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THE ROLE OF REAL WORLD EVIDENCE IN THE COST-EFFECTIVENESS ANALYSES FOR PHARMACOLOGICAL TREATMENTS IN OVERACTIVE BLADDER

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Abstract

The aim of this thesis is to evaluate the extent to which cost-effectiveness of a recently launched drug in the treatment of overactive bladder is supported by real world evidence. The demand for real world effectiveness data by Payers and decision-makers is increasing to better manage the uncertainty at the time of making reimbursement decisions. Real world data can help to fill the knowledge gap between clinical trials and actual clinical practice.

Overactive bladder is one of many chronic conditions likely to impact people as they age. It is a common condition characterised by a group of lower urinary tract storage symptoms, which has a profound and measurable negative effect on patient health-related quality of life (HRQoL). The economic burden of OAB is also considerable. Antimuscarincs have been the mainstay pharmacological treatment for OAB for over 30 years, but adverse events and persistence on medication remain a key issue. Mirabegron, a ß₃ adrenoceptor agonist provides an alternative option.

The thesis presents and critiques 9 peer-reviewed publications to demonstrate the value evidence generated pre-health-technology assessment (HTA) and that generated post-health -technology assessment in clinical practice. Each publication adds a new building block to the value proposition, and a sophistication of methods that help illustrate the value of the new drug compared to competing alternatives.

The impact of OAB on patient HRQoL is explored through analyses of both disease specific and generic validated patient reported outcome (PRO) instruments. Utility values are also derived for the purposes of health economic modelling. The comparison of efficacy and safety of mirabegron with other competing alternatives is assessed using network meta-analysis (NMA), a requirement from most HTA bodies in the absence of head-to-head evidence. The outputs from the NMA and the PRO analyses are then applied to a series of trial based and NMA based HE models to assess the cost-effectiveness of mirabegron. This is followed by an assessment of effectiveness through analysis of a large retrospective database to see if indeed cost-effectiveness is supported in the clinical practice.

The thesis concludes that cost-effectiveness of mirabegron is broadly supported by Real world evidence in terms of persistence and adherence while also highlighting the strengths and weaknesses of the current research and making recommendations for future research.

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Chapter 1: Introduction

1.1 The Role of Real World Evidence (RWE) in Drug Development and Commercialisation

Real world evidence (RWE) is becoming an increasingly important component of Bio-pharmaceutical drug development and commercialization. There is a growing demand from regulators, public and private payers and prescribers for broader information on real-world effectiveness and safety in order to better understand the impact of the new product in the real-world setting. As a result, plans to generate RWE are being included earlier in the research and development phase of new drugs (Annemans et al., 2007).

This demand for RWE is driven by the unsustainable cost explosion in major healthcare systems, resulting in cost-containment measures and a more demanding reimbursement environment which continues to raise the bar with respect to evidence. This has also been compounded by the growing emergence of health technology assessments (HTA) in many healthcare systems (Volker et al., 2014). An example of the greater scrutiny placed on demonstrating value can be seen with the United Kingdom (UK) HTA body, National Institute of Clinical Excellence (NICE). Between March 2000 and April 2014, NICE gave a negative recommendation for 36 out of 141 single technology appraisals (rejection rate of 26%) and the rejection rate for new oncology products was higher at 42% (24/57) (Volker et al., 2014).

Another example of the HTA effect is Germany's Act on the Reform of the Market for Medicinal Products (AMNOG) which between Jan 2011 and December 2013 assessed 51 out of 62 products to have less than significant incremental benefit, a rejection rate of 82% (Volker et al., 2014). These developments are leading to increased demand for demonstration of impact in the real world setting and the level of that impact may also influence varying payments for different patient subgroups, potentially leading to a more outcomes based paradigm shift. Therefore, while Regulatory authorities may for example require post-approval studies to determine the safety of the new product

when it is widely prescribed, payers require validation of a products real-world clinical effectiveness and cost-effectiveness to make more informed decisions on reimbursement, pricing and formulary placement (Christel M., 2014; Annemans et al., 2007).

Data generated from real-world patient experience can potentially help in understanding how to incorporate new technologies in to clinical practice. In doing so it can help to improve the quality and delivery of medical care, reduce overall costs and improve outcomes. These are essentially data to help fill the knowledge gap between clinical trials and actual clinical practice. There are several other reasons why the push towards real-world evidence is happening so quickly. Randomized controlled trials (RCTs) although they form the 'gold standard' for establishing efficacy and gaining regulatory approval, this is in an idealised environment and can often only measure efficacy in a limited population, thereby not providing a true indication of effectiveness (Cziraky, 2014). More information may also be required on how drugs perform in the real-world in specific subgroups such as age, gender, patient with co-morbid conditions, disease severity (Figure 1). Real-life data can provide insights that are not usually provided by RCTs such as epidemiology, adherence, compliance and cost and healthcare resource utilization insights (Cziraky, 2014). Finally, and more importantly payers are taking more of an interest in real world effectiveness data to better manage the uncertainty at the time of making reimbursement decisions (Annemans et al., 2007).
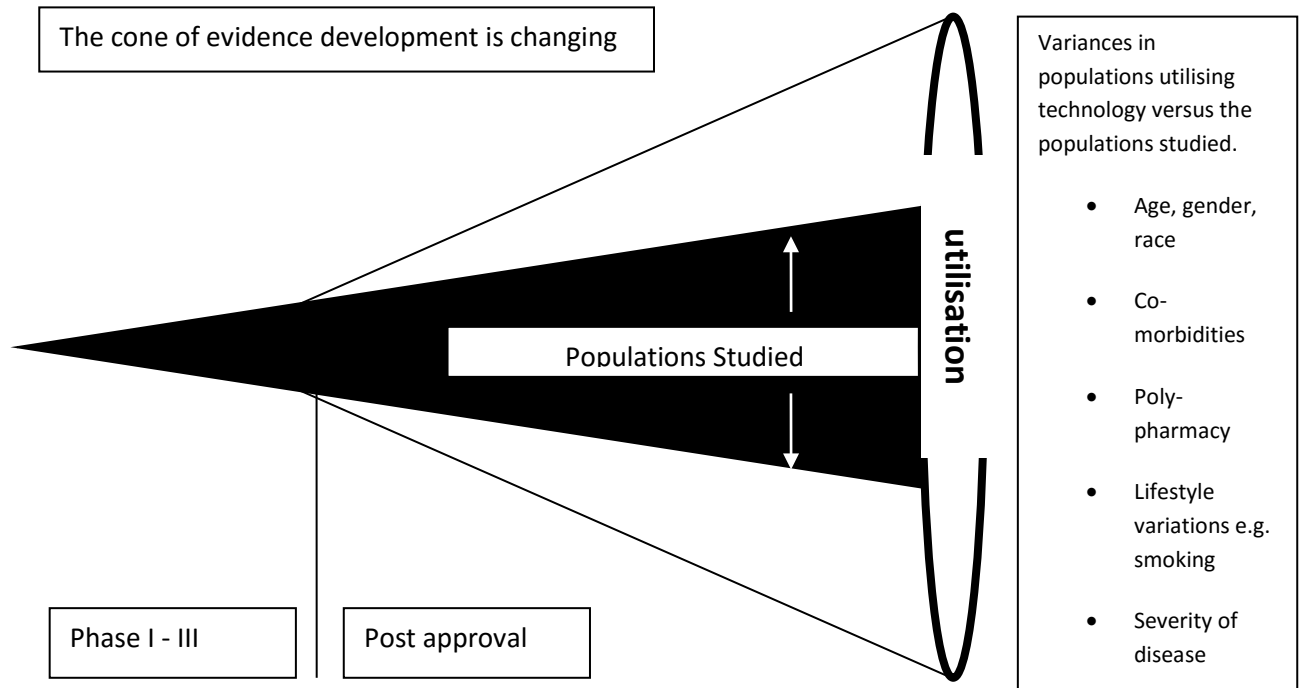
Figure 1: Real-world evidence studies: Applied Clinical Trials. (Adapted fromCziraky Mark, Pollock Michael. http://www.appliedclinicaltrialsonline.com/real-world-evidence-studies)

An increased demand for robust evidence has led to the integration of Health economics and outcomes research (HEOR) within traditional Research and Development (R&D), impacting clinical trial design and the management of economic endpoints within these trials. HEOR generates evidence of the economic value of new and existing products and helps decision-makers and payers determine reimbursement policies and insurance coverage for new and existing therapies. A growing number of Phase III trials now include economic endpoints and analyses, alongside the clinical outcome measures, to demonstrate the cost-effectiveness of new products (Annemans et al, 2007).

Therefore, from a HEOR perspective there are obvious benefits of working on real life or observational data before launch of a new product. Reimbursement authorities at pre-launch are always asking for more evidence with respect to cost-effectiveness in the real world but the industry argues that this is not possible given that the product is not available until a decision on its reimbursement is reached. As a result

reimbursement authorities will accept or even request Health Economic modeling. The modeling is based on different available evidence, observational data and RCT data. In addition to this some payers may approve conditionally pending collection of real-world data post-launch for validation (Cziraky, 2014). This is however not common practice in all countries and in countries where HE modeling or modeling assumptions are not accepted reimbursement and pricing negotiations may be negatively impacted. It is therefore important that the opportunity to collect real-world data post launch is fully utilized. This will not only help to validate modeling assumptions, but also provides the opportunity to prove effectiveness in a large pragmatic trial against key competitors which addresses outcomes such as adherence, persistence and other relevant long-term outcomes. Finally, it will also enable us to assess the value of a range of treatments options and evaluate the changing environment (Figure 2) (Annemans et al., 2007).
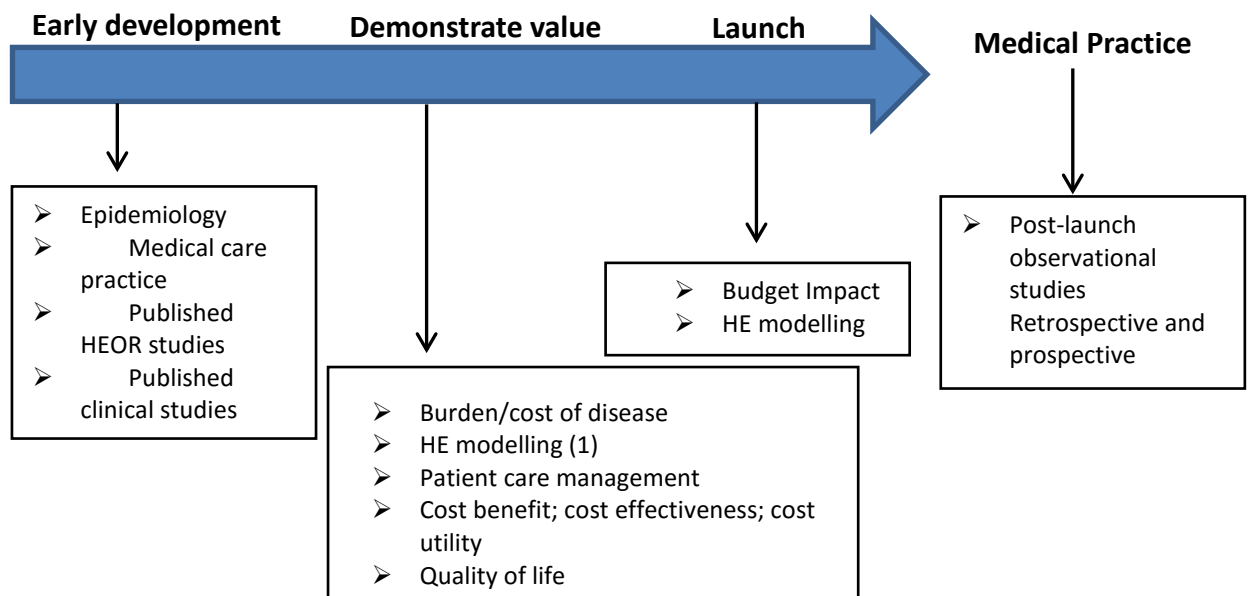
Figure 2: Phases of HEOR (adapted from https://www.ispor.org/News/articles/Oct07/RLD.asp)

As stated before, managing uncertainty for payers and decision makers during reimbursement processes is essential. RWE supporting effectiveness can help manage this to some extent and therefore is becoming a vital component of the body of evidence submitted by the pharmaceutical industry pre and post launch.

With an ageing population as one of the major factors impacting health care spending, effective management of chronic conditions will become a major priority for healthcare systems across the world (Kaplan et al., 2004). RWE will therefore play an instrumental part in helping payers to make difficult decisions when allocating resources. Overactive bladder (OAB) is one of many chronic conditions likely to impact people as they age. However, while there is considerable evidence that OAB has a significant humanistic and economic burden (Coyne et al., 2011b; Hawken et al., 2016; Sung et al., 2012) due to the non-life threatening nature of the disease there is a danger that it could fall below the radar and down the list of priorities when compared to conditions such as heart disease and diabetes. It is therefore vital that strategies are put in place to generate evidence to highlight the humanistic burden placed on patients suffering from this disease, and fill the current gap in cost-effectiveness and real world effectiveness data for pharmacological treatments used in the treatment of OAB.

OAB has a profound and negative impact on patient health-related quality of life (HRQoL) (Coyne et al., 2011b) and poses considerable economic burden (Irwin et al.,2009). For the past 30 years, anitmuscarinics have been the mainstay in terms of pharmacological interventions. However, although with established efficacy (Buser et al, 2012; Nabi et al., 2006), antimuscarinic agents have several limitations which include unwanted adverse events and high rates of discontinuation (Oefelein et al., 2011). Mirabegron, a β_3-adrenergic agonist is the first new class of treatment in OAB in over 30 years. It has a mechanism of action that is distinct from antimuscarinics and therefore is associated with a lower incidence of antimuscarinic related adverse events such as dry mouth and constipation (Khullar et al., 2015). Economic analyses of Mirabergon have not been available in literature prior to the publications submitted in this thesis. Previous cost-effectiveness analyses have been predominantly focussed on

antimuscarinic agents, and have mainly centred on data from clinical trials (Aballea et al., 2015). There has been very little emphasis on demonstrating cost-effectiveness in the real world setting.

1.2 Aims of the Thesis

The aim of the present thesis therefore, was to firstly, demonstrate the cost-effectiveness of Mirabegron in the pre-HTA submission phase. Secondly, to assess the extent to which cost-effectiveness of Mirabegron is supported using RWE. The overall aim is to try and reduce the uncertainty in value demonstration between clinical trial and clinical practice.

The thesis will achieve this aim through the presentation of nine published papers, for which the present author was either a first author or co-author. Two major themes are included in the body of work (Figure 3):

1. Predictive assessment of value pre-HTA assessment (pre-launch)
2. Real world assessment post-HTA assessment (post-launch)

The predictive assessment of value essentially includes research that would normally be assessed by a HTA body such as NICE for a single technology appraisal while the RWE evidence includes the post HTA assessment (post-launch) that assesses the effectiveness of the drug in clinical practice. The thesis will provide strengths and limitations of the evidence generated to support the predictive and real world assessment, and try to evaluate the extent to which they support each other. Finally, this thesis will try to draw plausible conclusions and make recommendations on areas where future research may be focussed.
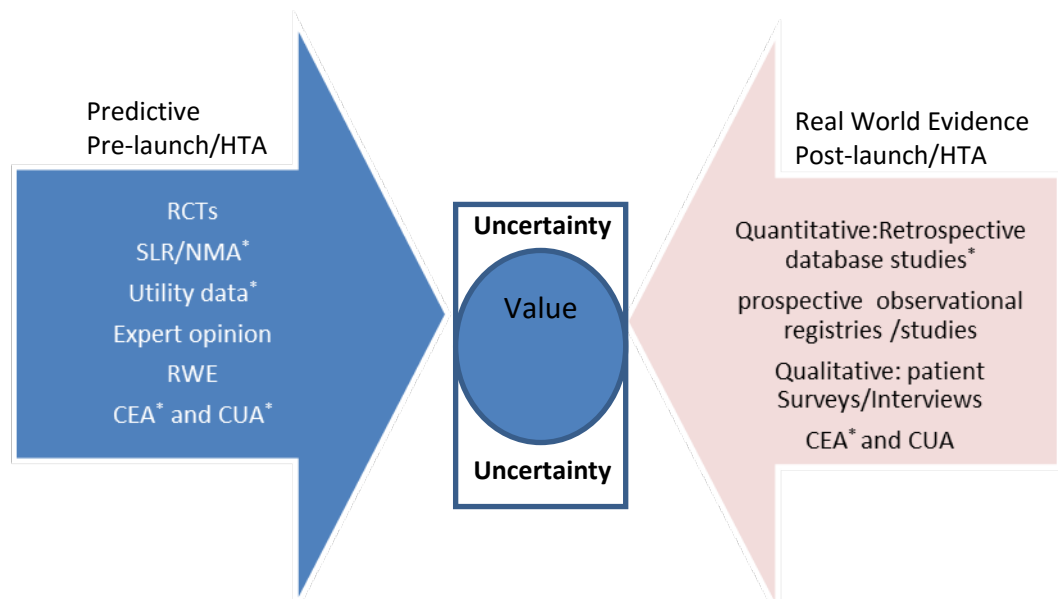
Figure 3: Summary of predcitve assessment pre-HTA and post-HTA assessment

RCT = Randomized Controlled Trial, SLR= systematic literature review, RWE= real world evidence, CEA = Cost-effectiveness analysis, CUA = Cost-utility analysis

*represents evidence (peer-reviewed publications) that have been submitted in this thesis

1.3 Overview of the Thesis

Chapter 1 provides an overview of the evidence requirements at the various stages of drug development. This chapter is particularly focussed on the increasing demand for RWE by payers and HTA bodies, to better manage the uncertainty at the time of making reimbursement decisions. General aims and structure of the thesis are also included.

Chapter 2 will provide a comprehensive background to OAB in terms of definitions, epidemiology, humanistic and economic burden, current treatment guidelines and treatment options. It also introduces Mirabegron, the latest option in pharmacological treatments in OAB.

Chapter 3 is focussed on patient reported outcomes (PROs) in OAB. The impact of OAB treatments on health-related quality of life (HRQoL) is discussed through research conducted using both generic and disease-specific instruments. The strength and limitations of both approaches is highlighted.

Chapter 4 discusses the importance of comparative effectiveness to payers. The network meta-analysis comparing efficacy and safety of treatment for OAB is introduced, and how this adds to previous literature reviews and meta-analyses. Strengths, limitations and application of this research are also discussed.

In Chapter 5, a critique of health economic modelling in OAB is provided. The learning from this is then applied to two different approaches to health economic modelling in OAB. This approach modelled progression of OAB symptoms separately, pays more attention to the treatment pathways and treatment sequences in OAB.

Chapter 6 introduces the persistence and adherence to OAB medications using RWE. In this chapter the methodology, results and interpretation of a large UK retrospective database study are discussed. A HE model developed using the main outputs of this study provides the basis of further discussion on the economic impact of persistence and adherence. The model also allows for broad comparisons between HE modelling described in Chapter 5 (pre-launch).

Chapter 7 presents a summary, conclusions, and recommendations for future research. In this chapter the extent to which RWE supports cost-effectiveness established previously (pre-launch and pre-HTA) is discussed along with the associated limitations. Areas for future research that would complement the current thesis are also highlighted.

Chapter 2: Background of OAB

2.1 Introduction

Chapter 1 has already examined the growing need for RWE to support effectiveness and focussed attention on the need for such evidence as well as cost-effectiveness evidence to support pharmacological interventions in OAB. Chapter 2 aims to provide

some more background on overactive bladder in terms of definitions, epidemiology, humanistic and economic burden, current treatments, guidelines and challenges.

2.2 Definition of Overactive Bladder

Overactive bladder (OAB) is a common condition characterised by a group of lower urinary tract storage symptoms. The condition is defined by the International Continence Society (ICS) as a disorder involving urgency, with or without urge incontinence, usually with frequency and nocturia in the absence of proven infection or other obvious pathology (Abrams et al., 2003). The ICS definition of OAB is widely applied and accepted. ICS definitions for each of the four lower urinary tract symptoms that make up OAB are shown in **Table 1** (Abrams et al., 2003). OAB is sometimes further categorised as OAB_{wet}, which is OAB that occurs with urinary incontinence, and OAB_{dry}, that is OAB without urinary incontinence (NICE 2013). It is estimated that approximately 30% of those affected with OAB have OAB_{wet} and 70% have OAB_{dry} (Tikkinen et al., 2007; Wen et al., 2014).

Table 2.1 Definitions of the lower urinary storage symptoms that constitute OAB

Symptom	Definition
Urgency	Sudden compelling desire to pass urine which is difficult to deter
Increased daytime frequency	Voiding too often by day
Nocturia	Waking at night one or more times to void
Urge urinary incontinence	Involuntary leakage accompanied by, or immediately preceded by, urgency

Source: Adapted from Abrams et al. (2003)

2.3 Epidemiology of OAB

In large population-based or community-based studies conducted in Europe, North America, South America and Asia, estimates of the prevalence of OAB ranged from 2.1% to 24.7%; most estimates were within the range of 12% to 19% (**Table 2.2**). No population-based estimates for the prevalence of OAB are currently available for

Australia or Africa (Corocos et al., 2004; Coyne et al., 2008; Coyne et al., 2011a; Coyne et al., 2011b; Coyne et al.,2012b; Coyne et al., 2013b).

Table 2.2: Prevalence of OAB in large population-based or community-based surveys that included both sexes (>800 respondents)

Reference	Country	Respondents, n	Age range, yr	OAB prevalence, %
Europe				
Irwin (2006a)	Germany, Italy, Sweden, UK, Canada	19,165	18–≥70	11.8
Milsom (2001)	France, Germany, Italy, Spain, Sweden, UK	16,776	40–≥75	16.6
Tikkinen (2007)	Finland	3727	18–79	8.4[a]
North America				
Corcos 2004	Canada	3249	35–≥75	18.5
Coyne 2011a	United States	20,000	40–95	24.7[b]
Herschorn 2008	Canada	1000	18–90	13.9
Stewart 2003	United States	5204	18–≥75	16.5
South America				
Teloken 2006	Brazil	848	15–55	18.9
Asia				
Homma 2005	Japan	4570	40–100	12.4
Lee 2011a	Korea	2000	18–96	12.2
Wang 2011	China	14,844	18–≥70	6.0[c]
Wen 2014	China	9805	40–≥70	2.1
Yu 2005	Taiwan	1827	30–79	18.2

a Age-standardised estimate.

b OAB symptoms reported as occurring at least "often".

c Weighted for age, gender, and city size.

Modelled data from one the largest population-based surveys of urinary incontinence, overactive bladder and other lower urinary tract symptoms (EPIC study) suggest that OAB burden is expected to increase because of population growth and ageing of the

population. The greatest increases are projected in Africa (31.1% increase from 2008 to 2018), followed by South America (22.4%), Asia (22.1%), North America (18.4%) and Europe (4.4%[30]). Overall, an estimated 500 million individuals worldwide were affected by OAB using the ICS definition in 2013, which is anticipated to increase to 546 million by 2018 (20.1% increase) (Irwin et al., 2011).

2.4 Burden of OAB

2.4.1 Quality of Life and Work Productivity

OAB symptoms have a profound and measureable negative effect on patient health-related quality of life (HRQoL). Adults with OAB have statistically significantly lower scores on recognised generic HRQoL instruments such as short-form (SF)-36 and EuroQol 5-Dimensions (EQ-5D)] compared with matched controls (Coyne et al., 2008). Lower scores on both instruments indicate poorer quality of life.

HRQoL impairment is influenced by the degree of symptom bother. In the EpiLUTS study, SF-12 mental and physical component summary scores were significantly lower (indicating worse HRQoL) for respondents with OAB symptom bother versus those with no/minimal symptoms or with OAB without symptom bother (Coyne et al.,2011b; Milsom et al., 2012).

HRQoL scores are also negatively affected by the presence of urinary incontinence, with respondents with OAB and urge incontinence reporting lower HRQoL scores than those without urge incontinence (Milsom et al., 2012; Stewart et al., 2003; Tang et al., 2012). Further, an increasing number of incontinence episodes per day were significantly associated with reduced scores on both generic and disease-specific HRQoL instruments in patients with OAB (Lee et al., 2011a).

OAB symptoms increase the likelihood of affective disorders when compared with controls. Individuals with OAB had significantly higher scores on the Centre for Epidemiologic Studies Depression Scale (CES-D) than matched controls (Stewart et al., 2003). In the EPIC study, a clinically elevated CES-D score of ≥21 was reported in 11.4% of OAB cases compared with 3.6% of matched controls (p < 0.001) (Coyne et al., 2008). Similarly in the EpiLUTS study, significantly higher rates of anxiety and depression,

defined as Hospital Anxiety and Depression Scale (HADS) scores ≥8, were reported in those with OAB compared with those with no or minimal OAB symptoms (Coyne et al., 2011b; Milsom et al., 2012).

In terms of productivity, data from several large surveys conducted in Europe and the US indicate that OAB symptoms affect employment status. Individuals with OAB were less likely to be employed (i.e. full-time, part-time or other paid work) compared with matched controls or compared with those with no or minimal symptoms; the differences between groups were statistically significant in most analyses (Coyne et al., 2008; Coyne et al., 2012b; Sexton et al.,2009).

2.4.2 Cost of Illness

A summary of cost-of-illness studies, which estimate the overall economic burden of OAB in different countries and regions, is presented in Table 3. All study estimates were dependent on prevalence data, which may explain some of the variability of the results reported. Most studies adopted a societal perspective and considered a broad range of direct medical costs, including those associated with OAB-related consequences such as urinary tract infections, skin conditions, falls and fractures. Several studies also considered indirect costs resulting from OAB such as productivity losses, travel expenses and home services (Ganz et al., 2010; Hu et al., 2003; Inoue et al., 2008; Irwin et al., 2009; Klotz et al., 2007; Reeves et al., 2006; Onukwugha et al., 2009; Sung et al., 2012).

Table 2.3:   Annual disease-specific costs for OAB; summary of cost-of-illness studies

Reference	Country(ies)	Costs included	Total annual cost (cost year)
Europe			
Irwin et al (2009)	Germany, Italy, Spain, Sweden, UK, Canada	**Direct:** GP consultations; drug therapy; diagnostic procedures; pads; OAB-related consequences (UTI, fractures, skin infections, depression); nursing home admissions **Indirect:** productivity loss	€9.7 billion (2005)
Klotz et al 2007	Germany	**Direct:** physician visits; diagnostic procedures; specialist care; nursing home care; physiotherapy; drug therapy; medical aids/devices; OAB-related consequences (UTI, skin infections, depression, falls, fractures)	€4.0 billion (not stated)
Reeves et al 2006	Germany, Italy, Spain, Sweden, UK	**Direct:** physician visits; drug therapy, pads; OAB-related consequences (UTI, skin conditions, falls, fractures)	€4.2 billion (2000)
North America			
Ganz et al 2010	United States	**Direct:** primary care; specialist care; diagnostic procedures; drug therapy; surgery; physical therapy; emergency department; pads; pantiliners; diapers; latex gloves; bedside toilets; skin protection; OAB-related consequences (UTI, falls, fractures, depression, nursing home admission) **Indirect:** productivity loss	$US65.9 billion (2007)
Hu et al 2003	United States	**Direct:** diagnostic; physician; surgery; drug therapy; home care; routine care; OAB-related consequences (UTI, falls, fractures, skin conditions, nursing home admission,	$US12.0 billion (2000)

		hospital stays) **Indirect:** productivity loss	
Onukwugha et al 2009	United States	**Direct**: outpatient; inpatient services; drug therapy; pads; OAB-related consequences (UTI, falls, fractures, skin infections) **Indirect:** productivity loss	$US24.9 billion (2007)
Asia			
Inoue et al 2008	Japan	**Direct:** physician visits; hospital admission; drug therapy; surgery; behavioural therapy; travel; OAB-related consequences (UTI, falls, fractures, skin infections) **Indirect:** productivity loss	¥956.2 billion (not stated)
Sung et al 2012	South Korea	**Direct:** physician visits; drug therapy; diagnostic costs; pads; diapers; cleaning **Indirect:** productivity loss	KRW117.5 billion (2006)

Abbreviations: GP, general practitioner; KRW, Korean Won; UTI, urinary tract infection.

Although the methodologies and assumptions used in each of the studies differed, the annual cost-of-illness estimates suggest that the economic burden of OAB is considerable.

2.5 Current Treatment Options

OAB is typically treated in a stepwise manner, following a pathway beginning with conservative measures and moving through pharmacological treatment to invasive/surgical interventions. Conservative measures include lifestyle and behavioural modifications, such as reducing caffeine intake, optimising fluid intake, and weight loss. Some patients may benefit from bladder training, which can be combined with pelvic floor exercises.

Oral pharmacotherapies, antimuscarinic agents and the β_3-adrenoceptor agonist Mirabegron represent an alternative option either alone or in combination with

lifestyle and behavioural changes for those in whom these measures do not produce a satisfactory response. Minimally invasive treatments, including botulinum toxin-A (BoNT-A) injection, are generally used for patients refractory to oral pharmacotherapies (Abrams et al., 2013; Gromley et al., 2015; Lucas et al.,2015).

2.6 Treatment Guidelines

Several international urology bodies and national urology/clinical bodies have developed clinical practice guidelines for the management of OAB. All of the clinical guidelines follow a stepwise management approach, and treatment strategies are similar for men and women (Abrams et al., 2013; Gormley et al., 2015; Lucas et al., 2015).

Generally, clinicians should offer patient education and recommend lifestyle modification with behavioural and physical therapy following initial assessment. Of note, the International Consultation on Incontinence (ICI) and American Urological Association/Society for Urodynamics, Female (AUA/SUFU) suggest to consider adding oral pharmacotherapy in combination with lifestyle/behavioural treatment (Table 2.5). Second-line treatment consists of oral pharmacotherapy if lifestyle/behavioural treatment is not successful. The AUA/SUFU guidelines recommend trying a different oral therapy if a patient experiences inadequate symptom control and/or unacceptable adverse events with the initial oral therapy. The minimally invasive surgical techniques of BoNT-A, peripheral tibial nerve stimulation and sacral neuromodulation are options for patients who are refractory or intolerant to one or two oral therapies. However, patients should first be evaluated by an appropriate specialist.

Table 2.4: Summary of the key international guidelines for the management of OAB.

		Recommendations				
Group	Last update (data cut-off)	First-line	Second-line	Third-line	Fourth-line	Mirabegron comments
ICI	2013 (Dec 2012)	Lifestyle advice, pelvic floor muscle training, scheduled voiding regimes, behavioural therapies and antimuscarinics	BoNT-A, neuromodulation and bladder augmentation	–	–	Not currently recommended (last update was prior to Mirabegron launch; phase II and III data reviewed in text)
AUA/SUFA	2015 (Feb 2014)	Behavioural therapies ± Mirabegron or an antimuscarinic	Mirabegron or an antimuscarinic	BoNT-A, peripheral tibial nerve stimulation or sacral neuromodulation	–	Included as first- or second-line option.
EUA	2015 (April 2014)	Individualised behavioural and physical therapies including pelvic floor muscle training	Mirabegron or an antimuscarinic	Peripheral tibial nerve stimulation	BoNT-A, sacral nerve stimulation, bladder augmentation or urinary divertion	Recommends Mirabegron, but cautions that possible long-term side effects remain uncertain

Most of the national guidelines for OAB management mirror the advice offered by the international societies, with some key differences. Notably, the National Institute for Health and Clinical Excellence (NICE) provide some specific guidance about which antimuscarinic to prescribe (NICE 2013a). NICE also provides separate and specific guidelines for the use of Mirabegron (NICE 2013b), where it is recommended as an option for treating the symptoms of OAB in patients for whom antimuscarinic drugs are contraindicated or clinically ineffective, or who have unacceptable side effects. Similarly, Mirabegron is specifically recommended as a first- or second-line option by the AUA/SUFA and EAU guidelines (Gormley et al., 2015; Lucas et al., 2015), but the latter advises caution that the risk of possible long-term side effects remain uncertain (Lucas et al., 2015).

2.7 Unmet Need

Antimuscarinic agents have established efficacy in the treatment of OAB symptoms, and reduce the daily number of micturitions, urgency episodes and incontinence episodes compared with placebo (Buser et al., 2012; Nabi et al., 2006). However, antimuscarinic agents have several limitations which include unwanted adverse events and high rates of discontinuation (Oefelein et al., 2011). For many patients, the benefits of antimuscarinic agents do not outweigh the drawbacks despite the bothersome nature of their symptoms, highlighting a clear unmet need for individuals with OAB (Sexton et al., 2011).

Muscarinic receptors, the target of antimuscarinic agents, are present not only in the bladder, but also in other organs including the salivary glands, gastrointestinal tract, eyes, heart and brain (Abrams et al., 2006). Systemic blockade of muscarinic receptors by antimuscarinic agents leads to several class-related (i.e. anticholinergic) adverse events, the most common of which are dry mouth, constipation, headache and blurred vision. Although these events are generally mild to moderate in nature, they can affect adherence and persistence on therapy.

Antimuscarinic agents also have the potential to cause more serious adverse events involving the CNS (Oefelein et al., 2011). These events include somnolence, dizziness, depression, cognitive impairment, psychosis, electroencephalogram changes, sleep deficits, hallucinations, confusion and behavioural disturbances (O'Mahony et al., 2015). The elderly, in particular, may be at increased risk of CNS events because of anticholinergic load or burden.

2.8 Adherence and Persistence

Adherence and persistence are important factors for the effective treatment of OAB, as patients may require long-term medication. Adherence (or compliance) is the extent to which a patient acts in accordance with the prescribed dose and interval of a dosing regimen; it is often expressed as the number of doses prescribed in relation to the dispensing period, i.e. the medication possession ratio (MPR). Persistence is the time

from initiation of therapy to discontinuation of therapy. Persistence can be reported either as a continuous variable, i.e. the number of days for which therapy was available, or as a dichotomous variable measured at the end of a predefined time period, i.e. proportion of "persistent" or "non-persistent" patients (Wagg et al., 2015).

By either measure, adherence and persistence with antimuscarinic agents is low. Persistence with antimuscarinic agents appears to drop off rapidly after treatment initiation, with 43% to 83% of patients discontinuing their medication within the first 30 days (Sexton et al; 2011).

Several studies have identified risk factors associated with non-persistence with antimuscarinic agents, which have been captured in the systematic review by Veenboer & Bosch (2014). These include:

- Oxybutinin use;

- Immediate-release formulation use;

- Age (i.e. lower persistence among younger adults);

- Gender (i.e. better persistence in women).

The reasons most commonly given for discontinuing antimuscarinic agents were that treatment was not effective or did not work as expected or because of adverse events (Krhut et al., 2014; Schabert et al., 2009; Benner et al., 2010; Campbell et al., 2008; Dmochowski et al., 2007).

Long-term persistence rates with OAB medications are lower than those observed with medications used for other common chronic conditions according to a retrospective analysis of US prescription claims. After 6 months, persistence rates were 47% for intraocular prostaglandin analogs, 56% for statins, 56% for bisphosphonates, 66% for oral antidiabetics, 63% for angiotensin II receptor blockers, and 28% for OAB medications. At 1 year, these rates decreased to 32%, 43%, 41%, 54%, 50%, and 18%, respectively (Yeaw et al., 2009).

There is both a humanistic and economic cost of discontinuing antimuscarinic agents. Even if therapy has been successful, symptoms relapse rapidly and HRQoL scores deteriorate within 1 month of discontinuing treatment (Lee et al., 2011b).

2.9 Mirabegron

Mirabegron has received Marketing Authorization in Europe, North America, Asia, and Australia (Astellas Pharma Australia Pty Ltd 2016; Astellas Pharma Europe B.V. 2012; Astellas Pharma US 2012; Astellas Pharma Inc. 2011; Astellas Pharma Canada Inc 2015). Mirabegron offers the first new class of treatment for OAB in over 30 years and a different mechanism of action to the antimuscarinics (Chapple et al., 2014). Mirabegron is indicated in adults with OAB for treatment of symptoms of urgency, increased micturition frequency and/or urgency incontinence (Astellas Pharma Europe B.V. 2012; Astellas Pharma US 2012; Astellas Pharma Inc. 2011; Astellas Pharma Canada Inc 2015).

2.10 Chapter Summary

This chapter provided a good overview of OAB. The ICS definition of OAB is now widely applied and accepted. The prevalence of OAB is estimated to increase to 546 million world-wide by 2018, representing an increase of around 20%. OAB symptoms have a profound impact on HRQoL as measured by both disease-specific and generic PRO measures and also impact productivity (employment status) when compared to matched controls or those with no or minimal symptoms. Thus the economic burden of OAB is considerable. Current treatment options and clinical guidelines put oral pharmacotherapies as second line if lifestyle and behavioural treatment is not successful. Antimuscarinic agents have been the mainstay pharmacological treatment for the past 30 years, but the recent launch of Mirabegron which has a different mechanism of action and not associated with antimuscarinc related side-effects presents a different option. Long term persistence rates with OAB medications are lower than those observed with medications used for other common chronic

conditions. There are humanistic and economic costs of discontinuing antimuscarinc agents.

The next chapter will focus on the impact on HRQoL of treatment of OAB, as measured by generic and disease-specific instruments.

Chapter 3: Assessing Patient Reported Outcomes in OAB

3.1 Introduction

Chapter 2 provided the background to OAB as a disease, including current treatment options, unmet need and the introduction of Mirabegron as the latest addition to the armamentarium available to clinicians in the treatment of OAB. As OAB is a symptom based condition the significant impact on a patient health-related quality of life (HRQoL) was also discussed. This chapter will continue with discussion on the impact on quality of life and their measurement through use of patient reported outcomes (PROs) in OAB.

3.2 Patient Reported Outcomes (PROs) in OAB

OAB is a disease prevalent condition which has a profound impact on health-related quality of life (HRQoL) (Coyne et al., 2008). The efficacy of OAB treatments has been traditionally assessed using 3-7 day bladder diaries capturing information on objective end-points such as micturition frequency and number of incontinence episodes (Benner et al., 2010). However, data pertaining to the clinical significance of these end-points have only recently been seen in the literature (Thomas et al., 2014). As these objective measures do not capture the patient perception of treatment or quality of life, inclusion within clinical trials of validated PROs allow both objective and subjective endpoints to be captured. This generates important insights in to the performance of treatments that can subsequently be shared with regulatory bodies, Payers and for clinical decision making. Subjective outcomes provide essential information on the impact of bothersome side effects as these can impact persistence and adherence

(Benner et al., 2010; Khullar et al., 2013). Furthermore, subjective outcomes enable for an understanding of patient expectations which can also influence the impact of OAB on HRQoL (Khullar et al., 2013). In this chapter the strengths, limitations and insights in to the impact on HRQoL of treatment for OAB will be discussed using the three PRO-related publications submitted as part of this thesis. The research includes both disease specific and generic PRO measures.

3.3   Patient-Reported Outcomes with the ß₃-Adrenoceptor Agonist Mirabegron in a Phase 3 Trial in Patients with Overactive Bladder.

http://onlinelibrary.wiley.com/doi/10.1002/nau.22844/full

This paper includes pre-specified analyses and post-hoc analysis of the pivotal phase 3 study (SCORPIO:NCT00689104) in which 1,987 patients were randomised to placebo, Mirabegron 50 or 100mg/day or Tolterodine extended release (ER) 4mg/day as an active control. Although the incidence of overall treatment emergent adverse events were similar in all arms, the incidence of dry mouth with Tolterodine ER 4mg was 10.1% and Mirabegron 50mg/day was 2.8%. It is reasonable therefore to hypothesise that the improvements in the balance between efficacy and tolerability may translate in to HRQoL improvements. The PROs used in this study included Treatment Satisfaction-Visual Analogue Scale (TS-VAS), OAB questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC) and work productivity and activity impairment: specific health problem (WPAI-SHP) instrument. Incontinent pad use was also monitored to evaluate the effect of therapy on OAB-related medical care resources. Of these, PROs TS-VAS, Symptom Bother component of the OAB-q and PPBC showed significant improvement with Mirabegron 50 and 10mg versus placebo and is reported in the pivotal trial [85]. Data for other PROs (secondary endpoints) were reported in this trial including a post-hoc analysis in the subgroup of patients with incontinence at baseline.

The results showed significant improvements with 12 weeks of therapy with Mirabegron at the approved dose compared to placebo in OAB-q components and

PPBC. These improvements were not seen with Tolterodine 4mg ER compared to placebo. Numerical improvements were also seen with Mirabegron with respect to WPAI-SHP scores and with at least numerical reductions in incontinence pad use at 4 weeks. With regards to whether or not these differences were clinically meaningful with WPAI-SHP, it was not possible to ascertain as minimal clinically important differences do not appear to have been established. The lack of significant differences in pad use at 12 weeks may also be due to patients even when continent using them as reassurance, a high placebo response, and a lack of drug effect or other types of incontinence. The differences seen in the incontinent group were even greater than that seen in the overall population, suggesting that patients with incontinence perceive the benefits of Mirabegron to be greater than those who do not have incontinence. This was despite the fact the placebo effect was also greater in this subgroup. These findings also support the efficacy of Mirabegron in terms of urinary frequency, urgency and urgency incontinence reported in this trial and the PRO analyses in the pooled phase 3 trials reported previously (Khullar et al., 2013; Hershorn et al., 2013). They also support the findings from the generic EuroQol questionnaire (EQ-5D) analysis which reported significant changes from baseline for EuroQol five dimensions questionnaire utilities for Mirabegron 50mg/day versus Tolterodine ER 4mg/day. This paper will be discussed in more depth in the next section.

The limitations of this analysis lie in the 12 week duration of the study which is typical for registration trials in OAB. It is therefore difficult to assess the long term impact Mirabegron may have on HRQoL. The study design was also not powered to compare Mirabegron head-to-head with Tolterodine 4mg ER which in the real-world setting would be a key comparator. In addition, consistent with the primary efficacy analysis (Hershorn et al., 2013; Nitti et al., 2013) there is a large placebo effect which may to some extent obscure treatment effects.

3.4 Paper 2: Understanding the effects on HR-QoL of treatment for overactive bladder: a detailed analysis of EQ-5D clinical data for Mirabegron.

http://www.tandfonline.com/doi/full/10.3111/13696998.2013.802240

For the purposes of cost-effectiveness analyses, especially where the requirement is to provide an estimate of the Quality Adjusted Life years (QALYs) it has become increasingly important to include generic PRO measures in clinical trials. The EuroQoL five dimensions questionnaire (EQ-5D) is one of the most widely used for this purpose and in fact preferred by some prominent HTA bodies such as NICE (NICE, 2008).

Traditionally, EQ-5D data collected in clinical trials is focussed on utility-weighted EQ-5D profiles required to estimate QALYs. However, this is a rich dataset comprising of both patients self-reported health on the EQ-5D dimensions as well as patients overall assessment of their health on a visual-analogue scale (the EQ-VAS), therefore apart from estimating utility gains it may also provide further insights in to the underlying changes in HRQoL. Simply collapsing the EQ-5D health profile data in to a single value by means of weighting may result in loss of additional information and introduce exogenous variation that can bias statistical inference (Parkin et al., 2010). Also, analysis of EQ-VAS provides useful insights in to the patient perspective given that there are differences between public preferences and those of patients. Thus the aims of this paper were to demonstrate the insights possible from a range of statistical analyses of the EQ-5D data.

The overall objectives were to estimate the changes in utility with Mirabegron using pooled EQ-5D data collected from three large scale multicentre phase 3 trials completed in Australia and Europe (178-CL-046, NCT00689104);USA and Canada (178-CL-047, NCT06612909); and US, Canada and Europe(178-CL-074, NCT00912964). Additional objectives were to investigate changes in EQ-5D profiles that drive the changes in utility and if these changes are consistent with the patient's own views of their health on the EQ-VAS. This analysis also reported comparisons of each patient's EQ-5D profiles between each study time point and baseline evaluation using the Paretian Classification of Health Change (PCHC) as defined by Devlin et al (2010). Finally in order to investigate the idea that some treatments may be faster acting than others even if there is no difference in outcomes at 12 weeks, a comparison of the

Areas Under the Curve (AUC) of changes from baseline in UK utility scores 4, 8 and 12 weeks was performed.

The results showed Mirabegron to be effective on the EQ-VAS and the EQ index .The EQ-VAS was the most consistent in showing superior outcomes with Mirabegron, especially when compared to Tolterodine with the Mirabegron 100mg dose also showing superiority when compared to placebo. On the EQ index however, Mirabegron 50mg showed statistically significant improvement compared to Tolterodine at 12 weeks in the modified intention-to-treat analysis (Mod-ITT), but it did not do so for the 25mg and 100mg dose and over placebo. The changes seen in the EQ-5D utility index, although small are consistent with other studies which used EQ-5D in OAB patients. The analysis showed Mirabegron to have a consistently stronger effect on the EQ-VAS which raises the questions about the ability of the EQ-index (descriptive system) to reflect aspects of HRQoL relevant to OAB. The descriptive system at the time had only three levels of severity which may make it less sensitive to smaller variations in effectiveness. This is especially relevant in OAB where patients generally score in 1or 2 in most dimensions as they do not have severe health problems. In this study there was also a high ceiling effect (11111- no problems on any EQ-5D dimensions) at baseline, although this was similar across all arms. A re-analysis that excluded these patients at baseline (11111) showed statistically significant results between groups were maintained, although effect size of between group differences increased. It should also be remembered that EQ-Index values represent the general public whereas the EQ-VAS captures the patients' overall assessment of their health.

Another interesting finding was the rapid effect of Mirabegron 50mg at 4 weeks shown in EQ-VAS and EQ-index when compared to Tolterodine. This may be explained by the higher incidence of bothersome anti-muscarinic side effects for example, dry mouth seen with Tolterodine. Focussing solely on differences at 12 weeks may not adequately represent these gains, which is why the AUC analyses is a very good representation of the significant gains seen with Mirabegron 50mg compared to placebo and Tolterodine (using change from baseline in the VAS). On the other hand, the new method (the PCHC approach) did not show any advantages with Mirabegron at any dose. This new

approach would allow departure from the utility weights and allow more exploitation of the responses to the descriptive system but again it may not have detected the changes between treatment and control groups due to the limitations of the EQ-5D in detecting quality of life impacts in OAB mentioned earlier. The question as to how adverse events may impact the EQ-Index or EQ-VAS was also asked and analysis performed in which the incidence of most relevant side-effects in all groups was assessed and then the impact on EQ-Index and EQ-VAS. Although a higher incidence of dry mouth at any time point was noticed with Tolterodine, this did not translate in to any significant changes in EQ-index or EQ-VAS scores.

There are several limitations of this study. These pivotal phase 3 studies were designed to assess efficacy of Mirabegron and not specifically to assess improvements in quality of life as measured by EQ-5D. The analysis excluded patients who did not have EQ-5D data available at 12 weeks and those with major protocol deviations to allow for a much clearer understanding of mirabegron's impact on a patient's HRQoL as measured by EQ-5D. However, when the analysis was repeated with inclusion of patients who took at least one dose of study drug, similar results were seen with the EQ-VAS with Mirabegron (all doses) showing significantly better results than Tolterodine at 12 weeks with two of them better then placebo. However, results were similar for the EQ-5D index but not statistically significant. The inclusion of those patients with protocol deviations and last observation carried forward approach may have had a 'watering down' effect. Finally, the EQ-5D data in these pivotal studies came from patients in Europe, US, Canada and Australia, yet the UK EQ-5D value sets were used which may have an impact on the results.

3.5 Paper 3: Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder.

www.hqlo.com/content/11/1/200

Despite the analysis discussed in the previous section, utility data in OAB is still lacking. EQ-5D has a number of limitations especially in terms of sensitivity in specific disease

contexts (Stolk et al., 2003; Eurich et al., 2006). In the previous section the limitations of EQ-5D instrument were discussed in the context of measuring impact on quality of life for treatment in OAB. The analysis pointed to a lack of sensitivity of the EQ-5D instrument with respect to subtle changes in OAB symptomology. Desroziers et al (2013), therefore explores this concept further by deriving utility values from a disease-specific instrument such as the OAB-q.

To overcome the limitations of the EQ-5D, Yang et al (2009), developed a 5-dimensional preference based disease-specific measure, named OAB-5D which was derived from the overactive bladder questionnaire (OABq)(Yang et al., 2009; Young et al., 2009). Even though OAB-q was not originally designed to generate utility values, using the Time Trade-off method (TTO) and UK general population survey, Yang et al (2009) built a model to derive utilities from the 5 items forming the OAB-5D. The objective of the analysis in this paper was to estimate utility values in patients with OAB using data from the three pooled clinical trials for Mirabegron and using the generic and disease specific instruments (EQ-5D and OAB-5D respectively). In addition, this analysis investigates the relationship between utilities and symptoms and evaluates the sensitivity to changes in OAB symptoms of both preference based instruments.

In the clinical trials patients had to complete a 3-day bladder diary before each scheduled visit. The main end-points derived from the diary were mean number of micturition episodes per 24 hours, mean number of frequency episodes per 24 hours, mean number of urgency episodes (grade 3 and 4) per 24 hours and mean volume voided per micturition. For micturitions and incontinence episodes 5 severity levels were defined based on the distribution (quintiles) of events observed in the pooled trials. To value the OAB health states, Yang et al (2009) chose five items from the OAB-q to construct the new health state classification system (OAB-5D). These consisted of: urge to urinate, urine loss, sleep impact, coping strategy, and concern with OAB, where each dimension has five levels of severity with level 1 denoting no problem and level 5 indicating extreme problem (Yang et al., 2009). This resulted in a total of 3125 health states that can be defined using the OAB-5D classification system (versus 243 from the

EQ-5D system). Therefore all OAB-q data which contain these five items can be mapped to a specific OAB-5D health state.

In terms of the statistical analysis utility scores from EQ-5D and OAB-5D were described as means and standard deviations and then estimated by symptom severity. For each symptom (micturition and incontinence) a liner regression model was used to estimate utility by symptom level (1-5) adjusting for age, gender, study and geographical region. Differences between OAB-5D and EQ-5D utilities were also estimated by symptom level using similar methods. Finally, as a test of sensitivity of the instruments, utility changes from baseline to 12 weeks were tested according to response in symptoms, defined as 3possible items: 'improvement higher than 1 level of symptoms', 'stable', or 'worsening higher than 1 level of symptoms'.

The results showed that the mean EQ-5D and OAB-5D utility decreased with symptom severity (i.e. from level 1 to 5) with OAB-5D showing a slighter larger change than EQ-5D (0.1 versus 0.07 respectively). After making adjustments using linear regression modelling the differences at the higher severity levels for micturitions and incontinence episodes (levels 4 and 5) were not significant between OAB-5D and EQ-5D. However, at the milder end of the spectrum (levels 1 and 2) a significant difference was observed in utility values between OAB-5D and EQ-5D.

The estimated regression coefficients confirmed that utilities decreased with symptom severity after adjusting for patient characteristics. Micturitions and incontinence has a similar impact on EQ-5D utilities, but micturitions seemed to have a greater impact on OAB-5D utilities than incontinence. For example, at equal micturition symptoms, an improvement in incontinence level from level 5 to 1 (> 3 incontinence episodes per day to 0) was associated with an increase in EQ-5D utility of 0.052 (p < 0.0001) and 0.076 in OAB-5D utility (p < 0.0001).

In terms of responsiveness of HRQoL and clinical symptoms, the mean changes from baseline in utility were positive in all groups of patients (improving, stable and worsening) and were greater in responders than in non-responders. There were no significant changes from baseline utility between worsening response and stable

response with EQ-5D but differences were significant with OAB-5D. In patients with mild micturition frequency and incontinence episodes, there was again no significant change in utility with EQ-5D between improvement and stable response. However, with OAB-5D differences in utility were significant. However, in severe cases differences in utility were significant for both EQ-5D and OAB-5D between improvement and stable response. No significant differences were observed between worsening response and stable response in severe cases for both preference based instruments.

Finally, overall changes in utility from baseline were greater with OAB-5D when compared to EQ-5D for all symptoms, in both improving and stable patients. Although both OAB-5D and EQ-5D demonstrated that utility scores increased as symptoms improved, OAB-5D had a greater range of variation according to symptom severity. Incremental utilities at different symptom levels were also different between OAB-5D and EQ-5D which is surprising considering both instruments are expected to provide value on the same scale (0 to 1) and use the TTO method. The correlation between OAB-5D and EQ-5D in the general population was moderate (r = 0.34: p < 0.0001) which maybe be explained by the larger standard deviation in the EQ-5D utilities reflecting natural variation in health status not related to OAB.

It must also be noted that the equation used for EQ-5D had low predictive power, which means that a much larger number of patients would be required to detect changes in utility between different groups of patients. Another limitation of the regression models used was that they do not capture the effect of potential non-urology related dimensions. Measuring the impact of adverse events using trial data is also difficult since the periods when patients experience these events rarely coincide with the assessment dates. The OAB-5D instrument does not have a dimension to detect the impact of adverse events, whereas the EQ-5D instrument as generic measure is expected to capture deteriorations in HRQoL related to adverse events.

Another important finding in this analysis was to learn that micturition frequency does affect the utility score even when adjusting for incontinence episodes. The interaction between micturition frequency and incontinence episodes using the liner regression

models (p = 0.1283) was found not be significant suggesting that micturition frequency and incontinence episodes impact utility independently of each other and therefore the effects of the different symptoms are additive.

Finally, this study demonstrated the greater responsiveness of the OAB-5D instrument in patients with mild OAB compared to EQ-5D. However, using EQ-5D to measure utilities does have the advantage to compare the values across other conditions and it can capture the impact of adverse events. However, larger sample sizes may be required to detect differences between treatments or patient groups. In conclusion, therefore both sets of utilities can be used for cost-effectiveness modelling although they will lead to different incremental cost-effectiveness ratios.

3.6 Chapter Summary

The patient reported outcomes included in the pivotal studies for Mirabegron demonstrate significant improvement with 12 weeks of therapy (OAB-q and PPBC). The differences seen in the incontinent sub-group were greater than the overall population. However, the studies are of 12 week duration, therefore difficult to assess the long-term impact on HRQoL. Tolterodine was an active control in only one of the studies and all three studies were focussed on efficacy, therefore not powered to detect differences in quality of life.

The pooled analysis of EQ-5D demonstrated Mirabegron to be effective on both the EQ index and EQ-VAS, but only showed statistical significance versus Tolterodine on the modified intention-to-treat analysis. A high ceiling effect (11111) was observed at baseline although when excluded statistically significant results between groups were maintained. Deriving utility values from a disease-specific instrument using an established mapping algorithm is one way to counter the lack of sensitivity seen in the generic EQ-5D questionnaire. This analysis showed a greater responsiveness of the OAB-5D instrument in patients with mild OAB compared to EQ-5D. However, using EQ-5D to measure utilities does have the advantage to compare the values across other conditions and it can capture the impact of adverse events. Both sets of utilities can be

used for cost-effectiveness modelling although they will lead to different incremental cost-effectiveness ratios.

In this chapter the impact of Mirabegron on HRQoL was presented using three published papers. The next chapter is focussed on how Mirabegron compares to other pharmacological treatments in terms of efficacy and safety.

Chapter 4: Comparing Efficacy and Safety of Mirabegron with Antimuscarinics

4.1 Introduction

In the previous chapter the PROs specifically within the context of OAB and treatment with Mirabegron were discussed. These analyses are based on the pivotal studies for Mirabegron which are predominantly placebo controlled trials with only one of them including Tolterodine but only as an active control. However, HTA, treatment guidelines and reimbursement policies requires comparison of all competing interventions. The ideal scenario would be to have well designed and conducted RCTs that simultaneously compare all competing interventions. Pivotal trials aiming to obtain regulatory approval often compare with placebo or standard of care as there is no commercial incentive to compare the new treatment with active control treatment.

Also, interventions of interest may vary by country and change over time due to new evidence and insights. Therefore, in the absence of direct comparisons between treatments of interest an indirect treatment comparison can provide useful evidence to estimate differences in treatment effects between competing interventions. There is now an increasing acceptance of Network Meta-analysis (NMA) by HTA bodies such as CADTH (Canada), NICE (UK), SMC (Scotland), IQWiG (Germany) and HAS (France) and they form a key part of healthcare decision-making (Laws et al., 2014). A recent study reviewed NMA guidelines from 33 countries: of these 9 countries had very detailed recommendations on the conduct of NMA (UK, Australia, Belgium, France, Spain, Germany, Scotland, South Africa and Canada) (Laws et al., 2014). It is possible to

perform one NMA for submission to multiple HTA and reimbursement bodies (Lumley et al., 2002).

The aim of the Maman et al (2014) is therefore to compare the clinical efficacy and safety of the most widely used OAB treatments and more specifically to estimate the efficacy and safety of Mirabegron compared with antimuscarinics. This NMA was also submitted as part of a NICE *single technology appraisal* assessment of Mirabegron in 2012.

4.2   Comparative Efficacy and Safety of Medical Treatments for the Management of Overactive Bladder: A Systematic Literature Review and Mixed Treatment Comparison.

http://dx.doi.org/10.1016/j.eururo.2013.11.010

This review considered all RCTs studying the efficacy or the safety of pharmacologic treatments in the management of OAB and also considered studies on most approved drugs used in Europe for the management of OAB.

A Bayesian Mixed Treatment Comparison (MTC) was conducted to estimate relative efficacy and safety of Mirabegron compared to all OAB treatments. The MTC (or NMA) is essentially an extension of a meta-analysis Lumley (2002). The main advantage of conducting a MTC compared to a meta-analysis is that the estimation of the relative effect between two treatments uses all the information available from the network of evidence available including both direct and indirect evidence.

This MTC was conducted in both the general OAB population and the subgroup of patients incontinent at baseline. The parameters included in the analysis were micturition frequency, incontinence and urge urinary incontinence (UUI) per 24 hours. Eligibility criteria, for a study to be included was that it had to have reported changes in these efficacy symptoms over 8-16 weeks (reported changes over 12 weeks were retained). Studies reporting safety outcomes if number of patients reporting dry

mouth, constipation, and/or blurred vision over 4-16 weeks could be derived from publications.

Overall, after applying the inclusion/exclusion criteria 44 studies were included in the MTC, enrolling 27,309 patients. Most of the studies were conducted in North America or Europe from 2000 to 2013. Over 70% of the studies were placebo controlled. In total, there were 129 treatment arms included in the MTC. Fixed effect models were used for most outcomes with the exception of dry mouth for which random-effect model was used due to heterogeneity between studies. The probability of each treatment being more effective then Mirabegron was calculated for different superiority margins.

In terms of the efficacy outcomes, for micturitions (26 studies, 22,040 patients) demonstrated that the effect of Mirabegron 50mg did not differ significantly from other treatments, except solifenacin 10mg which is more effective. For incontinence episodes (17 studies, 13,101 patients) the MTC demonstrated that Mirabegron did not differ significantly from the other treatments in terms of reduction of incontinence episodes and was statistically superior to placebo. However, solifenacin 5mg had a probability of 97% of being superior to Mirabegron and solifenacin 10mg had an equal probability. With respect to UUI (18 studies, 16,044 patients) again the Mirabegron demonstrated similar results to other antimuscarinics except for solifenacin 10mg which was significantly more efficacious.

In terms of the safety outcomes, in particular dry mouth (44 studies, 27,309 patients), Mirabegron 50mg had an incidence of dry mouth similar to placebo (OR: 1.344; 95%Crl 0.863-2.004). Not surprisingly all antimuscarinics were associated with a higher risk of dry mouth compared with Mirabegron 50mg. Similarly, the incidence of constipation associated with Mirabegron was similar to placebo. Blurred vision was relatively rare and no significant differences in risk of developing blurred vision were found between treatments.

Results from this MTC suggest that Mirabegron 50mg is similar to antimuscarinics in terms of efficacy (micturition frequency, incontinence, UUI) except for solifenacin

10mg (UUI and micturition frequency). However, solfenacin 10mg and fesoterodine 8mg were among the treatments with the highest adverse events, especially dry mouth. The drug with the most favourable tolerability profile was Mirabegron 50mg with an incidence of dry mouth and constipation comparable to placebo and significantly lower than the antimuscarinics.

This analysis adds on the previous literature reviews and meta-analysis conducted by Chapple et al, 2008, which showed that antimuscarinics are more efficacious than placebo (Chapple et al., 2008) by firstly including a new treatment (Mirabegron 50mg), secondly it included twenty more studies since 2007 and finally with the MTC approach it uses both head-to head comparisons as well as comparisons versus placebo.

One criticism of our MTC could be on the safety outcomes. The MTC considered only the adverse events associated with antimuscarinics such as dry mouth, constipation and blurred vision, yet ignored adverse events associated with Mirabegron. The pivotal studies for Mirabegron 50mg reported hypertension (7.5%), nasopharyngitis (3.9%), headache (3.4%), and UTIs (2.9%) (Nitti et al., 2013). The proportions of patients experiencing these adverse events however, were not significantly different from placebo arms based on pooled analysis except for nasopharyngitis. An MTC analysis could not be conducted on this adverse event because this event is not reported in the publications on antimuscarinics.

The efficacy outcomes included in the MTC did not include urgency symptoms which could also be seen as a potential weakness given that this forms part of the ICS definition for OAB. While this is an important symptom, the measurement of this symptom is very subjective and several instruments have been used to try and measure urgency, making it difficult to make any credible comparisons. The volume voided per micturition was also not included as this is seen as more of a surrogate end-point and of less clinical relevance. Other outcomes such as dry rate or resolution of incontinence, mean change in day and night time micturitions, urgency driven micturitions are relevant but not as frequently reported and therefore not considered in the MTC.

There were a few sources of heterogeneity with our MTC, namely between studies and the variability in follow-up periods between trials. The between study heterogeneity could arise from the differences in baseline characteristics of patients in different studies e.g. OAB severity at baseline, proportion of previously treated patients etc. Fesoterodine studies had more severe OAB at baseline (two studies had more than six urgency episodes per day at baseline) therefore with more potential for improvement. The FACT-2 placebo controlled trial comparing fesoterodine 8mg and Tolterodine ER 4mg included approximately 30% previously treated patients, whereas a placebo – controlled trial of Tolterodine reported efficacy results in a population with 70% previously treated patients.

The other source of heterogeneity was the follow-up periods between trials (from 8-16 weeks for efficacy and 4-16 weeks for safety outcomes). However, over 72% of the trials had a 12-week follow up period and we verified that relative effects at 8 weeks and 12 weeks or 12 and 16 weeks were similar when results at both times were reported., therefore in the end this was not a major concern.

One way to account for the heterogeneity is to use random-effect models which assumes that every RCT measures the same effect with a degree of variation, therefore the CrL around the treatment effect estimated from the MTC accounts for variability between studies. The presence of heterogeneity will lead to wide CrL. The fact the CrLs do not overlap between two treatments despite the heterogeneity indicates that estimated difference in treatment effects between two treatments exceeds the difference potentially due to heterogeneity. The fixed-effect model was selected for all outcomes except dry mouth suggesting that for this outcome the heterogeneity between studies affected the estimation of differences between treatments in the probability of dry mouth. However, the reported CrLs around the ORs for dry mouth account for this heterogeneity. We can therefore conclude the probability of dry mouth with Mirabegron is significantly lower compared to antimuscarinics despite the presence of heterogeneity between studies.

Another way to balance the baseline characteristics and account for heterogeneity would be to use meta-regression techniques to adjust for bias associated with effect-

modifying covariates (Dias et al., 2013a). This would only be feasible however, if these variables that drive heterogeneity such as OAB severity and treatment experience are systematically reported in publications. It would therefore significantly reduce the number of publications included in the MTC.

Finally, another limitation of this analysis maybe that we only included studies after 2000. The main reason for this was to ensure greater homogeneity between study populations because prior to 2000 more patients were treatment naïve (only oxybutynin IR available) and the current definition of OAB was introduced in 2001. This did mean that there were fewer studies including oxybutynin IR (hence the wider CrLs) but a head-to-head trial of oxybutynin IR with Tolterodine ER 4mg in Asian patients did demonstrate that Tolterodine ER 4mg was similar in efficacy but better tolerated compared to oxybutynin IR (Dias et al., 2013b).

4.3   Chapter Summary

The NMA forms a key piece of evidence, given that HTA, treatment guidelines and reimbursement policies require a comparison of all competing interventions. In the absence of direct comparisons between the treatments of interest, an indirect treatment comparison can provide useful evidence to estimate the differences in treatment effects between competing interventions. The results of this analysis demonstrated that Mirabegron was similar in efficacy to antimuscarinics but with a more favourable tolerability profile. The analysis adds to the previously conducted meta-analyses by firstly including Mirabegron, twenty more studies since 2007 and finally the whole NMA approach means that it uses both head-to-head and comparisons versus placebo.

Chapter 5:   Cost-effectiveness Analyses of Treatments in OAB

5.1 Introduction

Thus far the thesis has extensively discussed the quality of life impact of OAB medications and the comparative efficacy and safety of these interventions. In this chapter, the thesis will discuss how some of these findings and other relevant data sources are used to develop the cost-effectiveness analyses.

In previous cost-effectiveness analyses, Markov models have been based on the extensively applied model by Kobelt et al (1998). This model consists of five health states each representing a differing level of disease severity with an absorbing state for drop-outs who are considered to remain off treatment. In chapter 3, it was shown that the main symptoms of OAB (urinary incontinence and micturition frequency) had a significant impact on utility independently of each other with moderate correlations between changes in these symptoms. We have therefore tried to model the progression of these symptoms separately. Apart from this principle change in approach we paid more attention to the patient pathways after treatment discontinuation due to the high rates of switching and treatment discontinuation observed with OAB patients and we chose a time horizon that more accurately represents the costs and outcomes of managing a chronic condition.

There are essentially three publications which will be discussed in this model; a trial-based cost-effectiveness model; a cost-effectiveness model based on the outputs of the network meta-analysis discussed in the previous chapter; and a model that quantifies the cost and outcomes of different treatment sequences of OAB interventions and tailored for a more regional payer archetype. The trial-based model and the model using outputs from the network meta-analysis were both submitted to NICE in 2012 as part of the *single technology appraisal*

5.2 Cost-effectiveness of Mirabegron compared with Tolterodine Extended Release for the Treatment of Adults with Overactive Bladder in the United Kingdom.

https://link.springer.com/article/10.1007%2Fs40261-014-0240-

This was the first economic analysis that compared Mirabegron with currently available antimuscarinics agents for the treatment of OAB. A Markov model was developed to simulate the therapeutic management, course of disease, and the effect of complications in hypothetical cohorts of OAB patients over a 5-year period. As mentioned previously, the commonly used Kobelt et al (1998) model was limited to a 1-year time horizon, and did not model treatment pathways after treatment discontinuation, an important limitation given the high discontinuation rates with antimuscarinics. We therefore captured the impact of treatment discontinuation and switching on costs and OAB symptoms, since persistence affects HRQoL, health status and health care resource utilisation (Balikrishnan et al., 2006). HRQoL was assumed to be dependent on both variations in symptoms over time and the side effects of treatment.

The model simulated changes in symptoms (micturitions and incontinence) for which the model was run in parallel at monthly intervals (60 in total). Every month patients could remain on treatment (Mirabegron or Tolterodine as this was based on the phase 3 SCOPIO study), switch to another treatment with better efficacy and price similar to solifenacin or discontinue (go to no treatment). A small proportion would be eligible for botulinum toxin (BTX) after the next line of therapy (not allowed directly after Mirabegron or Tolterodine).

The probabilities of discontinuation and switching were dependent on adverse events. Patients with adverse events could stay on treatment, but incurred a disutility. Patients who discontinued therapy could naturally improve and thereby transition to a lower severity category after 1 month, or could worsen or stay the same. These patients could also restart the previous treatment, could move to a new treatment or remain off treatment. If patients were successful on BTX it was assumed they would transition to the lowest level of severity and remain there until the end of the simulation. The model assumed that the probability of improvement was greatest in the first month after which it decreased progressively until month three and then assumed to remain constant for the remainder of the simulation.

Apart from the general OAB population, the model considered several subgroups such as those dissatisfied with previous treatment either due to lack of efficacy or side effects, treatment naïve, treatment experienced, elderly patients, female and male patients and patients incontinent at baseline.

Another key feature that distinguishes this model from Kobelt et al's model is the non-arbitrary nature of the health states/symptom severity levels. Symptom severity in the model was determined using the SCORPIO trial (Khullar et al., 2013). Initial distributions of patients with symptom severity (Incontinence and micturition frequency) were based on SCORPIO trial base lines and there were five severity levels for each symptom. Transition probabilities between symptom level for Mirabegron 50m and Tolterodine ER 4mg were estimated using multinomial logistic regression models. Finally, both deterministic and probabilistic sensitivity analyses were conducted.

The results showed that in the base case Mirabegron 50mg was cost-effective compared to Tolterodine ER 4mg at a willingness to pay (WTP) threshold of £20,000/QALY and £30,000/QALY. This is generally the threshold applied by UK NICE. Both the deterministic and probabilistic sensitivity analysis demonstrated that the model was robust. The incremental cost-effectiveness ratios (ICERs) were also consistent in the subgroups analysed.

Key strengths of this model have already been highlighted by counteracting the potential limitations of the Kobelt et al model. One of the key strengths of this model were that it captured the effects on HRQoL of variations in symptom severity over a longer time horizon as well as capturing the impact beyond treatment discontinuation and switching on costs and health outcomes. It therefore more accurately represents the clinical management of OAB. Another strength, of this model, is that it also analysed cost-effectiveness in key subgroups.

In contrast, limitations of this model are centred on the lack of real-world evidence or persistence data on Mirabegron. In this context the rates of discontinuation other than

adverse events were assumed to be similar for Mirabegron and Tolterodine ER 4mg. Given the efficacy and safety profile of Mirabegron 50mg, this assumption was quite conservative. The NMA (Chapter 4.2) did show that the probability of Mirabegron 50mg being more effective than Tolterodine ER 4mg in terms of micturition frequency and incontinence is 87.4 and 88.3% respectively. Also, there was no information available on the number of patients who receive Botulinum toxin (BTX) therapy following drug therapy, so we assume only a small number (1%). Again, this was conservative given that BTX is a relatively high cost treatment. There was also uncertainly around the potential number of specialist visits. However, it was reassuring to see that the sensitivity analyses conducted with all of these parameters, showed that the ICERs remained relatively stable and below the thresholds. Finally, another potential limitation of the model was influenced by the perspective (Payer/HTA) which meant that only direct healthcare costs were captured. The main analysis did not capture the indirect costs for example, productivity, and work hours lost, that may be incurred in OAB especially when considering some of the subgroups within this analysis.

5.3 Cost-effectiveness of Mirabegron Compared with Antimuscarinic Agents for the Treatment of Adults with Overactive Bladder in the United Kingdom.

https://doi.org/10.1016/j.jval.2015.05.011

This model was almost identical to the model discussed in 5.1. The previous model was based on the SCORPIO trial and only compared Mirabegron 50mg with Tolterodine ER 4mg. However, the reality is that in clinical practice there are several antimuscarinics that form standard of care. Furthermore, most of these are also generic therefore it is essential that the incremental value of Mirabegron 50mg is also demonstrated compared to these pharmacological interventions which are almost all within the antimuscarinic class.

In the absence of head-to head trials of Mirabegron 50mg versus each antimuscarinic agent the Bayesian NMA (Chapter 4.2), was used to estimate the relative efficacy and

safety of Mirabegron compared with placebo and all the antimuscarinic agents (Tolterodine ER 4mg; Tolterodine IR 4mg; darifenacin 7.5 and 15mg; solifenacin 5 and 10mg; fesoterodine 4 and 8mg; Oxybutynin ER 10mg and IR 10 or 15mg and trospium chloride modified release 60mg).

Again, baseline symptom severity was taken from SCORPIO as with the previous model, with five severity levels and four coefficients capturing the effect of treatment on the probability of moving from one severity level to another (regression analysis, including other covariates as well such as age, gender, current severity level). The key difference in this model was that in order to incorporate the results of the NMA (efficacy and safety) a calibration method was used to fit the model to mean changes in symptoms at 3 months determined by the results from the NMA for different products. Finally, like the previous model the discontinuation rates were disaggregated to reflect those patients who discontinued due to adverse events and those that discontinued due to other reasons such as lack of efficacy.

The results were consistent with the previous model. From a UK NHS perspective Mirabegron was cost-effective compared with oral antimuscarinics agents commonly used for OAB. This was mainly driven by better persistence and improved patient quality of life due to lower risk of adverse events. All ICERs were below the £20,000/QALY threshold. Deterministic sensitivity analysis showed that the model was most sensitive to transition probabilities between symptom severity levels and probabilities of discontinuation. However, the probabilistic sensitivity analysis showed that the probability of ICERs being below the £20,000/QALY threshold was high.

Strengths and limitations of this model have already been discussed in 5.1. However, specific to this model the calibration techniques used to incorporate the NMA data in this model improved the accuracy of the estimates from the economic model and were also viewed positively by NICE during the Single Technology Appraisal (STA) for Mirabegron. A potential weakness may be that the model assumes similar efficacy between the IR and ER formulations whereas the associated incidence of dry mouth, blurred vision and constipation varies. In the NMA data was pooled from studies using IR and ER formulations to estimate efficacy and safety. However, we know that the IR

formulations are associated with higher incidence of dry mouth and would expect decreased persistence therefore ICERs potentially in favour of Mirabegron (depending on price).

5.4 Economic evaluation of pharmacological treatments for overactive bladder from the perspective of UK National Health Service (NHS).

http://dx.doi.org/10.3111/13696998.2014.995300

While the previous analyses have evaluated the cost of individual therapies for OAB, the cost and consequences of sequences of drugs incorporating recently approved agents such as Mirabegron have not been evaluated. Therefore, the objective of this analysis was to quantify the costs and outcomes associated with different sequences of oral antimuscarinic agents and ß$_3$adrencoceptor agonist from the perspective of the UK NHS.

The original idea was to develop a simple, interactive tool that can be used to estimate the cost of using different sequences of available therapies for OAB. The model focussed on the more tangible outcomes such as patients with controlled symptoms (e.g. < then 8 micturition's/24 hours and <2 incontinence episodes/24 hours, zero incontinence episodes or dry rates) which would appeal to local decision makers where the cost/QALY argumentation is not always relevant or prioritised. With an armamentarium of generic options available for a condition often perceived as a 'life style' condition the focus of local decision makers is usually on the unit cost or price. The aim of this analysis was to aid decision-makers to not only consider the medication acquisition costs but also to consider other factors such as efficacy, side –effect management, medication adherence as well as the sequence of treatments used in the treatment pathway.

By comparing a treatment sequence consisting of low-cost generic treatments with one incorporating branded agents such as Mirabegron, the model demonstrates that it

is not necessarily more cost-efficient to use generic therapies. In this analysis, a sequence consisting of two generic agents and a third –line branded agent was less effective than and was associated with costs similar to a sequence consisting of three branded agents. This is mainly a result of these drugs having a better efficacy tolerability balance in the branded sequence than the standard sequence. These drugs are also associated with better persistence rates and therefore overall lower treatment costs (Wagg et al., 2012). The sensitivity analysis also showed that the results are sensitive to persistence rates. Current UK guidelines however, continue to recommend initial antimuscarinic therapy for the patients with OAB (NICE 171). Furthermore, these guidelines stipulate that if initial therapy is not effective or not well tolerated another drug with the lowest acquisition cost should be offered (Irwin et al., 2009). The outputs from this model therefore challenge these guidelines from a cost and outcomes perspective.

In terms of overall strengths of this analysis, the model can be considered comprehensive as it includes multiple factors that affect the overall economic burden of OAB in addition to the direct cost of the therapy. These additional factors include pad use and costs of co-morbidities like depression and UTI's arising due to lack of control of OAB. However, work-related productivity costs were not included in this analysis and inclusion of these may have led to further cost-savings.

Again, a limitation of this model was the lack of real-world data on persistence rates for some of the agents such as Mirabegron and fesoterodine. These rates are currently only available in clinical trials, which is not reflective of clinical practice. As Tolterodine was either an active control or comparator in these trials we were able to use these persistence rates reported in real-world data for Tolterodine. Patients in this model were able to switch medication after 30 days. This is in line with treatment guidelines which suggest informing patients that they may not experience full benefits of treatment until they have taken therapy for 4 weeks (Nicolson et al., 2008). However, the guidelines also recommend that patients should be offered a review of therapy before 4 weeks if adverse events are intolerable. Our estimates of persistence also suggest that a proportion stop before 30 days, therefore using a minimum of 30-day

duration of therapy in the model may not reflect clinical practice in a proportion of patients.

Other limitations are associated with the fact that this model did not include data related to the impact on HRQoL. As communicated earlier urinary frequency, urgency and incontinence have a significant impact on HRQoL with those who are incontinent having a worse HRQoL than continent patients (Coyne et al., 2004; Liberman et al., 2001). Although HRQoL was not included in this model, the assessment included a measure combining urinary frequency and incontinence episodes (controlled versus uncontrolled) which are determinants of HRQoL. It was also not possible in this analysis to determine accurately the efficacy for second or third line treatments, therefore first line efficacy data for all treatments was used.

Overall, this analysis demonstrates that real-world disease management-related costs need to be considered when making recommendations on therapy to ensure that benefits to patients are maximised and that funds are spent in the most efficient manner.

5.5   Chapter Summary

The trial-based model and the NMA model advances the modelling approach used in OAB, when compared to previous models developed in this area. For example, the non-arbitrary nature of the health states and symptom severity was determined using one of the phase 3 studies. The models discussed also captured the changes in HRQoL over a longer time horizon as well as capturing cost and health outcomes beyond treatment discontinuation. The NMA based model used a calibration method to incorporate the results from the NMA. Results in both models were consistent and demonstrated that Mirabegron was cost-effective compared to antimuscarinics used in clinical practice. The ICERs were driven in favour of Mirabegron by better persistence and improved patient quality of life.

The final model in this chapter focusses on different treatment sequences and the impact on cost and health outcomes. This model is aimed at local payers as well as challenging the current clinical guidelines that favour the use of generic animuscarinics.

It separates the unit costs and highlights other disease management-related costs often not considered by local payers.

Chapters 3, 4 and 5 have focussed predominantly on insights gained from the Phase 3 program for Mirabegron (the PRO analyses, NMA and cost-effectiveness models). While the efficacy of Mirabegron has been well established in the RCT setting, chapter 6 turns the attention to effectiveness using RWE, collected once Mirabegron has been launched and is used widely in clinical practice.

Chapter 6:   Assessing the Impact of OAB Treatments using Real World Evidence

6.1 Introduction

In the previous chapters the value of OAB medications has been predominantly assessed using a combination of randomised controlled trials (RCTs), some real world evidence that does not include Mirabegron and other data sources such as national cost data   and other published data sources. In this chapter, the value of OAB medications will be assessed using real world evidence that includes Mirabegron (post-launch). Essentially, this is an assessment of effectiveness in the real world setting.

There are two papers which will be discussed (Paper 8 and 9). The first publication was a retrospective database study using a UK primary care database, the CPRD, while the second publication is a model based on the retrospective database study. As discussed in chapter 1, this type of evidence is now becoming essential, with some authorities for negotiating funding of new drugs and price negotiations.

6.2   Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice.

http://dx.doi.org/10.1016/j.eururo.2017.01.037

This was a retrospective, longitudinal, observational study of anonymised data from the United Kingdom (UK) Clinical Practice Research Data link database (CPRD). Eligible patients were aged ≥18 years, had ≥1 prescription for a target OAB drug (between 1 May 2013 and 29 June 2014) and 12 months of continuous enrolment before and after the index prescription date.

In this study, patients prescribed Mirabegron were significantly more likely to continue treatment long term than those prescribed Tolterodine ER with 12-month persistence rates of 37.7% and 20.2%, respectively, and median times to discontinuation of 169 days and 56 days, respectively. Persistence with Mirabegron was also significantly better with each of the other nine antimuscarinics commonly prescribed in the UK. These improvements in persistence were also maintained in the predefined sub-cohorts of treatment-naïve, treatment-experienced and older patients, as well as after matching to control for potentially confounding differences in baseline characteristics. The superior persistence of Mirabegron is supported with other recent real world evidence studies under different healthcare systems in the US, Japan, and Canada (Wagg et al., 2015; Nitti et al., 2016; Ogihara et al., 2014).

Persistence and adherence in this context may serve as a good proxy for efficacy/safety balance that leads to an improvement in quality of life due to symptom relief. The clinical significance has been highlighted in a prospective study which showed that women who adhered to OAB medication had significantly greater improvements in urinary symptoms compared with non-adherent women (Andy et al., 2016). However, due to the fact that this is a retrospective database study, one limitation of this study is that we are unable to examine the reasons for discontinuation.

A large US survey of approximately 5000 respondents suggested that the most common reasons for discontinuation of antimuscarinics were related to efficacy (treatment did not work as expected), switching to a new medication, coping without medication and side effects (Benner et al., 2010). It is therefore feasible to assume that

the differences in early discontinuation between Mirabegron and antimuscarinics could be explained by the lack of anticholinergic side effects such as dry mouth. However, the gradient of the Kaplan-Meier curves was generally comparable after 3 months, suggesting the reasons for later discontinuations may have been similar for both drug classes. Therefore, it is important to focus further research on trying to understand the reasons for discontinuation of OAB medications and how to support patients so they achieve long-term compliance.

Some key strengths of this study are that it uses a large database (CPRD) and therefore a large population sample which is broadly representative of the UK population. Unlike RCT evidence that is collected in a controlled or often idealised environment, and can often only measure efficacy in a limited population, thereby not providing a true indication of effectiveness, this study provides real world evidence demonstrating the effectiveness of Mirabegron. The study design also uses matching to control for baseline imbalances, notably the proportion of treatment-experienced patients which was greater in the Mirabegron-cohort at baseline. The main study limitations were the retrospective design and the use of prescription-event data rather than patient-derived data to estimate outcomes such as patient diaries. The inability to capture reasons for discontinuations as mentioned earlier, as well as potential health benefits resulting from increased persistence in terms of symptom severity and health related quality of life (HRQoL) were other limitations of this study. Also the prescribing of Mirabegron came relatively later than Tolterodine ER due to launch in February 2013 and the release of updated guidelines even later, which may explain the reason for the higher proportion of treatment-experienced patients in the Mirabegron cohort.

The analysis of the healthcare resource use was not reported here due to the unavailability of the HES data at the time of this analysis. This will be important data especially when estimating the economic impact of better persistence and adherence. There are also large prospective observational studies of Mirabegron on-going in the US (PERSPECTIVE; ClinicalTrials.gov.NCT02386072) and Europe (BELIEVE; ClinicalTrials.gov NCT02320772), which will include persistence and HRQoL outcomes in a real-life setting. These studies will yield important information on the impact of

treatment on patient's quality of life in the real world setting and will provide more insights in to the reasons for patient discontinuations.

6.3 Economic Impact of Mirabegron versus Antimuscarinics for the Treatment of Overactive Bladder in the UK.

http://dx.doi.org/10.1007/s41669-017-0011-x

The previous section (Chapter 6, section 6.2) discussed the impact of treatments for OAB in the real-world setting. In particular, the paper focussed on persistence and adherence as potential proxy's to efficacy and safety balance in the real world. Also as highlighted in the models discussed in Chapter 5, persistence was an important driver of value (cost-effectiveness) in OAB. These models were largely based on data from the RCTs and real world data that did not include Mirabegron (pre-launch). As such the assumptions were conservative because in the base case models the persistence of Mirabegron was assumed to be similar to antimuscarinics (solifenacin). The previous models were also largely developed from the payer perspective. This model (Paper 9) therefore provides the opportunity to estimate the economic and clinical impact of using Mirabegron 50mg versus antimuscarinics agents from a societal perspective by largely employing real-world data (specifically persistence rates) that includes Mirabegron 50mg. In section 6.1, the persistence rates for Mirabegron were superior compared to other antimuscarinics (range 8-25%), but what does this improved persistence mean in terms of economic and clinical impact from a payer and societal perspective? Thus, a Markov model was developed in Microsoft Excel with a 12 month time horizon and monthly cycles. The model compared a hypothetical cohort of 100 patients (Mirabegron versus antimuscarinics) and inputs included were real-world treatment patterns data, healthcare resource use and both direct and indirect costs (e.g. drug acquisition and productivity loss). Model outputs included patient disposition, healthcare resource use, drug acquisition costs and other treatment-

related costs. The key aim of the model was to help understand and the value of improved persistence.

The model demonstrates that a greater number of patients persist on treatment with Mirabegron versus antimuscarinics, fewer patients switched treatment and fewer work hours were lost. Although as expected Mirabegron had higher medication costs over the 12 months versus antimuscarinics, these costs were largely offset by savings attributed to other direct and indirect costs. This was partly attributable to a lower proportion of non-persisters and switchers, who had a higher demand for healthcare resources and higher pad use, compared with patients who persisted on treatment. The results suggest that a greater number of patients in the UK who receive Mirabegron will persist on first-line treatment versus antimuscarinics over 12 months resulting in more patients with likely controlled symptoms. This would have a beneficial effect on the UK healthcare system in terms of lower resource use and overall treatment and containment of costs. Also while improvements in work productivity and lower healthcare resource use have been cited as benefits of increased treatment persistence (Liu-Seifret et al., 2011; Kim et al., 2016), better persistence rates could also be expected to improve patient quality of life, likely due to increased symptom control and an increased ability to continue daily activities. This model does not include the improvements likely to be seen in terms of quality of life (Herdman et al,. 2011).

The main strengths of this model are that it uses real-world data, related to treatment of OAB and healthcare resource use in the UK, therefore the total costs derived for Mirabegron versus antimuscarinics are based on effectiveness rather than efficacy. However, the benefits of Mirabegron are dependent on key assumptions such as 12 month persistence being independent of the dose received such as for Trospium and Tolterodine ER and IR (extended release and immediate release respectively), and patients switch treatment or undergo surgery are assumed have controlled symptoms for the remainder of the time within the model. The time horizon of the model was only 12 months, mainly driven by the design of the retrospective database study (CPRD) discussed in the previous chapter. However, as OAB is a chronic condition a

longer time-horizon would have been beneficial in order to accurately estimate the economic and clinical benefits of long-term treatment. Another limitation is that the model did not include any indirect and direct clinical data for estimates of efficacy or health-related QoL and therefore some patient perspectives have not been captured.

6.4 Chapter Summary

The retrospective database study using the CPRD database demonstrated that patients on Mirabegron were significantly more likely to continue treatment long term than those prescribed antimuscarinics. These results are consistent in the general population and in subgroups, when baseline covariates have been adjusted and when using matched controls. The large database with a large sample size and the matching to control for baseline imbalances adds to the robustness of this study.

The economic model based on the above study, uses persistence as a proxy for efficacy/safety balance and improvements in quality of life. The model is therefore based on real-world effectiveness and the results are consistent with previous models discussed in chapter 5. However, there are some limitations in terms of the shorter time horizon and the exclusion of indirect and direct clinical data for estimates of efficacy or HRQoL, and therefore some patient perspectives may not have been captured.

In the final chapter, the aims of this thesis will be revisited and a summary of how these have been achieved using the 9 published papers. Recommendations for future research and conclusions drawn from the current research will also be included.

Chapter 7:   Summary, Recommendations and Conclusions

7.1 Summary

The increasing demand by decision-makers for more robust evidence, in particular RWE to demonstrate the value of new products and technologies was highlighted in chapter 1. The lead causes of this have been unsustainable increases in healthcare expenditure as result of ageing population, emerging markets and advances in treatment. As a result, there has been a marked rise in barriers to entry or cost-

containment measures, mainly through the emergence of HTA in many healthcare systems (Volker et al., 2017).

It is discernible that due to the ageing population chronic conditions will need to be prioritised by healthcare systems across the world. However, due to the non-life threatening nature of OAB there is a danger that this may not be prioritised in the same way as perhaps other chronic conditions.

The aim of this thesis was to assess the extent to which cost-effectiveness of a recently launched drug in the treatment of overactive bladder is supported by RWE. Through the critical review of nine publications, the cost-effectiveness of Mirabegron was supported by RWE, especially with respect to persistence and adherence to treatment Each paper was used to demonstrate a concept of value and how this contributes to developing the overall value proposition for a new drug both in the pre-launch or pre-HTA submission phase and in the post-launch phase. The thesis highlights how these 9 publications form important building blocks to demonstrate the value of a new technology, and often submitted to decision makers to inform reimbursement decisions.

7.2 Implications of the Thesis

The thesis highlights the economic and humanistic burden of the disease and the unmet need in OAB with respect to current treatment options. Importantly, this work demonstrates the value of pharmacological treatments in OAB relative to each other using health economic evidence which includes RWE. The current body of work uses a range of clinical evidence, both RCT and RWE and NMA for comparative effectiveness purposes, several different modelling approaches in OAB and extensive PRO analyses which include both disease-specific and generic instruments. This adds rigor to how value has been assessed for pharmacological treatments in OAB. To date the value of pharmacological treatments in OAB may not have been evaluated with such completeness. The present thesis may also serve as a good template when developing evidence generation strategies in other therapy areas as well, especially in the current economic climate where decision makers are demanding that value is also

demonstrated in the real-world setting. However, it must be noted that the thesis does not go as far as comparing the value of OAB relative to other chronic conditions. Although this is an interesting research question in the context of priority setting for payers and decision-makers, it was not within the scope of this research.

The comparative effectiveness and safety research conducted through the NMA, although not without limitations, does provide good insights in to the value of OAB treatments relative to each other. NMA's have increased in importance over the last ten years as they utilise a larger network of evidence, both direct and indirect and are accepted by HTA bodies as an essential part of the evidence supporting the value of new technologies (Laws et al., 2014). In the absence of head-to-head studies this research aids comparative effectiveness and has been an integral part of reimbursement dossiers across Europe and Canada. The outputs from this NMA have also been applied to the HE models discussed in chapter 5, and have been included in HTA assessments in the UK (NICE, SMC, AWMSG) and adapted to other countries such as Sweden (TLV). As a result, Mirabegron is reimbursed in some of these countries at an acceptable price. Overall, the four articles on HE modelling in OAB included in this thesis (Chapter 5 and Chapter 6) appeal to both National and Local decision-makers in terms of demonstrating the relative value of OAB treatments and aiding with guidelines, reimbursement and pricing decisions. Finally, with respect to PRO's the research highlights the significant impact OAB has on patients HRQoL and clinically meaningful improvements seen through treatment with Mirabegron. OAB is not a life threatening condition and therefore not always at the forefront of the mind of payers and decision-makers, which is why evidence related to patients HRQoL, is pivotal to understanding the value of treatments used in OAB. The present research demonstrates that the small changes seen in efficacy during the pivotal trials are actually meaningful to the patient as reflected by the PRO analyses and subsequent HE modelling (ICERs). The objective measures are thus supported by the subjective measures thereby strengthening the overall value arguments for Mirabegron.

7.3   Limitations of the Thesis

There are some limitations of the current thesis. Regarding the PRO analyses, these are limited to the 12-week duration of the registration trials so long term impact of QoL cannot be assessed. These studies were not powered to detect differences compared to the active control, Tolterodine. There is also a large placebo effect which may water down the treatment effect and high ceiling effect with respect to EQ-5D. Finally, the HRQoL analysis is based only on the 12 week RCTs and the current research does not include any QoL data from RWE.

The retrospective design of the UK CPRD study and the fact that QoL data is not routinely collected in primary or secondary care means that the patient perspective in the real world is not fully captured. Future research needs to focus on prospective collection of QoL data in a real world setting and preferably for longer than 12 weeks.

Another key issue this research raises with respect to OAB is the generally low persistence observed with OAB medications. The CPRD analysis confirms that persistence with OAB medications is one of the lowest amongst major chronic conditions (Yeaw et al., 2009) but this research does not shed any light on the reasons for discontinuation. Independent research around the reasons for discontinuation have already been cited (Benner et al., 2010; Campbell et al.,2008; Cramer et al., 2008; Dmochowski et al.,2007; Krhut et al.,2014; Schabert et al., 2009). However, more qualitative research is required in this area in order to obtain a better understanding of why patients discontinue especially within the first 1-3 months. Also the definitions of persistence and adherence are confined to the rules set within the retrospective design of the study and the limitations of using a database. Therefore, there is a possibility that we may not have accounted for patients who take their medication on a PRN ("pro re nata", "as the thing is needed") basis for example, or in patients with whom the disease may wax and wane and in patients who may experience a resolution of symptoms. Again, further insights from a prospectively designed observational study that includes all the main pharmacological treatments available for OAB may complement the current thesis.

Finally, the present research on the whole is focussed on demonstrating the value of OAB treatments in the general OAB population. One reason for this is that decision-

makers currently do not recognise any subgroups in OAB as reimbursement or coverage is granted or not for the general OAB population with stipulations made on line of therapy, and not restricted to any subgroups. However, in some countries such as France, Germany and Italy the additional benefit of a medication like Mirabegron is currently not recognised and therefore not reimbursed. Subgroup analyses maybe a viable option in these countries.

7.4 Recommendations for Further Studies/Research

Based on the findings from this thesis several recommendations can be made as to where future research should be focussed to further enhance our understanding around the value of OAB medications.

With respect to PRO's, the EQ-5D-5L version is now available which has five response levels for each of the five dimensions of the EQ-5D. This may provide some further insights in to the sensitivity of the EQ-5D instrument to subtle changes in OAB symptomology. A 12-month, prospectively designed observational study using the EQ-5D-5L and other disease specific PRO instruments such as the OAB-q, would be ideal in understanding the impact on HRQoL of treatments for OAB in the real world. Although not part of this research, prospective observational studies are now in progress in both the US (PERSPECTIVE; ClinicalTrials.gov.NCT02386072) and Europe (BELIEVE; ClinicalTrials.gov NCT02320772) which will yield important information on the long-term impact of OAB treatments on HRQoL in the real world setting. This type of study design would complement the current research and may provide an accurate assessment of persistence and adherence to medication in the real world setting. They would also provide more insights in to the reasons patient continue or discontinue OAB medications.

Regarding the cost-utility analyses presented in chapter 5, the accuracy of these analyses may be improved if these were updated with the most up-to-date RWE that now includes Mirabegron (that is the CPRD study). Also, once the HRQoL data is available from the observational studies mentioned above, the cost-effectiveness model based on persistence presented in chapter 6 should also be updated to a cost-

utlity analysis. Such a cost-utility analysis, based purely on RWE would make for an interesting comparison with the cost-utility analysis based mainly on RCT evidence. The ICERs generated from both models would provide important insights in to the cost-effectiveness of OAB medications and how this translates in to the real-world setting, and would complement the current research.

RWE can also provide greater insights in to why such a large proportion of OAB patients discontinue medication. Understanding these reasons could help modify clinical practice such as more education for patients and better management of expectations. To this end more qualitative research is warranted. The knowledge Transfer Partnership (KTP) between Astellas and Manchester Metropolitan University has been set up recently to answer precisely this question. This is qualitative research that will conduct interviews with OAB patients in the UK who will be selected on the basis that they match the baseline characteristics of patients who have discontinued treatment within the first 3 months, versus a group who have continued taking their OAB medication for at least 12 months. In addition, the patients from the current CPRD study will also be similarly selected to administer a series of PRO's on-line.

Finally, this thesis has highlighted analyses conducted across various subgroups. However, the main focus has still been on the general OAB population. The need to focus on specific subgroups of patients has been highlighted by negative reimbursement decisions in Germany and France for example and regular price reviews in Sweden and Spain. The KTP program mentioned above will also try and address this issue by focussing on specific sub-groups such as the elderly (anti-cholinergic burden), neurogenic detrusor overactivity (NDO) patients, and on patients requiring an add-on or combination treatment.

7.5   Conclusions

In conclusion, the research presented in this thesis demonstrates that the cost-effectiveness of a recently launched drug in the treatment of OAB (Mirabegron) is by and large supported by RWE. However, some limitations of the current evidence may be complemented through prospectively designed observational studies to capture

HRQoL and other elements such as persistence and adherence in the real world setting. There is also an opportunity to build on the current work through qualitative research that would help to understand the reasons for early discontinuation of treatment by patients and may help modify current clinical practice.

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Appendices

Appendix A: Peer Reviewed Publication List

Appendix B: Declaration of Contributions

Appendix A: Peer Reviewed Publication List

Papers included in this thesis are marked with an asterix.

Hart WM, **Nazir J**, Baskin-Bey E. An incidence model of the cost of advanced prostate cancer in Spain. *J Med Econ 2014;17:125–31*

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MSc, Emad Siddiqui MD, Adrian Wagg MD. Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. *(Accepted for publication Eur Urol)*

Appendix   B: Declaration of Contributions

The table below summarises my percentage contribution towards each paper submitted in this thesis. The publications are cited in the order in which they are cited in the thesis.

Number	Publication	Percentage contribution
1	Khullar V, Amarenco G, Angulo JC, Blauwet MB, **Nazir J**, Odeyemi IA, Hakimi Z. Patient-reported outcomes with the β3 -adrenoceptor agonist mirabegron in a phase III trial in patients with overactive bladder. *Neurourol*	40%

	Urodyn 2015.DOI 10.1002/nau	
2	Pavesi M, Devlin N, Hakimi Z, **Nazir J**, Herdman M, Hoyle C, Odeyemi IA. Understanding the effects on HR-QoL of treatment for overactive bladder: a detailed analysis of EQ-5D clinical trial data for mirabegron. *J Med Econ 2013;16:866–76*.	40%
3	Desroziers K, Aballéa S, Maman K, **Nazir J**, Odeyemi I, Hakimi Z. Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder. *Health Qual Life Outcomes 2013;11:200.*	40%
4	Maman K, Aballea S, **Nazir J**, Desroziers K, Neine ME, Siddiqui E, Odeyemi I, Hakimi Z. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol 2014;65:755–65*	50%
5	Aballéa S, Maman K, Thokagevistk K, **Nazir J,** Odeyemi IA, Hakimi Z, Garnham A, Toumi M. Cost Effectiveness of Mirabegron Compared with Tolterodine Extended Release for the Treatment of Adults with Overactive Bladder in the United Kingdom. *Clin Drug Investig 2015;35:83–93*.	50%
6	**Nazir J,** Maman K, Neine ME, Briquet B, Odeyemi IA, Hakimi Z, Garnham A, Aballéa S. Cost Effectiveness of Mirabegron Compared with Antimuscarinic Agents for the Treatment of Adults with Overactive Bladder in the United Kingdom. *Value Health 2015;18:783–90*	70%
7	**Nazir J,** Posnett J, Walker A, Odeyemi IA, Hakimi Z, Garnham A. Economic evaluation of pharmacological treatments for overactive bladder from the perspective	70%

	of the UK National Health Service. *J Med Econ 2015;18:390–7.*	
8	Christopher R. Chapple MD, Jameel Nazir MSc, Zalmai Hakimi PharmD, Sally Bowditch MPH, Francis Fatoye PhD, Florent Guelfucci PhD, Amine Khemiri MSc, Emad Siddiqui MD, Adrian Wagg MD. Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. *(Accepted for publication Eur Urol)*	60%
9	**Jameel Nazir**, Malin Berling, Charles McCrea, Francis Fatoye, Sally Bowditch, Zalmai Hakimi, Adrian Wagg. Economic Impact of Mirabegron Versus Antimuscarinics for the Treatment of Overactive Bladder in the UK. *Accepted for publication in PharmacoEconomics-Open.*	80%