Informing coverage and reimbursement decisions of medical devices: evidence from acute wound care and musculoskeletal disorders

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Informing coverage and reimbursement decisions of medical devices: evidence from acute wound care and musculoskeletal disorders

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Abstract

The burden of wounds and musculoskeletal (MSK) disorders are rising, primarily due to higher life expectancy and the growing epidemic of associated chronic diseases. This has made identifying technologies that can improve patient outcomes at the lowest cost possible an increasingly important pursuit. The aim of this thesis was to evaluate the clinical and economic evidence used to inform coverage and reimbursement decisions of medical devices using examples from wound care and MSK disorders. This thesis presents and offers a critique of 8 of my publications, which either updated, and or contributed to new knowledge in the field. The clinical effectiveness of wound and MSK disorders was explored via systematic literature reviews, meta-analysis, and indirect treatment comparison. The clinical evidence was then used to inform the cost-effectiveness analysis of these interventions in these patient populations.

The result of the analyses assessed for this thesis demonstrate; that for burn wound care, ACTICOAT was the most cost-effective compared with other silver dressings, whereas the use of PICO negative pressure wound therapy following surgical incision was cost-saving from a payer's perspective compared with standard care. Lastly, in MSK disorders, the use of twin-screw intra-medullary nail InterTAN was found to be cost-saving from a payer's perspective compared with single-screw nails in patients with unstable trochanteric fractures. Using examples of wound and MSK disorders, the thesis demonstrates that when clinical and cost-evidence are utilised, clinicians and payers are able to make decisions that optimise patients' outcomes as well as their budgetary spend. This was illustrated in the United Kingdom's National Health Service, where PICO negative pressure wound therapy was granted widespread coverage, and the South Korean Health authority granting a 10% price increase for InterTAN citing evidence presented in this

thesis. The strengths and limitations of this thesis was highlighted and recommendations suggested for future research.

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1 Chapter 1: Introduction

Health care systems around the world are under increasing financial pressures. With the exponential growth in the introduction and uptake of health technologies, governments and health care providers are challenged to use available resources as efficiently as possible in order to maximize population health. As such, providers are expected to deliver higher-quality health care for patients with the same amount of money or at times less, (Hawkes, 2012). This has placed greater emphasis on purchasing interventions, which provide the best health outcomes at less costs, thus necessitating that choices are made between competing alternatives (Drummond *et al*., 2005).

Currently, the most common method to facilitate choice between competing medical technologies or devices is a health technology assessment (HTA), which is used to ascertain the relative costs and benefits of health care interventions (Ciani *et al.,* 2017). The information gained from HTA is then used to aid priority setting by supporting clinical, reimbursement, or coverage decisions (EUnetHTA, 2015; Ciani *et al.,* 2017). The European Network of Health Technology Assessment (EUnetHTA) has recommended that currently established evidence assessment methodology used in pharmaceutical evaluations be applied in medical devices. However, the Advanced Medical Technology Association (AdvaMed) observed that, given the diversity in medical technologies, a "one-size-fits-all" approach to evidence, would be unsuitable and impractical (Miller, 2017), thus, a more flexible approach to evidence evaluation should be considered.

In order to address the increasing needs for evidence, manufacturers have responded by hiring professionals with competencies in health economics and outcomes research (HEOR). HEOR departments within manufacturing organisations provide evidence for a payer audience through groups such as HTA bodies or Pricing and Reimbursement/Formulary committees. Clinical and health economic evidence is needed to support the value proposition of health care interventions. This proposition, in turn, must consider the impact of the intervention on health outcomes and the economic consequences of implementing the intervention.

1.1.1 Motivation for research

I have been working in the field of Health Economics and Outcomes Research (HEOR) for the past 16 years. In the past 7 years, I have specialised in medical devices, and my research has focused on wound care and orthopaedic trauma devices. My research interest in wound care and orthopaedics has been informed by the business needs of my employer Smith and Nephew Inc, who operates a three-franchise business model focusing on: Wound care, Orthopaedics, and Sports medicine. The research that I conducted as part of my employment forms the basis of my thesis and I used examples from wound care and musculoskeletal (MSK) disorders, to demonstrate the clinical and economic value of the devices to patients, the payers and clinical audience.

The use of wound care and MSK disorder publications in this thesis was deemed appropriate, as the methodology and evidence requirements for the medical devices are similar. Both wound care and MSK disorders require careful appraisal of clinical evidence

as they impose a major cost burden to society and healthcare systems which will grow further as the global population continues to age. The clinical evidence is then used to inform the economic modelling to generate cost-effectiveness evidence. The totality of clinical and cost-effectiveness evidence together with other considerations, is then used to inform coverage and reimbursement decisions, which optimises the health outcomes of the patients, budgets for payers and profits for manufacturers.

1.1.2 Medical devices and the challenges of conducting HTA

The term medical device is defined by the World Health Organisation, as an article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose. Typically, the mechanism of action of a medical device is physical which is not achieved by pharmacological, immunological or metabolic means (WHO Medical Devices Technical series, 2011). Medical devices therefore, cover a huge range of healthcare products and equipment such as surgical gloves, wound care dressings, orthopaedic implants and many other instruments. The thesis will adopt this definition, and also sometimes will use the term medical technologies as a synonym.

Medical devices have unique characteristics which can present challenges in performing Health technology Assessment and hence usually have a lower bar of evidence requirements when compared to pharmaceuticals (Miller, 2017). For instance, there is a learning curve challenge when working with medical devices owing to the interaction

between the operator and the device. The learning curve affects the clinical performance of new devices when compared to standard care since clinicians take time to reach levels of competency and proficiency when using new devices. This makes it difficult for early studies to find true difference between new device and the standard of care (Sorenson *et al.,* 2011; Taylor and Iglesias, 2009). As a result, medical devices work only if they are used correctly and their effectiveness relies on the skills and experience of the physician using them among other factors.

In addition, it is difficult to conduct RCTs of medical devices due to few candidate patients of a new device or the learning curve effect where clinicians are not certain of the merits of the new device especially if they are invasive (Sorenson *et al.,* 2011). Furthermore, the small sample sizes and short follow up makes it difficult to detect statistically significant differences and demonstration of the true value of the device which increases the uncertainty associated with the new medical devices (Taylor and Iglesias, 2009).

A further challenge in conducting HTA in medical devices is genericization and class effect, that is assuming a class effect. This can be a flawed assumption since devices differ in their mode of action and properties, making it difficult to extrapolate clinical evidence even of similar brands (Drummond *et al.,* 2009; Sorenson *et al.,* 2011). There is also a challenge of rapid incremental innovations for medical devices. This impacts on the ability to conduct RCTs which usually require longer periods to complete by which time the device will be obsolete (Drummond *et al.,* 2009; Taylor and Iglesias, 2009). For these and other reasons, it therefore important to consider a variety of sources of evidence when evaluating the

clinical and cost effectiveness of medical devices. This can include both RCTs, observational evidence from registry studies, or real-world evidence to ensure timely access of innovative technologies for patients. Equally, when medical devices have gathered enough evidence, rigorous assessment of evidence should be conducted similar to the one for pharmaceuticals.

1.1.3 Reimbursement

In this thesis, reimbursement is defined according to Bruen *et al.,* (2016) which is an umbrella term for the policies and practices that define the terms of coverage and payment for a medical device, it encompasses the implicit or explicit decisions by payers (such as Medicare and Medicaid in the United States of America (US), United Kingdom National Health Service (UK NHS). The policies establish whether or not a device delivers sufficient benefit to be covered, the terms under which a device is covered and define the method of payment to the provider, dispenser or supplier of a healthcare technology (Bruen *et al.,* 2016)

1.2 Overall aim of the thesis

Using previously published work by the researcher, this thesis evaluates the clinical and economic evidence used to inform coverage and reimbursement decisions for medical devices using examples from wound care and MSK disorders.

1.2.1 Objectives of the thesis are to:

1. Provide an overview of the types of clinical data and methods used to synthesize the evidence for coverage and reimbursement decisions making with reference to wound and MSK disorders

2. Give an overview of the main types of economic evaluations and economic modelling techniques used to support coverage and reimbursement decisions in both wound and MSK disorders

3. Critically appraise each of the author's published studies, noting the incremental contribution to the body of knowledge and the influence of the new insights in the field

4. Draw conclusions and suggest areas of future research

1.3 Thesis Overview

This thesis presents clinical and economic evidence used to inform coverage and reimbursement decisions of medical devices. It is based on 8 of the researcher's works published between 2017 and 2018: 5 in acute wound care and 3 in MSK disorders (in particular, orthopaedic hip fractures).

Chapter 1: Introduction and the aims of the PhD thesis.

Chapter 2: Highlight the burden of wound care and MSK disorders, with special reference to burn wounds, surgical site complications, and hip fractures, as well as the existing evidence gaps.

Chapter 3: Provides a brief overview of the types of clinical and economic evidence used for medical decision making.

Chapter 4: Examines the clinical effectiveness of advanced wound care devices, with a focus on silver dressings used in burn care, using systematic review and indirect treatment comparison methods.

Chapter 5: Examines the cost-effectiveness evidence in wound care, in particular

1. Cost-effectiveness evidence from burn wound care using clinical effectiveness publications presented in Chapter 4.
2. Cost-effectiveness evidence from single use negative pressure wound therapy device to prevent surgical site complications using clinical evidence from randomised controlled trials.

Chapter 6: Examines the clinical effectiveness evidence of orthopaedic implants in managing patients with trochanteric fractures, with a special focus on intramedullary nails.

Chapter 7: Examines the cost-effectiveness of intramedullary nails in patients with trochanteric fractures using evidence from the clinical effectiveness publications in Chapter 6.

Chapter 8: Provide a key summary of the research and conclusions highlighting implications for patients, clinical practice, healthcare policy, and recommendations for future research.

1.4 Conclusion

This chapter has introduced the motivation, and highlighted the motivation, aims and objectives of the thesis.

The following chapter will provide background on the burden of wounds, with particular reference to burn wounds and surgical site complications. Furthermore, evidence on the burden of MSK disorders, with special reference to hip fractures will be discussed including evidence gaps for both wound care and MSK disorders.

2 Chapter 2: Background to wound care and musculoskeletal disorders

2.1 Introduction

Chapter 1 outlined the aim of the thesis and the context as to why it is necessary to have good clinical and cost-effectiveness evidence to support clinicians and payers in their objective efforts to optimise health outcomes for their patients. This chapter provides background to wounds and MSK disorders, including the rational for conducting this research by outlining the evidence gaps.

2.2 Burden and costs of wound care

According to Guest *et al.,* (2017), wounds are managed across the spectrum of different healthcare disciplines, including general practice, specialist physicians, and allied healthcare practitioners. Wounds can either be chronic, (those that have not progressed through the normal process of healing and are open for more than a month) or acute, (those wounds that heals uneventfully with time) (Sen, 2019). Although the true burden of wounds is unknown, they have a rough prevalence estimates in developed countries of between 1-2% of the general population (Guest *et al.,* 2017).

Between 2012 and 2013, the United Kingdom's National Health Service (UK NHS) managed an estimated 2·2 million patients with a wound at an estimated annual cost of £5.3 billion including associated comorbidities (Guest *et al.,* 2017). Of the reported 2.2 million wounds, 4% were burn wounds and 11% were surgical wounds respectively. In the United States

(US) nearly 14% of Medicare beneficiaries had at least one type of wound or infection, and surgical infections were the largest prevalence category (4.0%). Total Medicare spending estimates for all wound types ranged from $28.1 to $96.8 billion (Nussbaum *et al.,* 2018). This thesis focused on burn and surgical wounds to illustrate how comparative clinical and cost-effectiveness evidence can be or has been used to inform coverage and reimbursement decisions in healthcare.

2.3 Burn wounds

Burns are a common type of traumatic injury that causes considerable morbidity and mortality (Brusselaers *et al.,* 2013). Globally burn injuries account for an estimated 180,000 deaths annually and non-fatal burns are a leading cause of morbidity, including prolonged hospitalization, disfigurement, and disability (WHO Burn Fact Sheet, 2018). In the United States alone, over 400,000 people require medical care for burn injuries each year, leading to 40,000 hospitalisations costing around $1 billion per year (American Burns Association, 2016). Furthermore, in the United Kingdom, one study found that a burn patient costs at least twice as much compared with other hospitalised patients (Pellatt *et al.,* 2010). Indirect costs of burn wounds, such as lost wages and prolonged care for emotional trauma, also contribute to the socioeconomic burden.

Treatment of burn injuries is aimed at controlling infection which remains the leading cause of morbidity and mortality. Treatment goals also include promoting healing, with good aesthetic outcomes and thus improving the quality of life of the patients (Wasiak *et al.,* 2013). Topical antimicrobial therapy is mainly used to treat burn wounds, and silver-

containing products are the preferred choice of treatment given their impact on infection control (Wounds International 2012, EBA 2017). Silver sulfadiazine (SSD) has been the standard treatment for partial-thickness burns, however, SSD has well documented challenges, such as the need for frequent dressing changes (Atiyeh *et al.,* 2007; Brusselaers *et al.,* 2010; Wounds International 2012; EBA, 2017). Newer, improved silver delivery systems designed to overcome some of these problems have become available over the past few decades. These include nanocrystalline silver (ACTICOAT™ Smith & Nephew Hull, UK), silver hydrofiber dressing (AQUACEL® Ag, ConvaTech, Bridgewater, NJ), and silver-impregnated foam dressings (Mepilex® Ag, Mölnlycke, Göteborg, Sweden), collectively referred to as "newer silver dressings" in this thesis.

2.3.1 Evidence gaps in burn wound care

A systematic literature review was conducted from various medical databases such as the MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews, assessing the use of silver dressings in burn wounds, in particular the use of SSD compared with ACTICOAT and other newer silver dressings. These databases are preferred as they contain up-to-date and relevant medical literature (Bramer *et al*., 2017). One systematic review and meta-analysis (Gravante *et al.,* 2009) was identified which compared ACTICOAT with SSD, and concluded that ACTICOAT was superior with regards to infection control and pain in burn patients. However, evidence on length of stay (LOS) was not conclusive and the incidence of surgical procedures was not reported in this study. Another review of ACTICOAT evidence (Khundkar *et al.,* 2011) found that ACTIOAT had superior antimicrobial activity and reduces healing time when compared to another available silver dressings.

Furthermore, no studies were identified which compared the newer silver dressings against each other both from a clinical and cost-effectiveness point of view in patients following burn injury, in spite of the fact that these dressings are widely used in clinical practice.

The European Burns Association's (EBA) clinical practice guidelines, which according to Paprottka *et al*., (2016) have the most comprehensive treatment recommendations, offer no definitive guidance as to which silver dressing should be preferred over the other when managing burn patients. Rather, the EBA advises clinicians to 'be creative in choosing silver burn dressings because there is no direct clinical evidence to support the choice of one dressing over another' (EBA, 2017 :39).

The research presented in this thesis addressed this evidence gap by comparing the clinical and cost-effectiveness of newer silver dressings in burn patients. This was achieved by conducting systematic literature review and meta-analysis of all available comparative evidence of randomised controlled trials (RCTs) and observational studies). The research further ranked the silver dressing according to cost-effectiveness in order to offer unambiguous guidance to clinicians and payers as to which silver dressing should be used first clinically and reimbursed.

2.4 Surgical site complications

One of the main goals of wound care after surgery is to ensure that the wounds heal rapidly without complications (such as infections and dehiscence) according to the World Union of Wound healing Societies (WUWHS, 2016). The most common surgical site complications

(SSCs) reported are surgical site infections (SSIs), dehiscence, seroma, and haematoma, which complicate 2-5% of surgeries in the United States and about 6% globally (WHO SSI Report, 2016; WUWHS, 2016; Curcio *et al.,* 2019). A person with an SSI has a poor quality of life and has a 2- to 11-fold risk of mortality (WHO SSI Report, 2016; WUWHS, 2016).

SSCs are often associated with protracted wound healing process resulting in increased length of hospital stay, higher rates of readmissions, and increased episode of care costs (WHO SSI Report, 2016; WUWHS, 2016). In the European Union (EU), SSIs cost the health care system between 1.4 and 19.1 billion Euros per year, whereas in the United States it costs between $5.94 to $14 billion dollars per year (Leaper *et al.,* 2004; Nussbaum *et al.,* 2018). These cost estimates do not include patients and caregivers' costs, and are therefore an under-representation of the true total cost to society.

Many strategies have been introduced to control SSI, including antibiotics prophylaxis, post-operative wound care dressings, and traditional negative pressure wound therapy devices. Negative pressure wound therapy applies controlled suction to a wound using a suction pump that delivers intermittent, continuous, or variable negative pressure evenly through a wound filler (foam or gauze) (WUWHS, 2016). There are a variety of smaller, single-use negative pressure wound therapy (sNPWT) devices currently being used following surgical procedures to prevent SSIs. However, there has been slow adoption of these sNPWT devices, as clinicians and particularly payers demand evidence of their clinical performance and in particular cost-effectiveness evidence of sNPWT which is particularly lacking.

2.4.1 Evidence gaps in the use of single-use negative pressure wound therapy (sNPWT) following surgery to prevent SSCs

Although there are a number of sNPWT used in the management of SSIs following surgery, this research focuses on the cost-effectiveness evidence of one of the devices, (PICO™, Smith & Nephew, Hull, UK). Following a review of the literature, there was an abundance of clinical evidence comparing PICO with standard care and no health economic evaluations on the use of PICO following surgical procedures. Health economic evaluations have become important in supporting the use and adoption of medical devices by clinicians, payers and policy makers, in today's in resource constrained healthcare systems.

The research presented in this thesis has addressed the health economic evidence gap of PICO in the prevention of SSIs in patients following cardiothoracic and orthopaedic surgery. PICO is indicated in a number of surgical procedures, and additional work was conducted in other surgical procedures which was not included in this thesis as it was still in abstract form. The research presented in this thesis has had demonstrable impact as evidenced by the widespread coverage of PICO by the UK NHS and increase in global sales of the device. The UK's National Institute for Health and Care Excellence (NICE) concluded that, "Evidence supports the case for adopting PICO negative pressure wound dressings for closed surgical incisions in the NHS," after considering evidence from Study 4 and 5 and additional research which I conducted (Nherera *et al.,* 2019a; Nherera *et al.,* 2019b).

2.5 Burden and costs of musculoskeletal disorders

MSK health refers to the health of the locomotor apparatus, which enables the individual to independently perform daily activities without functional restrictions (Woolf, 2015; Briggs *et al.,* 2018). MSK disorders range from inflammatory joint diseases such as rheumatoid arthritis, to fragility fractures, and are characterised by pain and reduced physical function (Woolf, 2015; Briggs *et al.,* 2018). Furthermore, MSK disorders significantly impair patients' health-related quality of life (HRQoL), as they normally experience loss of mobility and independence, as well as higher mortality rates (Beaudart *et al.,* 2017).

The prevalence estimates vary with respect to age and MSK condition. However, evidence suggests that 1 in 3 people worldwide live with a chronic, painful MSK condition (Cauely *et al.,* 2013; Papadimitriou *et al.,* 2017). In the United States, it is estimated that 1 in 2 adult Americans live with a MSK disorder (Woolf, 2015; Briggs *et al.,* 2018), which cost US taxpayers approximately $213 billion in 2011 (Briggs *et al.,* 2018). Despite the high prevalence and costs, MSK disorders have not received similar attention as that of other non-communicable diseases, such as heart diseases and obesity. President George W. Bush proclaimed the years 2002–2011 as the United States Bone and Joint Decade, providing national recognition to the fact that MSK disorders and diseases are the leading cause of physical disability in the country (https://www.govinfo.gov/content/pkg/CFR-2003-title3-vol1/pdf/CFR-2003-title3-vol1-proc7533.pdf). In 2006, the Royal College of General Practitioners estimated that over 1 million adults in the United Kingdom consult their

general practitioner each year with symptoms of osteoarthritis. Hospital admissions have been increasing due to hip and knee arthritis. In 2010/11, there were 207,041 such admissions, representing an 80% increase above that seen a decade prior (Chen *et al*., 2012).

Amongst the many MSK disorders, hip fractures are considered to be a major public health problem in terms of patient morbidity, mortality, and costs to health and social care (Swart *et al*., 2014). Worldwide, hip fractures are estimated to surpass 6.3 million by 2050. In the United States alone, the number of hip fractures is estimated to increase from about 320,000 per year to 580,000 by 2040, with healthcare costs exceeding $10 billion per year (Papadimitriou *et al.,* 2017). The rate of hip fractures is expected to continue to rise with the corresponding increase in life expectancy (Cauely *et al.,* 2013; Papadimitriou *et al.,* 2017). A similar trend is observed In the European Union, where there were an estimated 600,000 hip fractures costing €20 billion to the health system in 2010 (Cauely *et al.,* 2013; Leal *et al.,* 2016).

Hip fractures can be classified into intracapsular or extracapsular fractures, depending on whether the fracture is inside (intracapsular) or outside (extracapsular/intertrochanteric) the joint capsule of the hip, with surgical management the best treatment option for both (Bateman *et al.,* 2012). Intertrochanteric fractures are further classified as stable or unstable, and are managed with either a compression hip screw or an intramedullary (IM) nail. According, UK NICE guidelines and the American Academy of Orthopaedic Surgeons

(AAOS), IM nails should be used in unstable intertrochanteric fractures (Bateman *et al.,* 2012).

2.5.1 Evidence gaps in use of intramedullary (IM) nails in unstable intertrochanteric fractures

The literature review revealed that there are a number of IM nails currently being used in patients with unstable intertrochanteric fractures, yet there is no guidance as to which among the IM nails will optimise patient benefits due to lack of definitive published clinical and cost-effectiveness evidence. For payers, the goal would be to grant coverage and reimburse the IM nails that will both optimise patient outcomes and reduce the cost of treating hip fractures.

Due to the lack of definitive clinical and cost-effective evidence supporting the use of one IM nails over another in patients with unstable intertrochanteric fractures, this author conceived and conducted research to address this evidence gap. The thesis therefore presents comparative evidence that will help payers and clinicians choose the most clinically and cost-effective IM nail in patients with intertrochanteric fractures. The evidence presented has had demonstrable impact already in South Korea, where InterTAN nail was granted a 10% increase in price and increase in sales of the device as reported in Section 7.8 and 8.8. of the thesis.

2.6 Chapter summary

Overall, the burden of wound care and MSK disorders is huge and only expected to rise due to aging and chronic diseases. Clinically and cost-effective interventions for wound care and MSK disorders are therefore imperative to reduce the sociological and economic burdens. Producing such evidence can aid priority-setting and obtain optimal benefit from limited resources for the benefit of patients, payers, and manufactures alike. This chapter in addition to outlining the burden of wound care and MSK disease, also identified evidence gaps which forms the basis of this thesis

The next chapter will describe the types of clinical and economic evidence used to inform coverage and reimbursement decisions for medical devices.

3 Chapter 3: Types of evidence for coverage and reimbursement decision making in medical devices

3.1 Introduction

Decisions that shape health care should be grounded on a reliable evidence base. Archie Cochrane posed 3 critical questions for assessing clinical evidence for decision-making purposes. Firstly, "can it work?"; secondly, "will it work?"; and lastly, "Is it worth it?" (Fineberg, 2010). This chapter will briefly address all the 3 questions, and conclude by highlighting the types of evidence applicable to this thesis.

3.2 Types of clinical evidence for coverage and reimbursement decision making

Clinical evidence for medical devices is used for different purposes, such as approval by regulators, coverage and payment policies by payers, clinical decision making by clinicians, and for manufacturers to demonstrate the value of new medical devices (Dreyer *et al.,* 2010; Miller, 2017). There are a number of ways of generating this evidence via primary or secondary data sources. Primary data sources include any study design, qualitative or quantitative, where data are collected from individuals or groups of people, whereas secondary sources do not collect data directly from patients (Dreyer *et al.,* 2010).

The traditional clinical research model depicts evidence as a pyramid, with the strongest level of evidence (systematic reviews and meta-analysis) displayed at the top, and what is

considered the weakest evidences (ideas and opinions) at the bottom. This ranking of studies according to their research designs provides a guide to the strength of the evidence, and also indicates the confidence the end user can have in the research findings (Evans, 2003). Accordingly, this ranking of evidence has placed more emphasis on effectiveness of interventions and, as a result, randomised controlled trials have been commonly viewed as providing the highest level of evidence.

3.2.1 Randomised controlled trials (RCTs)

For treatment decisions, there is a consensus that the most reliable primary study type is the RCT. This type of study answers Cochrane's question "can it work?," which is about efficacy under controlled and replicable conditions (CADTH, 2017; Miller, 2017). In RCTs, patients are randomly assigned to have either the treatment being tested, or a comparison treatment using a strict inclusion criterion. RCTs ensure that the groups formed are similar in all aspects through randomisation except for chance differences (CADTH, 2017; Higgins, 2011). Randomisation enhances the internal validity of the studies, which is the extent to which the observed difference in outcomes between the study groups can be attributed to the intervention rather than other factors (Higgins, 2011).

The advantage of an RCT design is that it minimises selection biases and confounding, which are seen as threats to the internal validity of a study (Speith *et al.,* 2016). Selection bias is defined as a systematic error in creating intervention groups, causing them to differ with respect to measured or unmeasured baseline characteristics, whereas confounding is a situation in which the estimated intervention effect is biased, because of some difference

between the comparison groups apart from the planned interventions which can predict the outcome of interest (Dreyer *et al.,* 2010; Speith *et al.,* 2016).

The main limitation of RCTs is the poor external validity of their findings; that is, the results cannot easily be generalisable outside of the population that was studied because of their strict inclusion and exclusion criteria (Dreyer *et al.,* 2010; Speith *et al.,* 2016). It is not always possible to blind patients to treatment allocation when doing a study on dressings or surgical implants. Furthermore, RCTs are costly to conduct and focus on short-term effects of an intervention among a small population, and therefore relevant long-term outcomes are not captured (Dreyer *et al.,* 2010; Speith *et al.,* 2016). In the study of medical devices, there are further issues with timing of RCTs. Such studies normally take 2-3 years to complete, by which time the device will be outdated, as they are usually quickly produced based on incremental technological enhancements (Tarricone *et al.,* 2017; Drummond *et al.,* 2018). When it is not feasible or ethical to conduct RCTs, other forms of research that are less costly and quicker to conduct, such as observational studies, should be considered.

3.2.2 Observational studies

The assessment of a healthcare intervention must go beyond whether the intervention can work under ideal circumstances, to an understanding of its effectiveness, that is, how well the medical devices work in broad patient populations (Tarricone *et al.,* 2017). This type of evidence addresses the second question posed by Archie Cochrane, 'will it work?" Observational studies include the patient populations which are usually excluded from the

RCTs due to age, gender, or presence of comorbid conditions (Dreyer *et al.,* 2010; Tarricone *et al.,* 2017). They are therefore capable of assessing "real-world" health and economic outcomes to help guide decision making for patient care in a timelier manner, which increases external validity of the study findings.

Despite the increased external validity offered by observational studies, they do have the inherent limitations of bias and confounding. This is attributed to lack of randomisation, which often leads to a perception by clinicians and payers that observational studies are an inferior study design when compared with RCTs (Tarricone *et al*., 2017). However, modern analytical methods are available that minimise the impact of bias and confounding, such as matching or propensity score matching, which ensures equal representation of subjects with certain confounders among study groups. (Tarricone *et al*., 2017)

3.2.3 Systematic literature review

In general, a single study does not always provide a conclusive answer to a clinical question and hence the need to conduct a number of studies and summarise them together to increase confidence in clinical findings. One way of summarising evidence is conducting a systematic literature review (SLR), which summarises the results of available literature, and provides a high level of evidence on the effectiveness of medical devices (Lau *et al.,* 1997; Glasizou *et al.,* 2014). A SLR involves designing a comprehensive search strategy, which makes it explicit how the authors attempted to find all relevant studies and judged their individual scientific quality (Lau *et al.,* 1997). SLR differ from a narrative review which

tend to be descriptive in nature and do not involve a systematic literature search, which is prone to selection bias (Uman, 2011).

The results of the SLR can be summarised qualitatively or quantitatively. When the studies identified by the SLR are very different (heterogeneous), it is best to summarise the results qualitatively, whereas if they are sufficiently homogeneous, then a meta-analysis is recommended (Hunter *et al.,* 2002).

3.2.4 Meta-analysis

Systematic literature reviews often include a meta-analysis when the included studies are sufficiently homogeneous (Hunter *et al.,* 2002). Meta-analysis is defined as a set of statistical methods used to combine the results of two or more independent studies to derive a single, more precise estimate of effect, in order to evaluate the therapeutic effectiveness of medical devices (Egger *et al.,* 1997; Egger *et al.,* 2002; Uman, 2011). Meta-analysis helps to address controversy of conflicting findings from individual RCTs or observational studies.

The advantages of both a SLR and meta-analysis is that they use explicit methods which are intended to minimize bias. SLRs and meta-analysis are quick to perform, and less costly than primary studies, and when properly performed, they provide a powerful summary of the evidence (Higgins *et al.,* 2019). The main limitation of SLRs and meta-analysis is that their findings are only as good as the studies that they include. Poorly conducted studies may potentially give misleading or biased results. A further limitation is some of the studies becomes outdated by the time they are published. For instance, a study by Shojania *et al*

(2007) found that 7% of SLRs and meta-analysis needed updating at the time of publication, 4% within a year, and 11% within 2 years.

3.2.5 Summary of the types of clinical evidence

There are other types of clinical evidence which are not the focus of this thesis, such as Real-World Evidence which are gaining traction with payers, regulatory bodies and clinicians. It is clear that there is no type of clinical evidence that can answer all the relevant questions around efficacy and effectiveness of medical devices and therefore a one size fits all approach to clinical evidence is not advocated. Rather, the choice of evidence types should reflect the decision problem at hand. This thesis will focus on clinical evidence derived from both RCT and observational evidence using SLR and meta-analysis methods to summarise the available clinical evidence, to assist clinicians, payers and policy makers in their desire to optimise patient outcomes and reduce budgetary spend.

3.3 Economic evaluation

Section 3.2 above took a relatively narrow view of evidence, focusing predominantly on evidence types used for clinical decision making. Although such a focus is necessary to define the effect of a medical device, it is not sufficient to provide the breadth of evidence that clinicians and policy makers need to derive recommendations for coverage and reimbursement decisions (Eccles *et al.,* 2000). As mentioned in Section 3.1 above, Cochrane's third question ("Is it worth it?") requires a consideration of costs. Incorporating such cost considerations into clinical evaluations has been advocated by many national bodies tasked with making coverage and reimbursement decisions, such as the United

Kingdom's NICE, the Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany, the French National Authority for Health (HAS) in France, and the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada (Hoaglin *et al.,* 2011). Consequently, decision makers and health care practitioners are increasingly demanding evidence of economic value for healthcare interventions. Conducting high-quality economic evaluations has therefore become a priority in coverage and reimbursement decision-making process (Drummond *et al.,* 2018).

Economic evaluation is defined as the comparative analysis of at least two or more interventions, in this case medical devices, in terms of their costs and consequences (Drummond *et al.,* 2005). Economic evaluation has become an important tool in informing coverage and reimbursement decisions, especially in Europe and other publicly funded health systems such as those in Australia and Canada.

There are a number of economic evaluation methods in health care. Two commonly used approaches are cost-effectiveness analysis (CEA) or cost-utility analysis (CUA). The choice of technique in economic evaluation should reflect the decision that the economic evaluation is designed to inform (Hoang *et al.,* 2016). This section briefly considers the different types of economic evaluations and concludes by outlining the techniques that are applicable in this thesis.

3.3.1 Cost utility analysis (CUA)

The cost-utility analysis (CUA) is a type of economic evaluation that considers the improvement in quality of life and length of life following the use of a medical device for

the amount of resources used to generate those benefits (Drummond *et al.,* 2005; Mathes *et al.,* 2013). Clinical studies generate the increase in length of life as a result of the medical device. The length of is then adjusted for the quality of life by an index called "utility,". Utility is the measure of relative value or preference placed on a specific health status or an improvement in health status (Torrance, 1986). The most commonly used measure of utility is the quality adjusted life year (QALY), which aggregates the morbidity and mortality effects of a medical device (Torrance, 1986; Drummond *et al.,* 2005).

CUA is preferred by regulatory authorities because it uses explicit methodology for calculating QALYs, which facilitates the comparison of results of economic evaluations across programmes of work (Drummond *et al*., 2005; Heintz *et al.,* 2016). However, a CUA is not always possible to conduct, for instance, when information on quality of life is not available, it is impossible to calculate QALYs. There are also conflicting ideas about how to incorporate the patient's willingness to pay in decisions to reimburse new treatments (Drummond *et al*., 2005; Heintz *et al.,* 2016). In such cases a cost-effectiveness analysis can be conducted which does not require the quality of life measures.

3.3.2 Cost-effectiveness analysis (CEA)

CEA is an economic study design in which the consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, or complications avoided) (Drummond *et al.,* 2005). By comparing the cost and effectiveness (outcomes) of two or more devices, the decision maker is able to evaluate the benefits and limitations of new devices compared with the standard of care.

Results of both CEA and CUA are expressed as an incremental cost-effectiveness ratio (ICER), which is the ratio of the difference in cost between devices being compared divided by the difference in benefits measured either in natural units for CEA or QALY for CUA (Drummond *et al.,* 2005). However, the results of a CEA can only be compared with the results of other devices that are expressed in the same outcome measure/unit and is unidimensional, as only one domain of benefits can be explored at a time.

3.3.3 Other types of economic evaluation

There are other types of evaluations of healthcare resources, which are not the focus of this thesis. The cost-minimization analysis (CMA) is utilised in situations where alternative devices have been proven to deliver similar clinical benefits, and therefore focuses on the acquisition cost of the devices. CMA is considered to be too simplistic (Briggs and O'Brien, 2001; Drummond *et al.,* 2005). The cost consequence analysis (CCA) quantifies the clinical benefits in a disaggregated form and the associated resource impact. In a CCA the decision makers form their own opinion on the relevance and relative importance of different outcomes and their costs to the decision being considered (Drummond *et al.,* 2005). Finally, the cost-benefit analysis (CBA) values costs and outcomes in monetary terms. CBA considers all direct and indirect costs of healthcare; however, the method is computationally difficult and there are ethical issues regarding assigning monetary values to health outcomes (Drummond *et al.,* 2005).

3.3.4 Modelling techniques

Modelling is a decision analytic tool used within economic evaluation methods to synthesise the best available information. The two most frequently used modelling techniques are the decision trees and Markov models (Karnon and Brown, 1998; Hoang *et al* 2016).

3.3.5 Decision trees

Decision trees, the most widely used form of models in health economics. Decision trees consist of pathways representing different sequence of events and their associated probabilities (Karnon and Brown, 1998; Hoang *et al.,* 2016). They are a preferred modelling technique when the time-frame is short and reoccurring events are not important. The main advantage of decision trees is that they are easy to follow and simple to construct. Their main limitation is that they are not suitable for modelling recurring events, especially those with a longer horizon (Karnon and Brown, 1998; Drummond *et al.,* 2005; Hoang *et al.,* 2016).

3.3.6 Markov models

A Markov model is an analytical framework that consist of a set of health states that are mutually exclusive and represent all possible consequences of different medical device interventions (Sonnenberg and Beck, 1993; Hoang *et al.,* 2016). Since health states are mutually exclusive, the simulated individuals can only be in one state at a time as defined by the cycle length and the speed of movement between health states is determined by

transition probabilities (Sonnenberg and Beck, 1993; Karnon and Brown, 1998; Kuntz *et al.*, 2013; Hoang *et al.,* 2016).

Markov models are suitable for modelling clinical problems that occur over a longer time horizon, which involve risk over time. The ability of Markov models in handling the time component also gives them an advantage over decision tree especially where the sequencing of events is important (Karnon and Brown, 1998; Kuntz *et al*., 2013; Hoang *et al*., 2016). The primary limitation is the assumption known as the "Markovian property or memoryless assumption." This assumption states that the probability of moving from one health state to another is dependent on the time spent in that current health state, and does not depend on past history (Karnon and Brown, 1998; Hoang *et al*., 2016). In the real world, the 'Markovian property" does not always hold, as an individual's past medical history can impact on current clinical outcomes.

There are other modelling techniques that are more complex and are not the focus of this thesis, such as individual-based microsimulation and discrete event simulations (DES). These models are capable of simulating the life-time trajectories and recording participants' history. The transitions across different states may be conditional on previous history that participants have gone through (Hoang *et al.,* 2016).

In order for the results of an economic analysis to be meaningful, the choice of a modelling technique needs to reflect the problem being addressed and its context. This thesis used mainly the decision tree approach, because of the short-term nature of the data and

outcomes collected. Previous models in related areas also utilised decision tree approach and, therefore, partly informed the choice to adopt the decision tree approach.

3.4 Conclusions

There are different types of evidence, ranging from RCTs to observational evidence to SLRs with or without meta-analyses. The choice of evidence ultimately depends on specific questions being addressed to assist clinicians and those who make coverage and reimbursement decisions. There is no single type of evidence that can provide all the answers to a clinical question. Archie Cochrane's questions "Can it work and for whom" are addressed by both RCTs and observational studies, whereas his final question "is it worth it" is an economic question.

Payers and providers should recognize the range of legitimate evidence types. Doing so ensures that high-value devices reach their patients in a timely manner. This thesis used evidence from systematic reviews and meta-analyses of RCTs and observational studies to address the questions of clinical and cost-effectiveness of medical devices using examples from wound care and MSK disorders. For the economic analysis, cost-effectiveness and CUA using decision trees were conducted.

3.5 Chapter summary

The chapter briefly outlined the different types of clinical evidence and types of economic evaluations. The thesis used the highest-quality source of clinical evidence, which are the

SLR and meta-analysis. For the economic modelling, it adopted the CEA and CUA, the preferred methods of many national regulatory bodies.

The next chapter will examine the clinical evidence of medical devices with a focus on wound care, primarily the use of silver dressings in burn wound management.

4 Chapter 4: Clinical Effectiveness evidence of silver dressings in the management of burn wounds

In this chapter, two articles are presented describing the clinical evidence of advanced wound care products in the management of burn wounds using evidence from a SLR and meta-analysis. The EBA's clinical practice guidelines offer no definitive guidance as to which silver dressing should be preferred over the other when managing burn patients. Rather, the EBA advises clinicians to 'be creative in choosing silver burn dressings because there is no direct clinical evidence to support the choice of one dressing over another' (EBA, 2017:39). Given the lack of definitive guidance on the use of silver dressings in partial thickness burns, Study 1 was conceived to help answer the question around the clinical effectiveness of one of the new silver dressings ACTICOAT compared with standard of care silver sulphadiazine (SSD). Study 2 considered the use of commonly used newer silver dressings in burns compared against each other using indirect treatment comparison methods (ITC), as described in Sections 4.5.

4.1.1 Study 1: https://doi.org/10.1016/j.burns.2017.01.004

4.2 Description of Study 1

A systematic literature review and meta-analysis of RCT evidence by Gravante *et al.,* (2009) concluded that there was evidence suggesting the superiority of ACTICOAT compared with SSD with regard to infection control and pain using evidence from RCTs only. In the same study, no definitive evidence was reported with regards to length of hospital stay (LOS) and none was reported on the incidence of surgical procedures. Study 1, was conceived and aimed to address the efficacy and effectiveness of ACTICOAT compared with SSD using all available comparative evidence in burns. In addition to using all available evidence (RCTs and observational studies) Study 1, also included outcomes on the need for further surgical procedures which was not reported by Gravante et al., (2009), in order to determine the most clinically effective treatment strategy and thus guide treatment, coverage, and reimbursement decisions.

The methods of the research consisted of two stages: a) an SLR of all comparative evidence and b) a pairwise meta-analysis. For the SLR, searches of RCTs and comparative observational studies were carried out from bibliographic medical databases, PubMed, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), and the European Trials Register. This was supplemented by searching the references of included studies to ensure the search was as comprehensive as possible. The U.S. Agency for Healthcare Research and Quality (AHRQ), the UK Centre

for Reviews and Dissemination (CRD) and the International Cochrane Collaboration recommend that for optimal searches, one should search MEDLINE, EMBASE, and the Cochrane CENTRAL trials register as a minimum (Eden *et al.,* 2011; Bramer *et al.,* 2017). This study and subsequent systematic literature reviews reported in this thesis went over and above the minimum requirements, using a variety of databases since no single database contains all the available literature (Betran *et al.,* 2005). Thus, by being comprehensive, I can be confident that the majority if not all of the published studies were identified as far as was possible.

Since ACTICOAT was licensed in 1990, the search was restricted to between 1990 and May 2015. Outcomes of interest were: incidence of infection, LOS, incidence of surgical procedures, and pain. Study quality was assessed by Cochrane risk of bias tool and the GRACE checklist for RCT and observational studies, respectively (Higgins *et al.,* 2011; Dreyer *et al.,* 2014). The statistical model chosen for meta-analysis was dependent of the presence or absence of statistical heterogeneity. Sub-group analysis was performed where results were reported by study design.

After applying the inclusion/exclusion criteria, 9 studies were included in the meta-analysis with a total of 1194 patients. The study found that the use of ACTICOAT dressings resulted in shorter LOS ($p < 0.00001$), fewer surgical procedures ($p < 0.00001$), and reduced infection rates ($p = 0.005$) when compared with SSD. A sensitivity analysis was performed using different statistical model, random or fixed effects, and considering study designs

separately. The conclusions remained the same, that ACTICOAT offered superior clinical outcomes.

4.3 Evaluation of Study 1

This study showed that ACTICOAT resulted in less pain, fewer surgical procedures and shorter LOS when compared with SSD. The results also confirmed earlier findings of the meta-analysis by Gravante *et al.,* (2009). The study by Gravante *et al.,* (2009) found that ACTICOAT is significantly associated with fewer infections when compared with SSD ($p < 0.001$) and lower pain scores. However, unlike Study 1, Gravante *et al.,* (2009) did not report on the outcome of the incidence of surgical procedures and excluded evidence from observational studies.

The approach of combining both RCTs and observational studies ensured that all appropriate and useful evidence was included for evaluation. By combing RCT and observational evidence, results demonstrate the superiority of ACTICOAT on LOS outcomes and incidence of surgical procedures. Focusing on RCT evidence alone can potentially result in sub-optimal clinical decisions and recommendations, for example by excluding useful observational studies. A different conclusion would have been made regarding LOS or incidence of surgical procedures in this study, as evidenced by the EBA 2015 guideline (EBA, 2015) which concluded there was no difference in LOS based on the then published studies. This research has now been used to update the 2017 EBA guideline (EBA, 2017), which now states that there is a difference in LOS between ACTICOAT and SSD citing this Study 1, which is a positive contribution to policy and clinical guidelines used by clinicians and

payers in their routine work. However, this study also noted that the definitions of LOS and additional surgical procedures sometimes varied between studies. Future studies must be standardised to ensure they will be measuring the same outcome and thereby increase confidence in conclusions around the efficacy of the devices being evaluated.

Furthermore, the method of utilising both RCT and observational studies is a valid approach that has been used in other therapeutic areas, such as cardiovascular and cancer (Bonovas *et al.,* 2005; Shrier *et al.,* 2007). The approach ensures that a bigger sample size is included in the overall analysis, which increases the power needed to detect important clinical differences. Regulatory bodies such as the UK's NICE has endorsed the approach of combining RCT and observational evidence in the assessment of medical devices, as evidenced by the recently published guidance on the use of negative pressure wound therapy following surgical incisions (NICE MTG43, 2019 https://www.nice.org.uk/guidance/mtg43/chapter/1-Recommendations). The inclusion of observational studies also provides comprehensive and generalisable real-world data, which is especially useful in the field of burns clinical research where there is a lack of large RCTs. However, it is also clear that observational studies have well-documented limitations around bias and confounding that may hinder the overall conclusions.

Another noticeable limitation of the included studies was the small sample sizes, especially of the RCTs, which are associated with less precise estimates (Linacre, 1994). With small RCTs, there is a danger that the overall analysis is dominated by large observational data that are more prone to bias. However, smaller sample sizes in medical device RCTs are an

unavoidable reality of clinical research, where it is sometimes difficult to recruit patients into studies due to budgetary constraints and type of patients. By conducting a meta-analysis of small individual studies, the sample size problem is partly addressed, as the sample is increased and this increases the power to detect clinically meaningful differences between the different silver dressings.

4.4 Conclusion

This study has demonstrated the strength and utility of sythensising all available evidence to inform coverage and reimbursement decisions of medical devices. The study found that ACTICOAT is clinically superior compared with SSD in patients with deep and superficial partial-thickness burns, resulting in reduced infections rates, LOS, and need for surgical procedures. The study also confirmed previously non-contentious knowledge that ACTICOAT reduced infections compared with SSD. This research has already been used in updating the EBA 2017 guideline (EBA, 2017), which now states that there is a difference in LOS between ACTICOAT and SSD. However, clinical heterogeneity, especially regarding definitions of LOS and surgical procedures, was identified as an issue that future studies should consider standardising.

4.4.1 Study 2: https://doi.org/10.1111/wrr.12559

4.5 Description of Study 2

During the execution of Study 1, when the inclusion and exclusion criteria was being applied, I noticed that there were other silver dressings with evidence comparing their use with SSD. It became clear that a multiple technology assessment was necessary to directly compare all newer silver dressings against each other and hence the conception of Study 2.

Study 2 is a systematic review and an ITC of the commonly used newer silver dressings ACTICOAT, AQUACEL AG, and MEPILEX AG in the management of partial-thickness burns. Although the EBA's clinical practice guidelines offers no explicit recommendation to support the choice of one dressing over another (EBA, 2017), the results of this study can be used as part of the decision tools in recommending one dressing over another in the next round of the clinical guidelines. Indirect treatment comparisons methods are advocated in situations where there are many competing devices that have not been compared directly in clinical studies or such direct evidence is limited or insufficient (NICE, 2013; CADTH, 2017).

A systematic literature review was conducted comparing three commonly used newer silver dressings (ACTICOAT, AQUACEL AG and MEPILEX AG) via a common comparator between the three dressings, which was SSD. The methods were similar to those implemented in Study 1 Section 4.2 with regards to the search strategy, endpoints, study types, and the population. Pairwise meta-analyses were conducted for i) ACTICOAT compared to SSD, ii) AQUACEL AG compared to SSD and iii) MEPILEX AG compared to SSD.

Following the pairwise meta-analysis, an adjusted ITC using previously defined methods by (Bucher *et al.,* 1997) was then implemented comparing ACTICOAT vs AQUACEL AG, ACTICOAT vs MEPILEX AG and AQUACEL AG vs MEPILEX AG. Monte Carlo methods were used to rank the probability that each silver dressing was the most effective for each outcome that was assessed.

Following the application of the inclusion/exclusion criteria, nineteen studies met the inclusion criteria of which sixteen studies provided data for the pair-wise meta-analysis. These included 9 studies (4 RCTs and 5 observational studies; 1194 patients) comparing ACTICOAT with SSD; 5 studies (2 RCTs and 3 observational studies; 1001 patients) comparing AQUACEL AG with SSD; and 2 RCTs and no observational studies (252 patients) comparing MEPILEX AG with SSD in 252 patients.

The results of this ITC analysis showed that there was no difference in infection control and the need for further surgical procedures between the new silver dressings. There was statistically significant difference in LOS between the new silver dressings in favor of ACTICOAT when compared to AQUACEL AG ($p = 0.027$) and no difference compared to MEPILEX AG ($p = 0.207$). Furthermore, ACTICOAT resulted in shorter healing time when compared to MEPILEX AG ($p = 0.03$) and no difference when compared with AQUACEL AG ($p = 0.20$). A Monte Carlo simulation, which ranked the performance of each silver dressings on each individual outcome, demonstrated that ACTICOAT had the highest probability of being the most clinically effective silver dressing followed by AQUACEL AG for all the outcomes evaluated.

4.6 Evaluation of Study 2

The study results indicate that amongst the newer silver dressings, ACTICOAT is the most clinically effective, resulting in reduced LOS in hospital and non-significant reductions in infection and the need for further surgical procedures. These results confirm those of small studies comparing ACTICOAT with AQUACEL AG and MEPILEX AG, which found no difference in infection control (Vebelem *et al.,* 2014; Gee *et al.,* 2015). Furthermore, a study by Gravante and Montone, (2010) also reported that ACTICOAT had the shortest healing times compared with other dressings including AQUACEL AG in patients with superficial and partial thickness burns further corroborates the findings of Study 2.

Study 2 is the first ITC comparing all the new silver dressings with rankings for the performance of each dressing per outcome evaluated. Although there was no difference in infection control, the use of Monte Carlo simulation was able to rank the newer silver dressings and identified which was more clinically effective. With regard to all outcomes evaluated ACTICOAT had in all cases the highest probability of being the most clinically-effective burn dressings followed by AQUACEL AG, MEPILEX AG and lastly SSD. The findings from the Monte Carlo analysis is useful to inform decision making, in particular when it comes to choosing the appropriate dressings for burns. As was pointed out earlier in Section 4.1, the EBA could not advise clinicians on the choice of dressing when treating burns due to lack of direct evidence. This study helps to address this evidence gap, albeit using indirect treatment comparison methods. The latest Burn guidelines (EBA, 2017) were published before this research. The evidence presented in Study 2 should therefore be

considered in the next update of the EBA guideline to reflect the current state of knowledge. The findings of Study 2 were used to inform the cost-effectiveness analysis described in Section 5.2.

This study utilised the classical, validated statistical methods outlined by Bucher *et al.,* (1997) for conducting ICT. The strength of the approach is that the estimation of the relative effect between treatments was derived from all the information available from the network of evidence, which was both RCT and observational evidence. The adjusted ITC is the recommended approach by methodologists (Glenny *et al.,* 2005; Song *et al.,* 2005; Edwards *et al.,* 2009) and national HTA agencies such NICE, as opposed to other methods like the so-called naïve approaches or simply comparing point estimates. These other methods do not include a statistical analysis to enable quantification of the magnitude of difference between interventions (Edwards *et al.,* 2009).

The inclusion of both RCT and observational studies needs to be acknowledged. This strengthens both the internal validity of findings by including RCTs and the external validity by including observational studies. However, the advantage conferred by observational studies may be eroded by concerns regarding bias in observational studies, especially when the observational studies are not well conducted. Observational studies included in this study were of moderate-to-good quality, as assessed by the GRACE checklist (Dreyer *et al.,* 2014), and also had large sample sizes. As policymakers and providers seek to extend access to useful devices to patients in a timely manner, innovative methods of data analysis such as those described in this study should be embraced.

As was the case with Study 1 Section 4.2, clinical heterogeneity is one of the main limitations. There was also lack of uniform definition of time to healing/re-epithelialisation and surgical procedures, which can have a confounding effect on the outcomes, thereby affecting the accuracy of the results. A standadised definition of what constitutes time to healing or surgical procedures may be helpful for future studies to allow accurate assessment of these outcomes with confidence. However, the International Society of Pharmacoeconomic and Outcomes Research task force on indirect treatment comparisons and good research practices noted that a degree of relative variation in the patient populations and outcome measurement is welcome for comparative evaluations, as this reflects real-world clinical situations (Hoaglin *et al.,* 2011).

4.7 Conclusions

This study presented the clinical effectiveness of newer silver dressings in patients with superficial and deep partial-thickness burns. The results of this ITC suggest that ACTICOAT results in statistically significant reduction in LOS, when compared with other newer silver dressings. Results were comparable for infection control and the need for surgical procedures. Strengths and limitations of the study have been noted and suggestions for future research outlined. The outputs of this ITC were used in the economic analysis of these dressings, which is discussed in the following chapter.

4.8 Chapter Summary

This chapter presented the clinical evidence of silver delivery systems in patients with superficial and deep partial-thickness burns. Study 1, Section 4.2 used a meta-analysis

approach, whereas Study 2, Section 4.5 used an indirect treatment comparison method, which are widely used in clinical research to inform coverage and reimbursement decisions. Study 1, Section 4.2 confirmed existing knowledge about superiority of ACTICOAT with regards to infection control and pain compared with SSD. In addition, the study provided new insights with regard to LOS and surgical procedures, as it demonstrated a significant difference between ACTICOAT and SSD. This study has been used in the current updated EBA guidelines (EBA, 2017), which now specifically mentions that ACTICOAT results in reduced LOS. This is an important contribution to clinical decision making and the policy debate around the use silver dressings in burns.

Study 2, Section 4.5 is the first attempt to compare head to head the newer silver dressings in burn care, as currently the evidence compares newer silver dressings to standard of care SSD. Current evidence confirms the notion that there is no difference in infection control between the silver dressings, however, there is potentially a difference in LOS in favor of ACTICOAT. The study provided a ranking of the newer silver dressings in terms of clinical effectiveness, with ACTICOAT, AQUACEL AG, and MEPILEX AG ranked first, second, and third, respectively. This information can potentially be used to update existing guidance to clinicians on choosing appropriate dressing in order of effectiveness, something that currently does not exist. The next round of EBA guidelines is currently underway following their last meeting in September 2019.

Research limitations were identified and in particular the need for direct head-to-head studies to validate the results of ITC, this will help resolve the uncertainty around the

outcome of infection and impact on the incidence of surgical procedures. Standard definitions are needed, especially around time to healing and what constitutes surgical procedures. Furthermore, there is an additional need to ascertain cost-effectiveness evidence surrounding the question of whether the clinical value conferred by the silver dressings was worth paying for, which formed the basis of the next chapters.

The following chapter will address the economic impact of medical devices used in wound care with a focus on burn wound infection and SSCs.

5 Chapter 5: Cost-effectiveness evidence of medical devices, the case of wound care

5.1 Introduction

Ionic silver has been in use for wound healing for many years, in particular the topical agents such as silver sulphadiazine (SSD), which according to the World Union of Wounds (WUWHS, 2016), is considered the current standard of care for burns. The previous studies in Section 4.2 to Section 4.6 demonstrated that SSD is the least clinically effective silver dressing in the management of burns, and suggested that ACTICOAT was the most clinically effective silver dressing. Previously, there were no published cost-effectiveness studies comparing all these silver dressings, despite them being widely used. This study therefore sought to estimate the cost-effectiveness of commonly used silver dressings, using clinical data outputs generated from an ITC Study 2, described in the previous chapter in Section 4.6. The chapter further presents two additional cost-effectiveness studies that were conducted using data from single RCTs of negative pressure wound therapy used in the prevention of SSCs.

5.1.1 *Study 3:* https://www.woundsresearch.com/article/cost-effectiveness-analysis-silver-delivery-approaches-management-partial-thickness-burns

5.2 Description of Study 3

A decision analytic model using a decision tree was used to estimate the expected outcomes and mean costs of patients from the US health payer perspective, to provide clinicians and policymakers evidence on the most cost-effective silver dressing. The decision tree methodology was deemed suitable because of the short-term nature of the outcomes collected. No discounting of costs and outcomes was necessary due to a shorter time horizon. Three health states (healed wound, infected wound and additional surgery) were modelled, which were informed by the clinical co-authors (Dr Chris Roberts), an experienced microbiologist working in the infection area and (Professor Leena Berg MD), who is an experienced burn surgeon. Model data (inputs for standard care including clinical effectiveness) were derived from the ITC Study 2 presented in Chapter 4. Other inputs like costs and health-related quality of life were obtained from published literature. The study ranked the different silver dressings in order of cost-effectiveness. One-way sensitivity analyses were conducted to assess the impact of uncertainty on the results of the analysis, such as varying the effectiveness of silver dressings around the reported 95% confidence intervals (CI).

The results of the analysis showed ACTICOAT to be a dominant strategy. ACTICOAT resulted in lower overall treatment costs and improved clinical outcomes when compared with all other new silver dressings (AQUACEL AG, MEPILEX AG and SSD). Furthermore, the analysis also showed that AQUACEL AG and MEPILEX AG were cost-effective, when compared with SSD. Ranking the dressings in order of cost-effectiveness indicated that ACTICOAT was the

most cost-effective dressing, followed by AQUACEL AG, MEPILEX AG, and lastly SSD. The results remained cost saving from the US payers' perspective for ACTICOAT, when model inputs were changed in sensitivity analyses suggesting the model is robust.

5.3 Evaluation of Study 3

This analysis represents the first cost-utility analysis to be published on new silver dressings in patients with partial-thickness burns and therefore adds new insights in this therapy area. The study demonstrated that ACTICOAT is the most cost-effective silver dressing in patients with partial-thickness burns compared with other newer silver dressings. The second most cost-effective silver dressing was AQUACEL AG followed by MEPILEX AG. The results were stable when sensitivity analysis was performed such as varying the effectiveness of the dressings and their costs. Furthermore, the analysis further updates the current knowledge that the new silver dressings are cost-saving from the US payers' perspective when compared with SSD (Silverstein *et al.,* 2011; Shecketer *et al.,* 2014).

This analysis was conducted using robust clinical data from an ITC of different silver dressings used in the management of patients with superficial and partial-thickness burns. The choice of comparators is important in economic evaluations, as cost-effectiveness ratios are derived using alternatives, which in some cases include more than one for the same indication (Henrickson *et al.,* 2012). The strength of this study is that it considered the most commonly used newer silver dressings, which was important, as this study was able to rank them according to cost-effectiveness. This ranking information is critically

necessary for policymakers and healthcare providers who need to prioritise the use of these dressings, according to their incremental cost-effectiveness to optimise patients' outcomes. The findings of this research have been successfully used by Smith and Nephew's marketing team to gain market share including making new marketing claims around pain reduction and incidence of surgical procedures. The market share for ACTICOAT had been falling behind, and following the publication of this Study 3, the brand has been growing steadily from negative growth in 2015 to 6% globally in 2018 (Personal communication with Business Intelligence Analysts). The marketing team has started to engage key opinion leaders to emphasise and highlight the research findings of Study 3 and are aiming to influence the upcoming EBA 2020 clinical guideline.

The study had some inherent limitations. The clinical studies were conducted in different healthcare systems, which have different clinical practices. This can potentially confound the results of the clinical parameters that were applied in the economic analysis. Also, although the use of ITC methods is accepted, direct head-to-head evidence for the dressings are warranted in order to verify the results of ITC. Therefore, these results need to be interpreted with caution until such direct evidence becomes available and this analysis is updated.

A series of one-way sensitivity analyses were carried out and confirmed that the results were robust. However, the study could have benefited from a probabilistic sensitivity analysis, which would have quantified the level of confidence derived from the conclusions of the economic evaluation (Claxton *et al.,* 2008; Adalsteinsson and Toumi*,* 2013). Equally,

the model only considered costs from the payer's perspective, an approach that negates indirect costs such as productivity, patients and caregiver costs, which might underestimate the true cost or savings to society. These limitations, however, are not deemed to alter the overall conclusions of the analysis, because it is expected that the superior technology would lead to less overall costs whether they are societal or medical.

Another limitation is the focus on short-term outcomes and negating the long-term outcomes such as scarring, which are important to the patient. Scarring is one of the patient-related outcomes that may cause functional and cosmetic problems leading to impaired psychosocial well-being (Moi *et al.,* 2016; Tredget *et al.,* 2017). Future studies should not just address the needs of payers, but also incorporate those outcomes most relevant to patients. It is also acknowledged that the focus on a short time horizon, results in a failure of studies to capture the full value of an intervention (Kim *et al.,* 2017). However, in this analysis, this expected to bias the results against the more effective intervention thus making the findings of this study conservative.

5.4 Conclusion

This analysis found ACTICOAT to be the most cost-effective silver dressing, followed by AQUACEL AG and MEPILEX AG, whereas SSD is the least cost-effective from the perspective of the payer. These results were robust in sensitivity analysis. This conclusion supports the clinical evidence presented in Section 4.5, which showed greater reductions in LOS in favor of ACTICOAT dressing, when compared with other newer silver dressings included in this study. Prospective head-to-head research on the costs and outcomes of these newer silver

dressings in this patient population are necessary to validate the results of this economic evaluation. These studies should also consider the long-term patient outcomes, to acquire a comprehensive understanding of the value of these dressings. This study has the potential to transform burns management in developed countries, especially in those that are implementing value-based reimbursement.

The next papers will critically review the cost utility analysis of sNPWT in incision management to prevent SSCs following a) total hip and knee arthroplasty (THA/TKA) and b) cardiothoracic surgery based on data from single-center RCTs.

5.5 Cost-effectiveness evidence of single use negative pressure wound therapy in preventing surgical site complications (SSC)

The burden of SSC has been discussed in Section 2.4. A number of techniques are used to prevent or reduce the occurrence of SSC including the use of negative pressure wound therapy. There are a variety of sNPWT devices and one such is PICO™ (Smith & Nephew, Hull, United Kingdom), a canister-free system consisting of a sterile pump and multi-layered adhesive dressings. PICO has been evaluated by the UK National coverage and reimbursement body NICE, and was deemed to be cost neutral at the least and cost saving in most of the surgical procedures evaluated.

Two of the studies described below formed part of the evidence base that was used in the decision-making process to grant coverage for PICO by NICE in closed incision management. The two cost-effectiveness studies evaluated in this section were conducted in two different surgical procedures using clinical evidence from single RCTs, one study in patients following hip and knee replacement surgery in the UK (Karlakki *et al.,* 2016) and the second study, in patients following cardiothoracic surgery in Poland (Witt-Majchrzak *et al.,* 2015).

5.5.1 *Study 4:* https://onlinelibrary.wiley.com/doi/epdf/10.1111/wrr.12530

5.5.2 Study 5: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6171177/

5.6 Description of Studies 4 and 5

In both Studies 4 and 5, the economic study type was a cost utility analysis utilising a decision tree model designed to capture outcomes following a surgical procedure (THA/TKA or cardiothoracic). Both studies used clinical data from single-centre RCTs from the payer's perspective. As in Study 3, a decision tree was considered appropriate due to the short timeframe for which the outcomes were evaluated. Furthermore, PICO is used prophylactically to prevent the occurrence of SSC, which are measured within 6 weeks of the index procedure. Thus, the model did not capture recurring events, otherwise a Markov model would have been considered, which is suitable for handling recurring outcomes.

The outcome of interest was SSC, defined as (length of stay, surgical site infections and dehiscence), costs and health-related quality of life. Baseline data without PICO was sourced from relevant country specific literature, whereas effectiveness of PICO was taken from the individual RCTs. Local national resource use, rather than trial-based data, were used in order to enhance the generalisability of the cost-effectiveness results beyond the single centres where the RCTs were performed. Both outcomes and costs were not discounted because of a shorter time horizon. Sub-group analyses were performed to ascertain which groups of patients would benefit most from PICO treatment. One-way sensitivity analysis and probabilistic sensitivity analysis was implemented to capture the uncertainty around model inputs.

The results demonstrated that the use of PICO was associated with better clinical outcomes and was less costly when compared with standard of care for patients undergoing hip and

knee replacement. The estimated cost-saving was £1,132 per patient. Probabilistic sensitivity analysis showed that PICO was cost saving in 79% of the 2000 simulations that were conducted, suggesting that clinicians and payers can be confident that PICO is indeed cost saving.

Similarly, the results for patients undergoing cardiothoracic surgery demonstrated that PICO was associated with better clinical outcomes and lower costs when compared with SC. The estimated cost-saving were €586 per patient. Probabilistic sensitivity analysis demonstrated that the probability that PICO was cost saving is 100%, further suggesting that there is no uncertainty associated with this finding.

When a series of one-way sensitivity analyses were conducted, such as the effectiveness of PICO and its costs, the models remained cost-saving from the payer's perspective. Sub-group analysis demonstrated that patients at higher risk of SSC, such as those with higher body mass index, diabetes, smoking and American Society of Anesthesiologists (ASA) score greater than 3, benefited more from PICO treatment. There were huge savings associated with targeting such high-risk patients.

5.7 Evaluation of Studies 4 and 5

The two studies suggest that PICO is cost saving from the payer's perspective compared with standard of care when used prophylactically following primary hip and knee surgery or cardiothoracic surgery. Both Studies 4 and 5 were subjected to one-way sensitivity analysis, as well as probabilistic sensitivity analysis, and the results remained robust, suggesting the findings are unlikely to be a result of chance. There are no previous cost-

effectiveness publications in the use of PICO in these populations. Therefore, these findings can serve as reference point with which these can be compared in the future. However, another study was published after these two publications, which focused on prevention of SSCs following caesarean surgery (Hyldig *et al.,* 2019). The study concluded that PICO was a cost-saving intervention in this patient population.

Study 4 and 5, together with the additional research I did (Nherera *et al.,* 2019a; Nherera *et al.,* 2019b), were used by the UK Technology appraisal assessment body NICE, in reaching their decision to grant market access for PICO use in the UK NHS (https://www.nice.org.uk/guidance/mtg43/chapter/1-Recommendations). PICO has seen growth in market share, which among other factors is attributed to the publication of Study 4 and 5, including the additional research mentioned (Nherera *et al.,* 2019a; Nherera *et al.,* 2019b). For the first time, PICO sales have hit the $100 million mark in 2019, and is projected to continue growing (See attached confidential E-mail). The use of clinical and cost-effective evidence has clearly benefited patients, payers, and manufactures alike. Patients are receiving effective therapy, payers are optimising their budgets, and manufactures are getting a return on their investment.

One of the strengths of the two studies is the fact that the comparator used was chosen by the clinician, as they often do in daily clinical practice. Having an appropriate comparator is key to the external validity and generalisability of the results. Choosing an inappropriate comparator may weaken the utility of an analysis, or in the worst-case scenario, invalidates the results of a research (Henrickson *et al.,* 2012).

One of the main concerns for payers and providers of health services is over-utilisation of new devices, especially due to aggressive marketing from manufacturers. These studies were designed and conducted in a way that helps payers and providers to target the PICO, to those patients who will benefit the most. Sub-group analysis demonstrated that those at high risk would derive greater benefit in particular patients with a body mass index >30, those with diabetes, and an ASA score >3. This finding will allow a targeted approach to adoption, which will optimise efficiency and prevent over-utilisation of the device.

Both models adopted a payer perspective rather than a societal perspective, yet it is understood that the perspective chosen impacts not only on the type of costs included in the analysis and also the time horizon of the analysis. Payers are interested in a short time horizon, that coincides with their budgetary cycles where possible, because they want to realise the savings immediately not sometime in the future (Kim *et al.,* 2017). The societal perspective was deemed not necessary, as the studies were done to inform coverage and reimbursement decision making, which is adequately answered by the payer's perspective that was adopted. Furthermore, none of the studies considered the budget impact of adoption. The payers need to find the money to make the device available to their patients. This aspect of affordability was beyond the scope of Studies 4 and 5.

The RCTs that informed the economic models were conducted at single centers. It is acknowledged that each center has its own clinical protocol, which may have confounded the clinical outcomes presented, and therefore the estimated savings affecting the generalisability of this study. However, the use of a standard care dressing of clinician's

choice, and use of national cost data rather than center-specific costs, may have helped with this limitation. Caution is still urged in interpreting the results of the analysis in other healthcare systems, since the studies were conducted from the UK and Germany health payer perspectives. Other health care systems have different reimbursement systems and standard of care differs from one health care system to another, which may affect the overall cost-effectiveness conclusions.

The current studies compared PICO to standard care, however, there are other sNPWT devices on the market currently used by healthcare providers. The majority of them do not have clinical and economic evidence supporting their use. It is strongly recommended that head-to-head studies or ITC be conducted once there is enough evidence gathered for the other devices, to assist clinicians and policymakers to choose the most cost-effective sNPWT device, thereby increasing efficiency within healthcare systems.

I have committed myself to conduct an indirect treatment comparison between PICO and one its major competitors, Prevena™ Therapy (Acelity, San Antonio Texas, USA). Prevena now has accumulated data compared to standard care following cardiac and caesarean surgical procedures. This research is already underway, including the economic evaluation, and I am expecting to have preliminary results sometime in the second quarter of 2020.

5.8 Conclusions

These cost-utility analyses demonstrated that PICO is cost saving compared to standard care in preventing SSCs following primary hip and knee replacement, and cardiothoracic surgery. The analysis demonstrated improved clinical outcomes and lower overall costs

from the UK NHS and Germany payer's perspective. These studies provided new insights, as they were the first cost-effectiveness studies evaluating PICO in these indications. Furthermore, these studies contributed to PICO being widely recommended for use in the UK NHS. The studies helpfully suggested a targeted adoption of PICO, focusing on high-risk patients initially in order to optimise the limited healthcare budgets. Evidence suggests some sNPWT have accumulated some evidence, therefore, there is need to conduct direct head-to-head or ITC and also a cost-effectiveness study, in order to rank which among the different devices optmises the health benefits. As a result of this observation, I have embarked on further research assessing both the clinical and cost-effectiveness of PICO devices using clinical evidence from ICT. In the future, budget impact models need to be considered to ensure payers can afford the recommended devices.

5.9 Chapter Summary

This chapter has presented three wound care economic evaluations: one in the use of silver dressings in burns and two in the use of PICO in preventing SSCs. The studies on burns provided significant new knowledge, which will help providers to prioritise burn treatment as the new silver dressings were ranked in order of clinical and cost-effectiveness. However, there is need for more head-to-head studies considering long-term patient outcomes with standard definitions of some of the outcomes.

Studies 4 and 5 (Section 5.7) demonstrated that PICO was cost-effective compared with SC in managing post-surgical wounds. The studies were able to identify patients that should be prioritised for PICO treatment in the event of budgetary constraints. Furthermore, the

need for economic analysis based on head-to-head or indirect treatment comparison of negative pressure devices was identified, as there are a number of such devices in the market now. The two economic evaluations on PICO have already had a positive contribution to the policy debate around adoption of PICO in UK NHS, as they were used as part of evidence which led to the acceptance of PICO in the NHS through NICE approval MTG43 (https://www.nice.org.uk/guidance/mtg43/chapter/1-Recommendations). However, both studies did not consider budget impact of these interventions, which was beyond the scope of this analysis, but is nonetheless an important consideration if the new effective technologies are to be adopted and used in clinical practice.

The next chapter will present the generation and use of clinical evidence in MSK disorders, using the example of patients with intertrochanteric hip fractures. The methodology used in both clinical and economic evidence generation are similar to those presented in the wound care sections, as policymakers and health care providers are interested in approving medical devices that can improve the health of their populations and lower the cost of health care.

6 Chapter 6: Clinical evidence from musculoskeletal disorders: the case of intramedullary (IM) nails in unstable intertrochanteric fractures

6.1 Introduction

Amongst the many MSK disorders, hip fractures are considered to be a major public health problem given their contribution to patient morbidity, mortality, and health care and societal costs, as mentioned in Section 2.5. Health care services worldwide are facing severe financial pressures, which has created a strong clinical and economic incentive to prioritise devices that will optimise patient outcomes. As noted by Papadimitriou *et al.,* (2017), there are considerable opportunities to ameliorate the burden of hip fractures, by focusing on treatments that will facilitate a rapid and complete recovery.

Two studies are presented here that help answer questions on the use of IM nails in patients with unstable intertrochanteric fractures. Systematic review and meta-analysis methods were used in Study 6 to assess the performance of a twin-screw integrated cephalomedullary nail (InterTAN) compared with a single-screw cephalomedullary nail (Proximal Femoral Nail Antirotation) (PFNA™), (DePuy Synthes, Solothurn, Switzerland). Study 7 went a step further and pooled together evidence from single-screw nails (PFNA + Gamma3™; (Stryker, Schönkirchen, Germany) and compared this with twin-screw InterTAN in the same patient population. In Study 7, I further explored the hypothesis that there

could be a class effect between intramedullary devices in patients with unstable intertrochanteric hip fractures.

6.1.1 *Study 6:* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5834859/

6.2 Description of Study 6

PFNA and InterTAN are two of the market-leading IM nails used in the management of unstable fractures. A number of studies have been conducted directly comparing these two devices (Zhang *et al.,* 2013; Seyhan *et al.,* 2015; Yu *et al.,* 2015; Zehir *et al.,* 2015; Zhang *et al.,* 2017a; Zhang *et al.,* 2017b). The individual study findings are inconsistent for instance results on revisions show no difference between InterTAN and PFNA for studies by Zhang *et al* (2017a) and Zehir *et al* (2015), while Zhang *et al* (2017b) shows a significant difference in revisions. This makes it harder for surgeons to identify the ideal treatment option for their patients or payers to optimise their budgets. Study 6, was therefore conceived with aim of addressing this question of inconsistency between individual studies reported in literature as well as updating a recently published meta-analysis by Ma *et al*., (2018), by conducting a SLR and pairwise a meta-analysis.

For the SLR, searches of RCTs and comparative observational studies were carried out from the main clinical bibliographic databases mentioned earlier in Section 4.2. The search dates were limited to January 2005 to May 2016, because InterTAN was licensed from 2005. The study collected three types of outcomes: functional outcomes (Harris Hip Score [HHS]),

post-operative implant-related failures (revisions), and intra-operative procedure measures.

Studies were assessed for quality using the Cochrane risk of bias tool and the GRACE checklist for RCT and observational studies, respectively (Higgins *et al.,* 2011; Dreyer *et al.,* 2014). A meta-analysis was performed using either random or fixed-effects model, and summary measures for the meta-analysis were odds ratios (OR) for binary outcomes or mean differences (MD) continuous outcomes. The main analysis reported results for the combined RCT and observational studies. In sub-group analysis, results were then reported separately by study design.

After applying the inclusion/exclusion criteria, 6 studies (2 RCTs and 4 observational studies; 970 patients) were included in the meta-analysis. The analysis demonstrated that there was a statistically significant difference ($p < 0.05$) OR and 95% CI for revisions [0.27; 95% CI: 0.13 to 0.56], implant-related failures [0.16; 95% CI: 0.09 to 0.27], proportion of patients complaining of pain [0.50; 95% CI: 0.34 to 0.74) in favour of InterTAN. There was no difference in non-unions and HHS ($p > 0.05$) and operating times between the two devices. The study also showed significant differences in blood loss and fluoroscopy usage in favour of PFNA. Sensitivity analysis were conducted considering study design (RCTs and observational studies individually), using alternative analytical methods of random or fixed effects models. Furthermore, studies which contained mixed populations of stable and unstable patients were also removed from the analysis as part of sensitivity analysis. Changing these assumptions did not alter our base conclusions that InterTAN was superior

compared to PFNA. Furthermore, we removed three studies which had mixed population consisting of 25% stable patients (Seyhan *et al.,* 2015; Zhang *et al.,* 2017a; Zhang *et al.,* 2017b) and the conclusions did not change, suggesting the SLR and meta-analysis findings are robust.

6.2.1 *Study 7:* https://www.oatext.com/pdf/ROM-3-156.pdf

6.3 Description of Study 7

One of the limitations of Study 6 in Section 6.2 above was that the scope was too narrow and excluded another single-screw nail that had comparative evidence against the twin-screw nail InterTAN in this population. Study 7 is therefore an update of the previous Study 6 and another meta-analysis (Ma *et al*., 2017). Study 7 combined all single-screw nail studies of PFNA and Gamma3 and compared them to the twin-screw InterTAN, to comprehensively assess the difference in outcomes and test the hypothesis that there could be a class effect between twin-screw and single-screw IM nails in patients with unstable intertrochanteric fractures.

The study methods were similar to Study 6, as presented in Section 6.2 above, which consisted of an SLR and pairwise meta-analysis of RCTs and observational studies of single-screw IM nails compared to twin-screw InterTAN. Unlike Study 6, this study considered all single-screw IM nails that had comparative evidence against twin screw InterTAN (both PFNA and Gamma3 nails). The main analysis, therefore, reported the combined results of

single-screw studies together and sensitivity analysis considered the single screws individually.

Following the application of the inclusion and exclusion criteria, 12 studies with 1,661 patients were included in the meta-analysis: 8 comparing twin-screw InterTAN with PFNA, 2 additional studies from the previous Study 6, and 4 comparing twin-screw InterTAN with Gamma3. The results demonstrated that there were significant differences in device performance in favour of twin-screw InterTAN compared with single-screw nails for implant-related failures ($p < 0.0000$), fewer revisions ($p < 0.0001$), hip and thigh pain ($p = 0.0009$), and better function as measured by SF-36 ($p = 0.002$) and HHS ($p = 0.02$). Procedure outcomes, defined as operating time and fluoroscopy time, significantly favoured single-screw nails ($p = 0.02$ and $p = 0.0001$, respectively). No differences were observed in non-unions ($p = 0.28$), blood loss ($p = 0.35$), and other complications ($p = 0.94$).

6.4 Evaluation of Studies 6 and 7

The two studies presented in Sections 6.2 and 6.3 build the case for twin-screw nail InterTAN in the management of intertrochanteric fractures. Twin-screw nail InterTAN resulted in significantly fewer implant-related failures and revisions, less hip and thigh pain, and better function as measured by SF-36 and HHS compared with single-screw nails (PFNA and Gamma3). Procedure outcomes were favourable to single-screw IM nails, such as operating time, fluoroscopy time, and blood loss, and no differences were observed for non-unions.

There is one systematic review (Ma *et al.,* 2017) that considered the same question and had a different conclusion around revisions and HHS. Study 7 included three additional studies (Zhang *et al.,* 2017a; Zhang *et al.,* 2017b; Gavaskar *et al.,* 2018) published after Ma *et al.,* (2017), which explains the different conclusions. The findings of this study are thus the most up to date, and should be preferred for coverage and reimbursement decision making.

In a sub-group analysis, single-screw IM nails were considered individually, and the results showed that the twin-screw InterTAN had better outcomes when compared with PFNA as was demonstrated in Study 6. When compared to Gamma3, the only differences were seen on quality of life and implant-related failures. This suggests that more studies are needed to compare InterTAN with Gamma3, as in the overall analysis there were 8 studies comparing InterTAN with PFNA and 4 comparing InterTAN with Gamma3.

A comprehensive search strategy was implemented in the main clinical databases, which ensured all comparative evidence was captured and included in the analysis. This was evident, as this study was able to identify one additional study which an earlier analysis by Ma *et al.,* (2017) had missed, and 2 new publications. Furthermore, combing both observational and RCT evidence ensured that advantages of both study designs were optimised in a single analysis. The use of recommended checklist to assess study quality ensures that clinicians, patients, and policymakers have confidence in the research outputs, a necessary condition for implementation and adoption of the clinical findings.

One of the key limitations of Study 7 is the assumption that all single-screw IM nails are the same by combining of Gamma3 and PFNA studies in the analysis. This may have introduced substantial clinical heterogeneity in the analysis, which may have biased the results; the direction of the bias is unknown. However, sensitivity analysis was conducted assessing each individual single-screw nail separately. The results of the sensitivity analysis demonstrated that InterTAN was superior when compared with PFNA and that more evidence was needed for Gamma3, as the only difference was observed in implant-related failures and HHS.

Study 7 has had a positive impact for Smith and Nephew the manufacturer of the twin-screw InterTAN. The company's annual report for 2017 states that, "new clinical evidence supported increased uptake of our TRIGEN™ INTERTAN™ hip fracture system" and sales in the Trauma business increased by 13% from $475 million in 2016 to $495 million in 2017 (Smith and Nephew, 2017). Furthermore, the availability of good clinical evidence is being used to engage with clinicians and payers. For instance, in South Korea InterTAN has been granted a 10% increase in price based on the evidence presented in this Chapter and the Section 7.3 below.

6.5 Conclusion

The studies found that there was a significant difference between twin-screw InterTAN and single-screw IM nails (PFNA + Gamma3) with regards to implant-related failure outcomes, whereas procedure-related outcomes tend to favour single-screw nails. No difference was observed for the outcome of non-union, which is not widely reported in the studies. Future

studies should focus on reporting non-unions among other outcomes. Additional studies are also needed comparing InterTAN with Gamma3, as there are currently limited data in this area.

6.6 Chapter Summary

This chapter examined the evidence around the relative effectiveness of IM nails in patients with unstable intertrochanteric fractures. The first study (Study 6, Section 6.2) compared InterTAN with PFNA alone. It demonstrated that InterTAN was clinically superior compared to PFNA, except for procedure outcomes, which favoured PFNA. This is the first meta-analysis of its kind contributing to unambiguous understanding of the benefits of InterTAN. The study also confirmed what was already known regarding procedure outcomes, for instance, the increase in both operating time and blood loss. However, experts believe the clinical benefits far outweigh the negatives of procedural benefits. For non-unions, there was no difference between the performances of the devices.

Study 7, Section 6.3 further highlighted the superiority of two screw InterTAN when compared with the two most common single-screw IM nails. The study also helped to reject the notion that all IM nails are the same, as the twin screw nails was demonstrated to be a superior construct compared with single-screw IM nails. As in the Study 6, there were no differences on non-unions between the twin-screw and single-screw devices. This is partly explained by the fact that out of the 12 studies that were included in the analysis, only 4 reported on non-unions. Future studies should be encouraged to report on this outcome.

Also, more studies on Gamma3 and InterTAN are needed, as currently only 4 of the 12 included studies compared the two devices head to head.

Demonstrating clinical effectiveness is one step towards achieving coverage and reimbursement of medical devices in today's resource-constrained environments. Currently, there are no published cost-effectiveness studies comparing the different IM nails in patients with unstable fractures. Cost-effectiveness arguments have become so important for coverage and reimbursement decision making, as healthcare systems are faced with falling budgets. Therefore, the next chapter will look at the cost-effectiveness of IM nails InterTAN, Gamma3, and PFNA in patients with intertrochanteric fractures using the clinical data from the meta-analysis presented in Section 6.3.

7 Chapter 7: Cost-effectiveness evidence of Intramedullary (IM) nails in patients with unstable intertrochanteric fractures.

7.1 Introduction

The previous chapter focused on the clinical effectiveness evidence of IM nails, in particular the three commonly used IM nails InterTAN, PFNA, and Gamma3. The clinical evidence suggested that the twin-screw nail InterTAN was clinically superior when compared with single-screw IM nails in patients with unstable intertrochanteric fractures. However, the cost-effectiveness of these devices was not examined, to assess if the added clinical benefit represents value for money to payers. This chapter focuses on the economic evaluation of IM nails using the clinical findings of the previous Study 7, Section 6.3, as inputs of the economic analysis. The analysis is conducted from the perspective of US payer with a view to assist clinicians with device selection and payers with coverage and reimbursement decisions.

7.1.1 *Study 8* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6117956/

7.2 Description of Study 8

A decision analytic model using a decision tree was developed in Microsoft Excel to estimate the expected outcomes and mean costs of patients with unstable intertrochanteric hip fractures treated with either twin-screw InterTAN or single-screw nails (PFNA + Gamma3) from the US payer perspective. The choice of the modelling

technique was informed by previously published studies in this area and the clinical studies from which the data was sourced. The model timeframe was 12 months and therefore no discounting was done for both costs and benefits. Following surgery, patients would either experience no complications or they had complications (non-union, implant-related failure). The complication would result in revision surgery, including the possibility of death. Baseline model values were taken from the literature and the meta-analysis, including health-related quality of life inputs. The analysis also ranked the IM devices in order of cost-effectiveness. One-way and probabilistic sensitivity analysis were conducted to assess the impact of model inputs uncertainty on the results of the analysis.

The analysis demonstrated that twin-screw InterTAN was associated with improved clinical outcomes and lower costs overall when compared with single-screw IM nails. In such instances, when an intervention results in improved clinical outcomes and less overall treatment costs, it said to be dominant strategy or a cost saving intervention. The estimated savings was $2,700 per patient in the base case analysis. Sub-group analysis considering each individual single-screw IM nail demonstrated that twin-screw InterTAN saved $3,280 per patient compared with PFNA and $1,652 per patient compared with Gamma3. The results remained cost saving from the US payer's perspective, when model inputs such as the effectiveness of the devices on revisions, implant-related failures, and cost of implants were varied in one-way sensitivity analysis. Probabilistic sensitivity analysis confirmed the findings of one-way sensitivity analysis suggesting that these results are robust. Furthermore, the study also considered the analysis from a hospital perspective in sensitivity analysis and concluded that twin-screw InterTAN remained cost saving. The

estimated savings were calculated to be $414 per patient, when compared with single-screw IM nails.

7.3 Evaluation of the study

The cost-effectiveness of IM nails compared with sliding hip screws in patients with unstable fractures was established in a study by Swart *et al.,* (2014) without distinguishing which of the IM nails should be preferred first. This study represents the first economic evaluation that has compared different IM nail fixation devices in patients with unstable fractures, in order to assist clinicians in selecting amongst the commonly used IM nails. The study concluded that the twin-screw nail construct InterTAN is cost-saving when compared with the single-screw IM nail constructs. Furthermore, the analysis was also able to show that among the single-screw IM nails, Gamma3 is the most cost-effective when compared with PFNA. The ranking of devices is useful to payers and clinicians, as this assist them to prioritise the use of IM nails especially in resource-constrained environments.

In sensitivity analysis, the study also considered a different perspective, that of the hospital, and still concluded that the twin-screw nail construct InterTAN is cost-saving when compared with the single-screw IM nail constructs. This is an important consideration especially in privately funded healthcare systems where hospitals and decision makers want to optimise profitability. In such instances, hospitals may be interested in knowing whether particular devices will generate them profit before they make purchasing decisions. Equally important is the fact that a hospital with good surgical

outcomes is able to attract more patients, thereby boosting patient volumes and profitability.

This research has contributed to the coverage and reimbursement of the InterTAN in South Korea, where the device managed to achieve a 10% increase in price based on this evidence. InterTAN as a brand has grown globally by 8.6% between 2014 and 2019 (See attached confidential e-mails). Smith and Nephew, the manufacturer of the twin-screw InterTAN, mention in their annual report from 2017 and 2018 that their Trauma portfolio has seen an increase in sales, a key driver for which they attributed to the good evidence presented in Study 8. This evidence is thus benefiting patients and clinicians who see improved outcomes, payers who are getting the most out of their budgets, and manufacturer who are seeing increased profitability.

As with all modelling exercises, not all possible outcomes were captured. For example, this analysis did not explicitly model the progression of patients to total hip arthroplasty (THA). In reality, it is possible that patients who need a reoperation to treat a failed internal fixation may end up with a conversion to a THA within the first year. This information on the conversion rates to THA in patients treated with IM nails is not well characterised in the literature. Furthermore, the modelling framework of using a decision tree would have made it difficult to incorporate recurrent events such as re-revisions and the possibility of THA. In such a situation where there are recurring events that occur over time, a Markov modelling framework would have been appropriate. Therefore, one of the key implications

of this study is to encourage future researchers to collect information on progression of patients to THA and then update the model once such information becomes available.

This study was carried out from the perspective of the US healthcare payer's system and used average Medicare reimbursement as a proxy for the hospital costs. As in most economic evaluations, caution should be taken when interpreting these results in other healthcare systems and encourage the use of local costs to test the robustness of this analysis on individual healthcare systems.

The study also focused on short time horizon of one year which undoubtedly addresses the payer's needs in the time frame selected. However, IM nails are known to have longer survival or lasts for far longer periods beyond the one year considered in this study. By limiting the analysis to one year, there is an implicit assumption that incremental costs and health benefits are zero beyond the one year modelled, which under-estimates the true costs and benefits of the interventions (Kim *et al*., 2017). This however, is expected to bias the results against the more effective two nail fixation than the single nail and therefore is not expected to alter the conclusions of Study 8 which was found to have less implant related failures and costs less overall.

7.4 Conclusion

This study demonstrated that twin-screw InterTAN offers better clinical outcomes at lower overall costs when compared with single-screw nails in patients with unstable fractures. These findings remained robust when different assumptions were tested in sensitivity analysis, suggesting they are unlikely to be a chance finding. Given that currently there is

no guidance as to the choice of IM nailing system, this study can have huge implications and encourage clinicians and policymakers to adopt the most cost-effective technology. This research is having a demonstrable impact in other health care markets, such as South Korea. Smith and Nephew have seen increases in sales reported in their annual report. This is proof that when a technology is backed by good clinical and cost-effectiveness evidence, it will be adopted for the benefit of patients, payers, and manufacturers alike. Long-term follow-up studies are needed to ascertain the benefits beyond the 12 months reported in the clinical studies. Data on the possibility of conversion to THA following device failures are also needed to fully quantify the benefits of the different nailing systems.

7.5 Chapter summary

This chapter presented an economic evaluation of IM nails used in patients with unstable intertrochanteric fractures and supports the use of twin-screw InterTAN nail compared with single-screw IM nails (PFNA and Gamma3). The existing knowledge was around cost-effectiveness of IM when compared with sliding screws, and none looked at IM against each other. Therefore, this is the first study that has compared IM nails against each other and provided new insights in this patient population regarding the performance of the commonly used IM nails.

Studies with longer time horizon are needed to confirm if the benefits persist beyond the reported one year, and also include outcomes of possible conversion to THA for patients whose implants fail at one year. This will further assist clinicians and policy makers in choosing the technology that optimise the clinical benefits for their patients given the

limited budgets with which they are working. The current study has already had a positive impact with regards to reimbursement. For instance, twin-screw InterTAN has been granted a 10% increase in price in South Korea by their health watchdog Health Insurance Review and Assessment Service, over and above other IM nails because of the clinical and cost evidence presented in Study 8 [See attached confidential e-mail].

8 Chapter 8: Summary, Conclusions and Recommendations

8.1 Thesis Summary

Chapter 1 highlighted the increasing demand by decision makers for more robust evidence demonstrating the value of new medical devices in order to optimise patient health. This is particularly important given the burden of wounds and MSK disorders is increasing due in tandem with the rise in chronic diseases and life expectancy, among other factors. As a result of this increased burden, there are huge pressures on healthcare budgets and the need to ensure efficient allocation of the limited healthcare resources. One such method is using the best available clinical evidence and incorporating economic evaluations in the coverage and reimbursement decision-making process.

The overall aim of the thesis was to evaluate the clinical and health economic evidence used to inform coverage and reimbursement of medical devices using examples from wound care and MSK health. The thesis demonstrated that having good clinical evidence, and incorporating health economic evidence is a necessary but not sufficient condition for ensuring efficient allocation of limited resources. Study 1, presented in 4.5 has resulted in the update of the EBA clinical guideline in 2017, whereas Studies 2 and 3 in Sections 4.6 and 5.3 are yet to have a demonstrable impact on guidelines. Studies 4 and 5 in Section 5.6 and Studies 6,7 and 8, in Section 6.4 and 7.3 have demonstrated that using good clinical and economic evidence can result in positive coverage decisions benefiting manufacturers, patients, and payers.

The thesis presented and critically appraised 8 publications: 5 studies published by the researcher focused on wound care (burn and surgical site wounds) and 3 in MSK disorders (unstable intertrochanteric fractures). The thesis has shown how the different publications have formed a coherent body of evidence for wound care and MSK disorders, and demonstrate that good clinical and economic evidence can be a vehicle for optimal coverage and reimbursement decision for medical devices, which will benefit patients, payers, and manufacturers alike.

8.2 Contribution to Knowledge

Study 1, in Section 4.3, and Study 2 in Section 4.6, examined the relative effectiveness of silver dressings in patients with superficial and partial-thickness burns. Silver dressings are already known to be effective in preventing infections compared with standard care. However, what was unknown was which amongst the silver dressings was the most clinically and cost-effective. Both Studies 1 and 2 demonstrated that ACTICOAT was the most clinically effective silver dressing amongst the newer silver dressings. This clinical evidence was then used to inform the cost-effectiveness study, which confirmed that not only is ACTICOAT clinically effective, is also cost-saving.

As was identified in Section 4.1., there is currently no guidance as to which dressing should be preferred due to lack of evidence on newer antimicrobials (WUWHS, 2016; EBA, 2017). Study 2, Section 4.6 in particular has contributed to the debate of which among the newer silver dressings is clinically effective, by pointing clinicians and policymakers to the ranking of different dressings outlined in this thesis. The current EBA (2017) guideline now

acknowledges that ACTICOAT results in reduced length of hospital stay, citing evidence presented in Study 1 Section 4.3, which was published in 2016. It is anticipated that the next round of the EBA guideline update due in 2020 will incorporate evidence from the ICT and cost-effectiveness studies that provided a ranking of the silver dressing in order of clinical and cost-effectiveness. Smith and Nephew has seen its silver dressing market share grow as a result of the convincing evidence presented in this thesis. The sales and marketing have updated their claims based on the results of the meta-analysis to include claims around reduction in LOS, reduction incidence of surgical procedures and pain compared to standard of care.

Chapter 4 also demonstrated that performing an appropriate Health Technology Assessment does have a significant benefit for the patients, payers, and the manufacturers. SSCs are a huge drain on the health care budgets and using modern advanced wound care devices can help lessen their incidence. The cost-effectiveness of PICO following hip and knee or cardiothoracic surgery contributed new understanding on the performance of this device in these patient populations. Studies 4 and 5 in Section 5.6, have led to a positive recommendation for the widespread adoption of PICO (https://www.nice.org.uk/guidance/mtg43/chapter/1-Recommendations) in the UK NHS, which is an important practical contribution. Patients now have wider access to an effective intervention and the payers are optimising their budgets.

Equally, the systematic review and meta-analysis of IM nails presented in Chapter 6, updated an existing meta-analysis by Ma *et al.,* (2017) (Study 7, Section 6.3). No

controversy exists regards the superiority of the twin-screw nailing system around implant failures when compared with single-screw nailing system, and this analysis further confirmed this assertion. However, the study added new understanding around pain, health-related quality of life, and revision rates, which were all shown to favour the twin-screw nailing system. The hypothesis that all IM nails (twin-screw or single screws) are the same was also dismissed by this study, as the twin-screw nailing system was shown to be superior compared with the single-screw nailing system.

Chapter 7 summarised the cost-effectiveness of the IM nails utilizing data from the clinical meta-analysis presented in Chapter 6, Section 6.3. This is the first published economic analysis that considered the twin-screw InterTAN and concluded that it was cost-effective. Furthermore, the study provided additional information that among the single-screw nails, Gamma3 is the preferred choice compared with PFNA according the evidence presented in this thesis.

8.3 Implications of the Thesis

The research summary findings have been presented in the preceding Section 8.1. In Chapters 4 and Chapter 5, the thesis described the clinical effectiveness and cost-effectiveness evidence in burn wound care, respectively. The thesis concluded that ACTICOAT is clinically superior and the most cost-effective dressing among the newer silver dressings, as evidenced by fewer infections and reduced LOS. It is important to acknowledge that the evidence was not a direct comparison and some of the outcomes are not defined in a standard way. However, as stated in Section 4.1. there is currently no

guidance on which silver dressing should be preferred in this patient population, due to lack of evidence. The findings of this research can be used by clinicians, policy makers, and payers to give guidance regarding the most clinically and cost-effective dressing. This will be a great starting point while further head-to-head research between the main silver dressings is conducted.

One of the significant findings of this thesis is in Section 5.6, where a pertinent question was addressed regarding the use of negative pressure wound therapy in closed surgical incisions to prevent complications following surgery. Negative pressure is certainly an innovative advanced wound dressing. As with any new technology, it needs to have proven evidence before it can be widely used. Studies 4 and 5, in Section 5.6 used evidence from published RCTs and reported the cost-effectiveness results where PICO was found to be cost-saving in patients following hip/knee and cardiothoracic surgery. The studies further found that the dressing was more effective in patients at high risk of SSC. This has significant implications as the research not only proved that negative pressure wound therapy is cost-effective and therefore should be recommended for use, but also that the dressing should be targeted at those patients with increased risk of contracting SSC/I. This is important to payers as it potentially avoids over-use of new technologies in times when budgets are tight. The studies have already had a positive impact as they were used as part of the decision that led to PICO being recommended for widespread use in the UK NHS MTG43 (https://www.nice.org.uk/guidance/mtg43/chapter/1-Recommendations). The manufacturer is also benefiting from the wider use of their technology, thereby optimising

their return on investment. As of November 2019, the manufacturer of PICO has seen PICO sales hit the $100 million mark for the first time (See attached confidential e-mail).

This thesis also found evidence to support the use of twin-screw nailing system over single-screw nailing system in patients with unstable intertrochanteric fractures. This is significant new evidence which should be used by policymakers and clinicians to update their guidance with regard to device selection in this patient population. Furthermore, among single-screw IM nails, Gamma3 should be preferred over PFNA on cost-effectiveness grounds. The studies on MSK disorders have had a positive policy impact, resulting in an increase in a 10% price increase of InterTAN device for the manufacturer in South Korea as the healthcare insurer was convinced by the clinical and cost-effectiveness evidence presented in this thesis. InterTAN as a brand has grown globally by 8.6% between 2014 and 2019 according to the manufacturer (See attached Confidential E-mails in appendix).

Furthermore, medical devices do not always have the abundance of evidence as in pharmaceutical research. This thesis has shown that when the evidence is available, the same methodological rigor should be applied in assessing the device usefulness in clinical practice. In this thesis, good evidence underpinned the conclusions for wound care and MSK disorders where SLRs and meta-analyses were conducted and informed the conclusions. The idea of pulling together RCTs and observational studies has greater utility in medical devices where conducting trials is difficult, in particular due to obstacles in blinding and smaller numbers of study participants. It is therefore imperative for

policymakers to accept the utility of using all available evidence. The adoption of this methodology in medical devices, especially wound care and MSK disorders, is going to ensure that no clinical evidence is overlooked and that patients have access to clinically and cost-effective interventions.

8.4 Limitations of the Thesis

As discussed above in Section 8.2, this research has addressed gaps that existed in literature and at the same time contributes to new knowledge in the field. However, there are limitations of the thesis that need to be acknowledged. Regarding cost-effectiveness analyses, the economic models adopted the healthcare payer's perspective. This approach favours publicly funded healthcare systems where the tax payers are responsible for paying for health provision. In the cases where a mix of both public and private payers, as in the United States and other countries where co-payments exists, productivity costs and out-of-pocket expenses for the patient, family, and friends have not been accounted for, which may underestimate the total costs of associated with a medical device. Consequently, there is a need to formally assess the impact of modelling from a societal perspective. The societal perspective considers all costs, including productivity loss, and patient and care givers costs. However, the analyses presented in Sections 5.3, 5.6, and 7.3 can be considered conservative and therefore likely to underestimate the true cost benefits, as payer perspective does not include all relevant costs and benefits in their analyses. Furthermore, the economic evaluation studies focused on short-term time horizons. Limiting studies to shorter time horizons may address the needs of payers,

however, there is a danger of not adequately capturing the full costs and benefits of interventions, which tend to be underestimated over a shorter time horizon. Focusing on short-time horizon usually biases the results against the more effective interventions. In this thesis this is unlikely to alter the conclusions since the more effective interventions have been found to be cost-saving even in the short-term.

This thesis answered questions on clinical and cost-effectiveness with important implications around value for money. However, they are not the only important questions necessary for full implementation of research recommendations. Value for money does not address the affordability question, which is answered by a different type of research, the budget impact model. The thesis did not consider budget impact of the interventions, which is key in terms of product adoption and patient access to medical devices as this was outside the scope of the thesis. There is a lack of congruence between cost-effectiveness analysis and budget impact analysis as payers may refuse to pay for recommended interventions due to affordability issues.

Although ITC methods are accepted and well developed, it is always preferable to have direct comparative evidence. This thesis demonstrated the lack of such direct evidence in the use of silver dressings despite the dressings having been used for more than 2 decades. Also, the clinical studies assessed in this thesis for both wound care and MSK disorders had short-term follow-up data. In burn injury there are outcomes important to the patient, such as scarring, which are not routinely collected.

8.5 Recommendations for Further Research

The thesis presented evidence of clinical and cost-effectiveness for wound care and MSK disorders, with focus on burn injury, infection control, and unstable intertrochanteric fractures, respectively. The findings and issues raised in this thesis indicate several possible avenues for future research that can enhance our understanding of evidence around these medical devices in the respective populations.

For the burn wound care studies, the clinical evidence comprised both RCTs and observational studies compared with SSD. There was no direct head-to-head evidence for the newer silver dressings and a lack of long-term outcomes such as scarring and other cosmesis outcomes, including lack of standard definitions of some outcomes such as LOS. Head-to-head studies comparing the new silver dressing in patients with superficial and partial-thickness burns should be conducted collecting long-term outcomes, such as scarring. These studies are necessary to validate the results of the indirect treatment comparison presented in this thesis Section 4.6 and ensure the treatment guidelines are updated with confidence. Furthermore, as pointed out earlier in Section 4.8, using standardised outcomes ensures that homogeneous outcomes are collected.

Regarding the prevention of surgical complications, head-to-head studies comparing the negative pressure wound devices either directly or via indirect treatment comparison methods should be conducted. I have already started the ITC research of PICO compared with Prevena in patients following closed incision surgery to assess both the clinical and

cost-effectiveness of the two devices. The research is expected to guide payers and clinicians to choose the device that will optimise their patient outcomes and budgets.

For the MSK disorder studies, only 4 out 12 studies that were identified and included in the clinical meta-analysis reported on the outcome of non-unions and none reported on conversions to THA following revision surgery of unstable fractures. Currently, the evidence from this thesis suggests that there is no difference between the performances of all IM nails on the non-union outcome. It is not clear if this is genuinely the case or it is a result of lack of reporting. It is therefore recommended that future studies should collect this (non-union) outcome to enhance our understanding, and further give guidance to clinicians and payers of health care. As identified in Chapter 6, there are also few studies comparing twin-screw InterTAN with Gamma3 in general. Additional studies comparing these two devices in this population are also recommended.

Economic evaluations attempt to provide information about the most economically efficient ways to utilise or allocate available health care resources, and these studies do not address the question of affordability. On the other hand, a budget impact analysis estimates the financial and organisational consequences of adopting a new health care technology without directly taking health consequences into account. Regulatory bodies are concerned with value for money and safety of medical technologies, while commissioners/insurers or hospitals have to find the money from their budgets to pay for recommended interventions. This thesis did not present budget impact analysis of the various technologies assessed, which is a worthwhile direction for future research. Future

studies considering affordability are therefore recommended to help guide commissioners or payers. This will ensure widespread adoption and patient's access to the medical technologies.

The economic models presented in this thesis used a decision tree modelling technique. The advantage of using a decision tree is that they are easy to follow and laid out in a very logical and linear fashion. However, decision trees are not suitable in situations where there are recurring events and where the relevant time horizon is longer. This was certainly the case for the MSK model for intertrochanteric fractures that long-term outcomes could have been handled better by a different modelling approach, specifically a Markov modelling approach. Markov models are ideal for modelling clinical problems that involve risk over time, or when the timing of events is important. Future economic studies should consider using the Markov modelling approach especially as they seek to include loner-term outcomes such as conversion to THA following a failed revision surgery.

8.6 Conclusions

In conclusion, the research presented in this thesis has demonstrated that when there is good clinical and economic evidence, this can hypothetically result in efficient allocation of scarce healthcare resources. The thesis used examples from wound care, where ACTICOAT was demonstrated to be clinically and cost-effective in superficial and partial-thickness burns. Further evidence was presented proving the cost-effectiveness of PICO in preventing SSCs. The use of the PICO evidence is a practical example of how clinical and economic evidence can inform coverage and reimbursement decisions as illustrated by the

decision of NICE in the UK to recommend its use in the NHS. Using examples from MSK disorders, this thesis was able to show that the twin-screw InterTAN was the best IM nail compared with the single-screw IM nails. The studies on IM nails presented in this thesis have resulted in InterTAN price being increased by 10% as payers in South Korea acknowledged the value that the device brings to the patient and payers, and 8.6% growth in sales of InterTAN between 2014 and 2019.

The thesis was also able to show that similar evidence types and assessment methods are needed for both wound and MSK disorders. However, there were limitations and evidence gaps that were identified in the thesis. Necessary future research recommendations have been made, which will no doubt increase the understanding of the medical devices presented in this thesis and further update current and future guidance. More importantly, to ensure widespread adoption and hence access of these devices, budget impact models are also needed, and I have challenged myself to contribute to this further research.

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