and the last chapter will provide a summary of the thesis, critical analysis and recommendations for future research.

The articles have been chosen in conjunction with the academic supervisor of the research as they consist of research covering a comprehensive spectrum of data generation studies centered on health-related quality of life and required to support HTA assessment; from conceptual framework and identification of key elements of the patient relevant endpoints, patient preferences, interpretation of the patient reported outcomes with definition and use of clinical relevant improvements, estimation of utility values using preference-based instruments, and eventually use of

quality of life data in health economic modeling that has been successfully used in reimbursement submissions to several HTA bodies, including the UK national institute for health and care excellence.

Chapter 1: has provided background information on the need to assess the patient perspective in OAB, information on PRO validation and describes the aims and structure of the thesis.

Chapter 2: provides an overview of the key data from the literature on the burden of OAB including clinical features, prevalence, humanistic and economic impact of the condition.

Chapter 3: discusses the patient perspective and patient preferences in relation to OAB and its treatments.

Chapter 4: critically examines the interpretation on clinical relevant improvement based on PROs and other objective measures of treatment effect

Chapter 5: critically demonstrates the role of PRO assessment in economic evaluation in patients with OAB

Chapter 6: provides a critical analysis of the research, discusses the implications for patients, physicians and health technology assessment and provides recommendations for future research

The next chapter will provide an overview of the burden of OAB, including epidemiology and its humanistic and economic burden.

Chapter 2: Burden of illness and management of overactive bladder

Chapter 2 aims to provide information on the disease and its burden, including disease definition, diagnosis, risk factors, treatments, humanistic and economic burden of overactive bladder (OAB).

2.1 Disease definition

Overactive bladder (OAB) is a syndrome defined in 2003 by the International Continence Society (ICS) as disorder involving urinary urgency, with or without urge incontinence, usually with frequency and nocturia in the absence of proven infection or other obvious pathology (Abrams et al., 2003).

The ICS (2003) has defined each of the symptoms components of OAB as follows:

- Urinary urgency: Sudden compelling desire to pass urine which is difficult to defer - Urge incontinence: Involuntary leakage accompanied by, or immediately preceded by, urgency
- Increased daytime frequency: Voiding too often by day
- Nocturia: Waking at night one or more times to void

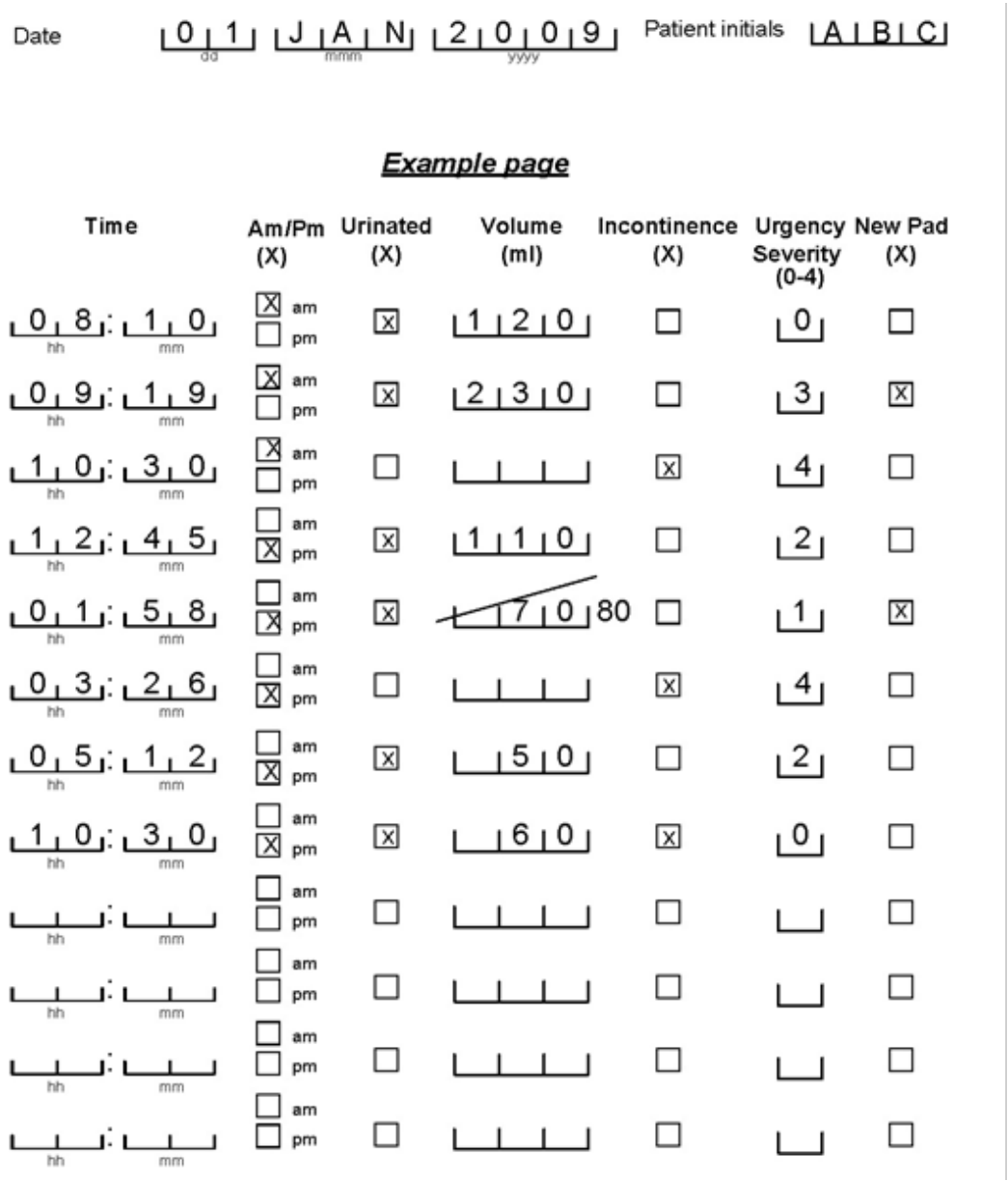
2.2 Diagnosis

Since the symptom-based definition of OAB is available, the diagnosis is no longer based on pressure flow studies (urodynamics), but based on objectively assessed symptoms using, using frequency-volume charts and voiding diaries (NICE, 2019). These are completed every day directly by the patients for a duration of 3 to 7 days. An example of a frequency-volume chart is presented in Figure 2.1. These usually capture the number of time the patient is going to the toilets, the volume of fluid intake, as well as the urine volume per urination.

Voiding diaries are completed after each urination or urine leakage and usually capture - besides the time and number of urinations and urine leakages – the urine volume, the number and severity of urinary urgency episodes, and sometimes the number of pad used per day. An example of voiding diary is presented in Figure 2.2.

	Day 1		Day 2		Day 3		Day 4	
	Drinks	Urine	Drinks	Urine	Drinks	Urine	Drinks	Urine
6 h								
7 h								
8 h	150mL		150mL					
9 h		100mL		300mL				
10 h	100mL							
11 h		40mL						
Midday	300mL	50mL	300mL	150mL				
13 h								
14 h		100mL						
15 h	150mL							
16 h								
17 h	250mL	100mL	250mL					
18 h				100mL				
19 h	300mL	150mL						
20 h		100mL						
21 h			200mL					
22 h	50mL							
23 h	150mL							
Midnight								
1 h				50mL				
2 h		150mL						
3 h				100mL				
4 h								
5 h								

Figure 2.1: Example of a frequency-volume chart


Date 01 (dd) JAN (mmm) 2009 (yyyy) Patient initials ABC

Example page

Time	Am/Pm (X)	Urinated (X)	Volume (ml)	Incontinence (X)	Urgency Severity (0-4)	New Pad (X)
08 (hh) : 10 (mm)	[X] am [ ] pm	[X]	120	[ ]	0	[ ]
09 (hh) : 19 (mm)	[X] am [ ] pm	[X]	230	[ ]	3	[X]
10 (hh) : 30 (mm)	[X] am [ ] pm	[ ]		[X]	4	[ ]
12 (hh) : 45 (mm)	[ ] am [X] pm	[X]	110	[ ]	2	[ ]
01 (hh) : 58 (mm)	[ ] am [X] pm	[X]	~~70~~ 80	[ ]	1	[X]
03 (hh) : 26 (mm)	[ ] am [X] pm	[ ]		[X]	4	[ ]
05 (hh) : 12 (mm)	[ ] am [X] pm	[X]	50	[ ]	2	[ ]
10 (hh) : 30 (mm)	[ ] am [X] pm	[X]	60	[X]	0	[ ]
(hh) : (mm)	[ ] am [ ] pm	[ ]		[ ]		[ ]
(hh) : (mm)	[ ] am [ ] pm	[ ]		[ ]		[ ]
(hh) : (mm)	[ ] am [ ] pm	[ ]		[ ]		[ ]
(hh) : (mm)	[ ] am [ ] pm	[ ]		[ ]		[ ]

Figure 2.2: Example page of a voiding diary

2.3 Risk factors

The risk factors of OAB were assessed in several studies, and although the findings are not always consistent, some factors independently associated with OAB have been identified. These include age, lower level of education, heart disease, stroke, constipation, urinary tract infection in the previous year, married status, and alcohol consumption (Wang et al., 2011; Irwin et al., 2011). There was also a strong

association between body mass index and OAB in some studies, although this was not a consistent finding (Chiu et al., 2012).

2.4 Epidemiology

Several large population or community based survey have been conducted in Europe, North America and Asia. In Europe and North America, the overall prevalence of OAB was estimated between 11.8% (Irwin et al., 2006) and 28.7% (Coyne et al., 2011), and between 2.1% (Wen et al., 2014) and 12.4% (Homma et al., 2005) in Asia. These variations can be explained by the methodological differences between studies and the criteria used to define OAB.

In the western world, the main epidemiological studies investigating lower urinary tract symptoms and OAB are:

- The survey reported by Milsom and colleagues (Milsom et al., 2001) conducted in 6 European countries: France, Germany, Italy, Spain, Sweden and UK
- The EPIC survey (Irwin et al., 2006) conducted in in Canada, Germany, Italy, Sweden, and the United Kingdom
- The EpiLUTS survey (Coyne et al., 2011) conducted in US, UK and Sweden

The first large epidemiological survey on LUTS, conducted by Milsom and colleagues, included 16,776 individuals aged 40 and older from the general population. The authors estimated the overall prevalence of overactive bladder to be 16.6% (Milsom et al., 2001).

The EPIC population based survey included 19,165 adults aged 18 and older, and found that 11.8% of respondents (with similar prevalence in both gender) had OAB symptoms. The prevalence of urgency incontinence or mixed incontinence (combination of urgency incontinence and stress incontinence) was 2.9% (Irwin et al., 2006). The EpiLUTS population-based survey included 30,000 adults over 40 years old.

Urgency, the cardinal symptom of OAB was reported at least ‘sometimes’ by 28.7% of individuals, with a higher prevalence in women (22.4%) of than in men (35.7%) (Coyne et al., 2011).

In Asia, the largest epidemiological studies have been conducted in Japan (Homma et al., 2005) and China (Wang et al., 2011 and Wen et al., 2014). In Japan, Homma and colleagues recruited 4570 respondents aged 40 and older (mean age 61 years) from the general population. The authors estimated the prevalence of OAB to be 12.4%, with a slightly higher prevalence in men than women with 14% and 11% respectively (Homma et al., 2005).

Wang and colleagues recruited 14,844 adults (7614 men and 7230 women) aged 18 and older from the general population in China. The prevalence of OAB was estimated to be 6.0%, including 4.2% individuals with dry OAB (without urgency incontinence) and 1.8% with wet OAB (with urgency incontinence) (Wang et al., 2011). Wen and colleagues performed a community-based survey including 10,160 residents aged 40 and older from the city of Zhengzhou in the middle of China. Data from 9805 residents were analysed, and the authors estimated the prevalence of OAB at 2.1%, with 1.0% having dry OAB and 1.1% wet OAB. For older patients (60 years and older), the prevalence of OAB was higher, with 4.6% of men and 2.6% of women having OAB symptoms (Wen et al., 2014).

The prevalence of OAB is expected to increase due to increasing ageing population worldwide. Based on the data from the EPIC study, Irwin and colleagues estimated that 546 million individuals will be affected by OAB in 2018, a 20.1% increase from the 455 million of individuals that were affected in 2008 (Irwin et al., 2011).

2.5 Treatments for overactive bladder

The initial management of OAB consists of lifestyle interventions (reduction of caffeine intake, fluid restriction, weight loss and smoking cessation if applicable) followed by behavioural and physical therapies (bladder training, pelvic floor muscle training). In case of insufficient symptom relief with conservative management, an oral pharmacological treatment can be initiated. This include either a muscarinic recertor antagonist (oxybutynin, solifenacin, tolterodine, fesoterodine, propiverine, or darifenacin), the beta 3 receptor agonist mirabegron or the combination of a muscarinic receptor antagonist and mirabegron. Percutaneous posterior tibial nerve stimulation can thereafter be considered after failure or insufficient symptom relief.

The last line of therapy consists of onabotulinum toxin A or sacral nerve stimulation (Burkhard et al., 2018).

2.6 Humanistic burden

Overactive bladder is known to be associated with significant impairment of several aspects on patient's QoL. OAB symptoms are known to be associated with increased level of anxiety and depression: in the EpiLUTS study, a significantly higher proportion of individuals with OAB reported anxiety and/depression based a Hospital Anxiety and Depression Scale (HADS) scores ≥8 (Coyne et al., 2011; Milsom et al., 2012).

Consistent findings were reported in the EPIC survey, where depression (defined as a Center for Epidemiologic Studies Depression Scale (CES-D) score >21) was present in in 11% of OAB cases compared with 4% of controls ($p < 0.001$) (Coyne et al., 2008).

The impact of OAB on quality of life has also been assess using generic quality of life measures: In the EpiLUTS survey, it has been demonstrated based on the mental and physical component scores of the Short Form 12 (SF-12), the HRQL was significantly lower in patients with no or minimal OAB symptoms compared with patients with bothersome OAB symptoms (Milsom et al., 2012; Coyne 2011). Similarly, based on the generic EuroQoL 5 Dimensions (EQ-5D) included in three large phase 3 studies comparing mirabegron and placebo, it was demonstrated that the EQ-5D Utility scores were lower (indicating worse HRQL) for patients with lower symptom intensity than in patients with severe OAB symptoms (Desroziers et al., 2013). OAB was found to be associated with erectile dysfunction (ED) in men and lower sexual QoL in men and women (Irwin et al., 2008; Coyne et al., 2011).

Another important consequence of OAB on patient's HRQL is the impact on satisfaction with sex life and erectile dysfunction (ED): a sub-analysis on 1004 males from the EPIC study demonstrated that men with OAB were 1.5 times more likely to suffer from ED than controls and less likely to be satisfied with their sex life ($p < 0.05$) (Coyne et al., 2008).

Chapter 3 will describe in more detail the evidence based on comprehensive qualitative research that investigated the quality of life dimensions affected by OAB.

2.7 Economic burden

The economic burden of OAB is substantial and has been evaluated in several cost of illness studies conducted in Europe and US (Irwin et al., 2009; Klotz et al., 2007; Reeves et al., 2006; Ganz et al., 2010; Hu et al., 2003 and Onukwugha et al., 2009). In six western countries (Canada, Germany, Italy, Spain, Sweden and the UK), the societal cost of has been estimated at 9.7 billion Euros, with direct costs estimated at 3.9 billion euros per year (Irwin et al., 2009). In five European countries, the largest cost driver have been found to be incontinence pads (63%) and physician consultations (20%), while drug acquisition (10%) and management of comorbidities (7%) represented the smallest costs (Reeves et al., 2006). In the US, the total cost of OAB has been estimated between 12 and 66 billion USD (Hu et al., 2003; Ganz et al., 2010), with direct medical costs accounting for 75% of the total economic burden (Ganz et al, 2010). The large difference in the estimated financial impact are primarily due to differences in epidemiology data sources used in these studies.

2.8 Chapter summary

This chapter provided an overview of the clinical features of OAB, the treatments options (non-pharmacologic and pharmacologic) and its humanistic and economic burden. It has be shown that OAB is a common symptomatic disorder that has a profound impact of patient's quality of life, and that is associated with significant financial burden. Although OAB is diagnosed using bladder diaries assessing the severity of urinary symptoms, it is critical to consider the impact of any treatment of patient's quality of life to assess the treatment benefit.

The next chapter will focus on qualitative research and patient preference studies conducted by the author of this thesis to comprehensively asses the quality of life aspects affected by OAB.

Chapter 3: Impact of overactive bladder on patient's quality of life and patients preferences for treatments

3.1 Introduction

Chapter 2 provided information on the burden of OAB, including epidemiology and its humanistic and economic burden. The significant impact of OAB on patient's HRQL was also discussed.

In order to ensure a robust identification of HRQoL domains affected by OAB, it is essential to conduct qualitative research with patients. Guidelines from ISPOR and regulators recommend to start by performing a literature search aiming at identification of relevant published qualitative research, hypothesise a disease conceptual framework, and then perform concept elicitation interviews with patients until "concept saturation". Clinician input should also be secured to understand the symptoms and impacts on quality of life that are related to the disease itself (EMA 2005; FDA 2009; Patrick et al., 2011a; Patrick et al., 2011b).

This chapter will discuss the author's research on the key HRQoL domains affected by OAB (Publication 1) as well as the attributes and patient preferences regarding determinant of choices for OAB treatments (Publication 2).

3.2 Publication 1: Hawken N, **Hakimi Z**, , Aballéa S, Nazir J , Odeyemi IAO, Toumi M Elicitation of Health-related Quality-of-life Concepts Associated with Overactive Bladder: A Qualitative Study Journal of Health Economics and Outcomes Research 2016;4(2):127-40

https://doi.org/10.36469/9816

Description and critical analysis of the study

This study has been conceptualized by the researcher and initiated due to the lack of supporting information on qualitative research to support a potential label claim in the US (FDA) to support a labeling language on urinary urgency for mirabegron. The researcher has defined the methods to bed used based on the FDA PRO guidance (FDA 2009). The researcher had a lead role in the design, analysis, interpretation and drafting of the manuscript. The other authors have mainly participated in the data collection as well as interpretation of the results and revision of the manuscript.

As qualitative research was lacking in the published literature on OAB, the aim of this paper was to elicit the key quality of life dimensions affected by OAB. This study was a qualitative research based on grounded theory and comprised of two distinct steps. In the first step, a literature review was performed using EMBASE to identify existing qualitative evidence regarding PRO related to OAB. The second step consisted of the primary research. It started with interviews with clinicians (two urologists) to identify the key aspects of the disease symptoms. Following clinician interviews, a semi structured interview guide to be used during patient interviews was developed. The interviews were conducted by an experienced psychologist in the United Kingdom with individual OAB patients. Ethical approval was obtained by the Solihull NRES committee (12/WM/0296). The main inclusion criteria were as follows: diagnosis of OAB with bothersome symptoms at least 6 months prior to the interview; English speaking; Living in the UK. In order to assess the whole spectrum of the disease severity an equal number of patients with (OAB wet) and without incontinence (OAB dry) was targeted. Another key consideration was to ensure sufficient representation of patients according to gender, age and education levels.

The interviews were transcribed verbatim and thematic analysis was performed using Atlas.ti software.

The literature review identified only three qualitative studies in which OAB patients were interviewed, either individually or though focus groups (Coyne et al., 2007; Anger et al., 2011; Nicolson et al., 2008). Although none of these studies were conducted according to the standards for PRO development, the following HRQoL aspects have been clearly identified: OAB is a debilitating disease with a serious impact on HRQL, affects self-esteem and relationships, can cause anxiety and depression (especially in wet OAB patients), and negatively impact sexual life. These findings were used to prepare an initial theoretical conceptual framework.

In the second step of this project, 30 OAB patients were interviewed, with 15 patients being incontinent and 15 patients having dry OAB. Data collection stopped when concept saturation was reached in both dry and wet patients, and that new information produced little or no change to the code book. The demographic characteristics were in line with the disease epidemiology, with a median age of 63 years old, and a predominant proportion of female OAB patients (73%). The analysis of these interviews showed that the following concepts were mostly affected by OAB: Role Functioning (shopping, impact on work), Sleep (waking up at night), Social functioning (going for a walk, traveling and holidays, socialising), Emotional/Mental functioning (embarrassment, shame) and Coping strategies (need to plan activities, restriction of places visited).

A key element is this study was the impact of urinary urgency on emotional and mental functioning, with more than 80% of OAB patients reporting feeling embarrassment or shame as a result of their condition. Patients used the terms ‘miserable’ and ‘ruined’ to describe the dramatic impact of OAB on their daily functioning. Another important finding is the negative impact on sleep as most patient reported waking-up at night because of their OAB symptoms (nocturia). The consequences of disrupted sleep were irritability, tiredness, difficulty to concentrate and impaired daytime functioning. Most OAB patients reported OAB coping strategies to manage their condition and alleviate their symptoms. These consisted mostly of restriction of fluid intake and limiting places visited, with patients organising their daily activities with careful planning of the location of the nearest toilets.

The concepts identified in this study are well represented in existing disease specific PRO instruments such as the OAB-q. It is however important to note that three concepts that were identified during the patient interviews and are not measured by the OAB-q: these include some coping strategies (restriction of fluid intake, and restriction of drinks containing alcohol or caffeine), sexual impact and ability to perform work. The difference between the concepts identified during the concept elicitation interviews and the OAB-q are presented in Table 3.1.

Concepts identified in the concept elicitation interviews (Publication 1)	Concept included in OAB-q
Role Functioning	
- Role at Work	No
- Role as a Caregiver or as Family Member	No
Sleep and Daytime Functioning	
- Waking up at night	Yes
- Impaired Daytime Functioning	Yes
- Daytime Sleeping	Yes
- Irritability, Anger, Annoyance	Yes
- Impaired Concentration	No
- Impaired Work Performance	No
- Impaired Social Life	Yes
- Disturbing Partner	Partially
Social Functioning	
- Avoiding Socializing / Going Out	Yes
-	
Emotional/Mental Functioning	
- Worry	Yes
- Anxiety	Yes
- Embarrassment / Shame	Yes
- Anger	No
Sexual Impact	No
Coping Strategies	
- Wearing Pads	No
- Need to Have Extra Clothing	No
- Restriction of Drink Types (Tea/Coffee/Soda/Juice/Alcohol)	No
- Drinking Only Decaffeinated Tea and Coffee	No

Table 3.1 Concepts identified during the concept elicitation interviews and concets included in the OAB-q

The strengths and importance of this study reside in the fact this constitutes the first published qualitative research that has been conducted according to the good practices for PRO development. The findings allows to validate the content of the existing PRO questionnaires; in particular, this research support the content validity of the OAB-q questionnaire that is widely used in OAB clinical trials (Coyne et al., 2002), and that has been developed before the guidelines of PRO development were published. The results are also being used by the present researcher to inform the development of a new instrument assessing the impact of OAB on HRQoL (Bladder Assessment Tool).

The study has some limitations: the sample size of the study was relatively small and although concept saturation has been reached, a selection bias cannot be excluded (patients that did not seek medical attention or had depression were under represented). This limit the applicability of the findings to the patient population that are not seeking medical attention and to those with depressive disorders. Another limitation is that the study was conducted only in the UK, and cross cultural aspects have not been explored. It is therefore possible that the findings would differ is other cultures and this research should be repeated in countries to confirm the applicability of these findings globally. Finally, another limitation of this study resides on the fact that it didn't include cognitive debriefing interviews designed at gathering the patient perspective on the relevance of items of existing OAB disease specific PRO instruments. This would have allowed to better assess the content validity of existing OAB disease specific PRO instruments.

Publication 2 will examine the patient and physician preferences for treatment attributes in OAB and how these preferences can influence treatment choices.

3.3 Publication 2: Heisen M, Baeten SA, Verheggen BG, Stoelzel M, **Hakimi Z**, Ridder A, van Maanen R, Stolk EA. Patient and physician preferences for oral pharmacotherapy for overactive bladder: two discrete choice experiments. *Current Medical Research Opinion. 2016;32(4):787-96*

https://doi.org/10.1185/03007995.2016.1142959

Description and critical analysis of the study

This study has been conceptualized by the researcher and initiated due a request from the EMA to gather data supporting the benefit risk of a fixed dose combination of mirabegron and solifenacin, as the fixed dose combination provided increased efficacy at the expense of additional side effects compared to either monotherapies. The choice of the methodology was made by the researcher as it allowed to understand the relative importance of efficacy and safety treatment attributes. The researcher has decided to conduct the discrete choice experiment in patients and physicians to take into account the patient perspective as well as the attributes considered by the physicians when prescribing OAB treatments. The researcher had a lead role in the conceptualization, interpretation of the results, drafting of the manuscript, and a key supportive role in the data analysis and data collection. The other authors were involved in data collection (as this was a large scope international study), analysis and interpretation of the data and revision of the manuscript.

Preference studies are an important element to consider for treatment decision making. Discrete Choice Experiment (DCE) - which is a form of conjoint analysis - is a well-established method to assess patient preferences (Ryan et al., 2004; Watson et al., 2004). This methodology is being used by prominent European HTA bodies such as the German Institute for Quality and Efficiency in Health Care (IQWiG) and the UK National Institute for Health and Care Excellence (NICE) to ensure that the patient perspective is taken into account when treatment recommendations are made (Mühlbacher et al., 2017; Shah et al., 2012). The present study consisted of two DCEs conducted in parallel. The first one was conducted in OAB patients and the second one with prescribing physicians (general practitioners, urologists and (uro)gynaecologists). The rationale for conducting two DCEs with patients and

physicians is that the patient is taking an increasingly active role with regards to the treatment decision making process (prescription of treatment) and the physician is no longer the only decision maker in the process. It has also been reported that an active role taken by the patient often lead to better outcomes (NICE 2019).

Both DCEs were conducted in accordance with the principle of the Declaration of Helsinki (WHO, 2013).

The initial selection of treatment attributes used in the DCEs was defined based on a review of the literature, the Summaries of Product Characteristics (SPCs) of a representative of the two pharmacological treatment classes (solifenacin and mirabegron), as well as patients and physician interviews (Astellas 2013; Astellas 2019). The final selection of attributes, description and levels were determined in two separate focus group sessions conducted in Netherlands with five patients and six physicians. Attributes were similar with eight and ten treatment attributes retained respectively in the patient and physician DCE (Table 3.1). These included key OAB symptoms, impact on HRQoL (Coping strategies in the physician DCE only), and potential side effects associated with OAB treatments.

Attribute	Patient DCE	Physician DCE
Micturition frequency	Yes	Yes
Incontinence	Yes	Yes
Nocturia	Yes	Yes
Urgency strategies	Yes	Yes
Coping	No	Yes
Dry mouth	Yes	Yes
Constipation	Yes	Yes
Increased heart rate	Yes	Yes
Increase blood pressure	Yes	Yes
Atrial fibrillation	No	Yes

Table 3.2 Attributes included in the patient and physician DCE

The DCE questionnaire consisted of 32 tasks in the patient study and 48 task in the physician study. For each task, participants were offered the choice ‘Medicine A’, ‘Medicine B’ or ‘No treatment’ with varying level of severity for each attribute. The survey was then launched in 5 European countries: UK, The Netherlands, Germany, France and Spain) with more than 500 OAB patients and 300 physicians.

The results of the study provided equation and coefficients informing about the tradeoff that patients and physicians make between attributes. In the patient study, the attributes that were ranked the most important to the least important were incontinence, nocturia, risk of increased heart disease, urgency, micturition frequency, risk of an increased blood pressure, risk of constipation and risk of dry mouth. In the physician study, the results were somewhat different with incontinence being the most important attribute, followed by urgency, nocturia, micturition frequency, risk of dry mouth, coping, risk of increased heart disease, risk of an increased blood pressure, risk of constipation and risk of atrial fibrilation. It became clear from these results that while both patients and physician consider that efficacy attributes (incontinence, nocturia) are the most important, the safety risks (cardiovascular risks) are considered more important by the patients than for physicians.

This research is the first to report patients and physician preference side by side and allow the assessment of key drivers in patient and physician preference. It has been conducted based on a comprehensive review of the literature as well as patient and physician input. The findings have been used in a multi criteria decision analysis that has been submitted to the EMA to evaluate the benefit risk of OAB treatments based on the importance of each treatment attribute from the patient and the physician perspective.

A key strength of this study is the large sample size of respondents allowing the results to form a robust representation of their preference.

These DCEs are particularly relevant in OAB as the efficacy and tolerability of OAB treatments differ significantly (Kelleher et al., 2018). These are therefore valuable additional tools when deciding treatments funding allocations alongside costeffectiveness analyses and relative effectiveness studies. The findings allow also to provide important insights into the benefit risk of new or existing drugs in OAB.

This study have some limitations: first, the definition of attributes, despite being developed based on robust patient input may have been misinterpreted by some patients or physicians. For instance, it might be difficult for a respondent to consider the risk of bothersome adverse events (such as dry mouth) in case these have never been experienced. This may have created a bias that influenced the rating of some attributes. Another limitation reside in the number of attributes (eight in the patient study and 10 in the physician study) that were included in the DCE questionnaire. This relatively high number of attributes may have rendered the questionnaire difficult to interpret by respondents. This implication of this limitation is that some of the respondent may not have performed a well informed and rationale treatment choice when completing the tasks from the questionnaire and this could have biased the results.

3.4 Chapter summary

The concept elicitation interviews conducted with OAB patients allowed the identification in a systematic manner of the key dimensions of HRQL that are affected by OAB symptoms. This research highlighted the significant impact of urinary symptoms on OAB patients, in particular on mental and emotional functioning. The findings can be used to support the development of new PRO instrument to assess the impact of OAB on HRQL and support the validation of existing PRO measures. It also inform the burden of the disease from the patient perspective and represent therefore a critical information to be taken into account in HTA appraisals.

The DCEs that were conducted in OAB patients and prescribing physicians provided important information on patient preferences. This is particularly relevant in OAB, as the efficacy and side effect profile of available treatments differ significantly. This research that mimic the real-world decision making context (where patient of physicians have to choose between available treatment alternatives having different attributes), is relevant to both drug approval (benefit risk assessment) and reimbursement decisions. It also informs treating physicians of the patient perspective and thereby can improve shared decision-making.

The next Chapter will focus on how PRO included in large multi-national randomised clinical trials in OAB patients have been used to demonstrate a patient relevant treatment benefit.

Chapter 4: Interpretation of clinical relevant improvement based on PROs and other objective measures of treatment effect

4.1 Introduction

The previous chapter discussed the importance of conducting qualitative research on HRQL dimensions affected by OAB as well as patients preferences related to OAB treatments.

In this chapter, the interpretation of clinically relevant patient benefit using PROs will be discussed, based on analyses from large clinical trials. Publications 3 to 5 will be presented and critically analysed in the context of HTA decision making process for OAB.

The regulatory guidelines applicable for drug development and approval recommend the use of micturition diaries as primary endpoints to assess the efficacy of OAB treatments in clinical trials. These micturition diaries allow to capture the severity of urinary symptoms, but the results are difficult to interpret as there is no consensus on the extent of improvement that represents a patient relevant benefit. It is therefore essential to consider the patient experience based PROs to not only for drug regulatory approval but also for HTA decision making.

Publication 3 will discuss responder analyses that were used to assess the clinical relevance of the symptom improvement of a new combination treatment for OAB.

4.2 Publication 3: MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, Saleem T, Huang M, Siddiqui E, Stölzel M, Hemsted C, Nazir J, **Hakimi Z**, Drake MJ Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy. *Journal of Urology 2016 Sep;196(3):809-18.*

https://doi.org/10.1016/j.juro.2016.03.174

Description and critical analysis of the Study

This study has been conceptualized by the researcher who had provided input during the phase 3 design of the combination of mirabegron and solifenacin and decided to include the following PROs in the phase 3 randomized clinical trial: PPBC, OAB-q, EQ-5D 5L and TS-VAS. The published worked has been designed by the researcher to generate data on the clinical relevance of the improvement in HRQoL for Health Technology Assessment. The researcher has conceptualized and designed the analysis, and led the interpretation and drafting of the manuscript. The other authors have participated in the data collection (clinical investigators of the multinational randomized phase 3 clinical trial), interpretation of the results and revision of the manuscript.

This objective of this analysis was to explore the clinical relevance of improvements in OAB symptoms associated with a new treatment combination of OAB treatments (mirabegron plus solifenacin). This was a pre-specified analysis of the BESIDE study (ClinicalTrials.gov NCT01908829) which demonstrated a statistically significant improvement in key OAB symptoms (mean number of incontinence per 24-hour and mean number of micturition per 24-hour) of solifenacin 5mg plus mirabegron compared to solifenacin 5mg and 10mg monotherapy (Drake et al., 2016). A total of 2174 patients were randomised in the 12-week duration study. The main inclusion criteria were as follows: adults with OAB symptoms since more than 3 months and at least 2 incontinence episodes per day. The results showed that the mean number of incontinence episodes was reduced by 0.27 incontinence episode per day with the combination therapy compared to the monotherapy. Although the results were statistically significant in favour of the combination treatment, the relevance of this modest improvement from the patient perspective was still unclear.

In order to assess the clinical relevance of the improvement, several responder analyses were conducted. These consisted of single responder analyses (based on one outcome measure) or double and triple responder analyses combining responder definitions for both an objective parameter (symptom severity as measured by voiding diaries) and PRO instruments. The BESIDE study included the following assessment measures: A voiding diary to assess objectively the severity of OAB

symptoms (urgency, micturition frequency and number incontinence episodes) as well several

PRO instruments. These included the Treatment-Satisfaction Visual Analog Scale (TSVAS) measuring the patient satisfaction with their treatment, the Patient Perception of Bladder Condition (PPBC) measuring the perceived severity of bladder symptoms, and the OAB-q questionnaire.

The OAB-q is a 33-item disease specific instrument measuring the degree of bother associated with OAB symptoms in addition to the following HRQL domains: coping strategies, concern due severity of symptoms, impairment in social interactions, as well as the impact on sleep and daytime functioning. Responder analyses using PRO instruments were based on established Minimally Important Difference (MID). The single responder analyses were based on two responder definitions: achievement of 50% reduction in mean number of incontinence episodes and achievement of zero incontinence episodes at the end of the treatment period (12 weeks). The double responder analyses included both a reduction of 50% of incontinence episodes and achievement of the MID on either the Symptom bother score of the OAB-q or the HRQL score of the OAB-q.

The results of the single responder analysis showed that compared to solifenacin 5 mg and 10 mg respectively, patients treated with the combination therapy were 47% and 28% more likely to achieve zero incontinence episode and 51% and 25% more likely to achieve at least 50% reduction in incontinence episodes (using odds ratios).

The double responder analyses indicated similarly that patients treated with the combination therapy were 66% and 25% more likely to achieve at least 50% reduction in incontinence episodes and reaching the 10-point MID on the OAB-q Symptom bother HRQL instrument. These were also 55% and 39% more likely to achieve triple responder status based on a minimum of 50% reduction in incontinence episodes, 10-point MID on the OAB-q HRQL Total score and 1-point improvement in PPBC. All these results were statistically significant. The results showed also that the objective parameters measured by the voiding diaries were correlated with the results from the PRO instruments included in the study.

This research is of particular importance at it allows to interpret the study results using responder analyses combining both objective outcomes and subjective

parameters. This allowed to provide a broader understanding of the treatment benefit and provide evidence that the new OAB combination treatment lead to a patient-relevant additional symptom relief compared to solifenacin 5 mg or 10mg monotherapy, which constituted the standard of care at the time of the research. This was indeed not possible when taking into account only the primary endpoint of the study (mean number of incontinence episodes). Due to its usefulness in interpreting the study outcomes, these responder analyses are now performed routinely in clinical trials investigating the OAB treatments. This research is also very informative from the HTA perspective to assess the clinical value of OAB treatments.

These analyses have some limitations. The most important one is that although these were pre-specified, no adjustment for multiplicity of endpoint has been performed. Another limitation resides in the fact the vast majority of the patients included in the BESIDE study consisted of female patients. This is in line with the epidemiology of OAB but this limits the applicability of the present analyses to the male patients. Although this analysis has been successfully used in reimbursement dossiers of solifenacin and mirabegron, these analyses based could have been strengthen by conducting an item-level analysis allowing to understand if a clinically meaningful improvement was also observed in the most patient-relevant items of the PRO instrument. It is indeed possible that within a domain of an existing PRO instrument, some items as more relevant than others. This type of item level analysis has been recently conducted by the researcher in another disease area (haemophilia) and published in a peer-reviewed journal (Astermark et al 2022). This item-level analysis allowed to explore in details the improvement is selected patient-relevant items (pain) that were not otherwise adequately analyzed based on the existing scoring of a PRO instrument, as these were part of domains that were multi-dimensional.

The next publication will discuss how the PROs included in a clinical trial of mirabegron were used to demonstrate the clinical relevance of the improvements of OAB symptoms by mirabegron in two subgroups of patients, using both objective (symptom alleviation) and subjective (HRQoL) assessments.

4.3 Publication 4: Khullar V, Amarenco G, Angulo JC, Blauwet MB, Nazir J, Odeyemi IA, **Hakimi Z** Patient-Reported Outcomes With the b3-Adrenoceptor Agonist Mirabegron in a Phase III Trial in Patients With Overactive Bladder *Neurourology and Urodynamics 35:987–994 (2016)*

https://doi.org/10.1002/nau.22844

Description and critical analysis of the study

This study has been conceptualized by the researcher in order to generate data on the improvement on HRQoL with mirabegron in the two most important subgroup of patients with OAB (continent and incontinent patients). These data are important from the HTA perspective as it allows to inform health care decision making and resource allocation based on the extent of the benefit in relevant subgroups of patients. It is important to understand is a drug should be restricted to a subgroup of patients that benefit the most, and this analysis has provided key insights in that regard. The researcher has conceptualized, designed the analysis, led the interpretation of the findings and drafted the manuscript. The other co-authors had participated in the data collection (investigators of the phase 3 clinical trial), participated in the interpretation of the data and in the revision of the manuscript.

This analysis assessed the results of PRO instruments included in a pivotal phase 3 clinical trial (ClinicalTrials.gov NCT00689104) investigating the efficacy and safety of mirabegron 50 mg compared to placebo. The study included also an active control arm with patients treated with tolterodine 4 mg. The results from the primary endpoints were published elsewhere and demonstrated that mirabegron was superior to placebo in reducing the mean number of incontinence episodes, the mean number of micturition per day, and the OAB-q Symptom bother score (Khullar et al., 2013) . In the incontinent subgroup of patients, the improvement in mean number of incontinence was modest with a difference of -0.37 incontinence per day compared to placebo, but no results of PRO analyses were available in this subgroup. It was therefore important to explore the patient relevance of these improvement based on PRO instruments, as the patient perception of efficacy and tolerability is known to be

the most important determinant of patient adherence and persistence with treatment (Benner et al., 2010).

Several PRO measures were included in the clinical trial: the TS-VAS assessing satisfaction with treatment, the OAB-q questionnaire, the PPBC and the Work Productivity and Activity Impairment – Special Health Problem (WPAI-SHP) assessing the impact on absenteeism presenteism, overall productivity and activity impairment.

A total of 1987 patients were randomised and 1429 were included in the Full Analysis Set (FAS). In the subgroup of incontinent patients, 884 patients were included in the FAS- Incontinent (FAS-I) data set, which represent 61.9% of the overall population.

The overall patient population reported statistically significant improvement with mirabegron 50mg compared to placebo on OAB-q symptom bother (4.7 points), OABq coping score (2.9 points), OAB-q concern score (2.6 points) OAB-q HRQL total score (2.3 points), 1 point improvement of PPBC after 12 weeks of treatment, and TS-VAS (0.7 points). Patients treated with tolterodine only reported statistically significant improvement over placebo on OAB-q symptom bother (3.5 points) and TS-VAS (0.6 points).

In the incontinent subgroup, mirabegron was associated with statistically significant improvement over placebo on OAB-q symptom bother (5.9 points), OAB-q coping score (4.6 points), OAB-q concern score (4.1 points), OAB-q HRQL total score (3.4 points), 2-point improvement on PPBC, and TS-VAS (0.9 points). Patient treated with tolterodine only reported statistically significant improvement over placebo on OAB-q symptom bother (3.9 points), TS-VAS (0.6 points) 1-point and 2-point improvement on PPBC.

These analyses allowed to better understand the extent of the treatment benefit associated with mirabegron to alleviate OAB symptoms and improve HRQoL. The results showed that mirabegron improved not only the OAB symptoms but also the improved satisfaction with treatment and several dimensions of HRQoL. These parameters we also improved with tolterodine, but to a lesser extent, indicating that the treatment benefit with mirabegron may be more important than with tolterodine. This has important implications in healthcare decision making due to the established association between HRQoL and treatment adherence in OAB (Benner et al., 2010).

In the subgroup of incontinent patients, the improvement of HRQL with mirabegron was even more important than in the overall population. This indicates that this patient population is anticipated to benefit the most from a treatment with mirabegron. It also allow to interpret the apparent modest improvement of 0.37 incontinence per day with mirabegron compared to placebo, by demonstrating that this improvement is clinically relevant. This analysis has been used as part of reimbursement submission and have positively influence reimbursement guidelines for mirabegron.

The present study is subject to some limitations, including the absence of adjustment for multiplicity of endpoints, similarly as in Publication 3. It can therefore not be excluded that these findings are due to chance. This analysis should therefore be confirmed in future research using a robust statistical methodology accounting for multiple endpoints as described in clinical development guidelines (EMA 2016).

Another limitation reside in the short duration of the study (12 weeks), as the maintenance of the quality of life improvements with mirabegron was not assessed over the long term. It is therefore important to conduct such analyses in a long-term study to gain certainty on the potential impact in patient persistence and adherence. Despite these limitations, these PRO results suggest a meaningful clinical benefit of mirabegron over placebo in OAB patients with or without incontinence at baseline.
The next publication will discuss responder analyses that have been conducted on a combination of solifenacin and tamsulosin that improved OAB symptoms in a patient population consisting exclusively of males.

4.4 Publication 5: Drake MJ, Sokol R, Coyne K, **Hakimi Z**, Nazir J, Dorey J, Klaver M, Traudtner K, Odeyemi IA, Oelke M, van Kerrebroeck P, on behalf of the NEPTUNE study group Responder and health-related quality of life analyses in men with lower urinary tract symptoms treated with a fixed-dose combination of solifenacin and tamsulosin oral-controlled absorption system: results from the NEPTUNE study *British Journal of Urology International 2016; 117: 165–172*

https://doi.org/10.1111/bju.13162

Description and critical analysis of the study

The researcher has conceptualized, designed the analysis, led the interpretation of the findings and drafted the manuscript. The other co-authors had participated in the data collection (investigators of the phase 3 clinical trial), participated in the analysis and interpretation of the data and in the revision of the manuscript.

This manuscript includes responder analyses of objectives outcomes as well as PRO analyses in a patient population of men with Lower Urinary Tract Symptoms (LUTS) with Benign Prostate Hyperplasia (BPH) and substantial storage symptoms. The storage symptoms correspond to key OAB symptoms and include urinary urgency, increase urinary frequency and nocturia (Gravas et al., 2018). The analyses were based on the NEPTUNE phase 3 clinical trial (ClinicalTrials.gov NCT 01018511) conducted in 13 European countries. The trial included 1245 patients and was designed to demonstrate the superiority a Fixed Dose Combination (FDC) of solifenacin + Tamsulosin Oral-Controlled Absorption System (TOCAS) compared to placebo and TOCAS monotherapy. The results of the clinical findings were published elsewhere (Van Kerrebroeck et al., 2013) and showed that the FDC was superior to placebo and TOCAS monotherapy on the primary endpoint Total Urgency and Frequency Score (TUFS).

The objectives of the present analyses were to assess the patient's perspective of the symptom relief seen with the FDC using responder analyses as well as to explore correlations between objective and subjective measures. The two objective measures included in NEPTUNE were the TUFS and the number of urinations per day. The

subjective measures consisted of the International Prostate Symptom Scale (IPSS), the OAB-q and the Patient Global Impression (PGI).

The correlation analyses assessed the correlation between the TUFS and four HRQL parameters using Spearman rank correlation coefficients: the IPSS QoL score, the OAB-q symptom bother score, the PGI bladder symptoms and the PGI general health. The single responder analyses were conducted as follows:

a) Improvement in TUFS of 6 points or more from baseline, corresponding the MID (Hakimi et al., 2013)
b) Improvement of at least 2 urination per day from baseline
c) Improvement in PGI bladder symptoms
d) Improvement in PGI general health

The double responder analyses combined improvement on TUFS or urinary frequency with PGI bladder symptoms or PGI general health.
The results of the correlation analyses showed that the change from baseline in TUFS was correlated with HRQoL: The Spearman rank correlation coefficients were statistically significant ($p < 0.001$) between TUFS and IPSS QoL score (0.34), OAB-q symptom bother score (0.35), PGI bladder symptoms (0.43) and PGI general health (0.36).

The results of the single responder analyse showed that the percentage of responders in the FDC treatment arm was significantly higher compared to placebo. The difference in response rate were 19% for urinary frequency, 19% for TUFS, 15% for PGI bladder symptoms and 14% for PGI general health. Similarly, the double responder analyses showed that the percentage of responders with the FDC were significantly higher than with placebo, with a difference in response rate ranging from 15% (urinary frequency and PGI general health) to 19% (urinary frequency and PGI bladder symptoms). The odds ratios were also all statistically significant ranging from 2.32 to 2.54, indicating a significantly higher likelihood to be responder with the FDC compared to placebo.

These findings establish the clinical relevance of the treatment benefit of the FDC compared to placebo as it demonstrates that objectives measures were significantly correlated with the patient's HRQL as measured by validated PRO instruments. The

findings from the single and double responder analyses demonstrated that when an improvement in OAB symptoms was present (based on objective measures), it was associated with an improvement of patient's HRQL.

The key strengths of this research reside in the consistency of the results comparing TOCAS and placebo, with all analyses leading to statistically significant results, and the fact that these analyses were based on a large and homogeneous patient population. The double blinded nature of the trial limited the potential bias that may have occurred with the assessment of patient's HRQoL.

The main limitations included the post-hoc nature of the responder analyses and the lack of adjustment for multiplicity of endpoints, similarly with Publications 3 and 4. Another limitation is the potential underestimation of the HRQL improvement with the FDC as the double blind of the trial did not allow to capture the benefit of a reduced pill burden from the patient perspective. It can be anticipated that the patient benefit is underestimated based on the present analysis. This could be further explored by conducting a similar study in a real world setting.

4.5 Chapter summary

Three articles were included in this chapter and summarised the association between improvement in OAB symptoms and patient's HRQL. The importance of measuring HRQL should not be underestimated in symptomatic conditions such as OAB as it is a key element of the evidence based medicine and complement the traditional measurement of treatment effectiveness using objective measures of symptom relief (Welch et al., 2012). The studies provided new knowledge on the clinical relevance of the symptom relief associated with recent treatments to treat OAB symptoms. It was also demonstrated that the extent of the clinical benefit was more important in the subgroup of incontinent patients than in the overall patient population.

The importance of conducting responder analyses and correlation analyses has been demonstrated and these clearly showed that an improvement in OAB symptoms was linked to an improvement in patient's HRQL. This was particularly important in OAB as the clinical relevance of the symptom relief (for instance an improvement in 0.37

incontinence per day in the BESIDE study) is difficult to interpret. The results of the studies discussed in this chapter have informed regulatory approval and/or HTA decision making as the finding are informative when assessing the benefit-risk and the clinical value of new OAB treatments.

A limitation in the approach taken in the analyses of these 2 manuscripts resides in the analyses being limited to pre-defined domains of the PRO instruments and absence of additional item-level analyses (similarly as for manuscript 3 presented in section 4.2). These would have been especially informative given that the PRO instruments considered in the analysis have been developed before the development of the FDA guidance on PRO development (FDA 2019) and some existing PRO domains may include items which are not all patient-relevant.

The next chapter will discuss how the PRO instruments have been used in the context of the HTA appraisal of mirabegron by estimating utility values using different techniques, and performing a cost-effectiveness analysis.

Chapter 5: Role of the patient perspective in economic evaluations and health technology appraisal

5.1 Introduction

In the previous chapter, the importance of assessing the clinical relevance of OAB symptom relief was discussed. Analyses of three large multinational clinical trials investigating the association between objective and subjective measures by conducting responder and correlation analyses were presented. These results provided critical information to address the treatment benefit of OAB treatments, and showed that despite a modest improvement in OAB symptoms, the symptom relief was associated with an improvement in patient's HRQL.

In this chapter, three articles will be discussed to address how the patient perspective is incorporated in HTA appraisal by estimating the utility values based on EQ-5D as well as using a mapping algorithm to derive utility value based on a disease specific instrument (OAB-5D). Finally, the cost effectiveness analysis of mirabegron compared to tolerodine will be discussed. This economic model has been submitted to NICE as part of the single technology appraisal of mirabegron.

5.2 Publication 6: Pavesi M, Devlin N, **Hakimi Z**, Nazir J, Herdman M, Hoyle C, Odeyemi IA. Understanding the effects on HR-QoL of treatment for overactive bladder: a detailed analysis of EQ-5D clinical trial data for mirabegron *Journal of Medical Economics. 2013 Jul;16(7):866-76*

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Description and critical analysis of the study

The researcher has conceptualized, designed the analysis, led the interpretation of the findings and drafted the manuscript. The researcher has developed this analysis in order to generate data on the preference-based instrument recommended by NICE (EQ-5D) and therefore obtain utility data for the cost-effectiveness modeling (NICE 2013). The other co-authors have participated in the analysis, interpretation of the findings and revision of the manuscript.

The utility values will thereafter be used to estimate the number of Quality-Adjusted Life Years (QALYs) gained with a new treatment and inform allocation of resources. The EQ-5D consists of a descriptive system and a visual analogue scale (VAS) on which respondents rate their overall health on a scale from 0 to 100. The descriptive measures HRQL in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension include three levels of severity (no problems; some problems; and extreme problems).

The main objective of this analysis was to estimate the effect of mirabegron compared to placebo and tolterodine on OAB patients' in EQ-5D utility values and VAS and the number and percentage of patients reporting no, some, or extreme problems on each dimension of the EQ-5D. In addition, an Paretian Classification of Health Change (PCHC) as defined in Devlin et al., (2007) was conducted. This study is the first detailed analysis of findings from EQ-5D in OAB patients.

The analyses were conducted using three pivotal trials comparing mirabegron and placebo. The SCORPIO trial (ClinicalTrials.gov NCT00689104), the ARIES trial (ClinicalTrials.gov NCT00662909) and the CAPRICORN trial (ClinicalTrials.gov NCT00912964). An active control arm with tolterodine was also included in the SCOPRIO trial. As the analyses were to be used in the HTA submission to NICE, the EQ-5D UK value set were used for the analyses.

For the estimation of the EQ-5D utility scores the results showed that mirabegron was superior to tolterodine and at the end of the treatment period (12 weeks), with a mean change from baseline of 0.045 for mirabegron and 0.026 for tolterodine. A difference of similar magnitude has been observed between mirabegron and placebo, although the difference was statistically significant only at 4-week and 8-week treatment, but no longer at 12-week treatment. In order to assess the extent of the utility gain over

time, an analysis estimating the Area Under the Curve (AUC) was conducted. This allowed to take into account not only the extent of the benefit at a given time point, but to use a similar approach as the QALY estimation, by taking into account the treatment benefit at each time point at which the EQ-5D has been included. This AUC analysis showed that mirabegron was statistically superior to both tolterodine and placebo with an AUC of 0.29 for mirabegron, 0.18 for placebo, and 0.11 for tolterodine.

On the EQ-VAS, mirabegron was statistically significantly superior to tolterodine after 12 weeks of treatment but yielded only numerically higher scores than placebo. The PCHC showed that the likelihood of patients reporting improved overall health status was not different for mirabegron compared to placebo or for tolterodine compared to placebo.

This analysis clearly showed that the EQ-5D utility index and the AUC was the most sensitive element of the EQ-5D to capture the treatment benefit of mirabegron compared to tolterodine, as the EQ-VAS and the PCHC were not able to differentiate between treatment arms. These results are of particular importance as the EQ-5D is a crude instrument that measures only 5 aspects of patient's HRQL and is not designed to adequately measure the improvement in OAB symptoms. Although EQ-5D is the preferred instrument for HTA appraisal, it is important to recognise that any treatment aiming at a symptomatic disease that affect another dimension than the ones captured by EQ-5D is unlikely demonstrate a significant treatment benefit using this instrument. This is illustrated by the high ceiling effect that has been shown when analysing the data, with the majority of the patients having no problem at baseline (scoring 'no problem' in each of the EQ-5D dimension) and thus could not improve during the course of the study.

The key strengths of these analyses were the large population included in these analyses, with EQ-5D data on more than 3700 OAB patients. The large sample size ensure a wide representation of degrees of symptom severity and therefore allows the conclusion to be generalisable across the full spectrum of severity of OAB. This research provided new information on the extent of the improvement of EQ-5D utility values associated with mirabegron, and confirmed that clinical relevance of the OAB symptom relief demonstrated in the previous chapter. These results were submitted

to NICE for the HTA appraisal for mirabegron and contributed to the positive recommendation of mirabegron for use in the UK national health service (NICE 2013c). This is a significant achievement as the outcome of this research has helped OAB patients in the UK gain access to an innovative therapy to treat their symptoms.

This research has several limitations, including the absence of adjustment for multiplicity of endpoint as also mentioned for publication 3 to 5. Another limitation is the pooling of three clinical trials resulting in the break of the randomisation between treatment arms and therefore potential imbalance in baseline characteristics. This has been addressed by conducting adjustments for potential confounding factors in case significant differences in baseline characteristics or comorbidities were found.

Although this analysis used pooled head to head clinical trials comparing mirabegron, tolterodine and placebo, an additional utility study could have been conducted usiong the vignette methodology (Matza et al 2021) to provide further data on utility values in OAB. This would have been especially important in light of the observed ceiling effect of EQ-5D in OAB and its inability to adequately capture the OAB symptoms and their impact on patients quality of life.

The publication 7 will discuss how utility studies were estimated for use in a future health economic evaluation in OAB, using both EQ-5D and a mapping technique linking the OAB-q and the EQ-5D.

5.3 Publication 7: Desroziers K, Aballéa S, Maman K, Nazir J, Odeyemi I, **Hakimi Z**. Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder *Health Quality of Life Outcomes. 2013 Nov 19;11:200*

https://doi.org/10.1186/1477-7525-11-200

Description and critical evaluation of the study

The researcher has developed the concept, designed the analysis, led the interpretation of the findings and drafted the manuscript. The other co-authors have participated in the analysis, interpretation of the findings and revision of the manuscript.

The objective of the analyses reported in this paper was to estimate the utility values to be used in health economic analyses in OAB. The economic model comparing mirabegron and tolterodine is presented in the section 5.4 of this thesis.

The EQ-5D is considered as the preferred measure of health-related quality of life in adults by several HTA bodies (NICE 2013a; HAS 2011). Although using a generic instrument allows to compare health benefit in a consistent manner across different diseases, EQ-5D has important limitations and may lack sensitivity or fail to capture important aspects of health in certain disease areas (Devlin et al., 2013). This has also been evidenced in Publication 6 with the substantial ceiling effect observed in OAB patients.

In order to estimate utility values for OAB health states, it become apparent that an alternative to method to EQ-5D was desirable. The algorithm developed by Yang (Yang et al., 2009) to map the disease specific OAB-q with the EQ-5D was used. Although OAB-q was not originally designed to assess utility values, Yang et al. (2009) built a model for deriving utilities from the 5 items forming the OAB-5D system based on a survey in the UK general population (South Yorkshire) using the Time Trade Off approach. The 5 items from the OAB-q retained in the OAB-5D covered the following HRQoL domains: urinary urgency, urine loss, impact on sleep, coping strategies, and concern due to severity of OAB symptoms. Each item had five levels of severity with 1 denoting no problem and 5 indicating an extreme problem.

Utility values were derived from three large international clinical trials (SCORPIO ARIES and CAPRICORN) comparing mirabegron with placebo and also used in the analyses performed in Publication 6. Both EQ-5D and OAB-q were included in the trials, in addition to the voiding diaries. Utility values were estimated according to OAB symptom severity according to the mean number of urination per day and the mean number of incontinence episode per day. These two outcome measures were selected as they are objective measures of OAB symptom severity and used as

primary endpoints in OAB trials. OAB symptom severity was defined on a 5 level scale as follows:

	Symptom frequency level	Level definition
Mean number of urination per day	1	<8
	2	8 - ≤ 10
	3	11 - ≤ 12
	4	12 - ≤ 14
	5	Over 14
Mean number of incontinence per day	1	0
	2	>0 - ≤ 1
	3	1 - ≤ 2
	4	2 - ≤ 3
	5	>3

Table 5.1 Definition of OAB symptom severity levels

Utility scores derived from the EQ-5D and OAB-5D were described as means and standard deviation for the overall population, and thereafter estimated by symptom severity. For each combination of number of urination and number of incontinence episodes, a linear regression model was used to estimate EQ-5D and OAB-5D utilities, adjusting for age, gender and study as fixed effect, and geographical region as random effect. In addition, Tobit and beta regression models were assessed with repeated measurements random effect. Minimizing the Root Mean Squared Error (RMSE) was used as a criterion to select the best model. Spearman correlation coefficient between EQ-5D and OAB-5D utilities were also estimated.

A test of sensitivity of the instruments was performed, with an assessment of the change in utility scores from baseline to week 12 according to change in symptoms severity.

The results showed that for the overall population, the mean utility score was lower with EQ-5D (0.82) than with OAB-5D, with values ranging from -0.59 to 1 for EQ-5D and from 0.61 to 1 for OAB-5D. A moderate correlation between EQ-5D and OAB-5D was found with a highly statistically significant spearman rank correlation coefficient of 0.34 ($p < 0.0001$). The mean EQ-5D and OAB-5D utility scores varied steadily with symptom severity with scores. Mean EQ-5D utilities ranged from 0.76 for the highest level of severity in mean number of urination to 0.85 to the lowest level of severity. Similarly, utility values ranged from 0.79 to 0.85 for the highest and the lowest level of severity in mean number of incontinence episodes, respectively. The mean OAB-5D utility values ranged from 0.80 to 0.90 depending on the severity in mean number of urination, and from 0.79 to 0.89 depending on the severity in mean number of incontinence episodes.

Difference in mean utilities between EQ-5D and OAB-5D were statistically significant for the lower levels in OAB symptom severity, indicating that the OAB-5D was more sensitive than EQ-5D to detect changes in patients with moderate symptoms.

Based on three models that were assessed, the linear model was selected as the best model for both EQ-5D and OAB-5D utility scores as it resulted in the lowest RMSE (0.08000 for EQ-5D and 0.20829 for OAB-5D). The estimated regression coefficients confirmed that utilities decreased with higher symptom severity after adjusting for patient characteristics. An improvement in severity in incontinence episodes from level 5 to level 1 was associated with an increase in 0.052 and 0.076 in EQ-5D and OAB-5D utility values, respectively.

The assessment of sensitivity to change for both instrument showed that the change from baseline in utility was greater with OAB-5D than with EQ-5D: the differences in utility change were +0.037 and +0.019 for severity in number of urination and +0.039 and +0.025 for OAB-5D and EQ-5D, respectively.

The analyses included in this paper were the first detailed analysis of EQ-5D and OAB5D utility scores in a large cohort of patients with OAB, and led to important information to be considered in HTA appraisal. The results showed that both EQ-5D and OAB-5D utilities increased when OAB symptoms improved. Utilities were similar between the two instruments for severe symptoms, but differed significantly for milder levels of severity, indicating that OAB-5D was able to assess a larger spectrum of

OAB symptoms due to its wider range of variation according to symptom severity. An important finding from the analysis is that despite the fact that incontinence is associated with higher impact on HRQoL as described in Publication 4, the number of urination also affect HRQoL significantly.

This study allowed to generate an equation for utilities for OAB health states based on OAB-5D and EQ-5D and can therefore be utilised in future research to estimate utility values from both instruments using clinical trials in which no utility instrument is included. This study has been part of the HTA submission for mirabegron in the UK (NICE 2013c) and several other HTA countries, and helped gained positive reimbursement recommendations for mirabegron.

These findings have been subsequently used in health economic evaluations that included OAB trials without utility measures (Nazir et al., 2015; Hakimi et al., 2018).

A limitation of this study include the fact that in the clinical trials that were used to perform these analyses, only a small proportion (8 to 12%) had a worsening of OAB symptoms from baseline to the end of the trials. This limits the applicability of this research for patient with worsening in symptoms. This is explained by the important placebo effect often observed in OAB trials in which even patients taking a placebo reach an improvement in OAB symptoms. This aspect should be explore in future research to assess if the findings of the present study is also applicable to patients with higher of symptom severity over time. Another limitation is that the models that were used did not account for potential effects of non-urological dimensions that may have been caused by bothersome side effect such as dry mouth or headache, which are often caused by OAB treatments. This was difficult to assess in the present research as the occurrence of side effects rarely coincide with the fixed time-points at which HQRoL was measured in clinical trials.

An important limitation of the approach taken in this study is related to the absence of alternative methods to derive utility values (such as vignette-based utilities). These would have been informative for the cost-effectiveness analysis of mirabegron by allowing a better characterization of the improvement with mirabegron in terms of utility values.

The next paper (Publication 8) will discuss how the utility values from both EQ-5D and OAB-5D were used in an economic analysis that has been used in the Single Technology Appraisal for mirabegron in the UK (NICE 2013c).

5.4 Publication 8: Aballéa S, Maman K, Thokagevistk K, Nazir J, Odeyemi IA, **Hakimi Z**, Garnham A, Toumi M. Cost Effectiveness of Mirabegron Compared with Tolterodine Extended Release for the Treatment of Adults with Overactive Bladder in the United Kingdom. *Clinical Drug Investigation 2015 Feb;35(2):83-93*

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Description and critical analysis of the study

The researcher has developed the model concept, designed the analysis, led the interpretation of the findings and drafted the manuscript. The other co-authors have participated in the analysis, interpretation of the findings and revision of the manuscript. The approach developed in this analysis has been further used by the research in another cost-effectiveness analysis conducted in 2018 (Hakimi et al. 2018) for another OAB product.

The objective of the study described reported in this paper was to perform a cost-effectiveness analysis of mirabegron compared to tolterodine from the UK National Health Service (NHS) payer perspective. This was the first health economic analysis of mirabegron since its launch in 2013 in the UK.

Mirabegron was the first representative of a new OAB drug class launched since several decades and it was important to assess its cost-effectiveness for health care decision-making purpose and reimbursement. A de novo Markov model was developed to analyse the cost-effectiveness of mirabegron 50mg per day as compared with tolterodine 4mg per day.

Several existing models in OAB based on a structure developed Kobelt et al., (1998) were available but had several limitations as they had a time horizon of 1 year and did not model after treatment drop-out. According to NICE, the time horizon should be sufficient to capture health outcomes and costs, which was only possible with a longer time horizon (NICE, 2013).

Efficacy and tolerability data for mirabegron and tolterodine were based on the SCORPIO (ClinicalTrials.gov NCT00689104), trial comparing mirabegron to placebo and included an active control arm with tolterodine. The model was programmed in Microsoft Excel 2007 and simulated changes in OAB symptom severity based on the number of urination and mean number of incontinence episodes, using the severity levels discussed in Publication 7. For each level of symptom severity, an utility value based on EQ-5D (base case) or OAB-5D (sensitivity analysis) was attached. For efficacy, the transition probabilities were based on the SCORPIO trial for the first 3 months of the model, and the efficacy was assumed constant after this period for the remaining time until the end of the time horizon.

Probabilities for switch and treatment discontinuations were dependent on adverse events as it is known that a primary reason for treatment discontinuation was due to the presence of bothersome adverse event due to OAB treatments (Sanchez et al., 2014).

The treatment discontinuation on mirabegron and the comparator was considered to be similar due to the absence of real world evidence studies assessing the persistence on mirabegron. Although not known at the time of the study, this hypothesis appeared to have been conservative as Chapple et al., (2017) demonstrated that mirabegron was associated with a higher persistence that antimuscarinics based on a large database analysis conducted in the UK.

Only direct costs were considered and were based on 2012 British pounds (GBP). An annual discount rate of 3.5% was applied on costs and outcomes. Several subgroups were considered (e.g previously treated, incontinent patients, elderly, men, women) to explore the costs effectiveness ratios amongst subgroup and identify those who may benefit the most.

The results of the model demonstrated that mirabegron was over 5 years, mirabegron was associated with a slightly higher costs than with tolterodine (1645 GBP compared to 1607 GBP). The utility gain, expressed in incremental QALY gained was higher with mirabegron than with tolterodine (0.013 vs 0.009). This is consist with the findings from Publication 7 which showed that the OAB-5D was more sensitive to change than EQ5D for changes in OAB symptom severity.

The incremental cost effectiveness ratios (ICERs) were 4386 GBP/QALY and 3008 GBP/QALY, which is well below the established willingness to pay threshold of 20000

GBP/QALY by NICE. Mirabegron remained cost-effective in all subgroup, with the exception of men, where the ICER was 38708 GBP/QALY.

The economic model has several strengths, as it was based on a head-to-head comparison of mirabegron and tolterodine, which limited the uncertainty based on indirect treatment comparisons. It demonstrated that mirabegron was highly cost-effective using both EQ-5D and OAB-5D utility values. The sensitivity analysis using OAB-5D reinforce the findings from the QALY gained based on EQ-5D as it has been shown in publication 7 that EQ-5D may not capture adequately the improvement in OAB symptoms for OAB patients with milder symptoms.

The findings of the study were instrumental in demonstrating the economic value of mirabegron from the NHS UK perspective and have influenced the reimbursement guidelines in the UK for mirabegron. This had a significant implication for OAB patients in the UK who gained access to mirabegron as an treatment alternative to treat OAB symptoms.

A limitation of the analysis is that the utility gained was not based on urinary urgency, which is the cornerstone symptoms of OAB. This has been decided when conducting the economic analysis as urinary urgency is measured using different scales in different trials and is somewhat subjective. It was therefore considered more robust to capture the effect on HRQoL based on objectively assessed symptoms (number of urinations and number of incontinence). In the future, in case urinary urgency can be assessed in a consistent manner across OAB trials based on a validated instrument, it could be included in cost-effectiveness analyses.

Although the model has been successfully submitted to NICE and led to the positive recommendation on the use of mirabegron in OAB patients, alternative model structures could have been tested. This includes the model structure published by Kobelt (Kobelt et al 1998) , as even if not considered suitable for the NICE submission of mirabegron due to the limitations described in this section, it would have allowed to compare the results with the published cost-effectiveness data on tolterodine, and further inform HTA decisions.

5.5 Chapter summary

The articles presented in this chapter critically appraised how utility values are estimated for OAB patients, and how these have been used in the first economic evaluation for mirabegron that has been submitted to the UK NICE as part of the Single Technology Appraisal. In the first paper, the analysis of EQ-5D based on three large clinical trials demonstrated that mirabegron was superior to tolterodine based on EQ5D utility values. The limitations of EQ-5D, including its ceiling effect and inability to capture some of the HRQoL aspect of OAB have been discussed. In the second paper, the utility calculations based on health states to be used in an economic model have been discussed. These included the estimation of OAB-5D utility values in addition to EQ-5D utility values in order to overcome some of the limitation of EQ-5D, especially its relative insensitivity to treatment effect in AOB.

In the third manuscript it has been demonstrated that mirabegron was a cost-effective treatment compared to tolterodine using utility values from both EQ-5D and OAB-5D. This was a critical finding as it led to the recommendation of mirabegron as a treatment for OAB by the UK NICE and therefore has a key impact on clinical practice.

The next chapter presents the summary, recommendations for future research and conclusions of the thesis.

Chapter 6: Summary, recommendations and conclusions

6.1 Summary

Health Technology Assessment bodies conduct an appraisal of the value of new treatments to optimise allocation of health care resources and improve clinical and humanistic outcomes. Value of innovative treatments in healthcare are usually considered in terms of clinical, economic, humanistic outcomes and public health benefits.

In order to inform appropriately the health care decision making process in relation to HTA appraisal, it is important to understand the patient perspective using robust methodologies and validated PRO instruments as presented in chapter 1 of this thesis. This is particularly relevant in overactive bladder as it is a symptomatic debilitating disease that although not life threatening, has a significant impact on patient's HRQoL and a high financial burden for the society.

The aim of this thesis was to provide an understanding and a critical assessment of HRQoL for treatments of OAB in relation to Health Technology Assessment. Through the presentation and critical review of eight manuscripts published in peer-reviewed journals, different aspects of the OAB patients perspective were assessed. Each paper was used to demonstrate an element of the patient perspective that is of importance for reimbursement decision and health technology appraisals.

The findings of this research have been part of the Single Technology Appraisal for mirabegron by the UK NICE, which has recommended the use of mirabegron within the UK NHS (NICE 2013c). It has also been used in part of totality for HTA submissions in Canada, South Korea and Sweden.

This chapter examines the contribution and implications of the research, its limitation and propose recommendations for future research.

6.2 Contribution to knowledge

Chapter 3 of this thesis investigated the patient perspective through qualitative research with OAB patients as well as patients and physicians preferences for efficacy and safety treatment attributes. Although several PRO instruments capturing patient's HRQoL have been developed in OAB over the past two decades, no adequate qualitative research - that should form that basis of PRO development (FDA, 2009) - were reported in the literature. The elicitation of HRQoL concepts was the first comprehensive qualitative research assessing the key HRQoL dimensions affected by OAB in both dry and wet OAB patients. The findings can be used to develop further new or modify existing PRO instruments, and to substantiate the burden of the disease for HTA or regulatory decision making.

Chapter 4 examined how the improvements of objectively assessed OAB symptoms (mean number of urinations per day and mean number of incontinence per day) were translated into patient relevant benefit. The single and double responder analyses on both objective and subjective endpoints reported in Publication 3 demonstrated for the first time that the combination of mirabegron and solifenacin was clearly superior to solifenacin monotherapy with a higher likelihood to be responder on both OAB symptoms and HRQoL. This type of analysis is now routinely performed in OAB trials to demonstrate the patient benefit of OAB treatments. Publication 4 was the first to assess the impact of mirabegron on HRQoL separately in dry and wet OAB patients, demonstrating that the impact of OAB symptoms on HRQoL was more profound in incontinent patients than in patients with no incontinence at baseline. The analyses reported on Publication 5 consisted of single and double responder analyses and were the first to assess the clinical relevance of a new fixed dose combination of solifenacin and Tamsulosin Oral-Controlled Absorption System. In this manuscript, it was also demonstrated that OAB symptoms were correlated with HRQoL. This was a specific requirement from the regulatory authorities in the Netherlands (MEB) who requested this to be demonstrated in the context of the regulatory approval of Vesomni.

Chapter 5 investigated how utility values were generated in OAB to inform health economic models that were used to support reimbursement decisions on mirabegron in the UK by NICE (NICE 2013c). The studies discussed in this chapter have

supported the demonstration of the economic value of mirabegron. The positive recommendation from NICE for mirabegron allowed OAB patients to gain access to mirabegron as a treatment alternative. Publication 6 was the first detailed analysis on EQ-5D in OAB based on three large OAB clinical trials. The study demonstrated that mirabegron was superior to tolterodine in terms of EQ-5D utility values. The study reported in Publication 7 was the first to assess both EQ-5D and OAB-5D utility values according to OAB symptom severity (based on incontinence and number of urination per day). These results allowed to perform the first economic analysis assessing the cost-effectiveness of mirabegron compared to tolterodine reported in Publication 8. The economic model has been submitted as part of the NICE Single Technology Appraisal for mirabegron and led to the recommendation to use mirabegron within the UK NHS.

Since the last manuscript presented in this thesis (2016), the researcher has published 22 peer-reviewed manuscripts, including real-world evidence studies, systematic reviews of the literature, cost-effectiveness analyses and PRO development and validation. The analyses included in these manuscripts were designed by the researcher to generate data necessary for HTA submissions of innovative medicines in different therapy areas, from urology (OAB, Interstitial Cystitis), to hematology (hemophilia), immunology (cytomegalovirus infections in transplant patients). The researcher is also a reviewer of several peer-reviewed journals, and is providing health economics lectures at the university of Aix-Marseille.

Due to the extensive knowledge and expertise gained by the researcher throughout his research career, the researcher is now (since 2021) leading a team of 4 health economists with global responsibilities in terms of evidence generation for HTA submissions.

6.3 Implications of the thesis

This thesis represents a well-integrated body of evidence demonstrating by different techniques and analyses how the patient perspective can be investigated to demonstrate the value of therapies in OAB and inform the HTA decision-making process. The scope of the work included in this thesis covered qualitative research,

preference studies, analysis of PRO data from clinical trials, utility values assessment and economic modelling. This work has been part of the reimbursement submissions for mirabegron monotherapy or in combination with solifenacin in several countries (UK, Sweden, Spain, Austria, Canada, South Korea) and led to positive recommendations and inclusion of mirabegron in formularies.

The findings from the studies included in this thesis have several implications, especially on the need for improved communication between patients and physicians. In chapter 3, it has been shown in the discrete choice experiments that the treatments attributes related to treatment choices differ greatly between patients and physicians. In this study, it was found that patients may overestimate the risk of safety events when they consider these serious (such as cardiovascular risk) even if the probability of these events is very low (well below 1%) and can be managed in routine clinical practice. This showed that there is a need to educate the patients to ensure they understand the implications of side effects described in the patient leaflets or mentioned by their treated physician, as this may have implication on treatment initiation or persistence.

On the other hand, treating physicians who consider efficacy attributes as the most important in their treatment decisions may not sufficiently consider the issues associated with bothersome side effects (such as dry mouth), even though this is known to be one of the leading causes of treatment discontinuation (Oefelein et al., 2011; Sexton et al. 2011). It is therefore important to ensure that physicians can apprehend better the occurrence of bothersome side effects to improve persistence with treatment.

Another implication of this work results from the detailed analysis of the EQ-5D, which demonstrated a clear ceiling effect in OAB patients, and an inability to capture treatment benefit in OAB patients with mild to moderate OAB symptoms. This indicates that EQ-5D may not be the appropriate instrument to be used in this patient population, and that other ways of assessing utility values should be used when assessing the cost-effectiveness of OAB treatments in patients with milder symptoms. This has been illustrated in this thesis when the utility values from EQ-5D and the disease specific OAB-5D have been compared, showing the lack of

sensitivity of EQ-5D in the patients with moderate symptoms, and the fact that OAB-5D was more appropriate in this setting.

Finally, a key implication of this research has been for OAB patients, as the demonstration of the value of mirabegron helped secured access to mirabegron in several HTA countries (including UK, Sweden, Canada and South Korea).

6.4 Learning trajectory

Since the completion of the studies presented in this thesis, the author has gained significant learnings and has become more methodically and research literate over time. One the elements that the author has improved since the studies published in 2016 is to systematically consider the inclusion of patients as part of the research team in studies involving HRQoL data collection (such as Publication 1, Chapter 3). Patient representatives have become an integral part of the regulatory and HTA processes and their perspective is has played a significant role in health care decision making, especially in rare diseases. One of the most recent example is the role played by the Parent Project Muscular Dystrophy advocacy group (advocacy group representing parents of patients with Duchesne Muscular Dystrophy), which has played a decisive role in the drug approval for a new treated for Duchesne Muscular Dystrophy in 2016 through close involvement in the regulatory process with FDA (Crossnohere et al. 2020). This was therefore identified by the author as one of important elements to improve in future studies, and is reflected in one of the latest research published by the author on the assessment of the burden of disease in patients with Paroxysmal Nocturnal in which patient representatives from UK and Germany have been integral part of the research team (Panse et al., 2022).

Another important element that the author has implemented in his research beyond the papers from 2016 is the conduct of in depth analysis of PRO instruments, beyond the analysis of existing domains and total scores as presented in Publications 3, 4 and 5 in Chapter 4). After careful review of several PRO instrument, the author has concluded that PRO instruments often violate the assumption of unidimensionality, and therefore their interpretability may be problematic. This limitation has also be reported in the literature by several researchers (Hudgens et al., 2018; McKenna and Heaney et al., 2021). In order to enhance the interpretability of the PRO results,

the researcher has therefore designed and conducted item-level analyses of the Haem-A-QoI in people with hemophilia A and B to improve the understanding of the improvement observed on the different items measuring pain from the 'Physical Health' domain. These studies have now been published in peer reviewed journals (Pasi et al., 2022; Astermark et al., 2022)

6.5 Limitations of the thesis

The work included in this thesis had some limitations. First, the studies conducted were conducted in the western world and therefore may not be applicable in different settings: The qualitative research and discrete choice experiment studies were conducted in different European countries with consistent findings, but the patient perspective and treatment decisions may differ in different regions of the world. This limits the applicability of the findings to countries with similar cultures or health care systems.

A second limitation resides in the relatively small sample size included in the qualitative research discussed in chapter 3. Qualitative studies generally require a limited sample size to identify key HRQoL concepts, but any bias in patient recruitment has the potential to influence the findings. These biases could be due to an over or underrepresentation of patients based on disease severity, gender, education or other important element that can influence the impact of the disease on HRQoL.

A third limitation is in the fact that findings from real-world evidence studies has not be part of the scope of this thesis. It is especially important for the analysis of PRO data from OAB clinical trials described in chapter 4 of this thesis. Although clinical trials represent the gold standard to demonstrate efficacy and safety of medical treatments, these have several limitations. It is known that clinical trials have highly selected patient populations, limited length of follow-up and are conducted in a controlled environment which often differ from clinical practice in the real world. This limitation should therefore be considered when interpreting the findings of the PRO analysis and the clinical relevance of the treatment benefit of mirabegron in real-world discussed in this chapter.

Finally, although consistent with epidemiology of OAB, the vast majority of the patients recruited in the studies presented in this thesis consisted of women. This also limits the conclusion that can be drawn from the thesis to this subgroup of patients as male OAB patients may have been underrepresented.

6.6 Recommendation for future research

Based on the findings and limitations from this thesis, several recommendations for future research can be defined to further improve how the patient perspective is taken into account when assessing the value of OAB medications or in HTA decision making process.

On the qualitative research and patient preference aspects discussed in chapter 3, there is a need to confirm the findings in other regions of the world including countries with different cultures and health care systems. The perception of the disease and its impact on HRQoL can be differ across countries and continents (Atkinson et al., 2006) and any additional qualitative study assessing the cross cultural difference in OAB is warranted to further assess how of these findings can be generalisable. Similarly, additional studies should be conducted in different of health care systems, with varying levels of health care cost coverage, access to physician or medications. This would provide valuable information to establish how differences in health care systems influence patient's and physician's decision making process when choosing medications.

The PRO analyses that demonstrated the clinical relevant of the improvement of OAB symptoms reported in Chapter 4 were conducted based on randomised clinical trials data, which have limitations described in section 6.4. It is recommended to repeat this research in large real-world studies with long term follow up to confirm these findings. Such studies could also explore how the improvement in HRQoL is linked to persistence with treatment which is an important element to be taken into account in health economic evaluations. It has to be noted that real world evidence studies have their inherent limitations (reference) and findings from such studies should also be assessed together with findings from clinical trial data.

On the assessment of utility values and economic evaluation, further research is warranted on estimation of utility across the spectrum of severity of OAB symptoms.

6.7 Conclusions

In conclusion, the research presented in this thesis demonstrated the impact on quality of life in patients with OAB and the influence of the condition on patients preferences and treatment choices. These studies helped characterised the key aspects evaluated during the HTA decision making process such as disease burden, preferences with treatment, clinical relevance of treatment benefit and health-economic evaluation. The studies discussed in this thesis were included in HTA submissions of several European countries, and influenced reimbursement guidelines in the management of OAB by different HTA bodies such as NICE in the UK, TLV in Sweden, CADTH in Canada and HIRA in South Korea. In particular, this research contributed to the recommendation of mirabegron as a treatment for OAB within the NHS in the UK due to the clinical relevance of the treatment benefit, improvement in HRQoL and value for money demonstrated through a robust cost-effectiveness analysis.

Although this work was conducted in OAB, this research on the patient perspective is generalisable to other diseases or conditions to demonstrate the impact of treatments on the patient HRQoL enabling efficient allocation of limited healthcare resource by decision makers to achieve optimal value for money.

The limitations of this research can be addressed by repeating some of the studies in different regions of the world to ensure consistency of the findings within different cultures and health care systems. This should be complemented by conducting real world evidence studies confirming that the treatment benefit of OAB drugs observed during clinical trials is also demonstrated in real life.

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Appendices

Appendix 1: List of Articles Included in the Thesis

1. Hawken N, **Hakimi Z**, Aballéa S, Nazir J, Odeyemi IAO, Toumi M. Elicitation of Health-related Quality-of-life Concepts Associated with Overactive Bladder: A Qualitative Study JHEOR 2016;4(2):127-40
2. Heisen M, Baeten SA, Verheggen BG, Stoelzel M, **Hakimi Z**, Ridder A, van Maanen R, Stolk EA. Patient and physician preferences for oral pharmacotherapy for overactive bladder: two discrete choice experiments. Curr Med Res Opin. 2016;32(4):787-96
3. MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, Saleem T, Huang M, Siddiqui E, Stölzel M, Hemsted C, Nazir J, **Hakimi Z**, Drake MJ. Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy. Urol. 2016 Sep;196(3):809-18
4. Khullar V, Amarenco G, Angulo JC, Blauwet MB, Nazir J, Odeyemi IA, **Hakimi Z**. Patient-reported outcomes with the β3 -adrenoceptor agonist mirabegron in a phase III trial in patients with overactive bladder. Neurourol Urodyn. 2016 Nov;35(8):987-994
5. Drake MJ, Sokol R, Coyne K, **Hakimi Z**, Nazir J, Dorey J, Klaver M, Traudtner K, Odeyemi IA, Oelke M, van Kerrebroeck P; NEPTUNE study group. Responder and health-related quality of life analyses in men with lower urinary tract symptoms treated with a fixed-dose combination of solifenacin and tamsulosin oral-controlled absorption system: results from the NEPTUNE study. BJU Int. 2016 Jan;117(1):165-72
6. Pavesi M, Devlin N, **Hakimi Z**, Nazir J, Herdman M, Hoyle C, Odeyem IA. Understanding the effects on HR-QoL of treatment for overactive bladder: a detailed analysis of EQ-5D clinical trial data for mirabegron. J Med Econ. 2013 Jul;16(7):866-76
7. Desroziers K, Aballéa S, Maman K, Nazir J, Odeyemi I, **Hakimi Z**. Estimating EQ5D and OAB-5D health state utilities for patients with overactive bladder. Health Qual Life Outcomes. 2013 Nov 19;11:200

8. Aballéa S, Maman K, Thokagevistk K, Nazir J, Odeyemi IA, **Hakimi Z**, Garnham A, Toumi M. Cost effectiveness of mirabegron compared with tolterodine extended release for the treatment of adults with overactive bladder in the United Kingdom. Clin Drug Investig. 2015 Feb;35(2):83-93

Appendix 2: Percentage Author's Contribution to the Articles Included in the Thesis

	Articles	**Percentage Contribution**
1	Hawken N, **Hakimi Z**, Aballéa S, Nazir J, Odeyemi IAO, Toumi M Elicitation of Health-related Quality-of-life Concepts Associated with Overactive Bladder: A Qualitative Study JHEOR 2016;4(2):127-40	40%
2	Heisen M, Baeten SA, Verheggen BG, Stoelzel M, **Hakimi Z**, Ridder A, van Maanen R, Stolk EA. Patient and physician preferences for oral pharmacotherapy for overactive bladder: two discrete choice experiments. Curr Med Res Opin. 2016;32(4):787-96	20%
3	MacDiarmid S, Al-Shukri S, Barkin J, Fianu-Jonasson A, Grise P, Herschorn S, Saleem T, Huang M, Siddiqui E, Stölzel M, Hemsted C, Nazir J, **Hakimi Z**, Drake MJ Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy. Urol. 2016 Sep;196(3):809-18	30%
4	Khullar V, Amarenco G, Angulo JC, Blauwet MB, Nazir J, Odeyemi IA, **Hakimi Z**. Patient-reported outcomes with the β3 -adrenoceptor agonist mirabegron in a phase III trial in patients with overactive bladder. Neurourol Urodyn. 2016 Nov;35(8):987-994	30%
5	Drake MJ, Sokol R, Coyne K, **Hakimi Z**, Nazir J, Dorey J, Klaver M, Traudtner K, Odeyemi IA, Oelke M, van Kerrebroeck P; NEPTUNE study group. Responder and health-related quality of life analyses in men with lower urinary tract symptoms treated with a fixed-dose combination of solifenacin and tamsulosin oral-controlled absorption system: results from the NEPTUNE study. BJU Int. 2016 Jan;117(1):165-72	25%
6	Pavesi M, Devlin N, **Hakimi Z**, Nazir J, Herdman M, Hoyle C, Odeyem IA. Understanding the effects on HR-QoL of treatment for	40%

	overactive bladder: a detailed analysis of EQ-5D clinical trial data for mirabegron. J Med Econ. 2013 Jul;16(7):866-76	
7	Desroziers K, Aballéa S, Maman K, Nazir J, Odeyemi I, **Hakimi Z**. Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder. Health Qual Life Outcomes. 2013 Nov 19;11:200	30%
8	Aballéa S, Maman K, Thokagevistk K, Nazir J, Odeyemi IA, **Hakimi Z**, Garnham A, Toumi M. Cost effectiveness of mirabegron compared with tolterodine extended release for the treatment of adults with overactive bladder in the United Kingdom. Clin Drug Investig. 2015 Feb;35(2):83-93	25%

Appendix 3: List of Publications by the Researcher in Peer Reviewed Journals

1. Mancuso ME, Castaman G, Pochopien M, Aballéa S, Drzewiecka A, **Hakimi Z**, Nazir J, Fatoye F. Cost-minimization analysis of recombinant factor VIII Fc versus emicizumab for treating patients with hemophilia A without inhibitors in Europe. J Med Econ. 2022 Jan-Dec;25(1):1068-1075.

2. Cella D, Sarda SP, Hsieh R, Fishman J, **Hakimi Z**, Hoffman K, Al-Adhami M, Nazir J, Cutts K, Lenderking WR. Changes in hemoglobin and clinical outcomes drive improvements in fatigue, quality of life, and physical function in patients with paroxysmal nocturnal hemoglobinuria: post hoc analyses from the phase III PEGASUS study. Ann Hematol. 2022 Jul 23

3. Panse J, Sicre de Fontbrune F, Burmester P, Piggin M, Matos JE, Costantino H, Wilson K, **Hakimi Z**, Nazir J, Desgraz R, Fishman J, Persson E, Kulasekararaj A. The burden of illness of patients with paroxysmal nocturnal haemoglobinuria receiving C5 inhibitors in France, Germany and the United Kingdom: Patient-reported insights on symptoms and quality of life. Eur J Haematol. 2022 Jun 23

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9. Astermark J, Wojciechowski P, Aballéa S, **Hakimi Z**, Nazir J, Klamroth R. Efficacy of rFIXFc versus rIX-FP for the Treatment of Patients with Hemophilia B: Matching-Adjusted Indirect Comparison of B-LONG and PROLONG-9FP Trials. J Blood Med. 2021 Jul 14;12:613-621

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