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Understanding medication adherence
Application of health psychology and behavioural economic theories

Holmes, Emily Anne Fargher

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Understanding medication adherence:

Application of health psychology and behavioural economic theories

Emily Anne Fargher Holmes

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This thesis is dedicated to my Dad, who instilled in me the tenacity required to complete this research over a remarkable seven years.

"Psychology and economics have a classic love-hate relationship. Members of each discipline often express positive sentiments about the other in the abstract, and acknowledge complementariness between disciplines in methods, subject matter and levels of analysis. Yet actual encounters often produce glassy eyes or, worse, overt hostility. Both disciplines set out to use scientific method to explain and describe human behaviour. They differ, however, in details of their respective paradigms. ...

A dispassionate mediator might think that both sides have merit, but might also propose that the two disciplines find some way of sorting out their differences and agree on a common ground that combines both their strengths to a greater whole. Now, more than ever before, there are ground for optimism that such reconciliation is beginning to occur."

(Lowenstien et al., 2003; p.1)

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Thesis Summary

Aims: This thesis explores the application of health psychology and behavioural economic theories to understanding adherence to medications in adult patients, to determine the most useful theoretical foundations to inform the development of adherence enhancing interventions in several countries and settings.

Methods and Results: A systematic review of the literature (Chapter 2) found that components from within sociocognitive (perceived barriers, perceived susceptibility) and self-regulation frameworks (necessity beliefs and medication concerns) are significantly associated with adherence to medication; and that self-efficacy was a proximal determinant of adherence in both frameworks. A multinational cross-sectional survey of self-reported nonadherence to antihypertensive medications (Chapter 3) found that low self-efficacy and a high number of perceived barriers are the main significant determinants of non-adherence, with country explaining 11% of the variance in non-adherence. A stated preference discrete choice (DCE) analysis (Chapter 4) found that medicine characteristics of benefit, harms and convenience have significant effect on stated persistence with medication and that psychosocial influences may modify these preferences. Concurrent application of the random utility maximisation framework and health psychology models showed that components of the theory of planned behaviour had greatest influence on probability of persistence with 5-aminosalicylic acid for ulcerative colitis. Application of intertemporal choice theory to explain nonadherence (Chapter 5) showed a weak association between time preference rates. Time preference rates, however, were associated with factors from the self-regulation framework (illness consequences and concerns). A DCE of treatment harms and benefits for treatment for epilepsy (Chapter 6) found that people with epilepsy place a higher value on reduction in harms than improvements in treatment benefit, and that patients' preferences for treatment vary by patient group. When put into the context of actual event rates this has implications the interpretation of clinical studies. An empirical study of the familiarity of conditions used to elicit time preference (Chapter 7) using propensity score matched data, found a significant familiarity with condition explained between 38- 53% of the variance in time preference rates.

Conclusions: Consolidation of behavioural models may provide a strengthened theoretical basis for the development and assessment of adherence enhancing interventions. A tailored approach to adherence research is required to account for country and clinical differences in preferences and behaviour.

Thesis Structure

The Centre for Health Economics and Medicines Evaluations at Bangor University subscribes to a publication based PhD model, which requires the preparation of four or more publishable manuscripts.

Chapter 1 provides a general overview and the background necessary to the thesis. Each of the Chapters 2 to 7 is presented as a stand-alone manuscript, which inevitably involves a degree of overlap and repetition of current themes. Chapter 8 then provides an integrated discussion of the findings. Figure I shows the structure and layout of the thesis.

- **Thesis projects**

This thesis comprises research from two projects. The PhD candidate was the appointed Research Fellow in Health Economics on both of these projects:

Ascertaining Barriers to Compliance (ABC): polices for safe, effective and cost-effective use of medicines in Europe. *European Union's Seventh Framework Programme* FP7/2007-2013. Reference number 223477.

Defining patient preferences and priorities for treatment options and outcomes in epilepsy. *NIHR Research for Patient Benefit Programme* 2011-2013. Reference number: PB-PG-0909-20161.

Thesis Publications

Five peer-reviewed publications are contained within this thesis. Chapters 2,3 and 4 are published as:

Holmes, E. A., Hughes, D. A., & Morrison, V. L. (2014). Predicting Adherence to Medications Using Health Psychology Theories: A Systematic Review of 20 Years of Empirical Research. *Value in Health, 17*(8), 863-876. [Thesis Chapter 2]

Morrison, V. L., Holmes, E. A., Parveen, S., Plumpton, C. O., Clyne, W., De Geest, S., ... & Hughes, D. A. (2015). Predictors of self-reported adherence to antihypertensive medicines: a multinational, cross-sectional survey. *Value in Health, 18*(2), 206-216. [Thesis Chapter 3]

Holmes, E. A., Morrison, V. L., & Hughes, D. A. (2016). What influences persistence with medicines? A multinational discrete choice experiment of 2549 patients. *British Journal of Clinical Pharmacology, 82(2), 522-31.* [Thesis Chapter 4]

Appendix 1.1 and 6.5 have also been published as:

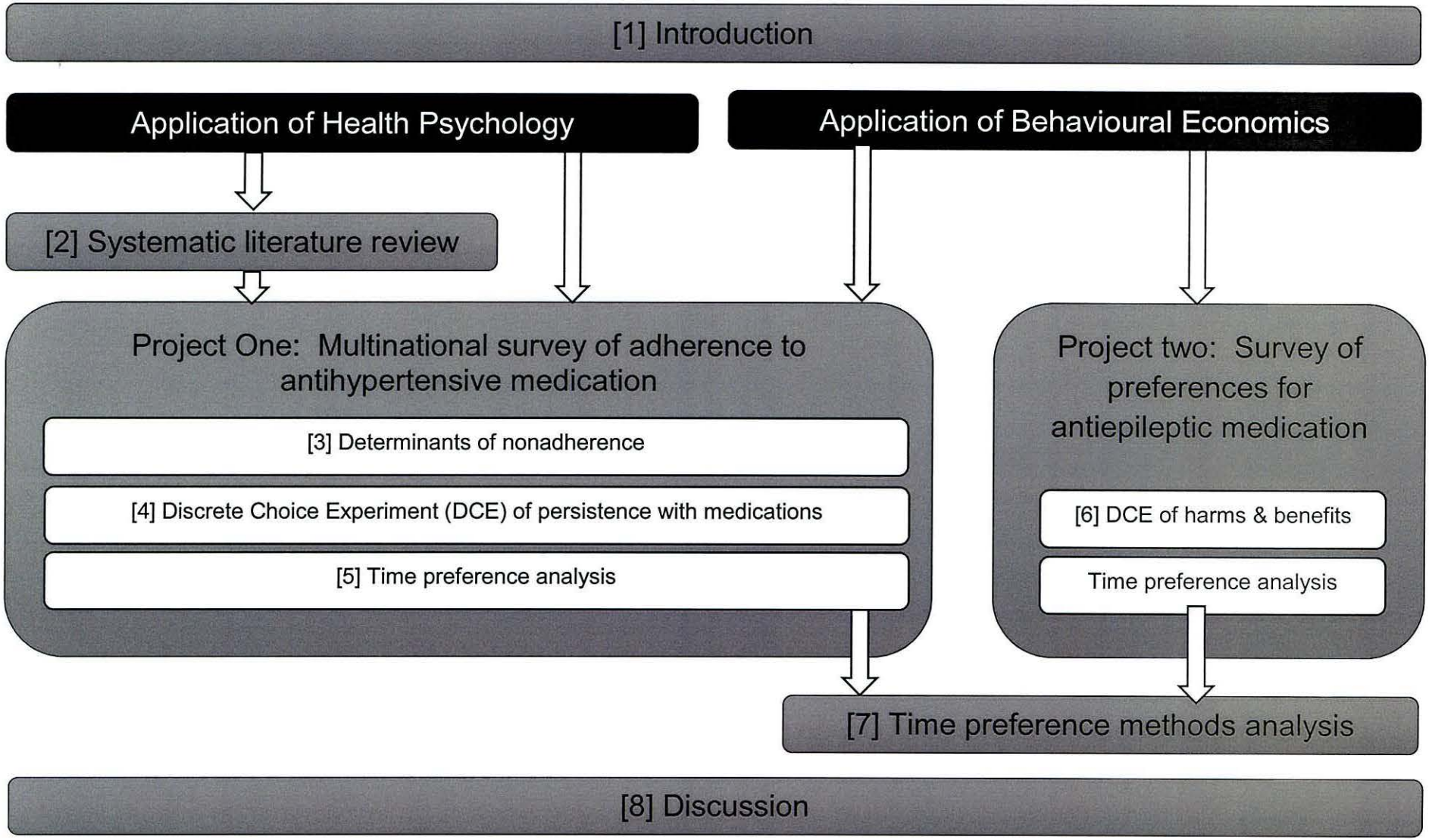
Powell, G., Holmes, E. A., Plumpton, C. O., Ring, A., Baker, G. A., Jacoby, A., ... & Hughes, D. A. (2015). Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: patients' and physicians' preferences for testing and service delivery. *British journal of clinical pharmacology,80*(5), 1149-1159. [Appendix to Chapter 6]

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., Dobbels, F., Fargher, E*., Morrison, V., Lewek, P., Matyjaszczyk, M., Mshelia, C., Clyne, W., Aronson, J., & Urquhart, J. (2012). A new taxonomy for describing and defining adherence to medications. *British Journal of Clinical Pharmacology, 73*(5), 691-705. [Appendix to Chapter 1]

* *Note.* The candidate's previous surname was "Fargher".

Chapters 5, 6 & 7 are manuscripts being prepared for submission for publication.

Figure I. Thesis Structure Diagram ([#] Chapter reference)



Chapter 1

Thesis introduction and background

1.1 Thesis overview

Adherence to medication is the process by which patients take their medication as prescribed (Vrijens et al., 2012). This process starts when the patient takes the first dose of a prescribed medication, continues with implementation of the dosing regimen, and ends when the patient stops taking the prescribed medication, for whatever reason(s). Poor adherence to treatment of chronic diseases is a worldwide problem of striking magnitude (Sabaté 2003, p. XIII); it is highly prevalent across a broad range of conditions and presents a significant challenge to safe, effective and cost-effective use of medicines. Evidence suggests that in the region of 50% of patients stop taking their medication within one-year (Vrijens et al., 2008). The financial implications of nonadherence are significant. In a study of adults diagnosed with diabetes, hypertension, or dyslipidaemia in the United States, the total direct national cost of nonadherence (suboptimal implementation) was estimated to be $105.8 billion ($453 per adult) (Nasseh et al., 2012). Sokol et al. (2005) also reported that patients with poor adherence to antihypertensives incur greater health care costs. This study was also based on prescription data. A study from the USA showed nonadherence to antiepileptic medications to result in almost a 20% increase in the incidence of accident and emergency attendance, 40% increase in hospital admissions and 76% increase in inpatient days, leading to significant additional costs (Faught et al., 2009).

It is thought that improving adherence to medications in general could have a greater impact on the health of the population than improvements in specific medical treatments (Haynes et al., 2002; yet research into the causes of suboptimal adherence has been of variable quality, often contradictory, and generally inconclusive (Sabaté 2003). In order to improve adherence to medications it is necessary to first understand what determines the behaviour nonadherence. This PhD explores theoretical reasons for nonadherence, drawing upon both the health psychology and behavioural economics literature. It seeks to identify and test models of behaviour that may explain the factors that determine adherence to prescribed medications in adult patients. The findings of this PhD further our understanding of adherence to medications from a theoretical (and empirical) perspective and have the potential to inform the development and evaluation of adherence-enhancing interventions.

1.1.1 Models of behaviour

A core component within psychology and economics is the study of behaviour that influences health. The focus is on determining the factors that influence whether a patient will or will not perform a behaviour, in this case adherence or nonadherence to medications. Conner and Norman (2005) outline two reasons for studying health-related behaviour. Firstly, we can attribute a substantial proportion of mortality, from the leading causes of death (WHO 2013) to patterns of behaviour and these patterns of behaviour are modifiable; for example the link between cardiovascular disease and diet or smoking. Secondly, there is increased recognition that individuals can contribute to their own health and wellbeing, by adopting health-enhancing behaviour and avoiding health-compromising behaviour.

Similarly, in economics health has been suggested as a means of investing in ones self (Grossman 1972). A common characteristic of all health-related behaviour is the trade-off between current costs and future benefits (Fuchs 1982). In this context, expected benefits relate to reductions in mortality or morbidity; and, costs cover a broad range of consequences such as time, money, resources, and emotions (Fuchs 1982). Economists have suggested several frameworks that are useful in explaining health-related behaviour (Becker 1964; Grossman 1972; Lancaster 1966).

Behavioural theories postulate a variety of factors as determinants of behaviour, including clinical, personal, social, emotional and cognitive factors. Such theories attempt to explain why behaviours differ within and between individuals (and behaviour change), with the goal of designing interventions to change the prevalence of such behaviours and produce improvements in individual and population health.

The theoretical underpinning of this thesis is models of behaviour, the behaviour of interest is adherence to medication, and the change is between nonadherence and adherence. The empirical research was conducted within two wider studies of (i) adherence to antihypertensive medications; and, (ii) patient preferences for antiepileptic medication. The empirical application of health psychology and behavioural economic theories therefore focuses on patients with hypertension and patients with epilepsy.

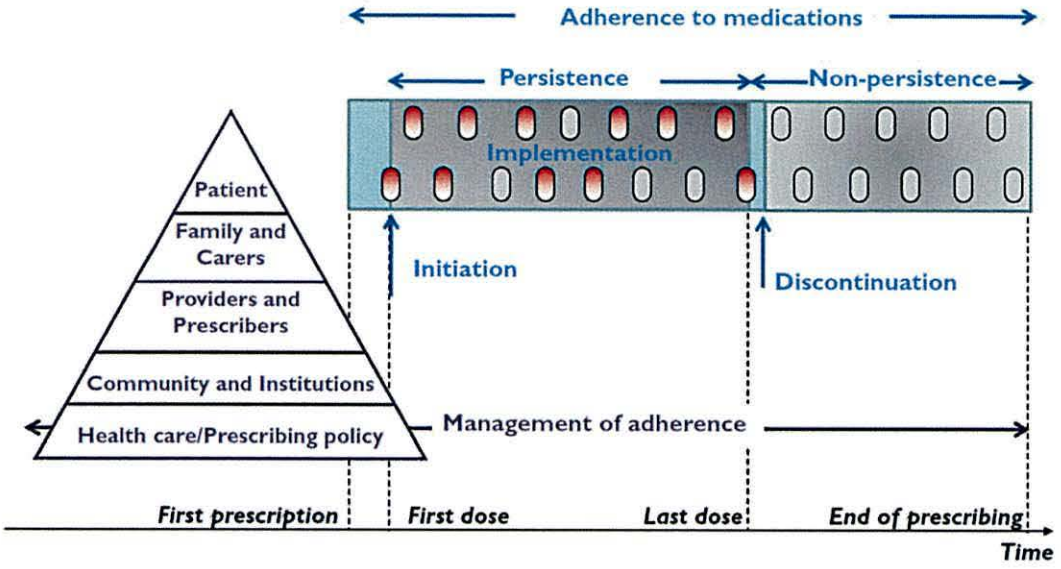
1.2 Adherence to medication

Over the past decade, there are been a considerable increase in research into adherence to medications (Vrijens et al., 2012). Reasons for this include an increased awareness of the magnitude of the problem of nonadherence across a broad range of conditions (Sabaté 2003) and, an increased recognition of the contribution this behaviour makes to variance in therapeutic response and health care resource use / costs (Osterbeg & Blaschke, 2005; Sokol et al., 2005). Historically, adherence to medications has been described using several terms including compliance and concordance (e.g., Friberg & Scherman, 2005; Snowden 2008). In 2012, Vrijens et al. published a new taxonomy for describing and defining adherence to medications (Appendix 1.1). The taxonomy was derived from a systematic review of conceptual approaches to adherence research that identified over ten different terms describing medication-taking behaviour (e.g. adherence, compliance); and was subsequently evaluated and discussed by experts at several international meetings. The candidate is a co-author of this taxonomy and was a member of the research team conducting the work. This thesis uses the taxonomy throughout, as described below.

1.2.1 Defining of adherence and nonadherence to medications

Adherence to medication is the process by which patients take their medication as prescribed, and is composed of three quantifiable phases: initiation, implementation and discontinuation (Figure 1.1) (Vrijens et al., 2012). Firstly, initiation occurs when the patient takes the first dose of a prescribed medication. The process continues with implementation of the dosing regimen. Implementation is the extent to which the patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Finally, discontinuation, signals the end of the process, and occurs when the patient stops taking the prescribed medication, for whatever reason(s). Persistence is the term used to describe the length of time between initiation and the last dose, which immediately precedes discontinuation.

Figure 1.1: Illustration of the process of adherence to medication (light blue) and the process of management of adherence (dark blue)



(Vrijens et al., 2012)

In the context of the taxonomy for describing adherence to medications, nonadherence to medication can occur in one or a combination of the following behaviours:-

- Late or non-initiation of the prescribed treatment: patient does not initiate treatment.
- Sub-optimal implementation of the dosing regimen: patient delays, omits or takes extra doses.
- Early discontinuation: patient discontinues treatment before end of prescribing.

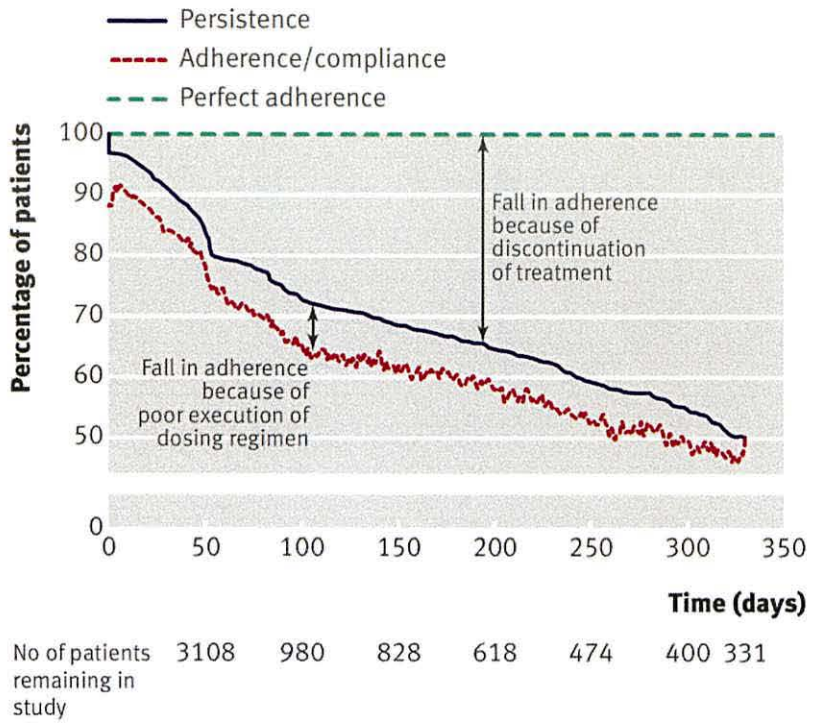
Many of the studies discussed in this thesis predate the publication of this taxonomy. As such, there is considerable inconsistency in terminology used to describe adherence behaviour and associated estimates. Often the information required to align previous empirical research with the taxonomy is unavailable, however, where possible adherence behaviour will be described in terms: initiation, implementation and persistence throughout this thesis.

1.2.2 Prevalence of nonadherence to medications

Nonadherence to medications is highly prevalent across a broad range of conditions (DiMatteo et al., 2004; Sabaté 2003), including hypertension (Naderi et al., 2012; Vrijens et al., 2008), epilepsy (Faught 2012), ulcerative colitis (Higgins et al., 2009), transplantation (Dobbels et al., 2010), HIV (Simoni et al., 2006), asthma (Mäkelä et al., 2013), diabetes (Davies et al., 2013), cancer (Bassan et al., 2014), and smoking cessation (Raupach et al., 2014). There is evidence of significant within and between condition variation in the prevalence of adherence (DiMatteo et al., 2002). This has greater impact depending on the pharmacological properties of the medication and the type of disease. Certain treatments, such as antiretroviral for HIV, have a narrower therapeutic window than other treatments, and may be more forgiving if doses are omitted. Furthermore, variable adherence may result in drug-specific issues such as drug resistance to antibiotics (Blaschke et al., 2012).

Evidence, from 20 studies, suggests the prevalence of initiation is between 2.3% and 50% (Zeber et al., 2013). In the context of a clinical trial, Vrijens et al. (2008) estimated one-year persistence with antihypertensive medication to be in the region of 50% (Figure 1.2). Whilst a meta-analysis of persistence with medication for the prevention of cardiovascular disease, measured using prescription refill, reported 57% of patients were persistent at 2-years (Naderi et al. 2012). Persistence with antiepileptic medication is in the region of 50-60% (Briesacher 2008; Davies 2008; Manjunath 2009), based on three studies that used 80% medication possession ratio at 1 year (Faught 2012). Estimates of implementation, however, prove difficult to summarise. In a highly cited paper, Osterberg & Blaschke (2005) reported average adherence rates in clinical trials ranged from 43% to 78% based on three studies (Cramer et al., 2003; Waeber et al., 1999; Claxton et al., 2001). Estimates of prevalence of "adherence" may not include patients who failed to initiate, or have discontinued. Furthermore, data must be interpreted with caution, as they can represent two confounding variables, percentages of patients within a trial being classified as adherent / nonadherent, and, the percentage threshold at which the patients are considered to be adherent.

Figure 1.2: Time course of implementation and persistence with antihypertensive medication



(Vrijens et al., 2008, p.1115)

1.2.3 Quantification of adherence to medications

It is important to note that the differences between the actions that comprise the process of adherence to medications (initiation, implementation, persistence) preclude a single quantitative parameter to describe all three. We can measure initiation and persistence as discontinuous behaviours using "time to event" variables i.e. time from prescription until first dose or from initiation until discontinuation. Standard survival analysis methods can measure these variables (e.g., Kaplan-Meier curves, median persistence etc. see Figure 1.2). Implementation, however, is a continuous process, that requires comparison of the prescribed dosing regimen and the patient's drug dosing history (actual behaviour). Estimation can be a single summary statistic (e.g., proportion of drugs taken over a defined interval of time) or a longitudinal comparison (e.g., electronically compiled dosing histories). Above, the variable type and measurement requirements are apparent due to the clearly defined taxonomy. Historically, however, most investigators classify patients dichotomously as being 'adherent' or 'nonadherent' according to some pre-specified (and often arbitrary) threshold (commonly 80%). This poses a serious methodological weakness and reduces the ability to assess the relative contribution of behavioural models to the various forms of

nonadherence, and represents an important limitation to the interpretation of adherence research. The use of a single dichotomous variable makes any assessment dependent upon the length of the study. For example, a patient who doses correctly for 90 days and then discontinues altogether will be classified as 100% adherent if observed for 90 days, 50% adherent if observed for 180 days, and 25% adherent if observed for 360 days. As such, estimates of adherence are not standardised or compatible across studies.

A major limitation of adherence research is in the accurate measurement and monitoring of the adherence. Table 1.1 summarises the wide range of methods for measuring adherence behaviour. Several studies have made comparisons between measures and/or validated methods (Vrijens et al., 2008; Blaschke et al., 2012; Garber et al., 2004; Wu et al., 2008). Vrijens et al. (2008) provide evidence of pharmacokinetic validation of MEMS and comparison to prescription refill; and, Blaschke et al. (2012) suggests that pre-electronic methods, such as medication measurement, and self-report, underestimate adherence; and as such it is clinically unrecognized as a frequent cause of failed treatment or underestimated effectiveness Blaschke et al. (2012).

1.2.4 Consequences of nonadherence to medications

Clinical impacts of nonadhernce

Suboptimal adherence to appropriately prescribed therapies is recognised as one of the major contributing factors to therapeutic nonresponse (Osterberg & Blaschke, 2005). DiMatteo at al. (2002) conducted a meta-analysis of 63 studies (44/63 studies of medication adherence, 20/44 cardiovascular disease), correlating adherence rate with objective measures of treatment outcomes. Findings suggest that patients with poor adherence have almost a 3-fold higher odds of experiencing a poor clinical outcome, and that this association is moderated by the method of adherence measurement. Adherence to medication is also associated with lower mortality. Simpson et al. (2006) found that 'good adherence' compared to 'poor adherence' (i.e. implementation) was associated with lower mortality (odds ratio 0.56, 95% confidence interval 0.50 to 0.63).

Table 1.1. Measuring adherence behaviour (e.g., Farmer et al., 1999; Vrijens et al., 2008)

Measurement category	Examples of methods	Advantages	Disadvantages
Direct, objective measurement			
Biochemical indicators / therapeutic drug monitoring	Blood / serum levels of targeted substances	Can tailor drug doses, confirms drug ingestion, free from memory lapse	May requires information on the dose and time of doses, can be affected by other factors , short-term, invasive, expensive
Observed behaviour	Directly observed therapy (DOT)	Can observe behaviour, can measure adherence on repeated occasions	Nonadherent patients may feign taking medication, often impractical
Biological indicators	Infection resolution; organ rejection, blood pressure	More useful for certain conditions	Imperfect reflections of actual behaviour
Sensor enabled pills	Proteous digital health® (Proteous 2016)	Provides patient and health care provider with objective longitudinal data, precise frequency and timing of dose obtained	Patient must wear patch, evidence of adverse reaction to skin patch, cost, dispensing issues
Indirect, objective measurement			
Electronic compilation of drug dosing histories	MEMS Cap® Medication Event Monitoring System (Westrock 2016a) Cerepak® (Westrock 2016b)	Provides patient and health care provider with objective longitudinal data, precise frequency and timing of dose obtained, validated by pharmacokinetic studies	Does not guarantee medications were ingested, cost, dispensing issues
Medication measurement	Counts of returned tablets	Easily obtained	Indirect measure of behaviour, no guarantee medications were ingested. pill dumping can occur, no information on time
Prescription data	Prescription refill records	Large data sets easily obtained, inexpensive	Does not guarantee medications were ingested, no information on time of doses
Subjective reports			
Patient self-report patient	Interviews Diaries Questionnaires e.g., Morisky Medication Adherence Scale; Medication Adherence Rating Scale (MARS)	Inexpensive, collected without technical expertise, clinically feasible	Inherently limited, may overestimate adherence, may requires recall of behavioural events
Healthcare provider or carer estimates	Proxy questionnaire Collateral report by family member or physician or carer	Inexpensive, collected without technical expertise, clinically feasible	Very subjective, not an accurate measure of behaviour

Bramley et al. (2006) found high adherence to antihypertensive medication (MPR 80-100%) was associated with higher odds of blood pressure control. Inversely, nonadherence to statins in the first year after hospitalisation for myocardial infarction is associated with a 12 to 25% increase in relative hazard ratio for mortality (Rasmussen et al., 2007). Evidence on adherence to antihypertensive medication suggests that patients with poor implementation (proportion of days covered ≤40%) experience significantly increased risk of acute cardiovascular events, compared with those who adhere adequately (≥80%) (Mazzaglia et al., 2009). Whilst, nonadherence with antiepileptic medication is associated with a 20% higher rate of seizures (Faught et al., 2012), and a 3-fold increase in mortality (Williams et al., 2006). Cramer et al. (2003) reported a higher estimate, with 71% of patients self-reporting dose omissions (suboptimal implementation) and 45% of these patients reporting a seizure after a missed dose, at some point during drug treatment.

Economic impacts of nonadherence

In 2015 world pharmaceutical market growth was 6.2% and sales were reported as $1,068.8 billion ($144 billion for the EU5; $27.7 billion in UK) (IMS Health 2015). Global spending on medicines is forecast to reach $1.4 trillion by 2020, with over 50% of the world's population consuming more than one dose per person per day (IMS Health 2015). Medicines expenditure is the second largest component of health expenditure for NHS providers, with most NHS Trusts spending between 5-10% of their total expenditure on drugs (Lafond et al., 2014). Latest figures show that in 2014, 1.1 billion prescription items were dispensed in the community in England (Health and Social Care Information Centre 2015), and 78.5 million in Wales (equivalent of 25.5 items per head) (Health and Social Care Information Centre 2015). However, it has been estimated that £300 million of NHS prescribed medicines are wasted each year (Trueman et al., 2010). This estimate included medication retained in patients' homes (£90 million), retained in nursing homes (£50 million) and, medication returned to community pharmacies (£110 million), over a one-year time frame. Hazell and Robson (2015) suggest in present terms this could be considered an underestimate.

Trueman et al. (2010) presented 6 case studies to illustrate the costs and benefits of nonadherence (asthma, type 2 diabetes, high cholesterol, use of statins, hypertension and schizophrenia). In their model for Ramipril for hypertension, they adopted a simplified representation of treatment pathways and outcomes, over one-year, using easily accessible data (published event and utility data, national resource use and costs). Adherence

(measured as a MPR, data source not specified) was assumed to be associated with higher event data, which in term influenced utility. The model used adherence rates of 13% of patients being adherent (MPR 80-100%), 75% being partially adherent (MPR 50-80%) 12% being nonadherent (MPR <50%), adherence was cost saving and improved quality adjusted life years (QALYs) (Table 1.2). The authors estimate, that based on prevalence of hypertension being 12.5%, increasing adherence to 80% would result in savings of over £100 million per year (compared to asthma £130 million, type 2 diabetes <£100 million, high cholesterol £9 million, use of statins £66 million, and schizophrenia £113 million).

Table 1.2 Summary of economic evidence for improved adherence in a cross-section of long term conditions which are high priorities for the NHS (Trueman et al., 2010).

Case study	Adherence Category*	Annual cost per patient (£)	QALYs	Net Benefit (£)^
Statins for secondary prevention of CVD	Adherent	246.64	0.830	
	Partially adherent	400.00	0.795	853.36
	Nonadherent	428.32	0.794	901.68
Type 2 Diabetes	Adherent	950.47	0.761	
	Partially adherent	1078.66	0.739	568.19
Hypertension	Adherent	573.80	0.786	
	Partially adherent	693.03	0.754	759.23
	Nonadherent	912.64	0.716	1738.84
Statins for primary prevention of CVD	Adherent	345.90	0.825	
	Partially adherent	383.89	0.820	137.99
	Nonadherent	393.10	0.820	147.20
Asthma	Adherent	435.61	0.833	
	Partially adherent	510.23	0.725	2234.62
Schizophrenia	Adherent	4,066.71	0.743	
	Partially adherent	7,421.98	0.625	5715.27

Note. *Medication possession ratios (MPR) used in economic models [no. days treatment dispensed / no. days between prescription refills]. Adherent >80%, Partially adherent 50-80%, Nonadherent <50%. Nonadherence only assumed in conditions where patients could potentially have a MPR of less than 50% adherent, without developing acute, life-threatening events. ^Incremental net benefit based on a conservative QALY value of £20,000

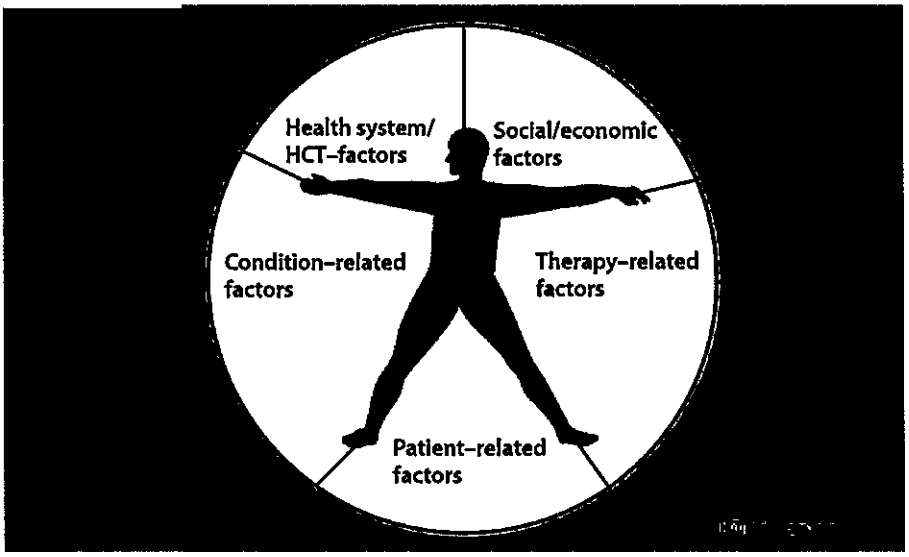
Trueman et al. (2010) provides a useful insight, but it should be noted that these models were only intended to give an idea of the issue. They used a simplistic approach but conclude that the findings are indicative of true scales. The authors acknowledge that their models were not informed by systematic reviews and more sophisticated modelling is recommended (Hughes 2007). The findings, however, highlight the potential for improvements in adherence to lead to decreased cost and improved patient outcomes. Table 1.2 details the net monetary benefit, calculated as the difference between the monetary value of incremental QALYs (incremental QALYs multiplied by £20,000) and

expected incremental costs. The net benefit approach is a good concept to use in these circumstances as it gives an idea of the amount that could be reallocated to adherence enhancing interventions (Trueman et al., 2010).

1.2.5 Determinants of nonadherence to medication

Reasons for nonadherence to medicines vary and are likely to include several factors that simultaneously influence behaviour. These factors may relate to one of several aspects of the problem. The World Health Organisation (WHO) have proposed five dimensions for the classification of factors (and subsequent interventions) that influence adherence (Sabaté 2003) (Figure 1.3). These five factors are introduced from the broad health care system level, down to the patient level, at which this thesis examines behaviour.

Figure 1.3: The five dimensions of adherence (Sabaté 2003)



(Sabaté 2003 p.27)

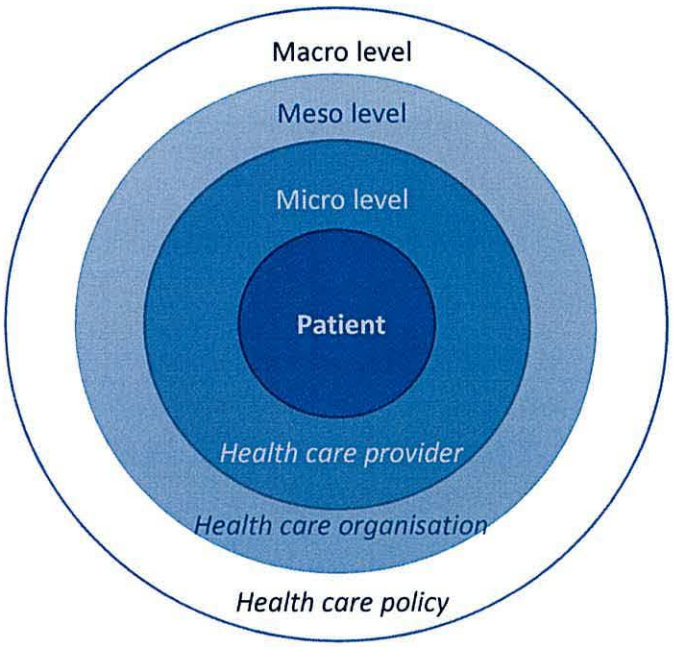
1.2.5.1 Health care team and system-related factors

There is an emerging literature on the effects of the health care system on adherence to medication. Healthcare team and system-related factors associated with adherence include: communication style (Zolnierek et al., 2009), lack of competencies in adherence management (Kruegar et al., 2005), time constraints; health care organisation (e.g. lack of

continuity and poor access to care) (Sabaté 2003); and, health care systems (e.g. health insurance coverage, or reimbursement schemes for drugs) (Berben et al., 2012).

Berben et al. (2012) explained that adherence is influenced not only by the patients but also by environmental factors and described influences in a framework of several levels, namely: micro (provider and social support), meso (health care organisation) and macro (health policy) (Figure 1.4). This represents the Ecological Model, the central premise of which is the need to consider these three system levels factors in order to gain a comprehensive understanding of adherence.

Figure 1.4. The Ecological Model of Bronfenbrenner (1977, 1980) adapted to adherence by Berben et al. (2012)



(Berben et al., 2012 p.640)

1.2.5.2 Condition-related factors

Sabaté (2003) reported several significant associations between adherence to medications and condition-related factors, such as severity of symptoms and time since diagnosis (Hekler et al., 2008). It is recognised that the strength of association between adherence and condition related factors may be influenced by co-morbidities and patients' risk perception (see patient-level determinants) (Sabaté 2003). Within the WHO framework, Sabaté (2003) suggests evidence pertaining to the patients' understanding of their disease and health care

professional communication, as condition related factors. These factors inevitably overlap with those in the health system and at the patient level.

1.2.5.3 Therapy-related factors

There is empirical evidence to suggest adherence to medication is associated with several therapy related factors, including: treatment satisfaction (Sweileh et al., 2011), route of administration (Lee et al., 2007), generic substitution (Bello 2012), side-effects (Lee et al., 2007; Youssef & Moubarak, 2002), dose frequency (Lee et al. 2007; Cramer et al., 2001), duration of treatment (Richardson et al., 1993), number of medications (Chen et al., 2009; Morrison et al., 2015), and mono versus combination therapy (Bautista & Gonzalez, 2012). Sabaté (2003) reports that characteristics of disease and treatment will modify the influence of these common therapy-related factors.

1.2.5.4 Social and economic factors

There is inconsistent evidence on social and economic factors as independent predictors of adherence (Sabaté 2003). Social and economic factors are often measured using 'convenience' variables that have been in included in the study as a population descriptor, with hypotheses based on previous empirical research (at best) from a biomedical perspective (as opposed to biopsychosocial). Factors found to have a significant association with higher adherence are: female (Faught 2008), older age (Hekler et al., 2008; Faught 2008), race (Faught 2008), live alone (Chen et al., 2009), higher education (DiMatteo et al., 2004), higher income/socioeconomic status (DiMatteo et al., 2004), and higher productivity (Hovinga et al., 2008); however there is also evidence of weak or no associations with many of these factors.

1.2.5.5 Patient-related factors

Patient-related factors are defined as the resources, knowledge, attitudes, beliefs, perceptions and expectations of the patient (Sabaté 2003). There is empirical evidence on associations between adherence and attitude (Bane et al., 2006), beliefs (Mann et al., 2009; Horne & Weinman, 2005), perceptions (Ross et al., 2004; Hekler et al., 2008; Chen et al., 2009), and feelings of knowledge and control (Bane et al., 2006; Chisholm et al., 2007; Barclay et al., 2007).

The biomedical literature most often tests correlations between adherence and demographic, therapy-related, and condition-related variables, as independent predictors. It has been argued that this is flawed conceptual model (Steiner, 2010), that is data driven rather than based on a solid theoretical foundation.

The World Health Organisation (WHO) has called for further research in understanding determinants of nonadherence to antihypertensive medication (AlGhurair et al., 2012). This requires consideration of all five factors described by Sabaté (2003), across several different countries. Solving problems related to each of these issues is necessary to improve behaviour. National Institute for Clinical and Health Evidence (2009) recommended a theory-based approach to supporting better adherence. The social science literature often shows stronger associations between adherence and factors, than studies relying on data collected for other purposes (e.g. Turner et al., 2009). Consequently, a range of models of behaviour, rooted in health psychology or economic theory, have been proposed and tested empirically.

1.3 Health psychology theories

Within health and social psychology there exist several theoretical frameworks and models for explaining variations in health-related behaviours, which can be applied to medication adherence (Munro 2007; Holmes et al., 2014).

The most common applications are of social cognitive theory (Bandura 1977; Bandura 1986; Bandura 1997), within which the health belief model (Rosenstock 1974; Becker 1974), the theory of reasoned action (Fishbein 1967), and the theory of planned behaviour (Ajzen 1991) are most prevalent. The self-regulatory model of illness and illness-related behaviour (Leventhal et al., 1992) and the transactional model of stress and coping (Folkman 1984) have also been used but to a lesser extent. Variables most often explicitly assessed within these theoretical models are considered proximal (close) to adherence behaviour (Webb et al., 2010); however, it has also been recognized that adherence behaviour varies according to more distal variables, such as social context, broad personality traits (i.e. the five factor

model of personality traits: agreeableness, openness, conscientiousness, extraversion, and neuroticism (Costa & McCrae, 1992), generic beliefs, such as multidimensional health locus of control (Wallston et al., 1978) and generalized efficacy beliefs (Bandura 1986), which more likely operate "indirectly" on outcomes.

1.3.1 Sociocognitive theory

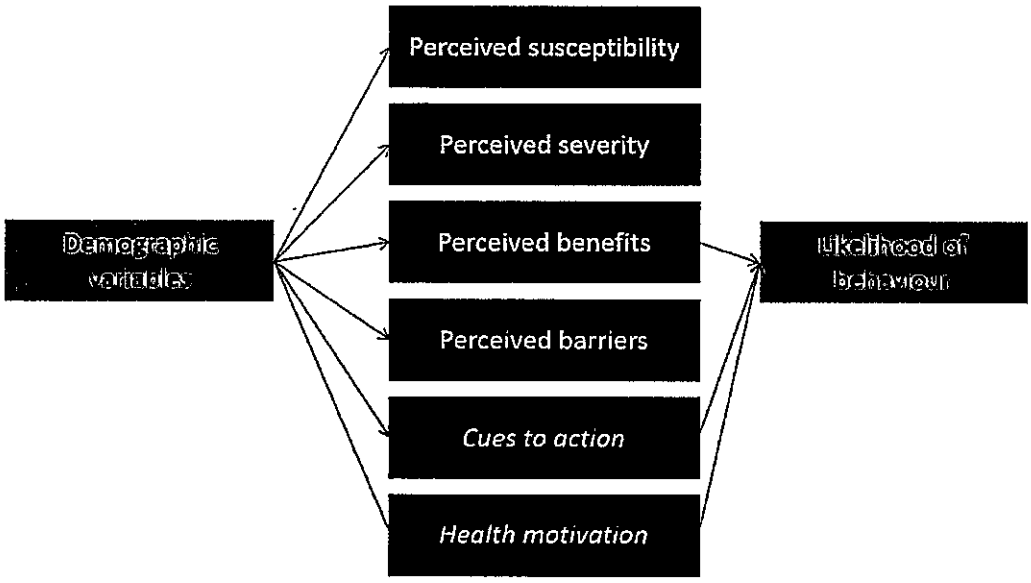
Sociocognitive theory assumes that persistence is motivated by outcome expectancies and goals (Bandura 1986) (such as improved health), which are determined by individuals' attitudes and beliefs (Fishbein 1966). Rooted in subjective expected utility theory these models are founded on a framework in which the individual evaluates expectancies or beliefs about the probability that a specific action will lead to a set of desired outcomes; and, selects the action with the highest subjective expected utility. They are based on two cognitions: expectancy of outcome of action; subjective value placed on that outcome. Models within sociocognitive theory that have been applied to persistence with medications include the Health Belief Model (Rosenstock 1974; Becker 1974) and The Theory of Planned Behaviour (Ajzen 1991).

The Health Belief Model

The likelihood of a health-behaviour, in this case adherence, is a function of the individual's beliefs about the threat posed by non action (behavioural evaluation of the consequences of nonadherence) i.e. severity of outcome and susceptibility to it, and the potential harms and benefits of the recommended course of action (behavioural evaluation of the consequences of adherence) (Figure 1.5).

In the context of adherence, the Health Belief Model postulates the likelihood of adherence is increased if the perceived threat of illness /ongoing symptoms from nonadherence is high, the benefits of adherence are greater than the barriers to carrying it out, and cues to action (e.g. reminders) are in place (Turner et al., 2007; Apter et al., 2003; Abraham et al., 1999).

Figure 1.5: The Health Belief Model



(Rosenstock 1974; Becker 1974; Strecher et al., 1997)

The HBM is relatively simplistic, conceptualising health-related behaviour as a single, static, decision – based on a cost benefit analysis. Other factors that need to be considered in the application to adherence are the social influences on behaviour, the influence of perceived behavioural control over the behaviour in question and that one needs to form an intention prior to action (Sheeran & Abraham 1996). These are addressed in another model, derived from theory - the Theory of Planned Behaviour (TPB).

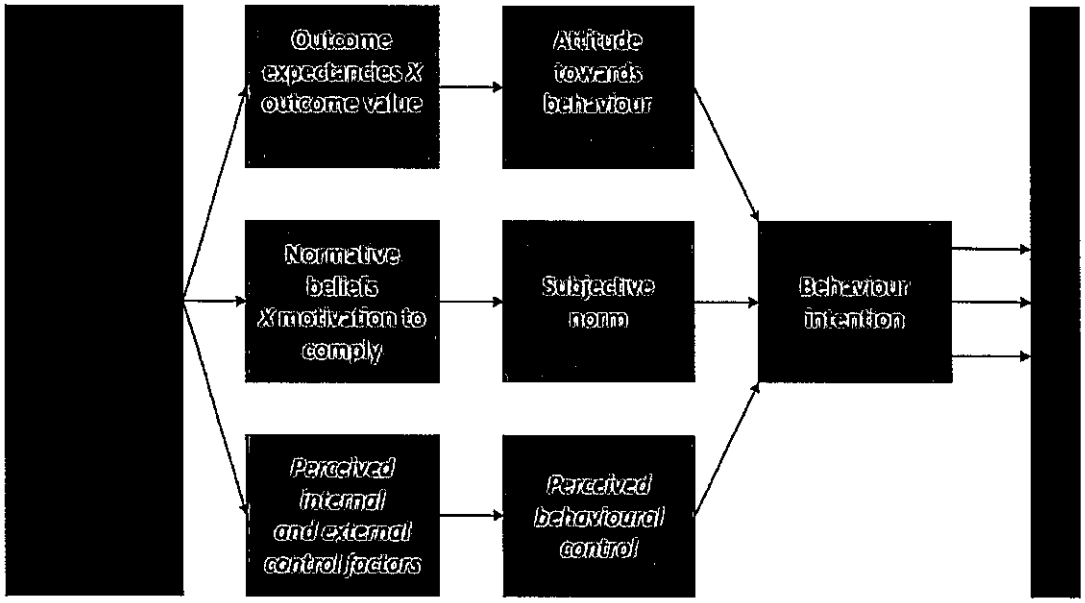
The Theory of Planned Behaviour

The Theory of Planned Behaviour (Ajzen 1985; Ajzen 1991) is an extension to the earlier Theory of Reasoned Action (Ajzen & Fishbein, 1970; Fishbein 1967), which explored the relationship between attitudes and behaviour and proposes a cognitive mechanism by which beliefs about preventative behaviour are translated into action via intention. The TPB further recognises the importance of self-efficacy beliefs (Bandura 1977) by introducing the concept of perceived behavioural control (PBC) i.e. the extent to which a person believes they have control over their own behaviour, even when facing barriers (Ajzen 1991, Schwarzer & Fuchs 1996) (Figure 1.6). This incorporates the possibility that behaviours are not

completely under a person's volitional control and will depend on perception of internal and external resources.

The Theory of Planned Behaviour suggests an individual's intention to adhere with medication increases if the perceived consequences of not doing so are high (attitudes towards behaviour and outcome expectancies are positive), they have strong positive beliefs about what others expect (perceived social norms); and they perceive a high level of personal control / self-efficacy with regards to adherence, even when facing barriers; this will depend on their perception of internal resources (e.g. knowledge) and external resources (e.g. social support).

Figure 1.6: Theory of Planned Behaviour



(Ajzan 1985; Aizen & Fishbein 1970, Fishbein 1967)

1.3.2 Proximal control beliefs

SCMs as described here have proved to be informative and useful predictors of health-related behaviour; however, certain personality traits are also considered influential, i.e. social-cognitions may vary according to the more distal and dispositional variables of locus of control (Rotter 1954) and generalised efficacy beliefs (Bandura 1986).

Locus of control (LOC) distinguishes between those who attribute responsibility for outcomes to themselves (internal LoC) or to external factors (external LoC). Specific to health, the Multidimensional Health Locus of Control (MLOC) scale (Wallston, Wallston, & DeVellis 1978) has also categorised control in terms of internal and external control beliefs – but with two aspects of external control beliefs: chance and powerful others (Levenson 1973). Thus an individual perceives that health is under their control, the control of health professionals, or fate.

Self-efficacy, defined as a belief in one's capability to 'organize and execute the sources of action required to manage prospective situations' (Bandura 1986). Given the potential for self-efficacy to be changed following feedback from past successes or failures, there is increasing interest in this factor with regards to adherence behaviour. This concept is closely related in that the degree of control one perceives one has over, for example, adherence, depends on the belief about competency in being able to perform the adherence behaviour. Self-efficacy beliefs are derived from an assessment of the outcome of one's actions/behaviour and from the behaviour and feedback of others (Bandura 1997). In application to adherence this could be considered assessment of the therapeutic outcome (or side-effects) of taking medicines; and, associated feedback from clinicians, relatives, or even intervention programmes e.g. MEMs feedback. By definition, self-efficacy beliefs may be considered more important the more difficult the behaviour – in the case of adherence, this may be a more complex regimen or complicated illness, as self-efficacy is associated with perseverance (Schwarzer & Fuchs, 1996).

Bandura (1992, 1997) argues that perceived self-efficacy influences motivation and behavioural control. Patients who believe they have the capabilities to adhere, are more likely to formulate an intention to adhere (initiate treatment), set themselves adherence goals, exert greater effort to execute a prescribed regimen, and persist with treatment; they would regard episodes of sub-optimal adherence as experience.

Self-efficacy beliefs have been shown to increase the prediction of SCMs such as the TPB (Schwarzer & Fuchs, 1996). The value of the concept of self-efficacy to SCMs is apparent in

the modified versions of the HBM (Rosenstock et al., 1988) and by the addition of PBC to the TRA to formulate the TPB (Ajzen & Madden, 1986).

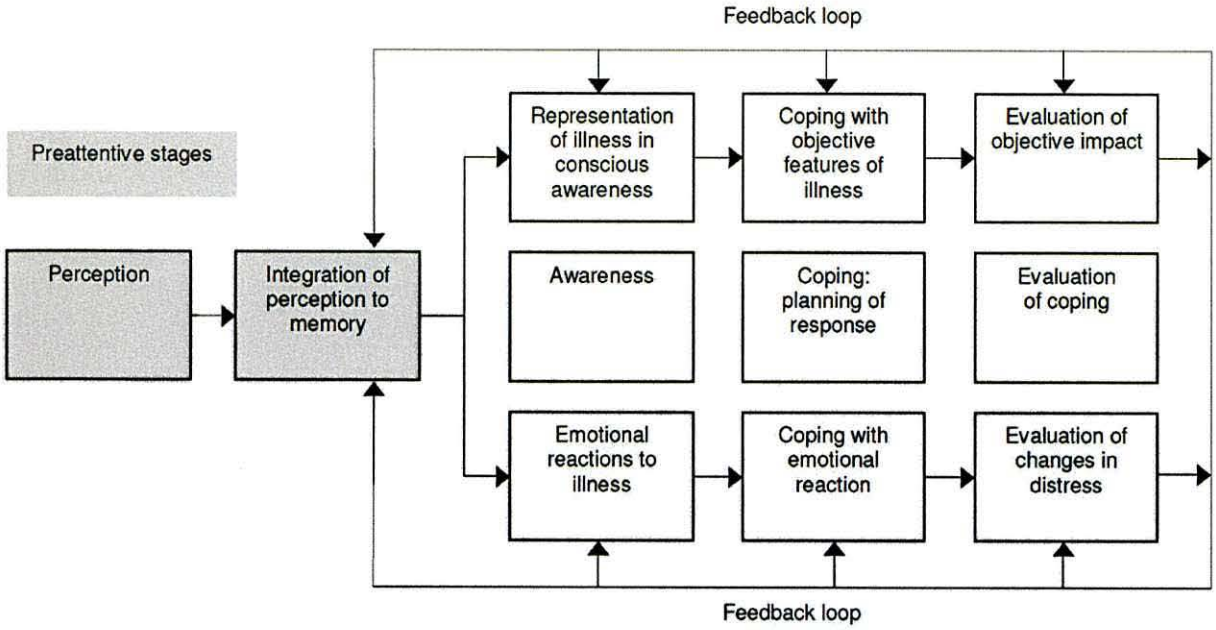
1.3.3 Self-regulation theory

A more dynamic link between cognitions, motivation and behaviour can be explored using self-regulation theory (Leventhal et al., 1992), which describes a 'common-sense model' of illness whereby a person's beliefs about their condition influences how they cope with both the objective and subjective aspects of the illness and any associated treatments.

Self-regulatory Model

Self-regulation theory describes the individual as an active problem solver, behaving in a manner to achieve their chosen goals and, when faced with the challenge of illness, they 'self-regulate' their thoughts, emotions and actions in order to try to return to 'normality'. Applied to medication adherence, the self-regulatory model would describe the cognitive and behavioural process by which individuals monitor and adjust their medication taking as the perceived solution to the problem of illness and its consequences (Abraham et al., 1999) (Figure 1.7). The problem solving response is based on: cognitive representations of the health threat (see illness representations below), developing and implementing an action plan (or coping procedure), and appraisal of that action plan, followed by re-adjustment if necessary to achieve the desired outcome. It is clear that this approach is potentially more dynamic than those previously discussed. The three stages described are processed in parallel at a cognitive and an emotional level.

Figure 1.7: Self-regulation theory (adapted from Leventhal, Nerenz, & Steele, 1984)



(Munro et al., 2007 p.1783)

Illness representations / Common sense model of illness

Illness representations or beliefs, together with treatment beliefs (later added by Horne & Weinman, 1999), shape coping responses e.g. adherence to medications. Beliefs about a particular illness and state of ill health are thought to form around five domains: Identity: signs and symptoms; Timeline: ideas about the time-frame of a condition (acute, chronic, cyclical); Cause: perception of cause (internal, external, stable, unstable etc.); Consequences: expected outcomes (physical, psychological and social); and, Control / cure: beliefs about potential cure and (internal/external) control. The specific content of each component is influenced by past experience, context, and opinions of significant others.

Self-regulations models are similar to SCMs in so much as they concentrate on a real or perceived health-threat in their explanation of behaviour; in fact, Bandura (1997) talked of a sociocognitive theory of self-regulation. SRMs are however more dynamic in considering coping appraisal and the consequence of feedback effects on cognition, emotion and behaviour and thus the explanation of behaviour is no longer thought of as a single decision at one fixed point in time.

1.4 Behavioural economics

There is emerging evidence of the role of behavioural economic theories in explaining patient adherence to prescribed medicines (Elliott et al., 2008). The most prevalent application of economic theory to medication adherence is that of consumer demand theory, which supports the negative impact of the costs of medicines on adherence (Goldman et al., 2007; Luiza et al., 2015). To date, however, there has been a lack of empirical evidence on the application of other behavioural economic frameworks, such as intertemporal choice and utility theory, to explain adherence to medications.

It is widely recognised in health economics that the demand for healthcare is a derived demand for health, and that the demand for health is, in part, a derived demand to enable individuals to do other things, such as participate in the labour market (McGuire et al., 1988). The study of health-related behaviour therefore involves a fundamental awareness of the features of the demand for health.

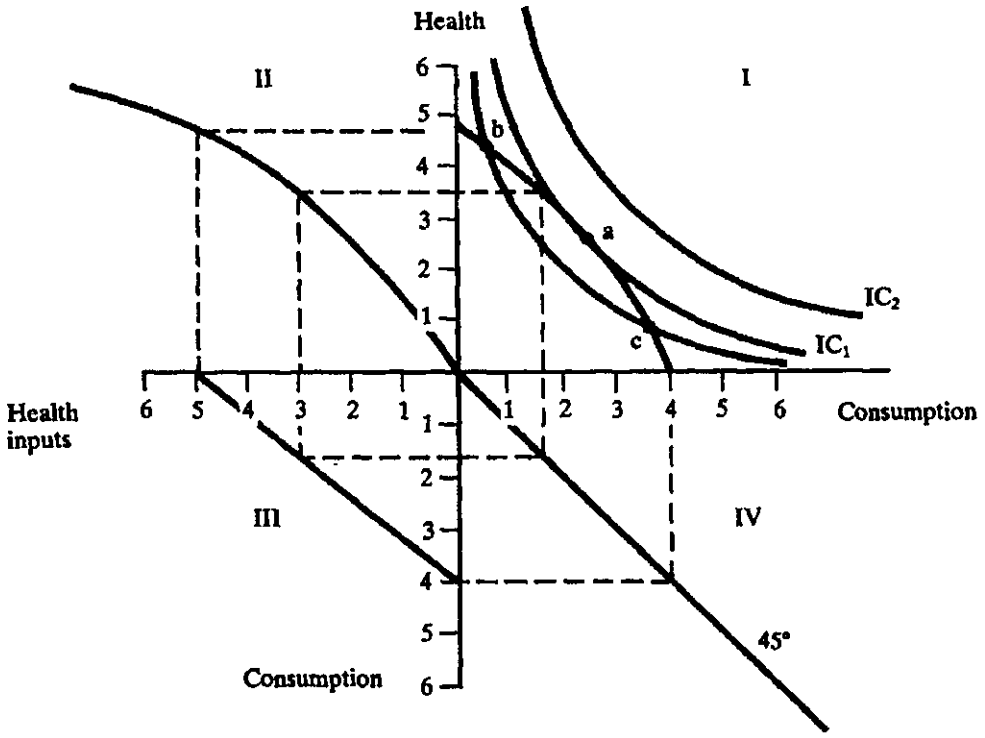
1.4.1 The Grossman Model

From an economic perspective, adherence to medications involves a trade-off between current costs and future benefits. The acceptance of the current cost (e.g., time to take medicine, experience of adverse events) for a future benefit (e.g., improvement in health) constitutes an investment. Traditional demand theory assumes that all goods and services purchased in the market enter the consumer's utility function. Becker (1964) however states that a household is both a consumer and a producer, contrary to the standard theory of considering individuals as consumers only. The notion that individuals invest in themselves is widely accepted in economics (Rosen 1999).

Grossman (1972) applied this theory specifically to health. Grossman (1972) argued that the analysis of the demand for health care must be undertaken after an initial analysis of the demand for the fundamental commodity health. Consumers are thought to demand health for two reasons; as a consumption good and as an investment good (Grossman 1972). As a consumption good, health enters the consumer utility function directly. As an investment good, health determines the amount of time available for work and leisure.

The Grossman model adapts household production theory to the analysis of the demand for health. The fundamental assumption of this theory is that an increase in a person's stock of knowledge or human capital will raise their productivity in both the market and nonmarket sectors of the economy. In order to realise potential gains from productivity individuals have an incentive to invest in education and training. They also incur the cost, however, of direct outlays on market goods and the opportunity cost of the time withdrawn from competing uses (Grossman 1972). Wagstaff (1986) suggested that an individual's utility maximising behaviour can be analysed with regards to a four-quadrant diagram (Figure 1.8).

Figure 1.8: Grossman Model: The household production of health (Wagstaff, 1986)



(McGuire, Henderson & Mooney, 1988 p.132)

First, consider Quadrant III, this is the budget constraint on utility maximising behaviour. Based on the assumptions of neoclassical economics, this assumes both health inputs (such as medical care) and other consumption incur costs and therefore the individual must allocate income between these activities. The budget constraint shows the maximum possible combinations of consumption on medical care and other goods, assuming the

individual has perfect knowledge of the costs of both medical care and other goods. Quadrant II contains the health production function; this illustrates the level of health that can be produced for each level of health input. The slope of this line represents the law of diminishing returns, which indicates the point at which the added health benefit is less than the amount invested.

Using the production function in Quadrant II and the budget constraint in Quadrant III, the combination of consumption and health input activity an individual chooses can be determined in Quadrant I, via the 45° line for Quadrant IV (simply used to map from one quadrant to another). Finally, the curves IC_1 and IC_2 represent the individual's indifference map (curves representing combinations of consumer preferences for consumption and health that generate equal utility). Finally, the concave curve in Quadrant I depicts the consumption possibility frontier. Point 'a' represents equilibrium, where the indifference curve IC_1 meets the consumption possibility frontier.

The four-quadrant illustration of the Grossman Model illustrates how individuals choose a combination of health (medical care) and other goods to maximise their utility and that the demand for health is a derived demand from that choice. In the context of medication adherence the a decision to invest in health is captured by initiation, implementation and persistence, but this may be at the expense of consumption of other goods; the health outcome will therefore depend on the combination of investment in medication adherence and other goods that yields the most utility (satisfaction) for the individual.

There are several caveats on the use of the Grossman Model on an individual level. The specification assumes that individuals have perfect information about their health, the rate of depreciation of their health, and the effect of other consumption on their health. Given the nature of the commodity health, this assumption is fundamentally flawed. Furthermore, the model fails to account for uncertainty; one particular area in which this is of interest is with respect to timing of adverse health events. Both the paucity of information on future health and the uncertainty of future health events have significant consequences for production and investment in the healthcare market (Morris et al., 2007).

If individuals differ in their willingness, or ability to undertake investments, we anticipate differences in health related behaviour. Fuchs (1967) postulated that the greatest potential for improving health was to be found in what people do and do not do for themselves. As such, theories that may explain decision making with regard to investment in health (e.g., intertemporal choice) are of interest.

1.4.2 Theory of intertemporal choice

Intertemporal choice describes the relative value of behaviour at an earlier date compared with its valuation at a later date (Maital & Maital, 1978). Intertemporal choice is central to almost every consequential decision. For example, the decision to exercise now, requires a trade-off between current costs of time, expenditure, and exhaustion; but with a future reward of weight loss and improved health. The study of what influences this trade-off represents a central theme in both psychology and economics (Loewenstein et al., 2003).

The central premise to time preference, is that people would prefer benefits sooner rather than later, whereas they would prefer to delay costs. For an individual to accept delayed benefit, they require a reward. The point of indifference between the earlier and later value of the behaviour represents the time preference rate.

1.4.3 The Discounted Utility Model

Economists have tested the validity and implications of the discounted utility model, which assumes people have a time preference rate that is used to discount the value of delayed events (Samuelson 1937). The utility function involving intertemporal choices is specified as:

$$U_{(c1,\,c2)} = u_{(c1)} + u_{(c2)} / (1 + \rho)$$

Where: $U_{(c1,\,c2)}$ = Utility of 'bundle' of consumption in time 1 and time 2

$u_{(c1)}$ = Utility of consumption in time 1

$u_{(c2)}$ = Utility of consumption in time 2

ρ = time preference rate

The model states the utility of the consumption bundle is given by the utility from consuming the amount in time 1, plus the utility gained from consuming the amount in time 2, divided by (1 + ρ). Hence, ρ discounts the utility gained from consumption in period 2. The present value of future consumption can therefore calculated using this weight.

In practical terms, discounting involves attaching declining weights to outcomes the further they occur in time:-

Discounting weight = $(1+ \rho)^{-t}$

Where: ρ = time preference rate

t = year in which the event occurs

The Discounted Utility Model calculates a constant time preference rate. Economists have also considered that people trade at different rates according to lengths of delay (being more impatient with trade-offs involving earlier reward than those involving a later); and on this premise they have explored the use of hyperbolic discounting (discussed by Frederick et al., 2002, van der Pol & Cairns, 2002).

In an emerging area of the relationship between intertemporal choice, health behaviour and health status, Fuchs (1982) conducted the first empirical investigation. Given the axioms of time preference, we expect people with high time preference rates (who prefer immediate consumption) to place a low value on future benefits, and therefore be less reluctant to engage in positive health-related behaviour (Fuchs 1982). When considering adherence to chronic medications, where the health benefit may not be immediate, but where patients may incur immediate costs of prescription payment, or adverse event, we anticipate an inverse relationship. As time preference decreases, adherence is likely to increase i.e. people who value the future are likely to take their medications as an investment for future health; whereas those who place a higher value on today are likely to risk the consequences of nonadherence. There is evidence of association between adherence to medications and low time preference in asthma (Brandt & Dickinson, 2013), and hypertension (Axon et al., 2009; Chapman et al., 2001). There is also empirical evidence for the association between time preference rates and socioeconomic and clinical factors (Axon et al., 2009) and, an

emerging literature on the influence of peoples beliefs on time preference (O'Donoghue & Robin, 2003; Liberman & Trope, 2003; Prelec & Bodner, 2003). Although this literature is not directly related to adherence to medications, it is of interest when considering the consolidation of behavioural models to explain multifaceted behaviour, such as adherence.

In recent years, the study of intertemporal choice has become an interdisciplinary project. This thesis adopts the economic perspective of intertemporal choice in application of the discounted utility model to explaining adherence to medications. The theory is modelled in terms of risk of negative health outcome and considered alongside health psychology theories, in anticipation that inferences may be drawn.

1.4.4 The Neoclassical School of Economics

Economists are essentially concerned with the allocation of scarce resources, which involves the production and consumption of goods and services (Sloman et al., 2013). Classical economics (18th and 19th century) focused on the theories of value and distribution, in which the value of a good or service depends on the cost of production (Smith 1776). In the late 19th century, however, economists began to consider the "perceived value" of a good or service, where value depends on the 'usefulness' of a good or service, referred to as its 'utility', and thus the Neoclassical School of Economics was founded. Neoclassical economics relates this concept of value to individual behaviour, based on three fundamental assumptions (Jevons 1937; Menger 1981; Walras 2013):

- Individuals have rational preferences that can be identified and valued
- Individuals maximise utility
- People act independently and with full information

1.4.5 Lancaster's Economic Theory of Value

The key feature of Lancaster's Economic Theory of Value is that utility is derived from underlying attributes as opposed to the actual commodity per se; and that individuals' preferences are revealed through the choices (described in terms of this bundle of attributes) (Lancaster 1966). We model these preferences using a random utility maximisation framework.

Random utility maximisation framework

It is assumed that the total value a consumer attaches to a good or service is described by the sum of the individual attributes. Application of the random utility maximisation framework allows researchers to assess the significance, direction, and relative importance of individual characteristics that comprise preferences (Ryan et al., 2008). The discrete choice analysis, within this framework, requires three extensions to classic consumer theory:

- Changes in attributes can cause a discrete change from one good to another, in order to maximise utility
- The choice of good is between a finite set of mutually exclusive alternatives
- Individual choice behaviour is intrinsically probabilistic

The basic utility function is presented as:-

$U = \beta 0 + \beta 1 + \beta 2 + \beta 3 + \beta 4 + \varepsilon$

U = utility derived by individual

$\beta 0$ = constant term

βi = estimated coefficient for each attribute (variable)

ε = error term

The probability that a sampled individual will choose an alternative (described by attributes) equals the probability that the difference between the random utility of any other alternative and the chosen alternative, is less than the difference between the systematic utility levels for all alternatives in the choice set (McFadden 1974).

Lamiraud & Geoffard (2007) were the first to apply this notion to persistence with medications. They postulated that if patients' utility (satisfaction) is maximised through taking their medications, their likelihood of persisting increases; but conversely if patients maximise their utility by not taking their medications, they will discontinue treatment persistence. In this regard, persistence is therefore considered an outcome of a decision

patients consciously make about whether the continued taking of their medication will increase their utility (according to a bundle of attributes and a choice to persist or discontinue). This is the most relevant application of the random utility framework to the understanding of adherence to medications. Further examples include influences of medication attributes on the utility to adhere to medication for type 2 diabetes (Hauber et al., 2009), and bipolar disorders (Johnson et al., 2007).

1.5 Theory to practice: Adherence enhancing interventions

Evidence from published reviews suggest that most effective solutions to nonadherence are complex interventions, based on multiple factors, targeting multiple aspects of care (e.g. patient, care giver, healthcare system), and repeated over an extended period of time (Sabaté 2003; Nieuwlaat et al., 2014; Conn et al., 2009; Zullig et al., 2013; Kripalani et al., 2007; Viswanathan et al., 2012, Al-aqeel & Al-sabhan, 2011). A Cochrane review (Nieuwlaat et al., 2014) of adherence enhancing interventions reported that 11 out of 17 studies with the lowest risk of bias, involved complex interventions with multiple components. The interventions were mainly cognitive / educational and aimed at overcoming barriers to adherence by means of tailored ongoing support from health professionals or family and/or peers. In keeping with previous versions of this review, only a small proportion of studies reported improvements in both adherence and health outcome; and even the most effective interventions did not lead to large improvements.

Stavri and Michie (2012) recently highlighted the importance of the application of theory-driven, evidence-based models in the development of effective interventions. They advocate the development of a hierarchical classification system of behaviour change techniques, which can be used to inform and evaluate interventions. More recently, they published a taxonomic method for reporting and describing behaviour change interventions (Michie et al., 2015). Interventions linked to components of evidence-based theories have the potential to be more successful than interventions based on observed associations with unknown mechanism for behaviour change (Michie et al., 2013). Such evidence based theories, not only provide a foundation for the assessment of potential associations (e.g. nonadherence and low self-efficacy), but offer explanations of how to modify behaviour (i.e. improve self-

efficacy through counselling to increase confidence and knowledge, with the aim of improving adherence).

Furthering our understanding of adherence to medications may help guide the development of interventions to improve adherence because they emphasise the considerations that patients themselves take into account as they decide whether to adhere to long-term treatment. Consolidation of behavioural economic models may provide a theoretical basis for the development and assessment of effective adherence-enhancing interventions.

1.6 Thesis aims

This aim of this thesis is to explore the application of health psychology and behavioural economic theories for predicting adherence to medications in adult patients, to determine the most useful theoretical foundations to inform the development of adherence enhancing interventions. Seven research questions are addressed in the following Chapters:-

Chapter 2:

Research question 1: *What do theoretical models of behaviour contribute to our understanding of adherence to medications? What empirical evidence exists and what is the quality of this evidence?*

Methods: Systematic literature review of 20 years of empirical research on health psychology theories predicting adherence to medications.

Unique contribution: In contrast to previous studies, this review has a broad scope by considering multiple theoretical frameworks. The review looked at all stages of the adherence process e.g. initiation, implementation and persistence, but did not combine any adherence behaviours that were not related to medication. The review was conducted to a high standard of methodological rigour – and makes a clear acknowledgement that meta-analysis was inappropriate whilst providing a narrative synthesis of the highest quality

evidence. This study makes an important contribution to the variable selection described in Chapter 3.

Chapter 3:

Research question 2: *What is the association between self-reported nonadherence to hypertensive medication and country, demographic, clinical and psychosocial factors?*

Methods: Primary data collection and analysis using a multilevel multivariate analysis to ascertain the determinants of adherence to anti-hypertensive medications in a multinational sample.

Unique contribution: This is the first study to test the combined contribution of a wide range of demographic, clinical, psychosocial and economic factors, simultaneously, across several countries to determine what predicts adherence to medication. This was a large study involving 2630 patients from 11 countries.

Chapter 4:

Research question 3: *Which attributes of medications do patients consider important in their decision to persist? How are trade-offs between medications affected by psychosocial and sociocognitive factors? How can empirical evidence on stated preferences be linked to actual clinical event data?*

Methods: Primary data collection using stated preference discrete choice methods to determine what predicts persistence with medication in a multinational sample of adults with hypertension; including a case study of 5-aminosalicylic acid for ulcerative colitis to illustrate an application of the findings.

Unique contribution: This is the first multinational assessment of influences on patients' decision to persist with medications, in terms of the utility they derive from medication characteristics and the influence of psychosocial characteristics associated with medication

preferences. This increases the possibilities for interventions which could be person or medicine based. This was a large study involving 2630 patients from 11 countries.

Chapter 5:

Research question 4: *What is the association between self-reported nonadherence to hypertensive medication and time preference for health benefits? What is the association between time preference rates and country, demographic, clinical and psychosocial factors?*

Methods: Primary data collection and analysis, using t-tests of adherence and time preference, and multilevel multivariate analysis to determine what predicts time preference, in a multinational sample of adults with hypertension.

Unique contribution: This is the first study to compare discount rates for adherence to medications across several countries and to explore the contribution that a wide range of demographic, clinical and psychosocial factors make to variance in discount rates across and within countries. This is one of very few studies to look at time preference for adherence to medication and the only study to use a large multinational sample: 2630 patients from 11 countries.

Chapter 6:

Research question 5: *How do people with epilepsy trade harms and benefits of antiepileptic medications? Does this vary by patient group? How do patient preferences for antiepileptic medications compare with recommendations based on clinical efficacy?*

Methods: Primary data collection using stated preference discrete choice methods to determine preferences for antiepileptic medication by people with epilepsy in the UK; and how this influences the utility and probability of drugs assessed in the SANAD trial.

Unique contribution: This is the first study to combine data on stated preferences for antiepileptic medications with clinical trial data to determine the utility and probability of uptake of drugs assessed in a recent clinical trial. This study is an advancement on the techniques described in Chapter 4.

Chapter 7:

Research question 6: *Are the time preference rates derived from hypothetical scenarios influenced by familiarity with the condition used?*

Methods: Primary data collection and analysis to estimate time preference rates for people with epilepsy. Secondary data analysis, using propensity scoring to match data from two independent samples, to test if differences in mean implied can be explored by familiarity of condition on the elicitation of time preference rates; and, using logistic regression to determine what predicts time preference rates.

Unique contribution: This is one of very few studies to explore the influence of familiarity with condition on time preference rates derived using survey based hypothetical scenarios.

Chapter 8:

Research question 7: *How can the behavioural theories be consolidated to provide a theoretical basis for the development and assessment of adherence enhancing interventions?*

Methods: Illustrated synthesis of the findings of the thesis classified according to frameworks, subordinate models, and individual components identified and tested.

Unique contribution: This the first study to our knowledge to test a range of theories across disciplines on a multinational sample, and consolidate and classify the findings. Concurrent assessment of influences on patients' decisions to persist with a medication in terms of the utility they derive from medication characteristics, and theory driven psychosocial characteristics associated with medication preferences, increases the possibilities for interventions which could be both medicine and person-based.

Chapter 2

Systematic Review of health psychology models of adherence

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2.1 Abstract

Objectives: This review sought to identify the empirical evidence for the application of models from sociocognitive theory, self-regulation theory, and social support theory at predicting patient adherence to medications.

Methods: A systematic review of the published literature (1990–2010) using MEDLINE, EMBASE, Cochrane Library, CINAHL, and PsychINFO identified studies examining the application of health psychology theory to adherence to medication in adult patients. Two independent reviewers extracted data on medication, indication, study population, adherence measure, theory, model, survey instruments, and results. Heterogeneity in theoretical model specification and empirical investigation precluded a meta-analysis of data.

Results: Of 1756 unique records, 67 articles were included (sociocognitive = 35, self-regulation = 21, social support = 11). Adherence was most commonly measured by self-report (50 of 67). Synthesis of studies highlighted the significance ($P \leq 0.05$) of self-efficacy (17 of 19), perceived barriers (11 of 17), perceived susceptibility (3 of 6), necessity beliefs (8 of 9), and medication concerns (7 of 8).

Conclusions: The results of this review provide a foundation for the development of theory-led adherence- enhancing interventions that could promote sustainable behaviour change in clinical practice.

2.2 Introduction

Adherence to medications can be defined as the process by which patients take their medication as prescribed, described by three quantifiable phases: initiation, implementation, and discontinuation (Vrijens et al., 2012). Suboptimal adherence to appropriately prescribed medicines is recognised as one of the major factors contributing to therapeutic nonresponse (Osterberg & Blaschke, 2005). It is highly prevalent across a broad range of conditions and presents a significant challenge to the safe, effective, and cost-effective use of medicines. It is estimated that between a third and a half of all medicines prescribed for long- term conditions are not taken as recommended (Osterberg & Blaschke, 2005). Even within the context of a clinical trial, 50% of the patients discontinue within the first year (Vrijens et al., 2008). In a study of adults diagnosed with diabetes, hypertension, or dyslipidemia in the United States, the total direct national cost of nonadherence was estimated to be $105.8 billion ($453 per adult) (Nasseh et al., 2012). It is argued that improving adherence to existing medication may generate more health benefits than any other improvement in medical treatment, yet research into the causes of suboptimal adherence has been of variable quality, often contradictory, and generally inconclusive (Sabate, 2003).

A Cochrane review (Haynes et al., 2012) identified that simple interventions, such as written information, improved adherence to short-term medications but only more complex interventions, such as education with follow-up, improved adherence to long-term treatments. The review found that even the most effective interventions did not lead to large improvements in adherence and health outcome. This is likely to reflect the multiplicity of factors determining adherence and the lack of attention to existing theories that may explain adherence behaviour. This is also an area of considerable heterogeneity with respect to patient characteristics, treatments, and illnesses, as well as adherence measurements and outcome variables.

The biomedical literature is abundant with studies in which patient and disease characteristics are examined as predictors of suboptimal adherence. It is argued that such research is based on a flawed conceptual model, in which variable selection is often based on availability rather than theoretical foundations (Steiner, 2010). Stavri and Michie (2012) recently highlighted the importance of the application of theory-driven, evidence-based models in the development of effective interventions. They advocate the development of a

hierarchical classification system of behaviour change techniques, derived from psychological theory that can be used to inform and evaluate interventions. Interventions linked to evidence-based theories have the potential to be more successful than interventions based on observed associations with unknown mechanism for behaviour change. This does not, however, exclude interventions based on other factors, including actual social context or support, regimen complexity, and cost of medication, which also have a significant impact on adherence to medication but are beyond the scope of this review.

There are several health psychology theories that have been used to predict adherence to medications (Munro, 2007). The most common applications are of social cognitive theory (Bandura, 1977; Bandura, 1986; Bandura, 1997), within which the health belief model (Rosenstock, 1974; Becker, 1974), the theory of reasoned action (Fishbein, 1967), and the theory of planned behaviour (Ajzen, 1991) are most prevalent. The self-regulatory model (Leventhal et al., 1992) and the transactional model of stress and coping (Folkman, 1984) have also been used but to a lesser extent. Variables most often explicitly assessed within these theoretical models are considered proximal (close) to adherence behaviour (Webb et al., 2010); however, it has also been recognized that adherence behaviour varies according to more distal variables, such as personality traits (including, e.g., conscientiousness, extraversion, and neuroticism), and more generic beliefs, such as multidimensional health locus of control (Wallston et al., 1978) and generalised efficacy beliefs (Bandura, 1986), which more likely operate "indirectly" on outcomes. To date, there has been little consistency in the type of control associated with adherence to medications (Bruhn, 1983; Wilson, 1995).

Consolidation of existing behavioural models may provide a theoretical basis for the development and assessment of adherence-enhancing interventions. Previous reviews of predictors of a range of health-related behaviours have found that a limited amount of variance in adult behaviour was explained by the health belief model (10%), the theory of planned behaviour (30%), and self- efficacy (4%–26%) (Armitage & Connor, 2001; Harrison et al., 1992; Keller et al., 1999). It should be noted, however, that these reviews relate to pooled estimates of various health-related behaviours within which predictors of adherence are likely to vary (DiMatteo, 2012). As such, these reviews have more limited generalisability to adherence to medications than those reported in a focused systematic review. There are clear benefits to theory-led findings informing the development of adherence-enhancing interventions, the full potential of which requires thorough and systematic selection of theory.

This article presents a systematic review of the application of behavioural models to the study and prediction of adherence to medications in adult patients. The review adds to the literature by providing a systematic and critical assessment of 20 years of empirical evidence on the determinants of adherence to medication in the context of three theoretical frameworks: the social cognitive theory, the self-regulation model, and the social support theory. The review findings will help to inform conceptual frameworks for behaviour change specific to adherence, which will further aid the development and implementation of theory-led adherence-enhancing interventions that seek to realize the full benefits of medicines.

2.3 Methods

A systematic review was conducted according to the methods of the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2008) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Liberati et al., 2009). Searches were conducted in MEDLINE via PubMed, EMBASE, the Cochrane Library, CINAHL, and PsychINFO from January 1990 to March 2010, using a range of search terms relating to adherence, medicines, theory, and health psychology, which were then combined using the Boolean "AND" operator (Appendix 2.1). Additional studies were also identified by experts convened at Ascertaining Barriers to Compliance Project Team internal meetings and by visually scanning reference lists of eligible studies.

2.3.1 Study Selection

Studies were included if they were published in peer-reviewed journals, contained empirical data on adherence to prescribed medicines in adult patients, investigated psychosocial determinants of adherence, and reported specific reference to an established theoretical framework. Studies were excluded if they concerned vaccines or involved participants who were dependent on others for the administration of medicine (e.g., children, inpatients, adults in care homes, or incarcerated). Studies involving complementary medicines (e.g., herbal remedies and homeopathy) were also excluded on account of these being available largely without prescription.

Eligibility assessment and data extraction were performed independently, unblinded, and in duplicate by two reviewers (E.A.F.H. [the candidate] and M.K./J.P./S.P.). Disagreements in assessment outcomes were resolved by a third opinion (V.L.M.). Data were extracted using predefined data fields on study characteristics, participant characteristics, adherence measure, application of health psychology (including theory, model, and instruments used to measure independent variables), and results of primary predictive model.

2.3.2 Risk of Bias

A scoring system was introduced to rank studies according to their quality (Table 2.1). This weighted three elements of each study: adherence measure, study design, and sample size. The method of adherence measure was weighted most because the extent to which variability may be explained by behavioural models of adherence depends on the accuracy, precision, and reliability of the methods used to detect it. Study design was weighted second, with longitudinal studies considered superior to cross-sectional analysis given that adherence varies over time.

Table 2.1 Quality assessment scoring system

Score	Adherence measure	Study design	Sample size
100	Directly observed therapy or electronic compilation of drug dosing histories	Randomised control trial or prospective cohort	≥1,000,000
75	Medication measurement: therapeutic drug monitoring or counts of returned tablets	Panel data	10,000 to 99,999
50	Prescription records	Retrospective cohort	1,000 to 9,999
25	Self-reported patient questionnaires and diaries	Cross-sectional	100 to 999
0	Assessment of patients' clinical responses and/or physiological marker or effect	Case report	≤99

Note. Quality Score = (Adherence measure score / 2) + (Study design score / 3) + (Sample size score / 6). Interpretation: 100 = highest quality, 0 = lowest quality.

Sample size was given the least weighting. The resulting overall quality score captured selection, performance, and detection bias. Attrition and reporting bias were assessed on an individual basis by inspecting the results of studies with multiple outcome measures and incomplete outcome data. All the studies included in the review were assigned a weighted score.

2.3.3 Evidence Synthesis

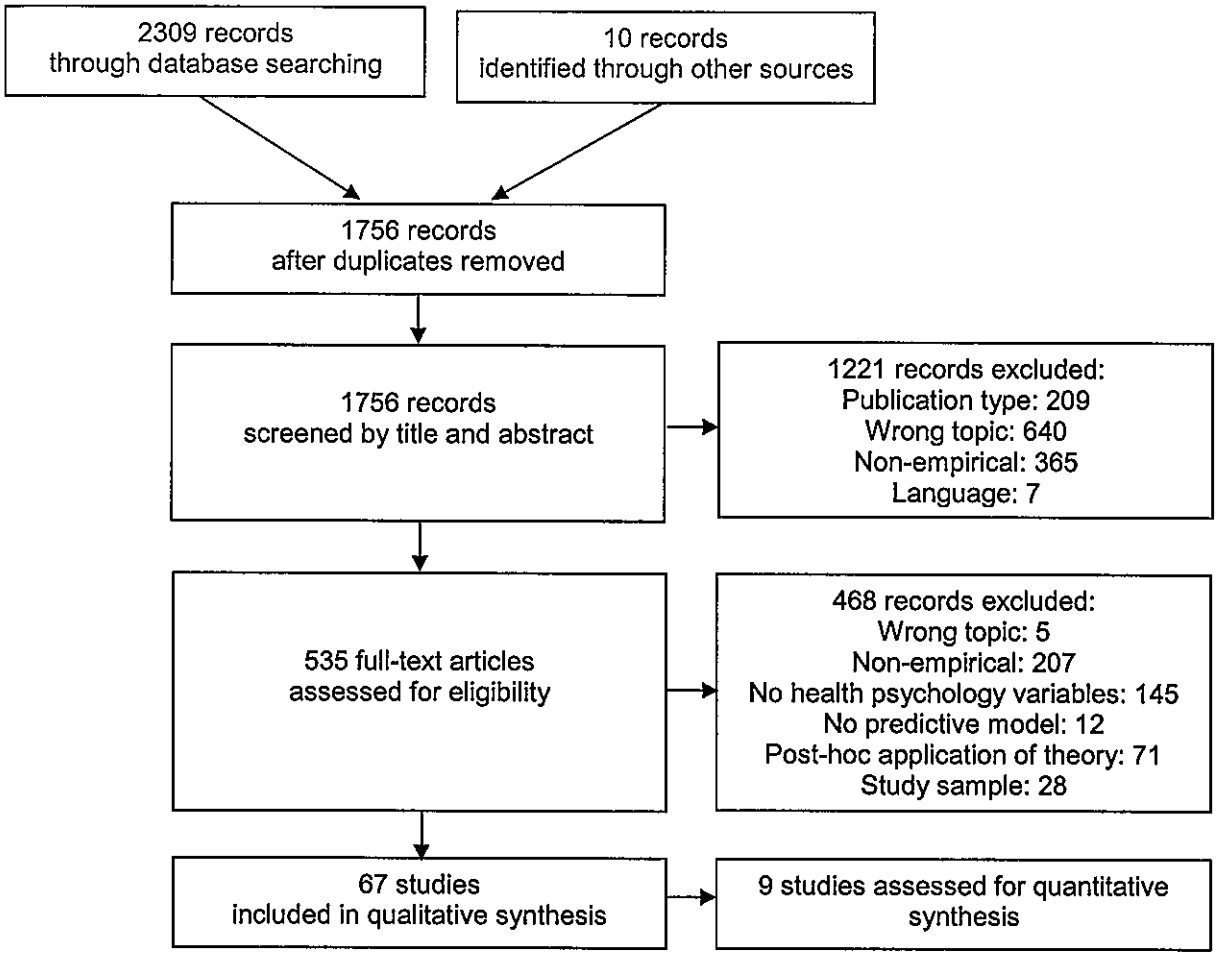
The plan for evidence synthesis was specified a priori and included an initial descriptive summary of all studies followed by a meta-analysis of three or more studies that were sufficiently homogeneous (contextually, methodologically, and statistically). In the event that a meta-analysis was not possible, we planned a narrative synthesis, using the general framework suggested by the Centre for Reviews and Dissemination (2008). This involved a primary synthesis to categorize the studies according to theoretical framework, model, and model components (factors), including a count of the number of studies that tested the relevant components and the ratio of how many times it research statistical significance ($P \leq 0.05$). All results were reviewed, including those that did not reach statistical significance in order to minimize the risk of selection bias. We then explored the relationships within and between studies by comparison of their application and the empirical performance of the postulated theory. This part of the review was to be restricted to studies of highest quality to ensure a more robust comparison (quality score ≥ 50).

2.4 Results

2.4.1 Study Selection

The search of electronic databases identified 2309 records; a further 10 were identified by experts and bibliographies. Following the removal of duplicates, resulting in 1756 records, 1221 were excluded on the basis of information provided in the titles and abstracts. Five hundred thirty-five full-text articles were assessed for eligibility, and 468 were excluded according to predefined exclusion criteria (Figure 2.1). Sixty-seven studies were included in the review (Appendix 2.2) and categorized into three frameworks: sociocognitive theory (n = 35), self-regulation theory (n = 21), and social support theory (n = 11).

Figure 2.1 Flow diagram of study selection



2.4.2 Study Characteristics

The characteristics of individual studies are summarised in Table 2.2.

2.4.3 Study design and participants

Studies were mainly cross-sectional (n = 49). Most of the studies reported participants on long-term treatment for chronic diseases with a mean age range of 34.1 to 80.5 years. The most common therapeutic indications were human immunodeficiency virus (HIV) (n = 22), hypertension (n = 8), and mental health disorders (n = 6).

Table 2.2 Selected characteristics of studies presented in order of study design then bias assessment score (longitudinal to cross-sectional; least to most prone to bias)

First author *N [model n]*	Therapeutic indication / Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality score[d]
Longitudinal studies						
Gonzalez [1] *N = 325 [325]*	HIV Antiretroviral	41 (8.5) 60	E: MEMS (>90%, 15-mths) S: ACTG	SRT: SRM *BMQ customised*	Structural Equation Model: Education* Pill burden* Symptoms* Necessity (specific)* Concerns (specific)* Distrust (general)*. Mediators: Distrust by concerns* Benefits by concerns* Benefits by necessity*.	87
Weaver [2] *N = 322 [322]*	HIV Antiretroviral	41(8.5) 58	E: MEMS (>90%, 15-mths) S: ACTG	SS: TMSC *COPE, SPS, ISEL*	Structural Equation Model: Age* Education, Income, Employment, Time since diagnosis* Regimen burden, Avoidant coping*. Mediators: Negative mood avoidant coping** SS by avoidant coping*.	87
Halkitis [3] *N = 300 [300]*	HIV Antiretroviral	42 (7.7) 100	E: MEMS (2-wks) S: Interview	SS: Coping/SE *Customised*	Structural Equation Model: Drug use* Socioeconomic status*. Mediators: Psychological state by drug use*.	87
Lynam [4] *N = 189 [189]*	HIV Antiretroviral	$ 73	E: MEMS (1-wk)	SRT: SDT *TSRQ, MHLC, SE-customised*	Structural Equation Model: MHLC Internal, MHLC: Chance, MHLC External** MHLC Powerful others, SE**. Mediators: Autonomous regulation by SE**.	87
Barclay [5] *N =185 [140]*	HIV Antiretroviral	44 (7.3) 78	E: MEMS (≥95%, 1-mth)	SCT: HBM ext. *ADQ, MHLC, SE-customised*	**Young** (n=140, age 41(5.0)) Drug abuse/dependence, Financial resource, Apathy/Indifference, MHLC Internal, MHLC Chance, SE* Perceived utility** Intention, Subjective norms, Support/Barriers. **Old** (n=45, age 56 (4.8)) Income, Sexual orientation, Global cognitive function* MHLC Internal, Subjective norms.	87
Stilley [6] *N = 158 [158]*	Cholesterol Lovastatin	46 (8.7) 54	E: MEMS (≥80%, 12-wks)	Distal: 5-FM *NEO PI-R*	Depression* Anxiety* Conscientiousness** IQ** Mental flexibility/Perceptual organisation.	87
Schmitz [7] *N = 97 [97]*	Smoking BupropionSR	49 (9.9) 0	E: MEMS (>50%, 7-wks)	SCT: HBM *HABQ*	Symptoms, Adherence feedback** Perceived barriers.	83
Apter [8] *N* = 88 [85]	Asthma Inhaled corticosteroids	47 (15) 28	E: MDILog (42-days)	SCT: HBM/TRA Customised	Race/Ethnicity* Symptoms, Treatment Knowledge, Inhaled adherence scale, Attitude**.	83
Cohen [9] *N = 65 [57]*	Depression Antidepressant	41(11.4) 42	E: MEMS (14-wks)	Distal: 5-FM *NEO PI-R*	NEO PI-R Activity** NEO PI-R Feeling, NEO PI-R Modesty**.	83
Brus [10] *N = 65 [55]*	Rheumatoid Arthritis Sulphasalazine	59 ($) 20	M: Pill count (≥80%, 3-mths)	SCT: SLT *Customised*	Age, Sex, Education, Health status, Symptoms, Disease severity, Patient education, SE** Barriers, Outcome expectation, Perceived social attitude, Perceived SS.	71
Abraham [11] *N = 176 [167]*	Malaria Mefloquine Chloroquine + Proguanil	$ 41 $ 34	S: Interview or questionnaire (at 6-7wks)	SCT: HBM/TPB *Customised*	**Mefloquine** (n=106) Adherence in malarious region, Perceived severity, Perceived susceptibility, Perceived side-effects* Perceived behavioural control(PBC), Intention** Attitude, Injunctive norm. **Chloroquine + Proguanil** (n=61) Adherence in malarious region** Perceived severity, Perceived susceptibility, Perceived side-effects, PBC, Intention, Attitude, Injunctive norm.	50
Simoni [12] *N = 136 [136]*	HIV Antiretroviral	43(8.9) 55	S: ACTG (at 3-mhs)	SS: *SSI, SBI*	Structural Equation Model: SE*. Mediators: Negative affect by SE** Spirituality by SE**.	50
Williams [13] *N = 186 [126]*	*Outpatients* *$ (≥ 1-mth)*	56 ($) 25	S: Pill count (at 14-days)	SRT: SDT *MHLC, TSRQ, HCCQ*	Structural Equation Model: Autonomous motivation*. Mediators: Autonomy support by autonomous motivation*.	50

First author *N [model n]*	Therapeutic indication / Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality score[d]
Lim **[14]** *N = 136 [126]*	Geriatric *poly-pharmacy*	81(8.1)/ 80 (7.7) 35	S: Interview (0 and 2-mths)	SCT: HBM *Customised*	Pharmacist intervention, Hospitalisation in last 6-mths, ADL, Responsibility for medicines taking, No. medication remembering methods, Barriers, Benefits, Severity*.	**50**
Farquharson **[15]** *N = 130 [94]*	Malaria Prophylaxis	37(13.1) 57	S: Interview (at 4.5-wks (4-7))	SCT: HBM/TPB *Customised*	**Full vs. Poor** (n=80) Benefits, Intentions, Length of stay, Info./questions, Adherence barriers discussion. **MLR: Full vs. Partial** (n=94) Benefits** Intentions, Length of stay** Info./questions* Adherence barriers discussion. **Partial vs. Poor** (n=40) Benefits, Intentions, Length of stay** Info./questions** Adherence barriers discussion.	**50**
Fraser **[16]** *N = 108 [104]*	Multiple sclerosis Glatiramer acetate	43 (8.8)/ 45 (9.5) 11	S: Interview or e-mail (dis/cont. at 6-mths)	SCT: Control Beliefs *MSSE, SES*	Individual hypotheses: SE total** SE control** SE function** Hope, Mobility** Spasticity** Fatigue-baseline*.	**50**
Turner **[17]** *N = 89 [85]*	Multiple sclerosis DMT	51(9.3) 80	S: Interview (per month for 6-mths)	SCT: HBM *ADQ, BACS*	**2-mth** (n=67) Age, Sex, Race, Yrs with MS, DMT type, Time on DMT, Cognitive status, Barriers, Benefits* Severity, Susceptibility. **4-mth** (n=80) Age* Sex, Race, Yrs with MS* DMT type, Time on DMT, Cognitive status, Barriers, Benefits* Severity* Susceptibility. **6-mth** (n=85) Age, Sex, Race, Yrs with MS, DMT type, Time on DMT, Cognitive status, Barriers, Benefits* Severity, Susceptibility.	**46**
Rudman **[18]** *N = 201 [190]*	Renal Immuno-suppressant	39($) 56	C: Laboratory report calls (over 12-mths)	SCT: PMT *Customised*	Structural Equation Model: Age at transplant* Side-effects complaints** MHLC External, SE** Threat appraisal* Protection motivation, Response costs, Response efficacy.	**21**
Cross-sectional studies						
George **[19]** *N = 819 [350]*	Heart failure *medication*	62 (12.6) 72	P: Refill data (≥90%, 14-mths)	SCT: HBM ext. *BMQ, MHLC and customised*	Born in North America, Smoker* Use of medications BD or less** Morisky score>0, Use of anti-depressants, Use of adherence aids, Self-reported adherence(%), Have you changed daily routine to accommodate your medication schedule** Perceived benefits .	**37**
Chisholm **[20]** *N = 158 [158]*	Renal Immuno-suppressant	51 (12.4) 60	P: Refill data (≥80%, 3-mths)	SCT: TPB *Customised*	Structural Equation Model Past behaviour ** Intention* Subjective norms, Perceived behavioural control, Attitude. Mediators: Attitudes by intentions, PBC by intentions.	**37**
Orensky **[21]** *N = 125 [75]*	Anti-coagulation Warfarin	60 ($) 49	P: Refill data (≥80%, 6-mths) S: Questionnaire	SCT: HBM *Customised*	Structural Equation Model: (i) Prescription refill = Divorced/never married** Perceived barriers**. (ii) Self-report = Living in a shelter* Living with a friend or relative* Perceived barriers**.	**37**
Johnson **[22]** *N = 2765 [2478]*	HIV Antiretroviral	41/42 69	S: Computerised interview (≥90%, 3-days)	SRT: SAT *SPS and customised*	Race/Ethnicity** Current crack cocaine use* Injection use** Homeless/shelter* In primary relationship** Doses/day** SE** Symptom bother** Treatment beliefs* Coping SE** Necessity beliefs** SE-beliefs**.	**29**
Horne **[23]** *N = [1871]*	IBD *maintenance therapies*	50 (16.0) 37	S: MARS *4-items*	SRT: SRM *BMQ, IPQ-R chronicity only*	Age** Sex, Outpatient visits** GP visits, Inpatient visits, Time since diagnosis** Diagnosis, Attitudinal groups compared to accepting: Ambivalent** Indifferent** Sceptical**.	**29**
Greenstein **[24]** *N=1402[1223]*	Renal Immuno-suppressant	47 (12.5) 49	S: Questionnaire (previous 4-wks)	SRT: SRM *Customised*	Age** White collar** Time since transplant* Need drugs even if my kidney is functioning well* Drugs should never be delayed** Immunosuppresants stay active in my system for ≥24 hours*.	**29**
Johnson **[25]** N = 244 [244]	HIV Antiretroviral	56 (4.8) 71	S: ACTG	SS: TMSC ext. PSR, WOC, CWI	Structural Equation Model: Time since diagnosis** Negative affect** Maladaptive coping** Perceived SS**.	**29**

First author *N [model n]*	Therapeutic indication / Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality score[d]
Byrne [26] *N* = 1611 [933]	Coronary Heart Disease *preventative*	66 (9.1) 65	S: MARS *5-items*	SRT: SRM *BMQ, IPQ-R*	Age* Sex, General Medical Services eligible** GP consultations, Time since diagnosis, Previous MI, Cause-stress, Cause-heredity, Cause-own behaviour, Identity, Timeline-chronic** Consequences, Personal control, Treatment control, Coherence, Timeline-cyclical, Emotional representations, Necessity (spec)** Concerns (spec)** Harm (gen)** Overuse (gen)**.	25
De Smet [27] *N =1270[573]*	Asthma Inhaled corticosteroids	41 (2.4) 29	S: Questionnaire	SCT: HBM ext. *Customised*	SF-36 MCS, Years since diagnosis, Perceived barriers** Perceived benefits** Perceived severity** Enabling.	25
Johnson [28] *N* = 545 [545]	HIV Antiretroviral	43 (7.8) 81	S: ACTG (≥90%, 3-days)	SS: SP-S *SPS, SPSI-R*	Structural Equation Model: Age, Sex, Ethnicity, Alcohol, drug use, Psychological health**. Mediators: Constructive SP-S by Psychological Health** Dysfunctional SP-S by Psychological Health**.	25
Ross [29] *N* = 514	Hypertension Anti-hypertensive	60 (12.2) 52	S: Morisky *4-items*	SRT: *BMQ, IPQ-R*	Age** Emotion** Personal control* Necessity (specific)**.	25
Chao[30] *N =1700[445]*	Diabetes (T2) Oral Hypo-glycaemic	56 (11.4) 50	S: Morisky / Horne 4-item	SCT: HBM ext. *Customised*	Structural Equation Model: Depression, SE** Perceived barriers** Perceived benefits, Perceived severity, Perceived susceptibility, Perceived side-effect barriers**.	25
Horne [31] *N* = 324	*Chronic Multiple*	$	S: Questionnaire	SRT: *BMQ*	Age** Illness group: cardiac** Illness group: asthma** Necessity-concerns (differential)**.	25
Youssef [32] *N* = 316	Hypertension Anti-hypertensive	59 (9.2) 60	S: Questionnaire (≥90%, 1-mth)	SCT: HBM *Customised*	Controlled blood pressure** Restriction of dietary salt and fat** Perceived benefits** Perceived susceptibility ** Drug side-effects*.	25
Chen [33] *N* = 277	Hypertension Anti-hypertensive	66 (12.3) 60	S: Medication Adherence Inventory + *customised*	SRT: SRM *IPQ-R*	Age, Live alone* History hyperlipidaemia* /hypertension, SPB, Drug number, Identity, Symptoms after-yes, Symptoms after-uncertain, Timeline, -cyclical, Consequence, Personal control, Treatment control* Coherence, Emotional, Balanced, Psychological** Cultural, Risk*.	25
Gatti [34] *N* = 301 [275]	*Pharmacy patients not reported*	54(12.5) 27	S: Morisky *8-items*	SRT: SRM *BMQ, SEAMS*	Age<65yrs** Literacy level of less than high school, Self-report of hyperlipidaemia * Low SE** BMQ (score ≥47)**.	25
Phatak [35] *N* = 250	*Chronic Multiple*	$ 38	S: Morisky *9-items*	SRT: SRM *BMQ*	Age** Conditions, Medications(n)* Necessity (specific)* Concerns (specific)** Harm (general), Overuse (general).	25
Brown [36] *N = 300 [241]*	Hypertension Anti-hypertensive	62 ($) 31	S: Interview (last 30-days)	SCT: HBM *Customised*	Age* Sex, Education, Poverty status, Perceived barriers-forgetting** Perceived barriers-refill, Perceived benefits, Perceived side-effect barriers**.	25
Clatworthy [37] *N = 259 [223]*	BPD Antimanic	48(11.2) 36	S: MARS *5-items*	SRT: SRM *BMQ*	Age, Sex, Age of diagnosis, Medications (n), Depression, Symptoms, Necessity (specific)** Concerns (specific)**.	25
Roh [38] *N* = 219 [219]	Hypertension Anti-hypertensive	65 (8.5) 61	S: Hill-Bone Compliance to High Blood Pressure Therapy Scale	SRT: SAT *GSES, PRA, KHS, MOS-SSS*	Structural Equation Model: Knowledge, SE*. Mediators: Depression by SE* SS by relationship and SE*	25
Cha [39] *N* = 215	HIV Antiretroviral	41 (7.6) 67	S: Morisky	SS: *ISEL*	Structural Equation Model: SE**. Mediators: Depression by SE** Perceived SS by self-efficacy beliefs**.	25
Sud [40] *N = 238 [208]*	Acute Coronary Syndromes	65(13.0) 61	S: Medication Adherence Scale	SRT: SRM *BMQ*	Age, Sex, Race, Education, Number of other people, Heart-related health status** Co-morbidities, Necessity (specific)** Concerns (specific), Harm (general), Overuse (general).	25

First author *N [model n]*	Therapeutic indication / Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality score[d]
Nageotte **[41]** *N* = 260 [202]	*Chronic mental health* Neuroleptic	35 (8.8) 68	S: Interview	SCT: HBM *Customised*	Sex , Race, Marital status, Urban/rural residence, Perceived barriers** Perceived benefits, Perceived threat* Perceived side-effect barriers.	**25**
Kennedy **[42]** *N =205 [201]*	HIV Antiretroviral	40 ($) 85	S: Interview P: Refill data for verification n=40	SRT: SDT *HCCQ, TSRQ, + SE*	Structural Equation Model: Psychological distress** Perceived competence** Autonomous motivation mediated by perceived competence** Autonomous support mediated by psychological distress**.	**25**
Ponieman **[43]** *N = 259 [*201]	Asthma Inhaled corticosteroids	48 (13) 18	S: MARS *10-items*	SRT: SRM *BMQ*	SE** Necessity (specific)** Concerns (specific)** Regimen hard to follow*.	**25**
Amico **[44]** *N = 200 [200]*	HIV Antiretroviral	39 (8.9) 65	S: ACTG-*reversed*	SCT: IMB *IMB questionnaire*	Structural Equation Model: Adherence Behavioural Skills*. Mediators: Adherence information by adherence behavioural skills* Adherence motivation by adherence behavioural skills*.	**25**
Richardson **[45]** *N = 201 [197]*	Hypertension Anti-hypertensive	54 (13.1) 22	S: Interview C: Blood Pressure	SCT: HBM *Customised*	Age* Duration of treatment* Salt restriction, Low net barriers, Medium net barriers* Perceived barriers*.	**25**
Pomeroy **[46]** *N = 225 [184]*	HIV Antiretroviral	43(7.3) 78	S: Medication Adherence Scale	SCT: IMB ext. *SSRS +* *customised*	Children in household, Medical care within 1-yr of diagnosis, Receiving mental health services* Intention** Information** Motivation- vulnerability* Motivation-provider, Perceived SS.	**25**
Cox **[47]** *N* = 179	HIV Antiretroviral	37 (7.7) 91	S: Patient rated and clinician rated	SS: *Customised*	Discriminant Function Analysis: Employment* Symptoms* Emotional support (actual)*.	**25**
Brewer **[48]** *N* = 169	High cholesterol *cholesterol-lowering*	67 (10) 61	S: Questionnaire C: Blood cholesterol	SRT: SRM *Customised*	Age, Sex, Ethnicity, Education, Smoker, CHD, Hypertension, Diabetes, Medication side-effects** Number of medications , Consequences* Timeline, Cause, Cure, Symptoms.	**25**
Valeberg **[49]** *N* = 164 [140]	Cancer Analgesic	58 (11.4) 21	S: Questionnaires	SCT: HBM ext *Customised*	Sex, Average pain score, Opioid or other pain medication** Pain relief** SE**.	**25**
Kopelowicz **[50]** *N* = 155	Schizophrenia Anti-psychotic	34(10.8) 63	S: Treatment Compliance Interview	SCT: TPB *TPB Inventory*	Perceived behavioural control**Attitude, Subjective norms**.	**25**
Mann **[51]** *N* = 151 [150]	T2 Diabetes PO Hypo-glycaemic	57 (11) 55	S: Morisky *4-items*	SRT: SRM *IPQ, BMQ +Customised SE*	SE* Necessity (specific), Concerns (specific)* Disease beliefs* Regimen hard to follow*.	**25**
Ferguson **[52]** *N = 149 [149]*	HIV Antiretroviral	39(8.6) 87	S: PMAQ [part 1]	SCT: HBM *barriers only* PMAQ [part 2]	*KAMED* Qualities of Medicine Schedule and Memory score* SS, Qualities of medicine* Schedule* Memory*.	**25**
Sajatovic **[53]** *N* = 140 [140]	BPD Antimanic	$ 50	S: Tablets Routine Questionnaire	SCT: Attitudes/ control *AMSQ, ITAQ, MHLC*	Age, Sex,Ethnicity, Education, Drug addiction** Illness duration, Psychiatric rating scale, Depression, Clinical Global Impression* ISEL, MHLC Internal, MHLC Chance, MHLC Powerful others* AMSQ** ITAQ** Rating of Medication Influences (ROMI)**.	**25**
Bane **[54]** *N* = 139	Hypertension Anti-hypertensive	52(12.1) 51	S: Questionnaire	SCT: SE / TPB *Customised*	Perceived behavioural control** Intention, Attitude** Subjective norms. *Note. Statistically significant difference in SE scores between adherent and non-adherent groups but this was not entered into the TPB regression.*	**25**
Atkinson **[55]** *N = 137 [130]*	HIV Antiretroviral	40(6.8) 74	S: ECAB	SS: TMSC *ECAB*	Structural Equation Model: SE* Optimism* Social isolation. Mediators: Stress by optimism* Psychological distress by patient-doctor relationship and optimism* SS by SE*.	**25**
Holstad **[56]** *N* = 120 [115]	HIV Antiretroviral	37(8.5) 60	S: Antiretroviral General Adherence Scale	SCT: HBM/TRA *ADQ adapted*	Sex, Alcohol, Years HIV** Existential well-being, Perceived severity, Support/Barriers**.	**25**

First author *N [model n]*	Therapeutic indication / Medication	Age (SD) Male %	Adherence measure (time)[a]	Theory: model *Instrument/s* [b]	Key findings [c]	Quality score[d]
Schmid-Mohler **[57]** *N* = 114 [110]	Renal Immuno-suppressant	54 (11.9) 65	S: BAASIS C: Nurse / Doctor reports	SCT: IMBP *Customised*	Barrier-feeling overwhelmed, Barrier-practical difficulties during intake, Barrier-no medication aids, Barrier-forgetfulness/interruption of daily routine* Intention.	**25**
Hekler **[58]** *N = 139 [102]*	Hypertension Anti-hypertensive	62 (10.2) 34	S: Interview	SRT: SRM *Customised*	Age* Sex, BMI, Education, Marital status, Time since diagnosis, Consequences, Timeline, Identity, Timeline-cyclical, Control/ cure beliefs, Disease cause/control.	**25**
Horne **[59]** *N = 119 [100]*	Asthma Inhaled corticosteroids	49 (18.8) 39	S: MARS *9-items*	SRT: SRM *IPQ, BMQ*	Age, Sex, Education, No. family doctor visits, Number of asthma-related hospital admissions* Duration of asthma, Consequences** Timeline, Identity, Cure, Necessity (specific)** Concerns (specific)**.	**25**
Starace **[60]** N = 100 [100]	HIV Antiretroviral	39 (7.3) 69	S: ACTG	SCT: IMB *IMB questionnaire*	Structural Equation Model: Adherence Behavioural Skills*. Mediators: Adherence information by adherence behavioural skills* Adherence motivation by adherence behavioural skills*.	**25**
van Servellen **[61]** *N* = 85 [77]	HIV Antiretroviral	40 (8.9) 90	S: ACTG	SS: *MOS-SSS + customised*	Months of antiretroviral treatment, Treatment Knowledge, Depression, SE, Emotional support (actual)* Patient-provider relationship**.	**21**
Frain **[62]** *N = 76 [76]*	HIV Antiretroviral	30-39 81	S: Questionnaire	SS: FRT *FIRM*	CD4 count, Health worries, Financial worries, Disclosure worries, Life satisfaction* Provider trust** Overall functioning, Medication concerns (QoL item), Sexual functioning, Global distress, HIV mastery** Optimism* Uncertainty, Family resiliency.	**21**
Muma **[63]** *N = 66 [52]*	HIV Antiretroviral	$ 83	S: Questionnaire C: Erythrocytes	SCT: HBM *Customised*	Ethnicity** Perceived barriers-problems taking and scepticism about medication*.	**21**
Simoni **[64]** *N* = 50 [50]	HIV Antiretroviral	41 (8.0) 38	S: ACTG	SS: *SSI + customised*	Depression** Anxiety* SE, SS (actual), Perceived SS , Treatment knowledge.	**21**
Fraser **[65]** *N* = 594 [199]	Multiple Sclerosis Glatiramer acetate	46 ($) 24	C: Record review (continued/dis-continued at 1-yr)	SCT: Control Beliefs *MSSE, SES*	Individual hypotheses: SE control* SE function** Hope, Self-esteem, Perceived support from spouse* Perceived support from physician*.	**8**
Christensen **[66]** *N = 112 [72]*	Renal *not reported*	46 ($) 54	C: Serum K levels / Serum P levels	Distal: 5-FM *NEO Five-factor Inventory*	Age* Conscientiousness*.	**8**
Budd **[67]** N = 40 [40]	Schizophrenia Neuroleptic	49 ($) 75	C: Accepted medication (>33%, 12-mths)	SCT: HBM Customised	Discriminant Function Analysis: Benefits, Severity, Perceived susceptibility**.	**8**

2.4.4 Adherence measure

Self-report was the most common method of adherence measurement (n = 50) (Table 2.3) usually by questionnaire (n = 24) such as the Medication Adherence Rating Scale (Horne & Weinman, 1999) (n = 5) and the Morisky questionnaire (Morisky et al., 2008) (n = 5). Half of the longitudinal studies used electronic compilations (9 of 18); within these studies, there was heterogeneity in the follow-up period and the threshold used to classify patients as being adherent (which ranged from >50% to ≥95% doses registered as being taken).

Table 2.3 Studies categorised by theoretical framework, adherence measurement and quality

	Sociocognitive Theory		Self-Regulation Theory		Social Support Theory	
Adherence Measure	n	Quality score median [range]	n	Quality score median [range]	n	Quality score median [range]
Electronic compilation	5	83 [83-87]	2	87 [87]	2	87 [87]
Medication measurement	1	71 [71]				
Prescription record	3	37 [33-37]				
Self-report	22	25 [21-50]	19	25 [25-50]	9	25 [21-50]
Clinical indicator	4	8 [8-21]				

Note: Quality score interpretation: 100 = highest quality, 0 = lowest quality.

2.4.5 Theoretical models

Studies most commonly used the health belief model (n = 20), self-regulation theory (n = 16), social support theory (n = 5), theory of planned behaviour (n = 3), self-determination theory (n = 3), and the transactional model of stress and coping (n = 3). Five studies tested more than one model within the same theoretical framework (sociocognitive), though there were no studies that compared models across frameworks.

All studies included more distal background factors alongside the independent variables specified within the theoretical model. Studies most commonly found associations ($P \leq 0.05$) between adherence and age and time since diagnosis. Twenty-two studies entered age as a distal variable, 13 reported significant association in a consistent direction. Older age was associated with adherence, or younger age was associated with nonadherence. These studies explored a range of conditions including hypertension (Brown & Segal., 1996; Hekler et al., 2008; Ross et al., 2004) and renal diseases (Greenstein & Siegal, 1998; Christensen & Smith, 1995; Rudman et al., 1999). Age appeared as a significant distal factor across frameworks, including self-regulation (n=8) and sociocognitive (n=3). Time since diagnosis was tested in 12 studies, five of which reported significant association, across a range of

conditions: HIV (Weaver et al., 2005; Johnson et al., 2009), multiple sclerosis (Turner et al., 2007), inflammoratory bowel disease (Horne et al., 2009) and renal disease (Greenstein & Siegal, 1998). Both studies of adherence to antiretroviral medication entered time since diagnosis as a distal variable to social support models. All studies found the same direction of association with longer time since diagnosis predicting nonadherence.

2.4.6 Quality assessment

Across the whole sample, the mean quality assessment score was 36 (median 25; range 8–87) (Table 2.2). Use of unweighted scoring as opposed to weighted scoring had no discernible effect on the order of studies when ranked by score. Several studies used financial incentives for participation, which may have introduced response bias (Apter et al., 2003; Williams et al., 1998; Johnson et al., 2009; De Smet et al., 2006; Amico et al., 2005; Brewer et al., 2002; Atkinson et al., 2008). Most of the studies reported both significant and nonsignificant predictors.

2.4.7 Synthesis of Results

2.4.7.1 Quantitative synthesis

There was considerable heterogeneity in terms of populations, theoretical and conceptual definition, adherence definition, adherence measurement, application of relevant theory in terms of independent variable selection, independent variable measurement (including use of validated instruments), study duration, and presentation of outcomes (Table 2.2). Nine studies were identified as using the same combination of adherence measure and health psychology measure as at least two other studies, and potentially amenable to meta-analysis (Horne et al., 2009; Byrne et al., 2005; Ross et al., 2004; Gatti et al., 2009; Phatak & Thomass, 2006; Clatworthy et al., 2009; Ponieman et al., 2009; Mann et al., 2009; Horne et al., 2002). On closer inspection, however, there were differences in the population they were applied to, the use of adherence and health psychology measures, and the data reported. The case for meta-analyses was consequently dismissed. Combining the explanatory power of models used to predict adherence to heterogeneous medications by heterogeneous populations could compromise the systematic and rigorous representation of empirical evidence that is more accurately reported in our narrative synthesis (Centre for Reviews and Dissemination, 2008; Sterne et al., 2011).

2.4.7.2 Narrative synthesis

Table 2.4 summarises predictors of medication adherence identified by model and factor, within their associated theoretical framework. It was not possible to compare the effect size because of heterogeneity in the measurement of both dependent and independent variables. Ratios of how many times factors reached statistical significance therefore provide a basis for a narrative summary of the direction of the empirical evidence for each factor, cross-referenced by study.

Self-efficacy was identified as the most prominent and significant determinant of adherence within sociocognitive theory (7 of 7), self-regulation theory (6 of 6), and social support theory (4 of 6). Significant associations with adherence were also frequently reported between components of the health belief model (perceived barriers = 11 of 17; perceived susceptibility = 3 of 6; perceived adverse effects = 4 of 5; perceived benefits = 5 of 11), the self-regulation model (beliefs about medicine necessity = 8 of 9; concerns about medicines = 7 of 8), and the theory of planned behaviour (perceived behavioural control = 2 of 4). Although widely entered, illness representations were rarely found to be associated with adherence. It should be noted, however, that two studies assessing illness representations were omitted from Table 2.4 because of inconsistency in their use of illness representation measures (Mann et al., 2009) and ambiguous use of customised items (Greenstein & Siegal, 1998). Direct comparison of models within the social-support framework was not possible because of the common use of structured equation models displaying unique mediated relationships.

Table 2.4 Summary of psychological predictors of medication adherence identified in the review, presented by theory model and factor

Independent variable	Measured n/N*	Reference no (Appendix 2.2). Significant / Non-significant studies
Proximal: General control beliefs		
Self-efficacy (total)	17/19	
- *with Sociocognitive Theory*	7/7	5, 10, 16, 18, 30, 49
- *with Self-Regulation Theory*	6/6	4, 22, 34, 38, 43, 51, 65
- *with Social Support Theory*	4/6	12, 39, 55, 62 / 61, 64
Sociocognitive Theory: HBM		
Perceived barriers	11/17	19, 21, 27, 30, 36, 41, 45, 52, 56, 57, 63 / 5, 7, 14, 15, 17
Perceived adverse effects	4/5	11, 30, 32. 36 / 41
Perceived benefits	5/11	5, 15, 17, 27, 32 / 14, 20, 30, 36, 41, 67
Perceived severity	3/7	14, 17, 27 / 11, 30, 56, 57
Perceived susceptibility	3/6	32, 41, 67 / 11, 17, 30
Sociocognitive Theory: TPB		
Perceived behavioural control	2/4	50, 54 / 11, 20
Intention	2/5	11, 20 / 5, 15, 54
Attitude	2/5	8, 54 / 7, 11, 50
Subjective norm	1/4	50 / 5, 6, 54
Self-Regulation Theory: SRM		
Treatment beliefs†		
Necessity (specific)	8/9	1, 26, 29, 35, 37, 40, 43, 51 / 59
Concerns (specific)	7/8	1, 26, 35, 37, 43, 51, 59 / 40
Harm (general)	1/3	26 / 35, 40
Overuse (general)	1/3	26 / 35, 40
Medication beliefs (not-BMQ)	2/2	22, 25
Illness representations		
Identity	0/6	26, 29, 33, 48, 58, 59
Consequences	1/6	48 / 26, 29, 33, 58, 59
Timeline	2/7	23, 26 / 29, 48, 58, 59
Timeline (cyclical)	0/5	26, 29, 33, 48, 58
Cause	0/5	26, 29, 33, 48, 58[d]
Personal control	2/6	29, 59 / 26, 33, 48, 58[d]
Treatment control	1/3	33 / 26, 29
Coherence	0/3	26, 29, 33
Emotional representations	1/3	29 / 26, 33

HBM Health Belief Model; *SRM* Self-regulation Model; *TPB* Theory of Planned Behaviour,.
*n number of studies reporting a statistically significant association with adherence, N number of studies that entered independent variable into the final regression model (results presented as counts due to heterogeneity between populations, study design and outcomes). †Horne et al. (23) compared attitudinal groups, Horne et al. (31) used the Necessities-concerns differential, Gonzalez et al. (1) also measured distrust (general). [d] merged medical belief / stress belief model.
"$p \leq 0.05$

2.4.7.3 Comparative Performance of Models (in Studies with Quality Assessment Score ≥50)

Further assessment of studies of the highest quality maintained the finding that self-efficacy was a consistent predictor of adherence. Applications of sociocognitive theory showed limited utility of the health belief model because most of the items failed to reach statistical significance and when they did, they explained a limited proportion of the variance in adherence. The prediction of adherence increased, however, when used in conjunction with the theory of planned behaviour and self-efficacy. Barclay et al. (2007) found that perceived utility and self-efficacy were highly significant predictors of adherence to antiretroviral therapy for younger participants and correctly classified 73% of the cases. In comparable populations of people prescribed malaria prophylaxis, Abraham et al.(1999) found that the theory of planned behaviour components explained approximately 40% to 50% of the variance in adherence to two different medications and Farquharson et al. (2004) found that perceived benefits of medication (a single factor of the health belief model), length of stay, and health professional discussion about adherence and travellers' questions independently predicted adherence among 73% of their population. Brus et al. (1999) identified self-efficacy as the only factor determining adherence ($P<0.01$). Fraser et al. (2004) also found that self-efficacy correctly classified 98.8% of the cases at 6-month follow-up.

Applications of self-regulation theory highlighted components of the self-regulation model and autonomous regulation as being significant predictors of adherence to medications. Symptoms, medication concerns, medication necessity, and dis- trust were found to predict up to 24% of the variance in adherence to antiretroviral therapy (Gonzalez et al., 2007). There was no evidence of testing this against other theories. Applications of self-determination theory found autonomous regulation to account for 68% of the variance in adherence of outpatients with various diagnoses prescribed long-term medication. Lynam et al. (2009) also found autonomous regulation to be a more robust predictor of antiretroviral therapy adherence than locus of control; however, again only self-efficacy predicted adherence directly.

Applications of social support theory again pointed toward the influence of more distal factors as well as self-efficacy beliefs. Simoni et al. (2006) found that social support was associated with less negative affect and greater spirituality, which, in turn, were associated

with adherence self-efficacy. This model explained 8% of the variance in adherence at 3 months and 8% of the variance in viral load at 6 months. Halkitis and Palamar (2007) found drug use and socioeconomic status to be the significant direct predictors of adherence, with drug use also significantly mediating the relationship between psychological states (level of social support, avoidant coping, self-efficacy) and adherence. Distal personality traits were also predictors of adherence.

Stilley et al. (2004) found that conscientiousness and estimated intelligence quotient accounted for 13% of the variance in adherence, whereas Cohen et al. (2004) found that activity (extraversion dimension) and modesty (agreeableness dimension) were significantly associated with adherence, both accounting for 12% of the variance.

2.5 Discussion

Overall, our comparison of the performance of models associated with three theoretical frameworks points toward the importance of both distal and proximal determinants, and most prominently self-efficacy or perceived control beliefs. The majority of evidence related to the application of the health belief model, the theory of planned behaviour, and beliefs about medicines (within the self- regulation model). Often, only single components of models explained the variance in adherence, and the variance explained was limited. The findings suggest that application of multiple or extended models improve predictions and that consideration of different populations within the same treatment area, or along the illness trajectory, yield different results.

Our review has emphasised the breadth of empirical research that has sought to predict adherence to medications using health psychology at various stages in the adherence process. Our results can be compared with those of a recent systematic review of psychosocial and behavioural factors associated with initial medication adherence (Zeber et al., 2013) that identified a limited number of studies (n = 5) addressing health beliefs within which medication beliefs, knowledge, and trust were identified as factors influencing initiation of medications. This review was, however, restricted to medication initiation, thus focusing on only one stage of the medication adherence process. These authors also stressed the methodological challenges of synthesising findings from empirical adherence studies.

DiMatteo et al. (2012) conclude that interventions should comprise three clinical actions: providing information and knowledge as to how to adhere, encouraging belief in treatment and motivation to adhere, and helping patients to overcome barriers. O'Carroll et al. (2011) also concluded that interventions to improve adherence should target patients' beliefs about medication. The importance of self-efficacy, treatment beliefs, perceived barriers, and social support, as identified in the literature, highlights the need for interventions to be multifaceted.

The application of theory-driven, evidence-based models is important in the development of effective interventions. Stavri and Michie (2012) conclude from their review that behaviour, in this case medication adherence, should be informed by an understanding of theoretical frameworks (e.g., sociocognitive, self-regulation, and social support) and within those a range of subordinate models (e.g., health belief model, theory of planned behaviour, and self-regulation model) and then the individual components (e.g., perceived barriers, perceived benefits, and treatment beliefs). We have summarised empirical evidence for each of these and have also identified that further credence should be given to more distal variables, such as personality traits, more generic beliefs, and generalised efficacy beliefs, which appear also to have a significant role in predicting adherence to medications. This may be achieved in practice via brief cognitive-behavioural intervention or improved communication with health care professionals, as evidenced in the Cochrane review of the effectiveness of adherence-enhancing interventions. In this, modest effects for self-efficacy enhancement using individually tailored telephone calls, information on self-management, checks on understanding, and concerns regarding medication and empowerment (Haynes et al. 2012) are reported, thus highlighting the potential for theory to inform practice.

Classification of the application of established theory may result in a move toward the development of conceptual models specific to adherence, rather than ad-hoc application of more generic theories. Findings from longitudinal studies reported here potentially add to an understanding of nonadherence and inform the development and evaluation of interventions targeted at different stages in the dynamic process of adherence. Turner et al. (2007), for example, demonstrate that predictors vary with time; this principle could help explain variance in behaviour across the various stages of adherence, that is, initiation, persistence, and discontinuation (Vrijens et al., 2012). Furthermore, the consistent use of definitions pertaining to medication adherence might improve the power of conceptual theories to

explain adherence behaviour at different stages; for example, medication beliefs may influence initiation (e.g., Bane et al., 2006), whereas higher self-efficacy may improve persistence (e.g., Barclay et al., 2007).

Overall, our findings support the notion that no single theory should be used to inform the development of adherence-enhancing interventions. Consolidation of existing models, however, could be used as a theoretical foundation from which to lead further empirical investigation of determinants of adherence. Identifying significant determinants from robust, reliable, and longitudinal evidence establishes targets for effective adherence-enhancing interventions with greater potential for sustainable behaviour change and improvements in health.

It should be noted, however, that the utility of these theories can be judged only by the quality of existing empirical evidence, which at present is limited. Further research in experimental health psychology relating to the development of evidence-based models of adherence to medications is encouraged, and the potential of theories from other disciplines (e.g., behavioural economics) should be explored. Similarly, the link between behaviour change intervention and theoretical mechanisms for change requires a clear definition of the behaviour in question (Michie et al., 2012). We therefore also suggest more robust adherence measurement, using techniques least prone to bias, and, crucially, the use of an agreed taxonomy of adherence to medications (Vrijens et al., 2012).

Key strengths of this review relate to the systematic methodology, the focus on studies of the highest quality, the consideration of multiple theoretical frameworks, and the acknowledgment that meta-analysis was inappropriate for the sample of studies included in our review. Most of the studies identified, however, were cross-sectional, which cannot accommodate dynamic theoretical propositions, capture the entire process of adherence, or make inferences concerning causality of effect. It is also recognized that studies investigating patients who are willing to participate in research may miss people who do not seek or have dropped out of health care, which may introduce sampling bias and limit generalisability to the least adherent patients. Our review also excluded studies with participants not responsible for the taking of their own medicines.

The review was limited by the degree to which the factors studied, and the theories/models on which they were based, compared with one another. The assignment of the independent variables to the theoretical constructs had to be assumed in some cases in which published articles lacked specificity. Only 5 of the 67 studies distinctly tested multiple models; all these studies were associated with sociocognitive theory. Heterogeneity among studies, originating from multiple sources, precluded any quantitative synthesis of the results although our narrative approach captured the key elements of the findings. The systematic approach to reviewing the studies ensured a rigorous assessment of quality and the combinability of studies in which to consider (and reject) the appropriateness of pooling the data (Sterne et al., 2011).

2.5.1 Conclusions

The findings of this systematic review suggest that health psychology theories are useful at predicting adherence to medications; however, in all cases, the determinants and variation in their measurement were sufficiently complicated that no individual theory or model ever explained more than a limited amount of the variability in adherence behaviour. Nonetheless, our findings have relevance for theory building and intervention development, and potentially for clinical practice. Consolidation of behavioural models and their components may provide a strengthened theoretical basis for the development and assessment of effective adherence-enhancing interventions.

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2.7 Candidates contribution

Under the supervision of DH and VM, EAFH wrote the protocol, designed the search strategy, ran the searches, screened publications for inclusion in the review, extracted data from papers, analysed the data, interpreted the results and drafted the manuscript. Maz Khalid, Sahdia Parveen, Joshua Pink, Colin Ridyard, and Todd Ruppar performed duplicate screening and data extraction. VM (supervisor) resolved disagreements in assessment. EAFH (the candidate), DAH (supervisor) and VM (supervisor) revised the manuscript for intellectual content. EAFH finalised the manuscript.

Chapter 3

Multinational cross-sectional survey of adherence to antihypertensive medication

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3.1 Preface

Chapter 2 presented a systematic review of 20 years of empirical research on the contribution of health psychology predictors of adherence to medication to our understanding of adherence to medications.

This chapter presents a multinational cross-sectional survey of predictors of self-reported adherence to antihypertensive medicines, in which potential determinants of nonadherence identified in Chapter 2 are tested. Simultaneous measurement of a wide range of predators on the same sample enables direct comparison of how theories perform. This is the first study to test such a wide range of theories, across several countries.

3.2 Abstract

Background: Nonadherence to antihypertensive medicines limits their effectiveness, increases the risk of adverse health outcome, and is associated with significant health care costs. The multiple causes of nonadherence differ both within and between patients and are influenced by patients' care settings.

Objectives: The objective of this article was to identify determinants of patient nonadherence to antihypertensive medicines, drawing from psychosocial and economic models of behaviour.

Methods: Outpatients with hypertension from Austria, Belgium, England, Germany, Greece, Hungary, The Netherlands, Poland, and Wales were recruited to a cross-sectional online survey. Nonadherence to medicines was assessed using the Morisky Medication Adherence Scale (primary outcome) and the Medication Adherence Rating Scale. Associations with adherence and nonadherence were tested for demographic, clinical, and Psychosocial factors.

Results: A total of 2595 patients completed the questionnaire. The percentage of patients classed as nonadherent ranged from 24% in The Netherlands to 70% in Hungary. Low age, low self- efficacy, and respondents' perceptions of their illness and cost-related barriers were associated with nonadherence measured on the Morisky Medication Adherence Scale across several countries. In multilevel, multivariate analysis, low self-efficacy (odds ratio = 0.73; 95% confidence interval 0.70–0.77) and a high number of perceived barriers to taking medicines (odds ratio = 1.70; 95% confidence interval 1.38–2.09) were the main significant determinants of non- adherence. Country differences explained 11% of the variance in nonadherence.

Conclusions: Among the variables measured, patients' adherence to antihypertensive medicines is influenced primarily by their self-efficacy, illness beliefs, and perceived barriers. These should be targets for interventions for improving adherence, as should an appreciation of differences among the countries in which they are being delivered.

3.3 Introduction

Adherence to antihypertensive treatments is suboptimal (Naderi et al., 2012), even among patients participating in clinical studies, whose median persistence with medicines is only about 1 year (Vrijens et al., 2008). Patients who are poorly adherent (proportion of days covered ≤40%) (Mazzaglia et al., 2009) experience significantly increased risk of acute cardiovascular events, compared with those who adhere adequately (≥80%), and incur greater health care costs (Sokol et al., 2005). The World Health Organization (AlGhurair et al., 2012) has called for further research to gain a better understanding of the determinants of nonadherence to antihypertensive medicines, and to identify common risk factors for nonadherence across different countries, to inform strategies for improving patient adherence.

Known determinants of nonadherence to antihypertensive treatments may broadly be categorized as factors related to the patients and their familial and cultural context, condition, treatment, socioeconomic characteristics, and health professional/health care system (AlGhurair et al., 2012; see also Brown and Segal, 1996; Chen et al., 2009; Hekler et al., 2008; Maimaris et al., 2013; Richardson et al., 1993; Ross et al., 2004; Youssef and Moubarak, 2002). Components of sociocognitive and self-regulatory theory including attitude, perceived behavioural control, low self-efficacy, lack of perceived treatment benefits, perceived barriers, illness perceptions, beliefs about medicines, and lack of social support are significantly associated with nonadherence (Holmes at al., 2014; see also Bane et al., 2006; Barclay et al., 2007; Brown and Segal, 1996; Cha et al., 2008; Chen et al., 2009; Chisholm et al., 2007; Hekler et al., 2008; Horne & Weinman, 2005; Mann et al., 2009; Richardson et al., 1993; Ross et al., 2004; Simoni, 2006; Youssef & Moubarak, 2002). Studies based on the consumer demand theory support the negative impact of the costs of medicines on adherence (Elliott et al., 2008), but there is a lack of empirical evidence on alternative behavioural economic theories such as time preference. We are unaware of any study in which a range of these factors has been tested simultaneously to assess their combined contribution to nonadherence across several countries.

The aim of this study, therefore, was to identify determinants of patient nonadherence to antihypertensive medicines, drawing from psychosocial and economic models of behaviour,

from a cross-sectional survey across a number of European countries with contrasting cultures, health care systems, and patient characteristics.

3.4 Methods

The research used an online, convenience cross-sectional sample of adults with hypertension recruited from 11 European countries. We tested the contribution of multiple, theory-driven determinants for association with antihypertensive treatment nonadherence, and reported our findings according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement on cross-sectional studies (Von Elm et al., 2007).

3.4.1 Procedure

After receipt of ethical approval from all relevant committees (Appendix 3.1), we invited ambulatory, adult patients with hypertension to participate in an online questionnaire. Patients self-selected into this study in response to advertisements placed in community pharmacies (Austria, Belgium, England, France, Germany, Greece, The Netherlands, Portugal, Poland, and Wales) or hypertension clinics (Hungary). Additional strategies were necessary to increase recruitment in some countries. These included recruiting patients via general practice surgeries (Poland and Hungary), placing advertisements in the press (England and Wales), and using online patient support groups (Poland). No incentive was offered for patients to participate. The survey was administered anonymously through Survey Monkey, with one entry allowed per Internet Protocol address to reduce the chance of multiple responses. Patient information sheets, consent forms, and eligibility checks were provided online.

3.4.2 Inclusion Criteria

We included patients who consented, and who self-reported as being 18 years or older, diagnosed by a doctor as having hypertension that lasted at least 3 months (ensuring an established diagnosis and commencement of treatment), currently prescribed antihypertensive medicine(s), and personally responsible for administering their medicines.

3.4.3 Exclusion Criteria

Respondents who self-reported as being diagnosed with a "psychiatric condition" or those living in a nursing home (or similar facility) were excluded.

3.4.4 Potential Determinants

Potential determinants of nonadherence were identified from published literature reviews (Holmes et al., 2014; Munro et al., 2007). The questionnaire was developed from validated instruments, where available, and covered participants' demographic characteristics, use of medicines, self-rated health (Lorig et al., 1996), and a battery of scales derived from economic (Elliott et al., 2008) and sociocognitive (Holmes et al., 2014; Munro et al., 2007) theories.

Affordability and cost-related behaviours were assessed by a dichotomous question asking whether respondents had to think about the money available to spend when obtaining their medicines and six related items, each measured on a five-point Likert scale (Schafheutle et al., 2004). Components of the European Social Survey (2008) assessed household income: participants reported their main source of income, their total annual income (in bands), whether they were coping with their present income, and the ease or difficulty in borrowing money when in need. We assessed participants' time preference for near versus distant enjoyment of health benefits (Chapman et al., 2001). The internationally standardized European Task Force on Patient Evaluations of General Practice (EUROPEP) measure (Grol & Wensing, 2006) assessed participants' evaluations of the health care they receive.

Validated, self-report tools were used to assess personal and sociocognitive determinants of nonadherence. Dispositional optimism was measured using the Life Orientation Test on five-point Likert scales (Scheir et al., 1994). Illness representations were measured using the Brief Illness Perception Questionnaire (Broadbent et al., 2006), which assessed personal beliefs about illness consequence, timeline, personal control, treatment control, illness identity, concern about illness, illness coherence, and emotional representations (the causal subscale was removed because of translation issues). The Beliefs about Medicines Questionnaire (Horne, 1996) assessed participants' belief in the necessity of their medicines and also concerns about their medicines. Components of the theory of planned behaviour

(Conner & Norman, 1996) measured attitudes/ behaviours toward taking medicines, subjective norms of adherence, barriers to, and facilitators of, adherence, intention to adhere, and self-efficacy for adherence behaviours, each scored on a five-point Likert scale. The Building Research Initiative Group Illness Management and Adherence in Transplantation (BRIGHT) questionnaire (Dobbels et al., 2008; Schmid-Mohler, 2010) was used to assess constraints/facilitators of adherence using subscales for barriers and social support.

3.4.5 Outcome Measures

The primary outcome measure was self-reported nonadherence, based on the four-item Morisky Medication Adherence Scale (Morisky et al., 2008). This classified patients as being nonadherent according to a single "yes" response to any of the four questions that made specific reference to "high blood pressure medicine." This validated scale is the most frequently used questionnaire measuring adherence to medication (Shi et al., 2010). An exploratory analysis was also conducted of those categorized as intentionally nonadherent on the basis of "yes" responses to two specific Morisky items that identify nonadherence as a result of feeling better/worse. A secondary outcome measure of adherence was provided by the Medication Adherence Rating Scale (MARS) (Horne 1999), which consisted of five items rated on a Likert scale, with a low score (on a range of 5–25) indicating lower levels of adherence. Our choice of outcome measures was informed by the theoretical and empirical literature on medication adherence spanning the behavioural and medical sciences from which the study questions emerged. These two conceptually different measures provided dichotomous data on nonadherence and continuous data on adherence to patients' antihypertensive medications. The final survey had a total of 135 items (Appendix 3.2).

3.4.6 Translation

Measures that were not validated and available in the required language were translated into the appropriate languages using accredited translators who were native speakers of the target languages and fluent in English. Translations were checked for compatibility with the original version in a process of back translation, performed by persons who were native English speakers and fluent in each target language, to ensure that none of the original meaning was lost. For each language, a third individual acted as a reviewer and highlighted any discrepancies between the forward and back translations, which were resolved by

discussion with the translators. All translations were coordinated by one project partner to ensure consistency. Piloting in each country enabled identification of any semantic inconsistencies.

3.4.7 Sample Size

Based on an expectation of 30% nonadherence (Ross et al., 2004) and a one- sided 5% level of significance, 323 completed Morisky scores were required per country for within-country analyses.

3.4.8 Data Analysis

Responses to the survey were coded in SPSS (version 19; IBM Corporation, Armonk, NY) and analysed in Stata (version 10; StataCorp LP, College Station, TX). Due to the length of the survey a level of missing data was to be expected, with respondents dropping out part way through or skipping questions (Plumpton et al., 2016). We therefore assumed missing responses to questions to be missing at random and imputed using multiple imputations by chained equations (Royston 2009), to create 25 data sets for each country. The assumption of missing at random is considered acceptable for statistical analysis of large well-conducted surveys; where data is not missing 'completely at random' and where missing responses can be predicted by other covariates that have been captured (Rubin, Stern, & Vehovar, 1995). For a single incomplete variable, multiple imputation constructs a model relating the incomplete variable to variables in the prediction model, and draws from the posterior predictive distribution of the missing data, conditional on the observed data. Using multiple imputations by chained equations, imputed values were initialized by drawing at random from observed values. Imputation of missing data was performed on variables ordered by level of "missingness," using observed and current imputed values of all predictors. To ensure stability, this imputation step was cycled 10 times for each of the 25 imputed data sets (White et al., 2011). Analyses were performed on each set, and imputation-specific coefficients were pooled according to Rubin's rules (Rubin 1987). Imputed data were used for all analyses with the exception of demo- graphic variables for which data from complete cases were used.

In the primary analysis, we calculated the percentage of patients classed as nonadherent according to the Morisky score in each country. Potential associations with nonadherence were initially tested univariately using chi-square and independent samples t-tests (associations with the use of medicines were adjusted for age), followed by a logistic regression with nonadherence as the dependent variable. We applied a bivariate method of selecting explanatory variables, whereby only variables found to be significant ($P < 0.05$) in the univariate analysis were entered into the regression model based on a theoretical order (Tabachnick & Fidell 2007; Malek et al., 2007), from determinants classified as demographic and medicine use characteristics (distal) to attitudes and behaviours (proximal). Assumptions regarding multicollinearity, singularity, normality, linearity, and homoscedasticity were tested and met. Country comparison analysis was conducted using chi-square tests. We adopted a similar approach for the secondary outcome of MARS adherence, but with a one-way analysis of variance to test differences among countries.

To account for both within-country and between-country variance, as a secondary analysis, two-level multilevel regression models with respondents nested within-country were specified for both Morisky (logit model) total and intentional nonadherence, and MARS adherence (linear regression model). Multilevel models with random intercepts and fixed effects were specified, initially with all variables common to all countries. Non-contributory variables were subsequently removed iteratively, determined by highest P value using backwards elimination (based on $P < 0.05$). We calculated the variance partition coefficient (Goldstein et al., 2002) to determine the attribution of country to the observed variance in nonadherence.

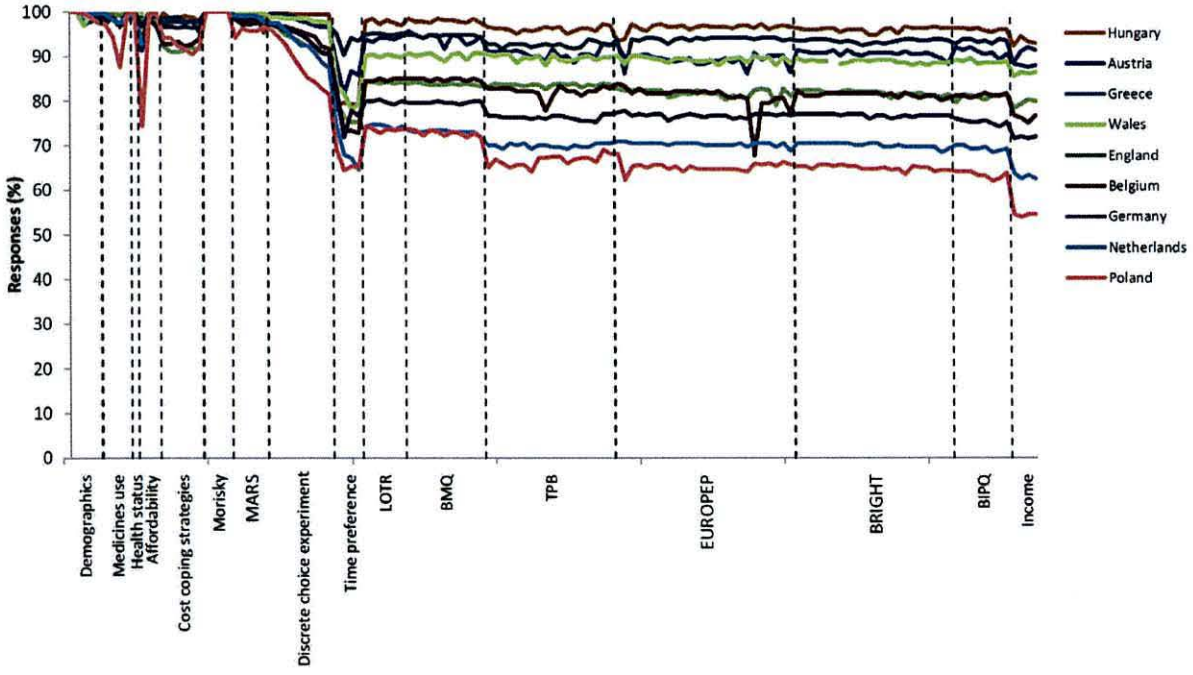
Sensitivity analyses were conducted to explore uncertainty around imputation of missing data and recruitment methods. A complete case analysis of Morisky total nonadherence was performed to assess the sensitivity of our main findings to assumptions relating to missing data. In a post hoc analysis, we assessed the impact of excluding Hungary from the analysis, given that Hungary alone recruited patients from hypertension clinics.

3.5 Results

3.5.1 Participants

A total of 2630 adults from 11 countries completed the questionnaire. Target recruitment was achieved in five countries (Austria, England, Hungary, Poland, and Wales). Study setup and initiation was delayed in Belgium, Germany, Greece, and The Netherlands, leading to nontarget recruitment. The analysis, therefore, includes these countries that each recruited more than 100 participants (n = 2595). There was an inadequate level of available research support in France and Portugal that resulted in low response (n = 11 and n = 33, respectively), and these were excluded from the analysis. Included participants' characteristics are presented in Table 3.1. The overall level of missing data by country ranged from 5% to 26%, with lowest rates seen on demographic and clinical questions (0%–8%), MARS (<2%), medicine necessity and concerns (14%), and self-efficacy (14%) and highest rates seen on the income questions (22%), time preference (22%), and BRIGHT barriers (23%) (Figure 3.1).

Figure 3.1 Percentage of complete responses according to country and individual question



Note. BIPQ, Brief Illness Perception Questionnaire; BMQ, Beliefs about Medicines Questionnaire; BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; EUROPEP, European Task Force on Patient Evaluations of General Practice; LOTR, Life Orientation Test Revised; MARS, Medication Adherence Rating Scale; TPB, theory of planned behaviour.

Table 3.1 Demographic data and cross-country comparison.

	Country (no. of respondents)									
Explanatory variable	Austria (323)	Belgium (180)	England (323)	Germany (274)	Greece (289)	Hungary (323)	The Netherlands (237)	Poland (323)	Wales (323)	X^2 *P* value
Age, mean (95% CI)	60.2 (58.8–61.5)	57.3 (55.6–59.1)	59.6 (58.5–60.7)	56.8 (55.4–58.2)	63.9 (62.6–65.2)	58.2 (56.8–59.7)	58.3 (57.0–59.5)	54.5 (53.2–55.8)	61.1 (59.9–62.2)	16.62 *P* < 0.001 *df* = 8
Sex										
Female	145 (44.9)	64 (35.6)	141 (43.7)	154 (56.2)	173 (59.9)	179 (55.4)	115 (48.5)	171 (52.9)	119 (36.8)	64.54 *P* < 0.001 *df* = 8
Education										
Secondary*	120 (37.2)	6 (3.3)	110 (34.1)	51 (18.6)	148 (51.2)	253 (78.3)	7 (3.0)	167 (51.7)	98 (30.3)	64.54 *P* < 0.001 *df* = 8
Higher	194 (60.1)	174 (96.7)	211 (65.3)	222 (81.0)	135 (46.7)	68 (21.1)	229 (96.6)	155 (48.0)	224 (69.3)	
Married	209 (64.7)	134 (74.4)	241 (74.6)	184 (67.2)	187 (64.7)	234 (72.4)	186 (78.5)	246 (76.2)	258 (79.9)	36.11 *P* < 0.001 *df* = 8
Student/ employed	119 (36.8)	98 (54.4)	166 (51.4)	150 (54.7)	119 (41.2)	124 (38.4)	151 (63.7)	169 (52.3)	143 (44.3)	70.47 *P* < 0.001 *df* = 8
Health status										
Poor	23 (7.1)	4 (2.2)	10 (3.1)	6 (2.2)	0 (0)	26 (8.0)	5 (2.1)	24 (7.4)	13 (4.0)	322.59
Fair	96 (29.7)	25 (13.9)	53 (16.4)	84 (30.7)	93 (32.2)	128 (39.6)	49 (20.7)	133 (41.2)	51 (15.8)	P < 0.001
Good	128 (39.6)	77 (42.8)	123 (38.1)	140 (51.1)	140 (48.4)	132 (40.9)	112 (47.3)	138 (42.7)	116 (35.9)	*df* =24
Very good	74 (22.9)	72 (40.0)	137 (42.4)	44 (16.1)	55 (19.0)	36 (11.1)	69 (29.1)	28 (8.6)	142 (44.0)	
Mean no. medical conditions (95% CI)	2.84 (2.59– 3.08)	2.29 (2.10–2.47)	2.28 (2.15–2.42)	2.13 (1.97–2.30)	2.85 (2.64–3.06)	2.85 (2.68–3.02)	2.08 (1.93–2.24)	2.15 (2.02–2.27)	2.42 (2.26–2.57)	13.16 *P* < 0.001 *df* = 8
Mean no. medicines (95% CI)	4.43 (4.06–4.79)	3.54 (3.19–3.90)	3.84 (3.58–4.10)	3.42 (3.14–3.70)	4.37 (3.99–4.75)	5.17 (4.80–5.53)	3.44 (3.09–3.79)	4.12 (3.83–4.42)	3.80 (3.54–4.06)	12.01 *P* < 0.001 *df* = 8
Mean units medicines per day (95% CI)	5.51 (4.95–6.07)	3.78 (3.33–4.23)	4.93 (4.45–5.40)	3.92 (3.56–4.27)	5.06 (4.57–5.54)	7.44 (6.90–7.98)	4.31 (3.45–5.16)	3.20 (2.89–3.51)	4.97 (4.45–5.49)	22.41 *P* < 0.001 *df* = 8
Most frequently dosed medicine										557.56
Once daily	114 (35.3)	123 (68.3)	224 (9.3)	100 (36.5)	51 (17.6)	54 (16.7)	157 (66.2)	131 (40.6)	241 (74.6)	
Twice daily	110 (34.1)	35 (19.4)	63 (19.5)	129 (47.1)	112 (38.8)	155 (48.0)	56 (23.6)	143 (44.3)	47 (14.6)	P < 0.001
≥Thrice daily	96 (29.7)	19 (10.6)	26 (8.0)	44 (16.1)	123 (42.6)	113 (35.0)	22 (9.3)	48 (14.9)	35 (10.8)	df = 16

Note. Data are counts (%), unless otherwise indicated. CI, confidence interval. *Secondary education meaning to secondary (high) school level, only.

There were significant differences between country samples on all demographic and clinical characteristics assessed. Self- rated health was more often rated as poor or fair in Poland (48.6%) and Hungary (47.6%) than in Belgium (16.1%), England (19.5%), and Wales (19.8%). Fewer respondents from Hungary, Greece, and Poland had received higher education than in other countries. Respondents from Greece tended to be older and more predominantly female, and together with Hungary and Austria had the greatest number of comorbidities and were more likely to be taking medicines more frequently than three times a day.

3.5.2 Prevalence of Nonadherence

Based on Morisky scores, it was found that nonadherence was least prevalent in The Netherlands and most prevalent in Hungary (Table 3.2). Intentional nonadherence was highest in Greece. Polish respondents had significantly lower levels of adherence, as measured by MARS, than did respondents from other countries.

Table 3.2 Prevalence of self-reported total nonadherence and intentional nonadherence across European countries based on Morisky responses, and adherence based on MARS.

Country	Morisky		MARS
	Respondents self-reporting as nonadherent (as a percentage of all respondents) (95% CI)	Respondents self-reporting as being intentionally nonadherent (as a percentage of all respondents) (95% CI)	Mean score (95% CI)*
The Netherlands	24.1 (18.6–29.5)	21.1 (10.5–31.6)	23.86 (23.64–24.16)
Germany	33.2 (27.6–38.8)	35.2 (25.4–45.0)	23.47 (23.28–23.75)
Austria	33.7 (28.6–38.9)	51.4 (42.0–60.8)	23.25 (23.03–23.56)
Wales	38.1 (32.8–43.4)	25.2 (17.5–32.9)	23.46 (23.30–23.77)
Belgium	38.9 (31.8–46.0)	17.1 (8.3–26.0)	23.59 (23.50–23.99)
England	41.5 (36.1–46.9)	23.9 (16.7–31.1)	23.41 (23.17–23.65)
Greece	50.2 (44.4–55.9)	57.2 (49.2–65.3)	22.08 (21.71–22.48)
Poland	57.6 (52.2–63.0)	44.6 (37.5–51.8)	18.19 (17.77–19.01)
Hungary	70.3 (65.3–75.3)	18.1 (13.1–23.1)	22.88 (22.74–23.26)
Cross-country comparison	χ^2: 191.52 df: 8 P = 0.000 Tests cross-country difference in self-reported nonadherence	χ^2: 108.87 df: 8 P = 0.000 Tests cross-country difference in self-reported intentional Nonadherence^	ANOVA F test: 106.08–115.49† (Complete case F: 103.24) P = 0.000

CI, confidence interval; MARS, Medication Adherence Rating Scale.
* 95% CI of mean based on imputed data.
† Range of Imputation-specific statistics.
^as a proportion of all self-reported nonadherence

3.5.3 Associations with Morisky Nonadherence and MARS Adherence

Among demographic factors, only age showed associations across several countries, with younger age associated with Morisky nonadherence in Austria, Belgium, The Netherlands, and Wales (Table 3.3) and older age associated with MARS adherence in The Netherlands (Table 3.4). Unemployment was associated with nonadherence in England and Hungary only. None of the medicine-related factors showed associations with nonadherence in more than one country. The perceived ease or difficulty in borrowing money was associated with nonadherence in England and Germany, and having available strategies to cope with the costs of medicines was significantly associated with MARS-rated adherence in Belgium, England, Greece, and Hungary.

No significant associations were evident for optimism, but, in contrast, beliefs about the illness did play a significant role. Brief Illness Perception Questionnaire factors of low perceived illness consequences, low concern about illness, and low beliefs in personal control over illness were significantly associated with nonadherence on the Morisky scale in Austria, Greece, Poland, and Wales (Table 3.3), and high belief in treatment control, high illness coherence, and high belief in personal control were significant in Austria, Greece, and Hungary based on MARS assessment of adherence (Table 3.4). Illness identity, perceived illness timeline, and emotional representations were not significant, neither were beliefs about medicines, in terms of their necessity or concerns about taking them (Beliefs about Medicines Questionnaire).

The sociocognitive variables, drawn mainly from the theory of planned behaviour, did not emerge consistently in the intercountry analysis. Perceived barriers to adherence (whether changes to daily routine makes taking medicines more difficult) were related to nonadherence only in Greece, although a high number of barriers assessed by BRIGHT (Dobbels et al., 2008; Schmid-Mohler et al., 2010) were associated with nonadherence in Austria and Poland. Intention to adhere was associated with adherence in Hungary and Wales. Low self- efficacy, however, emerged significant in relation to nonadherence in all countries except The Netherlands, and high self- efficacy explained adherence in all countries except Poland. Social support factors emerged significant only in Hungary but in a counterintuitive direction, in relation to low perceived environmental support and greater adherence.

Table 3.3 Summary of the logistic regression model using the Morisky nonadherence as the dependent variable* (1 of 2)

Explanatory variable†	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
Age	0.96 (0.93-0.99) *p* = 0.012	0.97 (0.95– 1.00) *p* = 0.047	0.98 (0.94–1.03) *p* = 0.431	0.97 (0.94–1.01) *p* = 0.012	*not entered*	*not entered*	0.94 (0.91–0.98) *p* = 0.001	0.98 (0.94–1.00) *p* = 0.088	0.97 (0.93–1.00) *p* = 0.037
Employment	1.32 (0.56-3.13) *p* = 0.521	*not entered*	3.14 (1.34–7.34) *p* = 0.008	1.25 (0.49–3.19) *p* = 0.646	*not entered*	2.93 (1.58–5.42) *p* = 0.001	*not entered*	1.12 (0.55–2.27) *p* = 0.762	0.82 (0.37–1.82) *p* = 0.618
Number of tablets	0.97 (0.88–1.07) *p* = 0.502	*not entered*	*not entered*	*not entered*	0.88 (0.78–0.98) *p* = 0.025	*not entered*	*not entered*	*not entered*	*not entered*
Dosing frequency Once daily Twice daily	*not entered*	*not entered*	*not entered*	0.08 (0.03-0.26) *p* < 0.001 0.24 (0.09–0.62) *p* = 0.004	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Income source	0.72 (0.31– 1.67) *p* = 0.445	*not entered*	0.99 (0.36–2.73) *p* = 0.977	3.83 (1.31–11.18) *p* = 0.014	*not entered*	*not entered*	*not entered*	*not entered*	1.08 (0.45–2.58) *p* = 0.864
Borrowing income Difficult Neither difficult nor easy Easy	*not entered*	*not entered*	6.26 (1.14–34.46) *p* = 0.035 5.28 (0.93–30.17) *p* = 0.061 5.47 (1.00–29.77) *p* = 0.050	*not entered*	3.01 (0.81–11.12) *p* = 0.098 1.82 (0.43–7.72) *p* = 0.418 3.08 (0.65–14.59) *p* = 0.157	1.30 (0.64–2.62) *p* = 0.469 3.36 (1.34–8.43) *p* = 0.010 0.59 (0.24–1.47) *p* = 0.261	*not entered*	*not entered*	*not entered*
Number of items prescribed	1.06 (0.95–1.19) *p* = 0.313	*not entered*	0.86 (0.76–0.97) *p* = 0.017	0.84 (0.70–1.00) *p* = 0.051	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*

Table 3.3 Summary of the logistic regression model using the Morisky nonadherence as the dependent variable* (2 of 2)

Explanatory variable†	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
Illness perceptions Illness consequences	0.89 (0.81– 0.99) *P* = 0.029	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Personal control	0.94 (0.84–1.04) P = 0.230	*not entered*	0.94 (0.83–1.07) *P* = 0.333	*not entered*	0.79 (0.66–0.95) *P* = 0.013	0.93 (0.82–1.06) P = 0.289	*not entered*	*not entered*	0.88 (0.79–0.99) *P* = 0.031
Concern about illness	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	0.79 (0.68–0.92) *P* = 0.002	*not entered*
Theory of planned behaviour Barrier	*not entered*	*not entered*	*not entered*	*not entered*	1.28 (1.03–1.60) *P* = 0.028	*not entered*	1.26 (0.97–1.63) P = 0.078	*not entered*	0.93 (0.72–1.22) P = 0.610
Self-efficacy	0.79 (0.70– 0.90) p < 0.001	0.82 (0.69– 0.96) *p* = 0.016	0.62 (0.52–0.74) p < 0.001	0.53 (0.43– 0.67) p < 0.001	0.82 (0.71–0.95) *P* = 0.006	0.84 (0.73–0.96) *P* = 0.013	0.81 (0.68–1.04) P = 0.111	0.70 (0.60–0.82) p < 0.001	0.66 (0.56–0.79) p < 0.001
BRIGHT Barriers	1.04 (1.00–1.08) P = 0.035	*not entered*	1.04 (0.98–1.10) P = 0.155	*not entered*	1.05 (1.00–1.10) *P* = 0.061	1.05 (1.00–1.10) P = 0.051	*not entered*	1.06 (1.00–1.11) P = 0.034	1.05 (0.99–1.11) P = 0.107
Constant	133.99 (6.92– 2593.41) P = 0.001	33.32 (4.06– 273.37) *P* = 0.001	11.78 (0.17–833.40) P = 0.256	649.33 (28.07– 15018.96) p<0.001	8.10 (0.36–183.93) P = 0.189	4.13 (0.49–35.10) *P* = 0.194	33.71 (1.92–591.49) P = 0.016	320.84 (9.36– 10993.92) P=0.001	124.91 (1.44– 10848.02) P=0.034
Other predictors in the model where P> 0.05§	2,18,19,22,24	20	6,7,8,9,15,6,17, 19,20,25	*not entered*	1,9,10,13,15,17 ,19,20,25	9,10,17,23,26	11,12	10,13,14,15,16, 22,25	3,4,5,15,17,20, 21,23,25
Final model χ^2 and P value‖	64.94, 78.87 p<0.001	14.36, 27.28 p<0.001	104.25, 145.31 p<0.001	89.41, 123.04 p<0.001	76.51, 89.42 p<0.001	64.02, 81.23 p<0.001	25.74, 47.98 p<0.001	76.56, 120.57 p<0.001	75.19, 94.15 p<0.001

not entered = independent variable did not reach statistical significance in univariate analysis (p>0.05)

BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; CI, confidence interval.

* Figures are reported as odds ratio (95% CI) and exact *P* values. † Only odds ratios for predictors with $P < 0.05$ for at least one country are presented.

‡ Constant reported for all values of *P*. § Number of medical conditions (1), number of different medicines (2), income deciles 1 to 4 (3), income deciles 5 to 7 (4), income deciles 8 to 10 (5), perception of income: living comfortably (6), perception of income: coping (7), perception of income: finding it difficult (8), affordability problem (9), cost-coping strategies (10), time preference: long (11), time preference: short (12), prescriber of medicines (13), sex of prescriber (14), satisfaction with practitioner (15), satisfaction with practice (16), optimism (17), timeline (18), treatment control (19), illness coherence (20), emotional representations (21), necessity of medicines (22), concern about medicine (23), attitude (24), intention (25), social support (26). ‖ Because χ^2 cannot be pooled, we report the range of imputation-specific χ^2. The degrees of freedom per imputation are given by (number of variables - 1). Imputation-specific *P* values were $P < 0.001$ in all cases, with the exception of three imputations in Belgium (which were *P* = 0.001, 0.001, 0.002).

Table 3.4 Summary of the final regression model (all variables) using the MARS adherence-dependent variable: β coefficient (95% CIs). (1 of 2)

Explanatory variable†	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
Age	0.01 (-0.02 to 0.03) P = 0.606	0.00 (-0.02 to 0.03) P = 0.922	0.02 (-0.01 to 0.05) P = 0.109	0.02 (-0.01 to 0.04) P = 0.153	*not entered*	*not entered*	0.03 (0.00– 0.06) *P* = 0.026	*not entered*	0.00 (-0.02 to 0.03) P = 0.976
Sex	*not entered*	*not entered*	*not entered*	0.39 (-0.10 to 0.88) P = 0.119	*not entered*	*not entered*	*not entered*	*not entered*	0.49 (0.00–0.98) P = 0.050
Cost-coping strategies	-0.01 (-0.22 to 0.01) P = 0.076	-0.17 (-0.30 to -0.06) P = 0.004	-0.12 (-0.21 to -0.02) P = 0.020	-0.06 (-0.16 to 0.05) P = 0.319	-0.35 (-0.42 to -0.28) P < 0.001	-0.21 (-0.28 to -0.15) P<0.001	*not entered*	-0.12 (-0.25 to 0.02) P = 0.094	*not entered*
Time preference Short	*not entered*	*not entered*	*not entered*	*not entered*	7.12 (2.14– 12.09) *P* = 0.005	*not entered*	*not entered*	*not entered*	*not entered*
Illness perceptions Personal control	*not entered*	*not entered*	0.01 (-0.10 to 0.11) P = 0.931	*not entered*	-0.11 (-0.26 to 0.04) *P* = 0.144	0.17 (0.04– 0.30) P = 0.011	0.11 (-0.02 to 0.24) *P* = 0.102	0.05 (-0.24 to 0.33) P = 0.735	0.05 (-0.05 to 0.15) P = 0.348
Treatment control	0.26 (0.13-0.39) P < 0.001	*not entered*	0.13 (-0.02 to 0.28) *P* = 0.095	-0.02 (-0.17 to 0.13) *P* = 0.794	0.08 (-0.08 to 0.24) *P* = 0.299	-0.09 (-0.25 to 0.07) *P* = 0.284	*not entered*	0.11 (-0.27 to 0.50) P = 0.558	0.07 (-0.08 to 0.20) P = 0.366
Illness coherence	*not entered*	*not entered*	-0.07 (-0.20 to 0.06) P = 0.274	*not entered*	0.17 (0.02– 0.32) P = 0.032	0.08 (-0.06 to 0.21) P = 0.257	*not entered*	*not entered*	-0.01 (-0.13 to 0.10) *P* = 0.814
Theory of planned behaviour Intention	-0.09 (-0.25 to 0.07) P = 0.286	*not entered*	0.06 (-0.17 to 0.28) P = 0.623	*not entered*	0.15 (-0.03 to 0.33) *P* = 0.112	0.32 (0.09– 0.55) P = 0.007	*not entered*	-0.01 (-0.53 to 0.51) P = 0.971	0.33 (0.04–0.62) P = 0.028
Self-efficacy	0.28 (0.16– 0.40) P < 0.001	0.19 (0.02– 0.36) P = 0.027	0.30 (0.17–0.42) P < 0.001	0.32 (0.19– 0.46) P < 0.001	0.39 (0.26– 0.52) P < 0.001	0.15 (0.03– 0.26) P = 0.016	0.25 (0.09– 0.41) *P* = 0.002	0.29 (-0.03 to 0.61) P = 0.072	0.37 (0.22–0.51) P < 0.001

Table 3.4 Summary of the final regression model (all variables) using the MARS adherence-dependent variable: β coefficient (95% CIs). (2 of 2)

Explanatory variable†	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
BRIGHT Barriers	-0.04 (-0.07 to 0.00) P = 0.062	-0.01 (-0.05 to 0.03) P = 0.698	-0.04 (-0.09 to 0.01) P = 0.081	-0.00 (-0.03 to 0.03) P = 0.893	-0.05 (-0.09 to 0.01) *P* = 0.010	-0.07 (-0.11 to -0.03) P = 0.101	*not entered*	-0.08 (-0.17 to 0.00) P = 0.057	-0.06 (-0.11 to 0.00) *P* = 0.060
Social support	-0.02 (-0.09 to 0.04) P = 0.520	*not entered*	0.00 (-0.04 to 0.05) P = 0.920	*not entered*	*not entered*	-0.05 (-0.10 to -0.01) P = 0.024	*not entered*	*not entered*	0.03 (-0.02 to 0.07) P = 0.270
Constant	18.97 (15.83– 22.10) P < 0.001	21.72 (19.04– 24.40) P < 0.001	17.83 (13.96– 21.69) P < 0.001	20.15 (17.35– 22.96) P < 0.001	19.06 (16.32– 21.80) P < 0.001	19.76 (16.70– 22.82) P < 0.001	19.48 (17.29– 21.68) P < 0.001	13.74 (8.97– 18.51) P < 0.001	19.37 (15.86– 22.88) P < 0.001
Other predictors in the model where P > 0.05†	2, 6, 11, 13, 14, 20, 22, 23	11, 14, 20	3, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24	13, 14, 16, 17, 19, 20, 22	3, 5, 7, 8, 10, 11, 12, 14, 15, 17, 19, 24	1, 7, 10, 13, 14, 15, 16, 17, 19, 20, 22, 23, 24	24	13, 21, 23	3, 4, 5, 8, 11, 13, 14, 15, 16, 17, 19, 20, 23, 24
Adjusted R2	0.2831	0.2005	0.3809	0.2223	0.6521	0.4589	0.1335	0.1482	0.3570

***not entered** = independent variable did not reach statistical significance in univariate analysis (p>0.05)*

BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; MARS, Medication Adherence Rating Scale.

* Only coefficients for predictors with P o 0.05 for at least one country are presented.

† Marital status (1), employment (2), dosage frequency (3), number of medicines (4), number of medical conditions (5), income source (6), total income (7), income perception (8), borrowing (9), affordability problem (10), health status (11), time preference: long (12), satisfaction with practitioner (13), satisfaction with practice (14), optimism (15), illness consequences (16), identity (17), concern about illness (18), emotional representations (19), concern about medicine (20), necessity of medicine (21), attitude (22), normative beliefs (23), barriers-theory of planned behaviour (24).

The variables examined in this study explained between 13.4% and 65.2% of the variability in MARS adherence (Table 3.4).

3.5.4 Multilevel Model

The multilevel logit model for Morisky nonadherence identified males, being of younger age, being employed, low number of medicines, high dosing frequency, high normative beliefs, low self-efficacy, high perceived barriers, low personal control, low concern about illness, and difficulty in borrowing money as being significantly associated with nonadherence (Table 3.5). Associations were consistent in the model specified with Morisky intentional nonadherence. Multilevel linear regression found that older age, a lower level of education, a greater number of medicines, less frequent dosing, having low perceived barriers, low perceptions of illness consequences, beliefs in treatment control, and high self-efficacy were connected to higher adherence as measured by MARS. Based on the Morisky scale, 11% and 7% of the explained variance in total and intentional nonadherence, respectively, was attributable to differences among countries and 23% of the variance in adherence based on MARS was attributable to differences among countries.

3.5.5 Sensitivity Analysis

The analysis of complete cases resulted in less precise estimators, as expected, altering the significance of some variables and hence their inclusion in the final model. Self-efficacy and perceived barriers (BRIGHT), however, remained significant as in the primary analysis.

When Hungary was excluded from the multilevel model (because of the aforementioned difference in recruitment method), we observed a reduction in between-country variance in Morisky nonadherence (from 11% to 4%). Other factors emerged as being significant, including education, number of medical conditions, attitudes, and intention to adhere, though self-efficacy and barriers remained significant.

Table 3.5 Summary of multilevel regression models for Morisky and MARS as outcome measures.

Explanatory variable	Morisky		MARS	
	Odds ratio	95% CI	β coefficient	95% CI
Sex	1.22*	1.01–1.47		
Age	0.98†	0.97–0.99	0.01*	0.00–0.02
Employment	0.74*	0.59–0.94		
Education			-0.34‡	-0.60 to -0.09
Number of medicines	0.89†	0.86–0.93	0.06*	0.01–0.10
Dosing frequency	1.30‡	1.12–1.52	-0.24‡	-0.42 to -0.06
Normative beliefs	1.05*	1.01–1.09		
Self-efficacy	0.73†	0.70–0.77	0.36†	0.30–0.42
Barriers (BRIGHT)	1.70†	1.38–2.09	-0.83†	-1.10 to -0.57
Illness consequences			-0.06*	-0.10 to -0.01
Personal control	0.94‡	0.90–0.97		
Treatment control			0.11‡	0.04–0.19
Concern about illness	0.94‡	0.91–0.98		
Borrowing money	0.85‡	0.78–0.94		
Constant	34.59†	13.5–88.5	19.45†	18.1–20.8
Random effects parameters	Variance	95% CI	Variance	95% CI
Between-country variance (σ^2_u)	0.40	0.15–1.07	2.14	0.79–5.80
Within-country variance (σ^2_e)			7.09	6.63–7.57
% variance attributable to differences between countries	10.82	4.35–24.49	23.20	10.63–43.40

Notes. For the logit model, $(\sigma^2_e) = \pi^2/3$
Variance partition coefficient = $\sigma^2_u / (\sigma^2_u + \sigma^2_e)$
Full model specification: age, sex, education, marital status, employment, number of medical conditions, number of different medicines,number of tablets, dosing frequency, number of items prescribed, health status, affordability problem, optimism, necessities, concerns about medicine, attitudes, normative beliefs, barrier (theory of planned behaviour), facilitators, intention, self-efficacy, prescriber of medicines, sex of prescriber, satisfaction with practitioner, satisfaction with practice, barriers (averaged as one less collected in Wales), social support, illness consequences, illness timeline, personal control, treatment control, illness symptomaticity, concern about illness, illness coherence, emotional representations, income source, income perception, ease of borrowing, total income.
BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; CI, confidence interval; MARS, Medication Adherence Rating Scale.
* $P < 0.05$.
‡ $P < 0.01$
† $P < 0.001$

3.6 Discussion

Self-reported nonadherence to antihypertensive medicines is prevalent, even among the sampled population who were in receipt of a current prescription for antihypertensive treatment. Prevalence differs significantly across countries, and although a proportion of this variance is explained by country-level effects and demographic characteristics, our principal finding is that potentially modifiable factors of low perceived self-efficacy and, to a lesser extent, low personal control beliefs and high perceived barriers are consistently associated with nonadherence. Perceived barriers to adherence included forgetfulness or interruption of daily routine, practical difficulties, and feeling overwhelmed by circumstances or complexity of regimen. Our finding of common associations with nonadherence across different countries supports the importance of these factors, particularly given the significant differences that exist in cultural, medical practices, and health care systems that contribute to a small proportion of the variance in nonadherence.

Adherence is generally explained by the converse of the above, but cost-related behaviour (i.e., strategies to cope with the cost of prescriptions) and intention also emerged as significant in several countries. The multilevel analysis of all countries shows that although many factors act in the opposite direction depending on whether we are addressing nonadherence or adherence, some uniquely explain nonadherence, for example, employment status, low normative beliefs, low personal control, low illness concern, and low borrowing potential, and others uniquely explain adherence, for example, lower education, low perceived illness consequences (both these are counterintuitive), and beliefs in treatment control. The multilevel analyses also suggest that where possible, a reduction in dose frequency and number of prescribed medicines might achieve improvements in adherence.

The literature on adherence to medicines contains many analyses that have tested the significance of clinical, treatment, and demographic characteristics as predictors of nonadherence, assuming that behaviour is a function of these characteristics alone. This approach has significant limitations. Our analysis is rooted in behavioural theories to reflect the notion that individual beliefs and social influences are potentially more relevant determinants of intentional and nonintentional nonadherence (and of adherence) than

relatively fixed attributes of the person or the clinical situation. Previous studies have shown that, based on sociocognitive and self-regulation theories, personal and perceived control (Ross et al., 2004; Chen et al., 2009; Bane et al., 2006; Barclay et al.,2007; Roh 2005), perceived benefits of treatment (Brown & Segal, 1996; Youssef & Moubarak, 2002), and perceived barriers—such as forgetfulness and experienced or anticipated adverse effects (Brown & Segal, 1996; Richardson et al., 1993) —are significant predictors of nonadherence in patients taking antihypertensive medicines. Associations between higher levels of self-efficacy and adherence in patients with hypertension have been noted previously (Bane et al., 2006; Criswell et al., 2010).

The novelty and key strength of our study is that a range of theoretically informed factors derived from behavioural theories in health psychology and economics were tested concurrently across several European countries. Our analysis also considered the distinction between intentional and unintentional non-adherence. Associations with intentional nonadherence were fewer, and although several overlapped with those associated with overall nonadherence, that is, age, self-efficacy, and perceived barriers, other factors included the number of medical conditions, concerns about medicines, perceived illness identity, and behavioural intention. The act of deliberately choosing to avoid taking medicines, therefore, warrants interventions that more explicitly target illness and treatment and behavioural beliefs. This is also of interest when considering the notable finding that the association between beliefs about medicine and adherence was not statistically significant in the primary analysis (multivariate by country and multilevel). Whereas the findings of the literature review (Chapter 2) found strong evidence of association between adherence and medication beliefs (10/11 studies reached statistical significance). The statistically significant association between high concerns about medicines and intentional nonadherence suggests that patients who have concerns about their medicines (e.g. worries, long-term effects, dependency on medicines, etc.) are more likely to deliberately stop taking their high blood pressure medicines. This has implications for future research that should consider the distinction between intentional and unintentional nonadherence.

There are several caveats to our analysis, however, which may limit the strength of the interpretations. First, only 5 of the intended 11 countries reached target recruitment. We pragmatically included all nine countries that recruited an appreciable number of patients; however, this reduced the precision of the estimates of nonadherence in each country and limited the strength of inferences. Second, our analyses might be confounded by differences

in methods of recruitment. Although all countries—except Hungary—recruited via community pharmacies, the exclusion of Hungary from the secondary analysis resulted in more variables being significant. The main findings of the primary (per country) analysis, however, remained unchanged. Third, because responses were elicited via self-administered questionnaires, we had no means of confirming hypertension diagnosis, nor other responses, or mitigate any self- presentation bias, which would reduce the external validity of our findings. Fourth, we were unable to assess the impact of nonresponse bias (Johnson & Wislar, 2012) because those who failed to complete the outcome measures—which were at the beginning of the questionnaire—were not allowed to progress through the remainder of the survey. The length of the survey represents a fifth limitation, which may have had an impact on completion rates. The variables ultimately emerging as being associated with nonadherence and adherence (i.e., theory of planned behaviour barriers and self-efficacy), however, had relatively low levels of missingness and we improved precision by performing multiple imputation. Although multiple imputation addresses problems in complete case analyses related to loss of efficiency and bias due to differences between observed and unobserved data, it is no substitute for a complete data set and requires an important but unverifiable assumption that data are missing at random. Moreover, only subscale totals rather than every individual item were imputed for health psychology measures. This may introduce bias because data from respondents who completed some, but not all, of the items in a subscale were discarded. Sixth, although we used validated scales wherever possible, full testing of the BRIGHT measure did not exist at the time of the study. Finally, self-reported measures of adherence are prone to bias (Shi et al., 2010), and may not distinguish among failure to initiate dosing, incorrect implementation of the dosing regimen, and treatment discontinuation (Vrijens et al., 2012). In mitigation, however, we used two measures of adherence and both had a significant association with self- efficacy.

Notwithstanding these limitations, the findings can inform the development of nonadherence-reducing (or adherence- enhancing) interventions. Most importantly, the common variables identified within our study are amenable to change through improved communication with health care professionals or brief cognitive-behavioural intervention. Reviews of adherence-improving interventions (Schroeder et al., 2004; Gwadry-Sridhar et al., 2013) offer support for self-efficacy enhancement, with modest effects reported in trials of supportive and individually tailored telephone calls, information on self- management, checks on understanding, and concerns regarding medicines and empowerment. Our analysis suggests that a theoretically informed, controlled trial of cognitive-behavioural interventions, focused on increasing self-efficacy and related control beliefs and reducing perceived

barriers to adherence behaviours, is warranted. Given the broad spectrum of potential barriers and the observation of independent, country-level differences, which may be related to cultural, health service, or other factors, interventions that are tailored specifically to the population in which they are being delivered are the most likely to be effective.

3.7 Acknowledgements

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3.8 Candidates contribution

DH and VM (supervisors) conceived the study. EAFH (the candidate) designed the survey and protocol (alongside co-authors and the ABC team), gained research governance approval in the UK, managed data collection and recruiting pharmacists in Wales. Catrin Plumpton managed and imputed the data. CP, Sadia Parveen and VM (supervisor) analysed the responses. CP, SP, VM (supervisor), EAFH (the candidate) and DH (supervisor) interpreted the results. VM (supervisor) and SP drafted the manuscript. EAFH (the candidate), DH (supervisor) and co-authors revised the manuscript for intellectual content. DH (supervisor) finalised the manuscript.

Chapter 4

Multinational discrete choice experiment of persistence with medications

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4.1 Preface

Chapter 3 presented the results of a multinational cross sectional survey of predictors of adherence to antihypertensive medications.

This chapter presents a stated preference discrete choice experiment. Discrete choice experiments (DCEs) are a survey method to measure patients' preferences for goods (including healthcare services, interventions, medicines), that can be used in the absence of any data on revealed (actual) preferences (de Bekker-Grob, 2012). Respondents choose between hypothetical but realistic alternatives, described in terms of a number of attributes (e.g. adverse events), each characterised by specific levels (e.g. frequency of adverse events). This allows for the estimation of the relative importance of each attribute, assessment of any trade-offs between attributes (e.g. treatment benefits versus mild but common adverse events), and of respondents' total satisfaction (utility) with the medication (Ryan & Farrar, 2000; de Bekker-Grob, 2012). This is of particular interest when considering risk benefit decisions (Mt-Isa et al., 2014), such as the choice of medication.

This DCE of persistence with medication explores how significant determinants of persistence (identified in Chapter 2) and adherence (identified in Chapter 3) influence utility and probability of persistence with medication. The findings of the study are presented in a case study of the probability of persistence with 5-aminosalicylic acid for ulcerative colitis, which serves as an exemplar of how this method could be applied to clinical trial data to model the impact of patient preferences in optimising the use of medicines.

This is the first concurrent assessment of influence on patient decision to persist with medication, in terms of utility they derive from medication characteristics and psychosocial characteristics associated with medication preferences.

4.2 Abstract

Objective: To examine patients' stated preferences to persist with medicines and to explore the influence of psychosocial and sociocognitive factors.

Methods: Community-dwelling, hypertensive patients recruited from 9 European countries were invited to complete a discrete choice experiment (DCE) with attributes for treatment benefits, mild yet common adverse drug reactions (ADR), rare but potentially life-threatening ADR and dosing frequency. Patients responded to the binary-choice of which medicine would they be most likely to continue taking. Data were analysed using a random effects logit model.

Results: 2549 patients from Austria (n=321), Belgium (n=175), England (n=315), Germany (n=266), Greece (n=288), Hungary (n=322), The Netherlands (n=231), Poland (n=312) and Wales (n=319) completed the DCE. All attributes significantly influenced patients' stated preference to persist with medications ($p<0.05$). Patients were willing to accept decreases in treatment benefits of: 50.6 percentage points (95%CI: 46.1-57.9) for a very rare (as opposed to rare) risk of severe ADR; 28.3 percentage points (95%CI: 25.2-33.1) for a once-daily instead of twice-daily dosing; and 0.74 percentage points (95%CI: 0.67-0.85) for a 1% point reduction in mild ADR. Models accounting for psychosocial and sociocognitive characteristics were significantly different from the base case.

Conclusion: Patients' intention to persist with treatment was associated with their willingness to trade potential benefits, harms, and dosing frequency. Psychosocial and sociocognitive factors influenced the extent of trading. The utility model may have value in assessing patients' likelihood of persisting with medicines, and to tailor treatment to maximise persistence.

4.3 Introduction

Medication adherence encompasses the processes of initiation, implementation of dosing and persistence (Vrijens et al., 2012). Reduced persistence with prescribed treatment is prevalent, with median length of time between patients' initiation of treatment for chronic diseases and their last dose being typically in the order of 1 year (Vrijens et al., 2008), despite failure to continue treatment having a detrimental effect on health (Osterberg & Blaschke, 2005). Reasons for the premature discontinuation of medicines are varied, and include factors related to patients, such as their beliefs and socioeconomic characteristics; the condition and its treatment; healthcare professionals and health systems (Osterberg & Blaschke, 2005; Sabaté, 2003). There is emerging evidence of the role of behavioural economic theories in explaining patients' choice to persist with their prescribed medicines (Elliott et al., 2008). This is based on a notion that persistence with medications may be an outcome of a decision patients consciously make about whether the continued taking of their medication will increase their utility (Lamiraud & Geoffard, 2007). That is, if patients' utility (satisfaction) is maximised through taking their medications, their likelihood of persisting increases; but conversely if patients maximise their utility by not taking their medications, they will discontinue treatment.

Patients' utility may be examined using stated preference techniques, such as a discrete choice experiment (DCE) (Ryan et al., 2008). DCEs are an attribute-based survey measure underpinned by a Lancastrian view of utility which contends that goods and services (or medicines in this case) can be described by their characteristics or attributes and that the utility yielded by a medicine is a function of its various attributes (Lancaster, 1974). Choices reveal information about the relative importance of each attribute, willingness to trade between attributes, and total utility (which patients aim to maximise).

DCEs represent a particularly effective method of eliciting preferences regarding health processes and outcomes that have gained extensive use in several contexts, including patients' preferences for medicines (de Bekker-Grob et al., 2012; Clark et al., 2014), but few empirical studies have made specific reference to the process of adherence to medication (Hauber et al., 2009; Johnson et al., 2007; Mohamed et al., 2015). Hauber et al., (2009) conducted a study of treatment preferences and adherence to oral glucose-lowering agents

amongst individuals with type 2 diabetes and found that while patients were willing to accept some adverse events in exchange for better glucose control, stated adherence would reduce with increasing risk of weight gain or myocardial infarction. Using a choice-format stated-preference survey, Johnson et al., (2007) identified severity of depressive episodes, weight gain and the cognitive effects of treatments for bipolar disorder to affect patients' likelihood to adhere.

The view that nonadherence may be considered a rational behaviour that reveals patient preferences, adds to more established health psychology research studies. Within health and social psychology there exist several theoretical frameworks and models for explaining variation in health-related behaviours, which can be applied to persistence with medications (Holmes et al., 2014). Sociocognitive theory assumes that persistence is motivated by outcome expectancies and goals (such as improved health), which are determined by individuals' attitudes and beliefs (Turner et al., 2007; Apter et al., 2003; Abraham et al., 1999). Models within sociocognitive theory that have been applied to persistence with medications include the Health Belief Model (Rosenstock, 1974; Becker, 1974) and The Theory of Planned Behaviour (Ajzen, 1991). In this context, the Health Belief Model postulates the likelihood of persistence is increased if the perceived threat of illness from sub-optimal persistence is high, the benefit of medicines-taking is greater than the barriers to medicines-taking, and cues to action (e.g. reminders) are in place. The Theory of Planned Behaviour suggests an individual's intention to persist with medication increases if the perceived consequences are high (attitudes towards behaviour and outcome expectancies are positive), they have strong positive beliefs about what others expect (perceived social norms); and they perceive a high level of personal control / self-efficacy with regards to persisting, even when facing barriers; this will depend on their perception of internal resources (e.g. knowledge) and external resources (e.g. social support).

A more dynamic link between cognitions, motivation and behaviour can be explored using self-regulation theory (Leventhal et al., 1992). Self-regulation theory describes the individual as an active problem solver and describes the cognitive and behavioural process by which individuals monitor and adjust their medication taking as the perceived solution to the problem of illness and its consequences (Abraham et al., 1999). Illness representations or beliefs, together with treatment beliefs, shape coping responses e.g. persistence with medications. Beliefs about a particular illness and state of ill health are thought to form around five domains: (i) Identity: signs and symptoms; (ii) Timeline: ideas about the time-

frame of a condition (acute, chronic, cyclical); (iii) Cause: perception of cause (internal, external, stable, unstable etc.); (iv) Consequences: expected outcomes (physical, psychological and social); and, (v) Control / cure: beliefs about potential cure and (internal/external) control. The contribution of the models described can be measured using self-report questionnaires for each component e.g. Barriers in the Theory of Planned Behaviour, or Illness consequences within Illness Perception Questionnaire.

Concurrent assessment of influences on patients' decisions to persist with a medication in terms of the utility they derive from medication characteristics, and theory driven psychosocial characteristics associated with medication preferences, increases the possibilities for interventions which could be both medicine and person-based. We are unaware of any study in which a range of health psychology theories have been tested simultaneously alongside preference elicitation methods in relation to medication persistence.

This study aims to (i) assess how patients from across Europe value the key attributes of medicines in their stated decision to persist with taking them and to examine the trade-off between potential benefit, harm and convenience; (ii) use a case study to estimate the relationship between these preferences and psychosocial and sociocognitive characteristics.

4.4 Methods

The study involved a multi-national, web-based survey of hypertensive adult patients containing a DCE designed to elicit the preferences of patients for attributes of a hypothetical medication. The survey was piloted and ethically approved for eleven European countries: Austria, Belgium, England, France, Germany, Greece, Hungary, The Netherlands, Poland, Portugal, and Wales. Patients were eligible for the study if they self-reported as being 18 years or older, diagnosed by a doctor as having hypertension that lasted at least 3 months, currently prescribed antihypertensive medication, and personally responsible for administering their medication. Respondents were excluded if they were aged less than 18 years, declared a psychiatric disorder, or lived in a nursing home or similar facility where they were not responsible for their own medicines taking. The target sample was for a minimum of 100 respondents per country (consistent with DCE studies de Bekker-Grob et

al., 2012; Clark et al., 2014) up to a maximum of 323 patients per country (Morrison et al., 2015). Respondents were principally recruited using advertisements in community pharmacies. Additional strategies included advertisements in hypertension clinics (Hungary), GP surgeries (Hungary and Poland) and local press (England and Wales). The survey was anonymous, hosted online and restricted to one respondent per Internet Protocol address.

4.4.1 DCE attributes, levels, and experimental design

We identified a list of potential attributes from 18 DCE studies of medicinal products identified in a systematic review (de Bekker-Grob et al., 2012). Attributes identified were categorised as follows: mild adverse drug reactions (n=14 studies), treatment outcome (n=13), severe adverse drug reactions (n=6), dose related (n=5), duration of treatment (n=4), location of treatment (n=3), cost (n=3), route of administration (n=1), quality of life (n=1). The four most commonly used attributes were selected: treatment benefit, risk of common mild adverse drug reactions (ADRs), risk of rare but potentially life-threatening ADRs and dosage frequency (Table 4.1). As stated, cost did not reach the pre-defined eligibility criteria for inclusion as an attribute in the DCE (only 3/18 studies included cost, attribute category ranked =6 of the attribute categories identified). Furthermore differences in prescription payments systems and currencies across countries would limit comparison of preferences between countries.

We hypothesised that benefits would have a positive influence on patients' stated intention to persist with treatment, while increased risk of harms and dose frequency would be negative.

Table 4.1 Attributes and Levels used in the Discrete Choice Experiment (DCE)

Attribute name	Attribute description	Level description	Rationale for levels
Benefit	Treatment benefits	1 in 20 2 in 20 4 in 20	Based on typical Numbers Needed to Treat for treatment for chronic conditions (e.g. hypertension, diabetes, ulcerative colitis)
Dose	Number of times you need to take the medicine	Once a day Twice a day Four times a day	The majority of chronic disease treatments are in the range of once to four times daily dosing
Mild ADR	Mild side-effects e.g. feeling sick, diarrhoea	1 in 10 3 in 10 5 in 10	Gastrointestinal irritation is a common ADR for many treatments. Frequency based on representative range
Severe ADR	Potentially life-threatening side-effects	Very rare: 1 in 10,000 Rare: 1 in 1,000 Uncommon: 1 in 100	Likelihood of life-threatening ADRs are typically uncommon to very rare

Each attribute was set to have three levels, representative of treatments used commonly for the management of chronic diseases. These were set at plausible values with a range sufficient to encourage respondents to trade, and limit potential dominance (Table 4.1), while allowing for scenarios (e.g. for improved benefit) to be modelled. For the DCE to be broadly generalizable across many common treatments, we used a hypothetical scenario of an unlabelled medicine and respondents were not given information on any specific condition or disease area. The question posed was: Which medicine would you be most likely to continue taking? Respondents were required to select either Medicine A or Medicine B. There was no option to opt-out of the decision, as the DCE was designed to measure preferences for persistence with medication (whereas an opt-out option would represent discontinuation). Figure 4.1 provides an example of the pairwise choice used in the experiment.

The number of possible choice scenarios in a full factorial design was $3^4 = 81$. As this would pose too great a burden on respondents, a fractional factorial design was selected with 9 profiles from a published design catalogue (Hahn & Shapiro, 1996). Binary choices were created using the fold-over method which replaces each attribute level with its opposite (Street & Burgess, 2001). The attribute and question order was randomised to avoid left or right selection bias. Rational trading was tested by examining responses to a dominant profile which had a lower risk of mild ADR, lower dosage frequency, higher treatment benefit and lower risk of severe ADR.

Figure 4.1 Example of pairwise choice

We would like you to imagine that you have been prescribed a **new** medicine that you should continue taking until your doctor advises otherwise. In the following questions the characteristics of two alternative medicines will be described to you, please indicate which medicine you would be most likely to continue taking, 'Medicine A or Medicine B'.

	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	5 in 10 	1 in 10 
Number of times you need to take the medicine	Once a day	Twice a day
Treatment benefits	4 in 20 	1 in 20 
Potentially life-threatening side-effects	Uncommon: 1 person in 100	Very Rare: 1 person in 10,000
Which medicine would you be most likely to continue taking?	☐	☐

4.4.2 Survey of psychosocial and sociocognitive factors

Validated self-report instruments were used to assess sociocognitive determinants of adherence (Morrison et al., 2015). Illness representations were measured using the Brief Illness Perception Questionnaire (B-IPQ) (Broadbent et al., 2006). Patient beliefs in the necessity and concerns of medications were measured using the Beliefs about Medicines Questionnaire (Horne, 1996). Constraints and facilitators of adherence were measured using barrier and social support subscales of the BRIGHT questionnaire (Dobbels et al., 2008; Schmid-Mohler et al., 2010. Attitudinal and belief components of the Theory of Planned Behaviour (TPB) were scored on a 5-point Likert scale (Conner & Norman, 1996; Farmer et al., 2006). Self-reported adherence was measured using the Morisky questionnaire (Morisky et al., 2008) which categorises participants as being non-adherent if they respond with a "yes" to at least one of four questions posed; and the Medication

Adherence Rating Scale (MARS) which results in a continuous score for adherence (range 5-25) (Horne, 1999). Details of the psychosocial measures used in the exploratory analysis are provided in Appendix 4.1. The full survey content is detailed elsewhere (Morrison et al., 2015).

4.4.3 Translation

Measures that were not validated and available in the required language were translated into the appropriate languages (and back-translated for checks of compatibility with the English version) using accredited translators who were native speakers of the target languages and fluent in English. Descriptions of ADR prevalence were taken from the European Medicines Agency's standard text for summaries of product characteristics, which is available in all European languages.

4.4.4 Data analysis

Results of the DCE were analysed in STATA (version 10; StataCorp LP, College Station, TX) using a random effects logit model that allowed for repeated observations from the same respondent:

$$U = \beta 0 + \beta 1 SEVERE\_ADR + \beta 2 DOSE + \beta 3 BENEFIT + \beta 4 MILD\_ADR + \varepsilon$$

U = utility derived by individual

β0 = constant term

βi = estimated coefficient for each attribute (variable)

ε = error term

Treatment benefit and risk of mild ADR were included in the analysis as linear continuous variables. We explored the assumption of linearity for frequency of dose and risk of severe ADR, using effects coding and plotting the resulting size of the coefficient against the level of each attribute. The level of the base case was calculated using the estimated levels: e.g.

$$\beta \text{very rare SEVERE\_ADR} = -(\beta \text{rare SEVERE\_ADR} + \beta \text{uncommon SEVERE\_ADR})$$

The DCE contained two value attributes: treatment benefit and risk of common, mild ADR, that were used to compare the rate at which patients were willing to give up a unit change in benefit or harm in exchange for a unit change in another, whilst maintaining the same utility (marginal rates of substitution, MRS). 95% confidence intervals were calculated by Bootstrapping with 1,000 replications. Left or right hand bias was explored by using counts of how many respondents continually selected medicine A or B. The random effects logit model was then estimated using data from all respondents, including those with dominant preferences, and then re-run excluding patients who showed dominant preferences. Coefficients and 95% confidence intervals were computed for the model with and without dominant preferences and the results were compared. The influence of psychosocial and sociocognitive factors on preferences for persistence was assessed using exploratory subgroup analyses. Subgroups were selected for analysis if they: (i) had a statistically significant association with adherence (as defined by Morisky or MARS) (Morrison et al., 2015); and (ii) were confirmed as significant predictors of persistence in other published studies (Holmes et al., 2014). Log likelihood ratio tests of the base case regression and the models comprising the two subgroups were performed at a 5% level of significance. If the subgroup model was significantly different, the MRS for harms and benefits were calculated for each category within the subgroup.

4.4.5 Application of results: Case study

To illustrate the application of the findings of the study, we chose 5-aminosalicylates (5-ASAs) for ulcerative colitis (UC) for a case study on the basis of there being several treatment options available, with each differing with respect to efficacy, harms, and dosing regimen. The four most commonly dispensed 5-ASAs in primary care in England (Health and Social Care Information Centre, 2013) were selected for analysis: sulfasalazine (Salazopyrin tablets 500mg), mesalazine (Asacol 400mg MR tablets), olsalazine (Dipentum 250mg capsules) and balsalazide (Colazide 750mg capsules). Ulcerative colitis is a chronic condition characterised by colon and rectum inflammation and small ulcers on the lining of the colon. Symptoms include diarrhoea, abdominal pain, increased frequency of bowel movements, fatigue, loss of appetite, and weight loss. The condition is relapsing and remitting, which may have implications for preferences for medication i.e. patients may be willing to accept a greater risk of adverse events if they are in remission and treatment benefits would mean they avoid a flare-up of the condition.

The probability of persisting with each 5-ASA was calculated from data on treatment characteristics and the results of the DCE. Data on efficacy and adverse events were

obtained from a published meta-analysis of RCTs of 5-ASAs versus placebo in inducing remission in active UC (Ford et al., 2011). Data on severe ADRs and dosing frequencies were obtained from summaries of product characteristics (Table 4.2). Patient utility was calculated by weighting the results of the DCE utility function against likely outcomes of treatment with each of these four drugs. The probability of persistence for each agent was then calculated as the exponential of the utility divided by the sum of the exponential of the utility. Changes to the probability of persisting were assessed for a range of patient characteristics.

Table 4.2 Values of regression variables used to estimate utility and probability of persistence with 5-ASAs for ulcerative colitis

	Drug name				References
	sulfasalazine	mesalamine	olsalazine	balsalazide	
Probability of remission	0.37	0.42	0.33	0.24	Ford et al., (2011)
Probability of ADR	0.34	0.13	0.20	0.10	Ford et al., (2011)
Frequency of severe ADR (aplastic anaemia)	Very rare	Rare	Very rare	Very rare	SmPC
Maintenance dose frequency	Four times daily	Once a day	Twice a day	Twice a day	SmPC

SmPC summary of product characteristics

4.5 Results

The analysis was restricted to nine countries that reached the target sample size. There was an inadequate level of available research support in France and Portugal that resulted in low response (n=11, n=33 respectively) thus these countries were excluded. Eighty-nine percent (n=2,549) of people who started the survey completed at least one DCE question. These were from Austria (n=321), Belgium (n=175), England (n=315), Germany (n=266), Greece (n=288), Hungary (n=322), The Netherlands (n=231), Poland (n=312) and Wales (n=319).

4.5.1 Sample characteristics

Participants' characteristics are presented in Table 4.3. Respondents were split almost equally according to gender (51% male) and employment status (52% employed), had a median age of 60 years, and were prescribed a median of 3 different medicines per day. The majority of patients (54%) were prescribed medicines that required more than once-daily dosing.

4.5.2 Magnitude and statistical significance of attributes

Among respondents to the DCE, 91.2% selected the dominant choice while only 2.5% of respondents showed left hand bias, consistently choosing medicine A (1.77%) or B (0.76%). There was no significant difference between models which either included or excluded these respondents, therefore the all respondents were included in the base case analysis.

All four attributes influenced respondents' stated intention to persist with treatment ($p<0.01$) (Table 4.4). Respondents were most likely to persist with the treatment offering greatest benefit ($\beta=0.031$), least risk of mild but common ADRs ($\beta=-0.023$), or severe but rare ADRs ($\beta=1.553$), and the least frequent dosing regimen ($\beta=0.869$). The signs and direction of the regression coefficients were consistent with expectation.

All else being equal, the odds of patients stating that they would continue taking their medicines increased by 3% for every 1 percentage point increase in the chance of treatment benefits, and increased 2% for every 1 percentage point decrease in the risk of common mild side-effects. A medicine with the lowest risk of severe ADR (very rare) increased the odds of persistence four-fold, and the lowest dose frequency (once daily) more than two-fold.

4.5.3 Comparing preferences

Marginal rates of substitution, using treatment benefit as the value attribute, suggest that patients were willing to forego improvements in treatment benefits in order to: reduce the risk of severe ADR (forego 50.6 percentage point improvement in treatment benefit for a 'very rare' risk of severe of ADR as opposed to a rare risk); reduce the frequency of dosing (forego 28.3 percentage point improvement in treatment benefit for once-daily dosage frequency as opposed to twice daily); and to reduce the risk of common mild side-effects (forego 7.4 percentage point improvement of treatment benefit for a 10 percentage point reduction in mild ADR) (Table 4.5). When considering harm as the value attribute, respondents were also willing to accept an increase in risk of mild ADR to avoid severe ADR (68.6 percentage point increase in risk of mild side-effects for a 'very rare' risk of severe ADR as opposed to rare); and to move to a less frequent dosing schedule (38.4 percentage point increase in risk of mild ADR for once daily dose frequency as opposed to twice daily).

Table 4.3 Patient characteristics

Characteristic		n	%	Mean (sd)	Median (range)
Sex (male)		1309	51.35		
Age (years)				58.95 (11.73)	60 (18-95)
Employment (in/out)		1315	51.98		
Education (higher)		1583	62.67		
Marital status (married)		1842	72.81		
Ability to borrow money					
	Very/quite difficult	934	45.69		
	Neutral	456	22.31		
	Quite/very easy	353	17.27		
	Not willing to provide	301	14.73		
Health status*					
	Poor/ fair	805	31.66		
	Good	1089	42.82		
	Very good/ excellent	649	25.52		
Morisky nonadherence					
	Non-adherent	1115	43.74		
	Intentionally non-adherent	366	14.36		
MARS adherence				22.75 (3.20)	24 (5-25)
Number of medicines per day				4.07 (2.84)	3 (0-22)
Most frequently dosed medicine					
	Once daily	1174	46.24		
	Twice daily or more	1365	53.76		
Sociocognitive theory:					
Theory of Planned Behaviour					
	Subjective norms of adherence {3-15}			13.03 (2.70)	15 (3-15)
	Barriers {3-15}			2.49 (1.43)	2 (1-5)
	Intention {2-10}			9.12 (1.46)	10 (2-10)
	Self-efficacy {2-10}			7.43 (2.31)	8 (2-10)
BRIGHT Environmental	Constraints / Facilitators				
	Social support {0-35}			3.93 (5.74)	2 (0-29)
	BRIGHT Barriers {0-60}			7.79 (9.09)	5 (0-75)
Self-regulation theory:					
Illness Representations					
	Illness consequences {0-10}			4.36 (3.21)	4 (0-10)
	Personal control {0-10}			6.27 (2.74)	7 (0-10)
	Treatment control {0-10}			7.74 (2.22)	8 (0-10)
	Illness concern {0-10}			5.39 (2.98)	5 (0-10)
Treatment Beliefs					
	Necessity of medicine {5-25}			18.47 (3.97)	18 (5-25)
	Concerns about medicine {6-30}			16.17 (5.26)	16 (6-30)

Note. * Stanford Self-rated Health (Lorig et al., 1996) Figures in curly brackets indicate the range (minimum to maximum) of scores for each scale.

Table 4.4 Random effects logit model

Attribute	Coefficient (95%CI)	p-value	Odds Ratio
Severe ADR - Very rare	1.553 (1.469 to 1.637)		4.726
Severe ADR - Rare	-0.444 (-0.488 to -0.401)	0.0000	0.641
Severe ADR - Uncommon	-1.109 (-1.149 to -1.068)	0.0000	0.330
Dose - Once a day	0.869 (0.776 to 0.961)		2.383
Dose - Twice a day	-0.296 (-0.341 to -0.250)	0.0000	0.744
Dose - Four times a day	-0.573 (-0.620 to -0.526)	0.0000	0.564
Treatment benefit	0.031 (0.028 to 0.034)	0.0000	1.031
Common mild side-effects	-0.023 (-0.024 to -0.022)	0.0000	0.978
Constant	0.452 (0.414 to 0.490)	0.0000	1.572
Number of observations	22277		
Number of groups	2549		
Wald chi^2 (6 degrees of freedom)	1465		
Log likelihood	-11952.52		

Table 4.5 Patients' marginal rates of substitution between treatment benefit or reduction in common mild side-effects and other attributes

Attribute	Marginal rate of substitution (MRS)	
	Treatment benefit % (95% CI)	Risk reduction of mild ADRs % (95% CI)
Severe ADR - Very rare	50.58 (46.07, 57.87)	68.60 (63.98, 72.35)
Severe ADR - Rare	-14.48 (-16.99, -12.77)	-19.64 (-21.60, -17.49)
Severe ADR - Uncommon	-36.10 (-41.24, -32.94)	-48.96 (-51.25, -45.90)
Dose - Once a day	28.29 (25.18, 33.11)	38.36 (34.77, 42.50)
Dose - Twice a day	-9.63 (-11.88, -8.14)	-13.05 (-15.33, -11.15)
Dose - Four times a day	-18.66 (-21.51, -16.67)	-25.31 (-27.60, -22.95)
Treatment benefit		1.36 (1.17, 1.49)
Common mild side-effects	-0.74 (-0.85, -0.67)	

4.5.4 Exploratory analysis

Regressions controlling for psychosocial variables were significantly different from the base-case regression in 10/12 cases (Table 4.6), but in each case, all four attributes were significant and in the expected directions. Respondents' willingness to trade treatment benefit for once daily dosing, as opposed to twice daily, was significantly higher for respondents who were unlikely to take their medicines regularly. These respondents, who had low intentions, were willing to forgo an additional 29.9 percentage point benefit to take medication once, rather than twice a day (i.e. Table 4.6; MRS of lower intentions 49.97 minus MRS of high intentions 20.06). Individuals with high concerns about medicines were

also willing to forgo an additional benefit to take medication once, rather than twice a day (22.2 percentage points); as where those who lacked confidence in their medicines-taking i.e. those with low self-efficacy (16.6 percentage points) and, those with higher illness concern (willing to forgo a 15.5 percentage point improvement in benefit to take medication once, rather than twice a day).

Respondents' willingness to trade treatment benefit for the lowest risk of ADR (very rare) opposed to a rare risk was significantly higher for respondents who (i) were unlikely to take their medicines regularly (people with low intention were willing to forgo a 32.4 percentage point additional benefit for a very rare risk of severe ADR, than those categorised as high TPB intentions); (ii) demonstrated high illness concern (24.5 percentage points); and (iii) had high concerns about medicines (23.8 percentage points).

4.5.5 Case study

Based on the characteristics of four 5-ASAs for ulcerative colitis, the probability (utility) of respondents choosing to persist was: olsalazine 31.3% (1.72), balsalazide 31.3% (1.72), sulfasalazine 23.7% (1.44), and mesalazine 13.7% (0.89). The influence of demographics, adherence, psychosocial and sociocognitive factors showed variation in these probabilities, although the proportion of patients preferring olsalazine and balsalazide remained comparatively constant (Figure 4.2).

Components of the Theory of Planned Behaviour had the greatest influence on the probability of persistence across all four drugs. A patient with high barriers (strongly agree with the statement: "changes to my daily routine would make it difficult for me to take my medicine") prescribed sulfasalazine will derive 1.20 utility from this drug with a 21.7% probability of persistence. If barriers (perceived and /or real) were reduced via an intervention aimed at improving the convenience of medicines taking, their utility would increase to 1.89 and a corresponding 25.6% probability of persistence. The perception that persistence is influenced by the approval of others e.g. doctor, nurse, partner, family (subjective norms) and individual intentions also have similar effects on probability of persistence across the four drugs.

Table 4.6 Results of exploratory subgroup analysis of willingness to trade benefit or mild ADR with other attributes, presented by psychological theory, model, and factor. (1 of 4)

Psychological theory, model, factor^	Trade-off	Subgroup MRS (95% confidence interval)	
Sociocognitive Theory			
Theory of Planned Behaviour			
Subjective norms:		Higher	Lower
Perception that persistence is influenced by approval of others: doctor, nurse, partner, family.		Influence of others	Influence of others
	Mild ADR / Benefit	-0.64 (-0.79, -0.56)	-0.77 (-0.94, -0.68)
	Once daily dose / Benefit	23.25 (19.23, 29.40)	31.77 (27.06, 39.57)
	Twice daily dose / Benefit	-8.39 (-11.58, -6.60)	-9.70 (-13.27, -7.77)
	Four times a day dose / Benefit	-14.86* (-18.26, -12.22)	-22.07* (-26.78, -19.04)
	Very rare severe ADR / Benefit	50.91 (43.99, 60.89)	45.56 (39.24, 54.81)
	Rare severe ADR / Benefit	-14.85 (-18.34, -12.39)	-12.23 (-15.39, -9.77)
	Uncommon severe ADR / Benefit	-36.06 (-43.10, -31.43)	-33.33 (-39.89, -29.10)
	Benefit / Mild ADR	-1.55 (-1.80, -1.27)	-1.29 (-1.48, -1.06)
	Once daily dose / Mild ADR	-36.14 (-42.92, -30.20)	-41.01 (-47.13, -35.56)
	Twice daily dose / Mild ADR	13.04 (10.11, 16.67)	12.52 (10.00, 15.72)
	Four times a day dose / Mild ADR	23.10 (19.24, 26.99)	28.49 (24.98, 32.02)
	Very rare severe ADR / Mild ADR	-79.14* (-86.43, -71.82)	-58.81* (-64.10, -53.07)
	Rare severe ADR / Mild ADR	23.08* (19.59, 26.38)	15.78* (12.99, 18.62)
	Uncommon severe ADR / Mild ADR	56.06* (50.93, 60.76)	43.03* (39.34, 46.50)
Barriers:		Higher	Lower
Changes to daily routine would make it more difficult to take medicines regularly		Barriers	Barriers
	Mild ADR / Benefit	-0.77 (-0.92, -0.67)	-0.59 (-0.74, -0.52)
	Once daily dose / Benefit	30.33 (25.80, 36.85)	22.68 (18.57, 28.91)
	Twice daily dose / Benefit	-9.49 (-12.40, -7.46)	-8.24 (-11.43, -6.24)
	Four times a day dose / Benefit	-20.84* (-24.68, -17.97)	-14.44* (-17.94, -11.98)
	Very rare severe ADR / Benefit	46.27 (40.24, 55.68)	49.72 (43.71, 59.66)
	Rare severe ADR / Benefit	-12.73 (-16.20, -10.49)	-14.27 (-18.07, -11.86)
	Uncommon severe ADR / Benefit	-33.53 (-39.42, -29.24)	-35.45 (-42.26, -31.38)
	Benefit / Mild ADR	-1.30* (-1.49, -1.09)	-1.69* (-1.93, 1.36)
	Once daily dose / Mild ADR	-39.43 (-44.74, -34.36)	-38.23 (-45.75, -31.34)
	Twice daily dose / Mild ADR	12.34 (9.84, 15.07)	13.89 (10.28, 18.00)
	Four times a day dose / Mild ADR	27.09 (23.74, 30.44)	24.35 (19.98, 29.05)
	Very rare severe ADR / Mild ADR	-60.15 (-64.87, -55.26)	-83.81* (-91.51, -75.28)
	Rare severe ADR / Mild ADR	16.55 (14.18, 19.01)	24.06* (20.23, 27.60)
	Uncommon severe ADR / Mild ADR	43.59 (40.27, 46.51)	59.75* (54.13, 64.69)
Intention:		Higher	Lower
Likely to and/or intend to take medicines		Intentions	Intentions
	Mild ADR / Benefit	-0.58* (-0.67, -0.52)	-1.10* (-1.58, -0.86)
	Once daily dose / Benefit	20.06* (17.08, 24.18)	49.97* (38.10, 70.71)
	Twice daily dose / Benefit	-6.67* (-8.77, -5.28)	-16.64* (-24.72, -11.80)
	Four times a day dose / Benefit	-13.39* (-15.72, -11.58)	-33.34* (-46.34, -25.70)
	Very rare severe ADR / Benefit	40.26* (36.21, 45.97)	72.70* (56.78, 101.43)
	Rare severe ADR / Benefit	-11.10* (-13.20, -9.48)	-21.31* (-31.12, -16.06)
	Uncommon severe ADR / Benefit	-29.16* (-33.11, -26.36)	-51.39* (-71.54, -40.64)
	Benefit / Mild ADR	-1.73* (-1.91, -1.50)	-0.91* (-1.16, -0.64)
	Once daily dose / Mild ADR	-34.64 (-40.38, -29.79)	-45.36 (-52.58, -38.07)
	Twice daily dose / Mild ADR	11.51 (9.09, 14.70)	15.10 (11.37, 18.86)
	Four times a day dose / Mild ADR	23.12 (20.00, 26.34)	30.26 (25.79, 34.79)
	Very rare severe ADR / Mild ADR	-69.53 (-74.41, -63.71)	-65.99 (-73.01, -59.12)
	Rare severe ADR / Mild ADR	19.17 (16.56, 21.79)	19.34 (16.13, 22.86)
	Uncommon severe ADR / Mild ADR	50.36 (46.44, 53.33)	46.65 (42.12, 50.80)

Table 4.6 Results of exploratory subgroup analysis of willingness to trade benefit or mild ADR with other attributes, presented by psychological theory, model, and factor. (2 of 4)

Psychological theory, model, factor^	Trade-off	Subgroup MRS (95% confidence interval)
Self-efficacy:	Higher	Lower
Confidence of taking medicines and/or at the prescribed times	Confidence	Confidence
Mild ADR / Benefit	-0.58* (-0.68, -0.52)	-0.93* (-1.17, -0.78)
Once daily dose / Benefit	21.31* (18.08, 25.71)	37.90* (30.67, 48.12)
Twice daily dose / Benefit	-7.26 (-9.63, -5.80)	-12.34 (-16.92, -9.20)
Four times a day dose / Benefit	-14.06* (-16.46, -12.10)	-25.56* (-32.06, -20.90)
Very rare severe ADR / Benefit	44.11 (39.51, 50.42)	55.71 (47.02, 68.98)
Rare severe ADR / Benefit	-12.25 (-14.64, -10.40)	-15.90 (-20.92, -12.80)
Uncommon severe ADR / Benefit	-31.86 (-36.06, -28.76)	-39.81 (-49.21, -33.43)
Benefit / Mild ADR	-1.71 (-1.91, -1.47)	-1.08* (-1.28, -0.86)
Once daily dose / Mild ADR	-36.50 (-42.82, -31.06)	-40.92 (-46.81, -35.06)
Twice daily dose / Mild ADR	12.43 (10.02, 16.01)	13.33 (10.27, 16.46)
Four times a day dose / Mild ADR	24.07 (20.54, 27.42)	27.59 (23.95, 31.05)
Very rare severe ADR / Mild ADR	-75.55* (-82.07, -68.88)	-60.14* (-66.36, -54.28)
Rare severe ADR / Mild ADR	20.99 (18.03, 24.01)	17.16 (14.27, 20.21)
Uncommon severe ADR / Mild ADR	54.56* (50.02, 58.65)	42.98* (39.13, 46.59)
Sociocognitive Theory		
Bright: Environmental Constraints / Facilitators		
Social support	Higher	Lower
Support from people in personal environment	Social support	Social support
Mild ADR / Benefit	-0.64 (0.78, -0.56)	-0.87 (-1.09, -0.74)
Once daily dose / Benefit	25.76 (21.93, 32.10)	30.73 (24.84, 39.28)
Twice daily dose / Benefit	-8.44 (-11.46, -6.69)	-10.67 (-14.99, -7.87)
Four times a day dose / Benefit	-17.32 (-21.13, -14.65)	-20.06 (-25.21, -16.61)
Very rare severe ADR / Benefit	42.01* (36.55, 50.80)	61.01* (51.62, 75.39)
Rare severe ADR / Benefit	-11.52 (-14.65, -9.44)	-17.24 (-22.12, -14.04)
Uncommon severe ADR / Benefit	-30.49* (-36.48, -26.85)	-43.76* (-53.90, -37.17)
Benefit / Mild ADR	-1.55* (-1.78, -1.29)	-1.15 (-1.36, -0.92)
Once daily dose / Mild ADR	-40.02 (-46.49, -34.07)	-35.39 (-41.63, -29.68)
Twice daily dose / Mild ADR	13.11 (10.32, 16.79)	12.29 (9.40, 15.65)
Four times a day dose / Mild ADR	26.91 (23.10, 30.77)	23.10 (19.43, 26.43)
Very rare severe ADR / Mild ADR	-65.25 (-71.52, -58.83)	-70.25 (-76.67, -63.43)
Rare severe ADR / Mild ADR	17.90 (14.93, 21.19)	19.86 (16.75, 23.03)
Uncommon severe ADR / Mild ADR	47.36 (43.06, 51.18)	50.40 (45.86. 54.30)
Self-regulation Theory		
Illness Representations		
Illness consequences	Higher	Lower
How much does your illness affect your life?	Illness consequences	Illness consequences
Mild ADR / Benefit	-0.77 (-0.94, -0.65)	-0.64 (-0.76, -0.57)
Once daily dose / Benefit	32.67 (27.43, 40.65)	22.58 (18.88, 28.03)
Twice daily dose / Benefit	-10.18 (-13.80, -7.87)	-8.07 (-10.83, -6.17)
Four times a day dose / Benefit	-22.50* (-27.20, -19.10)	-14.51* (-17.46, -12.22)
Very rare severe ADR / Benefit	53.76 (45.87, 64.60)	43.36 (38.35. 51.07)
Rare severe ADR / Benefit	-15.24 (-19.24, -12.56)	-12.16 (-14.94, -10.17)
Uncommon severe ADR / Benefit	-38.52 (-46.03, -33.07)	-31.20 (-36.62, -27.56)
Benefit / Mild ADR	-1.31* (-1.53, -1.07)	-1.56 (-1.76, -1.32)
Once daily dose / Mild ADR	-42.70 (-49.51, -36.83)	-35.34 (-41.33, -29.57)
Twice daily dose / Mild ADR	13.30 (10.37, 16.80)	12.63 (9.80, 15.77)
Four times a day dose / Mild ADR	29.40 (25.49, 33.59)	22.71 (19.28, 25.93)
Very rare severe ADR / Mild ADR	-70.26 (76.95, -64.03)	-67.84 (-73.64, -61.77)
Rare severe ADR / Mild ADR	19.92 (16.77, 23.28)	19.03 (16.27, 22.06)
Uncommon severe ADR / Mild ADR	50.34 (45.92, 54.69)	48.82 (44.94, 52.40)

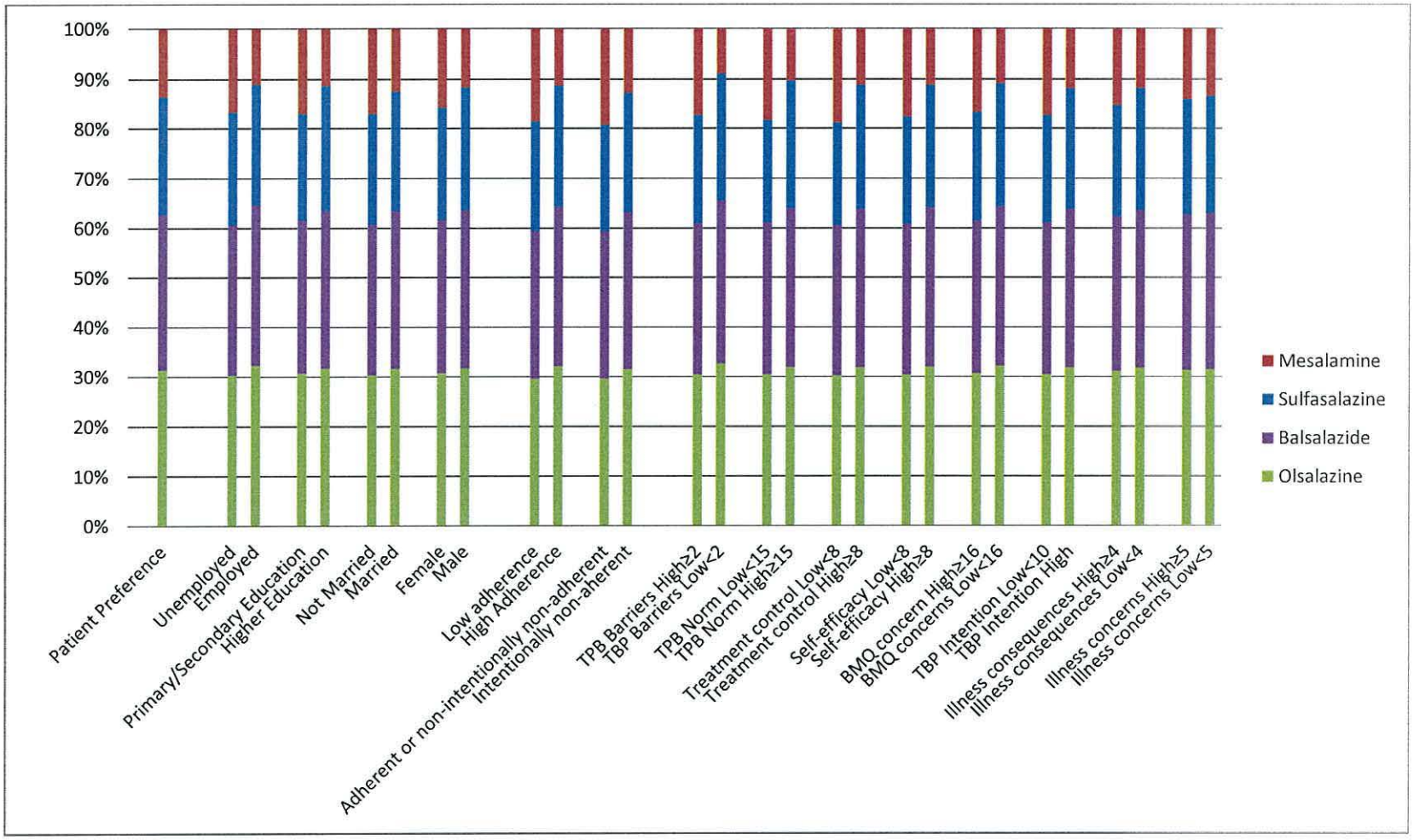
Table 4.6 Results of exploratory subgroup analysis of willingness to trade benefit or mild ADR with other attributes, presented by psychological theory, model, and factor. (3 of 4)

Psychological theory, model, factor^	Trade-off	Subgroup MRS (95% confidence interval)
Personal control	Higher	Lower
How much control do you feel you have over your illness?	Personal control	Personal control
Illness		
Mild ADR / Benefit	-0.83 (-1.01, -0.71)	-0.60 (-0.72, -0.53)
Once daily dose / Benefit	30.79 (24.97, 38.61)	24.53 (20.66, 30.01)
Twice daily dose / Benefit	-10.26 (-13.77, -7.52)	-8.25 (-11.03, -6.39)
Four times a day dose / Benefit	-20.53 (-25.22, -17.20)	-16.28 (-19.41, -13.96)
Very rare severe ADR / Benefit	58.86* (50.95, 71.72)	39.59* (34.61, 47.11)
Rare severe ADR / Benefit	-16.64 (-20.96, -13.42)	-11.08 (-14.01, -9.20)
Uncommon severe ADR / Benefit	-42.23* (-51.55, -36.86)	-28.51* (-33.68, -25.19)
Benefit / Mild ADR	-1.21 (-1.41, -0.99)	-1.67 (-1.89, -1.40)
Once daily dose / Mild ADR	-37.28 (-43.27, -31.74)	-40.96 (-47.13, -34.53)
Twice daily dose / Mild ADR	12.42 (9.48, 15.49)	13.78 (10.76, 17.26)
Four times a day dose / Mild ADR	24.85 (21.23, 28.23)	27.18 (23.19, 30.67)
Very rare severe ADR / Mild ADR	-71.27 (-77.02, -65.43)	-66.11 (-72.54, -59.50)
Rare severe ADR / Mild ADR	20.14 (17.28, 23.25)	18.50 (15.62, 21.65)
Uncommon severe ADR / Mild ADR	51.12 (47.16, 54.78)	47.61 (43.33, 51.46)
Treatment control	Higher	Lower
How much do you think your treatment can help your illness?	Treatment control	Treatment control
Mild ADR / Benefit	-0.67 (-0.80, -0.60)	-0.77 (-0.96, -0.65)
Once daily dose / Benefit	24.35 (20.81, 29.84)	32.92 (27.15, 41.82)
Twice daily dose / Benefit	-8.56 (-11.27, -6.77)	-10.19 (-14.33, -7.46)
Four times a day dose / Benefit	-15.79* (-18.89, -13.57)	-22.74* (-28.29, -19.18)
Very rare severe ADR / Benefit	49.91 (44.64, 58.58)	46.26 (39.16, 57.57)
Rare severe ADR / Benefit	-14.28 (-17.33, -12.30)	-12.60 (-16.86, -9.92)
Uncommon severe ADR / Benefit	-35.64 (-41.91, -31.83)	-33.66 (-41.27, -28.44)
Benefit / Mild ADR	-1.48 (-1.67, -1.25)	-1.30 (-1.54, -1.04)
Once daily dose / Mild ADR	-36.12 (-42.10, -30.87)	-42.90 (-49.92, -36.54)
Twice daily dose / Mild ADR	12.69 (10.16, 15.96)	13.27 (10.07, 16.82)
Four times a day dose / Mild ADR	23.43 (19.95, 26.71)	29.63 (25.71, 33.81)
Very rare severe ADR / Mild ADR	-74.05 (-79.96, -68.30)	-60.27* (-66.63, -53.91)
Rare severe ADR / Mild ADR	21.18 (18.46, 24.12)	16.41 (13.37, 20.09)
Uncommon severe ADR / Mild ADR	52.87 (48.71, 56.44)	43.85* (39.62, 47.88)
Illness concern	Higher	Lower
How concerned are you about your illness?	Illness concern	Illness concern
Mild ADR / Benefit	-0.90* (-1.10, -0.78)	-0.51* (-0.61, -0.44)
Once daily dose / Benefit	35.45* (29.60, 44.41)	19.98* (16.30, 25.06)
Twice daily dose / Benefit	-11.91 (-16.01, -9.30)	-6.61 (-9.32, -4.77)
Four times a day dose / Benefit	-23.54* (-28.63, -20.11)	-13.37* (-16.22, -11.12)
Very rare severe ADR / Benefit	60.83* (52.54, 73.78)	36.33* (31.85, 43.05)
Rare severe ADR / Benefit	-17.17* (-21.47, -14.36)	-10.07* (-12.86, -8.02)
Uncommon severe ADR / Benefit	-43.66* (-52.71, -37.86)	-26.26* (-30.82, -23.13)
Benefit / Mild ADR	-1.11* (-1.29, -0.91)	-1.98* (-2.25, -1.63)
Once daily dose / Mild ADR	-39.40 (-45.00, -34.82)	-39.55 (-47.39, -32.48)
Twice daily dose / Mild ADR	13.24 (10.82, 16.22)	13.09 (9.39, 17.41)
Four times a day dose / Mild ADR	26.16 (23.07, 29.40)	26.47 (21.82, 30.81)
Very rare severe ADR / Mild ADR	-67.61 (-73.02, -62.02)	-71.91 (-79.68, -63.11)
Rare severe ADR / Mild ADR	19.08 (16.56, 21.61)	19.93 (16.15, 23.72)
Uncommon severe ADR / Mild ADR	48.52 (44.84, 51.78)	51.98 (46.36, 56.85)

Psychological theory, model, factor^	Trade-off	Subgroup MRS (95% confidence interval)
Self-regulation Theory		
Treatment Beliefs		
Concerns about medicine	Higher Concerns about medicines	Lower Concerns about medicines
Mild ADR / Benefit	-1.01* (-1.33, -0.85	-0.53* (-0.63, -0.47
Once daily dose / Benefit	41.48* (33.90, 54.45)	19.31* (16.38, 23.61)
Twice daily dose / Benefit	-13.34* (18.84, -10.10)	-6.62* (-8.99, -5.13)
Four times a day dose / Benefit	-28.14* (-36.63, -23.24)	-12.70* (-15.11, 10.84)
Very rare severe ADR / Benefit	63.88* (52.54, 82.42)	40.06* (35.95, 46.87)
Rare severe ADR / Benefit	-17.70 (-23.79, -13.92)	-11.31 (-13.94, -9.60)
Uncommon severe ADR / Benefit	-46.17* (-59.47, -38.47)	-28.75* (-33.10, -25.81)
Benefit / Mild ADR	-0.99* (-1.18, -0.75)	-1.90* (-2.12, -1.60)
Once daily dose / Mild ADR	-40.89 (-46.88, -34.80)	-36.77 (-43.18, -30.91)
Twice daily dose / Mild ADR	13.15 (10.18, 16.36)	12.60 (9.62, 16.13)
Four times a day dose / Mild ADR	27.74 (24.20, 31.29)	24.17 (20.44, 27.60)
Very rare severe ADR / Mild ADR	-62.97* (-68.84, -57.12)	-76.27* (-83.20, -69.36)
Rare severe ADR / Mild ADR	17.45 (14.46, 20.80)	21.53 (18.31, 24.93)
Uncommon severe ADR / Mild ADR	45.52* (41.84, 48.88)	54.74* (49.92, 58.89)

Note. ^ Full details of the measures used in Appendix 4.1. *MRS*. Marginal Rate of Substitution between attributes. p<0.004 adjusted for multiple comparison n=12 subgroups. Spilt sample analysis not significantly different to base case for: Sociocognitive theory, BRIGHT Barriers: problems with taking medicines or taking them on time p=0.0093; and, Self-regulation Theory, Treatment beliefs: beliefs about the necessity of medicine P=0.0645; therefore marginal rates of substitution were not calculated.

Figure 4.2 Probability of persistence with 5-ASAs in ulcerative colitis by subgroup



4.6 Discussion

The results of the study suggest that, in addition to treatment benefits, patients place a high value on reduced risk of severe (but relatively rare) ADRs and less frequent dosing when stating that they choose to continue taking a medicine. Stated preference to persist is therefore associated with the willingness to trade potential benefits for reduced harm and increased convenience. The total utility produced by different combinations of these attributes may have value in assessing patients' likelihood of persisting with medicines, in the context of health care provider-patient communications, and the personalisation of medicines, or formulations thereof, to maximise persistence.

This study has shown that the evidence-based medicine model of health maximisation via use of treatments with the highest expected net benefit may not necessarily result in the best outcome for patients if there is misalignment in preferences. Persistence with medications can be considered as an outcome of a decision patients make about whether the continued taking of the medication will increase their utility (Lamiraud & Geoffard, 2007). Maximising utility may therefore increase persistence, which may lead to better health outcomes – even when using a less effective treatment. Our analysis therefore suggests a mechanism via which the prescribing of alternative treatments might improve persistence and hence health outcome. We have also found that patients' trade-offs between benefits, harm and convenience are influenced by psychosocial and sociocognitive factors. Interventions to improve persistence, grounded in theory and targeted towards psychosocial variables (e.g. barriers to medicines, self-efficacy / confidence in medicines taking) may therefore improve the probability of persistence directly (Morrison et al., 2015), and indirectly through changing patients' preferences for medicines-related attributes. The case study illustrated that improvements in sociocognitive factors could increase the utility of routinely prescribed drugs for ulcerative colitis and thus encourage persistence. Whilst this study has identified potential determinants of persistence, further research is necessary to design and provide evidence on the efficacy of potential interventions. Our findings suggest that several factors influence persistence, however a simple intervention, such as a guided conversation or a medicines review, could enable health care professionals to identify barriers to medicines taking and assess how other people influence perceptions of medicines (subjective norms), in order to increase an individual's self-efficacy via education or counselling.

Interestingly the stated preference model that controlled for intentions, as measured in the context of the Theory of Planned Behaviour, was significantly different from the base case model – suggesting that the medication characteristics (harms, benefits & convenience) are valued and traded differently by people high intentions to adhere, compared to those with low intentions to adhere (two items: "It is likely that I will take my medicines regularly", "I intend to take my medicines regularly"). Whilst this explains difference between those with high and low intention, what is also of interest is the potential gap between those with high intentions who ultimately do not persist (intention of behaviour, but no action). Similarities between theories would suggest that the stated preferences of these individuals will differ from their revealed preferences. Further research exploring stated versus revealed preferences, and analysing the factors that predict the gap between intention and action, is warranted.

Previous DCEs of preferences for medicines reveal that patients are willing to trade benefit for reduced harm (de Bekker-Grob et al., 2012; Clark et al., 2014). In the context of adherence, a DCE by Mohamed et al. (2015) showed that lower frequency of administration, shorter administration times, and milder ADR appear to improve stated adherence to antibiotic treatment of CF lung infections. A study of patients with HIV, using a modified adaptive conjoint analysis, identified pill burden, dosing frequency, and adverse events as having the greatest impact on patients' perceived ability to adhere to antiretroviral medication regimens (Stone et al., 2004). Our case study showed variation in utility among 5-ASAs, which would impact on stated persistence. This is consistent with claims data from the US showing median persistence to be higher with balsalazide (148 days) than with of sulfasalazine (98.5 days) or mesalamine (137 days) (Yen et al., 2012).

To our knowledge this is the first study of preferences for persistence with medication to survey a large multi-national sample; and, the first study to measure both stated preferences and a wide range of psychosocial factors concurrently. The DCE was generic, based on previously tested actionable attributes and used European Medicines Agency data and terminology where possible to enable general application. The selection of psychosocial and sociocognitive factors tested alongside the DCE attributes was guided by theory and based on empirical evidence. This adds to the DCE methodological literature by demonstrating how country and psychosocial characteristics can be considered in both the interpretation of preference weights and applied utility models. The results suggest that policy can be informed using both product and consumer (patient) characteristics. Furthermore, the case

study of 5-ASAs for UC also serves as an exemplar of how this method could be applied to clinical trial data to model the impact of patient preferences in optimising the use of medicines.

There were a number of limitations. Firstly, patients self-selected to participate in the study and we must therefore acknowledge the risk of selection bias which may influence the results insofar as only people who were actively interested in expressing their views on their medicines taking behaviour participated, which may reduce the external validity of our findings. Secondly, our study was restricted to four attributes to cover benefits, harms and convenience; findings from other studies of preferences for medications (not persistence with) suggest that attributes such as route of administration (Levitan et al., 2015), quality of life, location / provider, duration of treatment, among others, may also have a significant influence on preference. The risk attributes were also presented as probabilities with no indication of frequency or time horizon. It is acknowledged, however, that trading multiple attributes is cognitively challenging (Gigerenzer, 2003). We aimed to minimise this by piloting the DCE extensively and by using two methods of displaying risk. Event frequencies were supplemented by pictograms which were intended to aid interpretation by depicting probabilities graphically and colour-coding positive and negative effects. Respondents find it much easier to understand pictorial representations than probabilities presented in the form of 1 in X chance (Gigerenzer 1995). Thirdly, the respondents were diagnosed with hypertension whereas the case study used to illustrate the findings of the DCE was ulcerative colitis. The DCE description, however, did not provide details of the medication nor the condition and thus was not based on antihypertensive treatments. The DCE was not amenable to treatments for hypertension as they are mainly once daily. Fourthly, the length of the survey (135 items) represents a further limitation, but completion rates were high as the DCE was purposely put towards the beginning of the survey before participants were asked to complete any items that may have conditioned their choice (Morrison et al., 2015). Finally, as with any stated preference study, the findings need to be confirmed by studies of revealed preference.

Patients were willing to trade potential benefits, harms, and convenience in responding that they would persist with treatment. Potentially alterable, psychosocial factors influence the extent of the trade-offs between these attributes. Persistence may therefore be enhanced directly, through selection of medicines meeting preferred levels of attributes; or, indirectly through targeting modifiable psychosocial factors that affect trade-off choices. The novel

finding of an interaction between patients' stated preferences to persist with medication and their sociocognitive characteristics (i.e. high/low illness concerns, high/low self-efficacy etc.) provides a basis for synergistically effective approaches aimed to change behaviour (e.g. to increase self-efficacy) and treatment selection (e.g. reduced dose frequency).

4.7 Acknowledgements

The authors wish to acknowledge Dr Catrin Plumpton (Bangor University); and the Ascertaining Barriers to Compliance (ABC) Project Team for their participation in internal meetings, discussing the progress and findings of this research; and, for their internal review of the report to funders. The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

4.8 Candidates contribution

DH and VM (supervisors) conceived the study. Under the supervision of DH and VM, EAFH (the candidate) designed the survey and protocol (alongside co-authors and the ABC team), designed the discrete choice experiment, gained research governance approval in the UK, managed data collection and recruiting pharmacists in Wales. Catrin Plumpton managed and imputed the data. EAFH (the candidate) analysed the responses, interpreted the results with DH and VM, and drafted the manuscript. DH and VM (supervisors) revised the manuscript for intellectual content. EAFH (the candidate) finalised the manuscript.

Chapter 5

Multinational analysis of individual time preferences and adherence to medication

5.1 Preface

Chapter 4 presented the results of a stated preference discrete choice experiment of persistence with medication.

In a further application of behavioural economics to our understanding of adherence to medications, this chapter presents an empirical investigation of the association between time preference and nonadherence to medications. This is one of only a few studies to explore this association and the first to also assess how a wide range of demographic, clinical, psychosocial and sociocognitive factors contribute to the variance in time preference rates across countries.

Time preference rates can be derived using two broad approaches: revealed preference and stated preference methods (Cairns 2002). Revealed preference methods are based on actual behaviour, and analyse observed intertemporal choices, whereas, stated preference techniques model hypothetical scenarios. Whilst economists have traditionally preferred revealed preference data, the distinct nature of health as a commodity (in contrast to financial products) limits opportunities to obtain observed values, and thus there is an acceptance of stated preference methods to elicit time preferences for health (Cairns 2002). The time preference questionnaire described here was contained in the survey reported previously (Chapters 3 & 4). The time preference questionnaire is discussed from a methodological perspective in Chapter 7.

5.2 Abstract

Background: Time Preference is an economic theory that describes the extent to which an individual is willing to trade short-term costs and benefits for long-term costs and benefits. The time preference rate (discount rate) quantifies the relative value of behaviour at an earlier date, compared to its perceived value at a later date (Maital & Maital, 1978 cited in Fuchs, 1982). Individual time preferences may influence adherence to chronic medication, as patients are required to trade between immediate costs (both financial and intangible e.g. the inconvenience and potential adverse effects of treatment) and delayed benefits.

Objectives: To investigate empirically if discounting of delayed outcomes correspond to patients' adherence to medications. We hypothesised that patients with lower time preference rates may be more adherent to medication as they place a higher value on the future benefits of adherence.

Methods: Hypertensive adult patients across Europe were invited to complete a cross-sectional, web-based survey that had been translated and piloted. Patients' time preference (4-items) was assessed to calculate individual time preference rates for a 3-year and 6-year delay in event (treatment benefit). Medication nonadherence was measured using the Morisky questionnaire. Target sample size was 323 per country. Missing data was imputed using multiple imputation in STATA. Mean time preference rates were derived for the 3-year and 6-year delay. The significance of the association with nonadherence was assessed using the two-sample t-test with equal variances. Associations with time preference were tested for demographic, clinical and psychosocial factors using a multilevel multivariate regression model.

Results: 2272 antihypertensive patients across eight European countries completed the questionnaire. The mean time preference rate for the 6-year delay was 6.66% for the pooled sample (range 4.01% England to 9.77% Greece). The association between time preference and nonadherence was significant for the pooled sample but this result varied by country and only reached significance in two of eight countries (The Netherlands and Germany) where, contrary to our hypothesis, lower time preference rates were associated with nonadherence. The mean time preference rate for the 3-year delay was 13.37% for the pooled sample (all countries) (range 8.51% England to 21.4% Greece). In multilevel multivariate analysis of the time preference rates for the 3-year delay, low number of medication conditions, more comfortable perception of income, difficulty in borrowing income, and high perceived consequences of illness were associated with higher time preference rates. Difficulty to borrow income, being female, and high concerns about illness were associated with higher time preference rates for the hypothetical scenario of a 6-year

delay in experiencing benefit. Country differences explained 39.67% of the variance in time preference for the 3-year delay and 39.40% of the variance in time preference for the 6-year delay.

Conclusions: Time preference rates were aligned with those in the published literature. Evidence on the association between nonadherence and time preference was weak and varied by country. Perceptions of illness consequences and concerns about illness are amongst factors associated with time preference that are previously unreported and associate with time preference in the expected direction.

5.3 Introduction

Time preference is an economic theory that describes the relative value of behaviour at an earlier date, compared to its perceived value at a later date (Maital & Maital, 1978 cited in Fuchs, 1982). It describes the extent to which an individual is willing to trade short-term costs and benefits for long-term costs and benefits. Evidence suggests people prefer benefits sooner rather than later, whereas they would prefer to incur cost later (Cairns & van der Pol, 2000). For an individual to accept a delay in benefits, or an increase in immediate costs, they require a greater reward in the future. We quantify the point of indifference between the earlier and later value of the behaviour as a time preference rate (also known as the discount rate) (Sloman et al., 2013). An individual's time preference rate has been shown to affect health related behaviour (Hutson & Finke, 2003). People with a high time preference rate place a high value on today and a lower value on future health benefits (Fuchs, 1982). This has proved to be of interest when considering interventions such as smoking cessation and exercise, where perceptions of short-term costs (i.e. withdrawal, changes to routine) may be stronger than long-term benefits (i.e to health, reduced expenditure etc) (Gotto et al., 2009; Komlos et al., 2004).

Time preference is broadly relevant to health economics for two reasons. Firstly, application of time preference as a theoretical construct may help us to further our understanding of health related behaviours (e.g. Komlos et al., 2004). If we know how patients perceive future costs and benefits we can hypothesise about how such beliefs will affect their behaviour (Carins & van der Pol, 2000). Extending our understanding of behavioural predictors is useful to inform the design of policies and interventions to promote health e.g. smoking cessation, adherence-enhancing interventions (Cairns & van der Pol 2000; Holmes et al.,

2014). Secondly, time preference needs to be considered within economic evaluation to estimate the present value of new technologies. This is especially important as the timing of costs and benefits vary within and between interventions (Drummond et al., 2015), for example, a medication for hypertension may be more expensive but may have significantly higher long-term benefits than its comparator. Inappropriate use of discounting may lead to flawed results and could reduce the reliability of evidence and the credibility of consequent decisions (Cairns & van der Pol, 2000). In the UK a consistent societal discount rate of 3.5% per annum, as published in the Green Book (HM Treasury, 2003), is recommended.

5.3.1 Time preference rates

The time preference rate quantifies the difference between the perceived value of behaviour at an earlier date compared to its perceived value at a later date. Time preference rates are typically between 3-6% per annum (Cairns & van der Pol, 2000). Variation in the rate applied (often referred to as the discount rate) has a marked effect on studies with long time horizons, which is common in the economic evaluation of health prevention and medication for chronic conditions. In practical terms, discounting involves attaching declining weights to outcomes the further they occur in time:-

Discounting weight = $(1+r)^{-t}$

Where: r = time preference rate

t = year in which the event occurs

The aggregate time preference rate should reflect the time preferences of all members of a given population. Private time preferences are anticipated to have higher discount rates than societal, as they are based on a limited lifetime and/or the expectation that people will be better off in the future and therefore attach less value to future increments (van der Pol & Cairns, 2000; van der Pol & Cairns, 2001). At a societal level, people are more likely to accept deferring immediate benefit if it means everyone can enjoy more benefit in the future.

Individuals will differ in their time preferences, due to demographic, clinical and psychosocial factors. Known determinants of higher time preference for health include, older age (Cairns,

1994; Cropper et al., 1991; Cropper et al., 1992), being female (Carins, 1994; Johannesson & Johansson, 1997; Olsen, 1993); lower level of education (Olsen, 1993), higher income (Robberstad, 2005); being a smoker (Cairns, 1994), positive life expectancy (Bobinac et al., 2009), and small community size (Robberstad, 2005). Empirical evidence also suggests that higher time preferences are associated with: proximity of delay used to estimate time preference (Carins, 1994; van der Pol & Cairns, 2001), estimation using finance domains as opposed to health domains (Cairns, 1992) or life-saving health over financial (Cairns, 1994), and, health benefits for others (societal) compared to private health benefits (van der Pol & Cairns, 2001). To date there has been a lack of empirical evidence on the relationship between time preference and psychosocial / sociocognitive factors known to explain health related behaviour, such as health beliefs (Horne & Weinman, 1999) and illness representations (Broadbent, 2006; Leventhal et al., 1992). There is relatively consistent evidence that theoretical frameworks, such as sociocognitive theory (Abraham et al.,1999; Farquharson et al., 2004), and illness perceptions as described in the self-regulation model (Bryne et al., 2005; Ross et al., 2004) can explain behaviour, including in terms of medication adherence (Holmes et al., 2014). However, the amount of variance in behaviour explained is typically limited (less than 50%) and it is therefore of interest to test the association between time preference and these factors in order to extend our understanding.

5.3.2 Time preference and adherence

Adherence to medication is the process by which patients take their medication as prescribed, described by three quantifiable phases: initiation, implementation, and discontinuation (Vrijens, 2012). The period between initiation and discontinuation is referred to as persistence. Adherence is therefore a dynamic behaviour, and yet the majority of studies that test associations with demographic, clinical and psychosocial factors (Sabate, 2003) report static influences measured at single time point (Holmes et al., 2014). To date, applications in health psychology (such as the health belief model) have considered the value of future benefits of adherence, however, few studies have explored the association between the economic theory of Time Preference and adherence to medication.

In application of Time Preference theory to adherence to chronic medications, the health benefits of initiation of (and persistence with) medication for chronic conditions may not be immediate (or evident) whilst the patient may incur costs such as inconvenience, risk of adverse event, and monetary expense (Elliot et al., 2008). We therefore anticipate an

inverse relationship between time preference rates and adherence. Patients with a low time preference, who place a higher value on future benefits, are expected to be more persistent than patients with a high time preference, who live for today and place a lower value on future benefits in favour of more immediate gains. Patients with a high time preference are therefore more likely to have poor implementation, which may lead to reduced persistence and early discontinuation. Time preference theory highlights the importance of time on a patients' perception of costs and benefits of medications and it is proposed here that better understanding of peoples' time preferences for medicines taking and thus of adherence to medications would be of value in the design of patient-centred approaches to enhance adherence.

There is limited existing evidence on the association between time preference and adherence. In an online survey of a small sample of 47 students, Brandt & Dickinson (2013) explored the relationship between adherence and financial time preference, alongside asthma specific attitudes. This study found a significant association between low time preference and adherence to medication, together with feelings of embarrassment and concern about medication, and low risk preference. In a larger study of time preference in health behaviours among 422 hypertensive adults, Axon et al. (2009) found that low income and poor health were statistically significant predictors of time preference rates. They measured time preference for health using scenarios of blood pressure monitoring, diet, exercise, adherence to treatment plans, and smoking. They then conducted a logistic regression analyses adjusted for gender, age, race, income, and health status, which revealed mean health time preference rates of 43.8% per annum, and that a 1% increase in discount rate leads to a 1.6% increase in the likelihood respondents would not follow their treatment plan. The authors attribute the high estimate to a disproportionate sample of patients (low income and minority) but also suggest that high rates explain the short sighted decisions made by patients with hypertension regarding health behaviour. Chapman et al. (2001) in two studies of adherence to hypertension medication and cholesterol lowering medication, found either weak or no relationship between time preference for health and adherence to a medication. The differences in these studies may relate to differences in sampling and experimental design. It is therefore apparent that evidence to date on time preference and adherence to medication is sparse and inconclusive.

This study aims to (i) test the relationship between time preference rates and nonadherence to medications, and, (ii) identify demographic, clinical, psychosocial and sociocognitive

predictors of time preference rates; using a cross-sectional survey across a number of European countries with contrasting cultures, health care systems and patient characteristics. We are unaware of any study that has tested associations between time preference and nonadherence to medications across several countries.

5.4 Methods

5.4.1 Procedure

The data were collected within a survey of predictors of self-reported adherence to antihypertensive medicines, reported in full elsewhere (Chapter 3; (Morrison et al., 2015)). Briefly, hypertensive adult patients across Europe were invited to complete a web-based survey. Recruitment was via advertisements placed in community pharmacies. Advertisements were also placed in hypertension clinics and GP surgeries in Hungary, and in local press in England and Wales. Respondents were included if they self-reported as being 18 years or older, were diagnosed by a doctor as having hypertension that lasted at least 3 months, were currently prescribed antihypertensive medication, and personally responsible for administering their medication. Respondents were excluded if they self-reported as being diagnosed with a "psychiatric condition" or were living in a nursing home or similar facility. The survey was hosted by SurveyMonkey between August 2010 and March 2012. Responses were restricted to one per Internet Protocol Address. The survey contained 135 items with an estimated completion time of 30 minutes. Target sample size was 323 per country assuming 30% nonadherence with the Morisky measure on nonadherence and one-sided 5% level of significance (primary outcome measure of the main survey).

Ethical approval was obtained for each surveyed country (UK REC code 10/WNo01/57). Translations from English were provided by accredited translators and validated using forward and back translations, followed by review by a third person. The final version was piloted in each country and language. Patient information sheets, consent forms and eligibility checks were provided online.

5.4.2 Outcome measures

5.4.2.1 Time preference elicitation method

The time preference elicitation method used a stated preference technique. We used an open-ended experiment, based on private preferences (own health) (as described by van der Pol & Cairns, 2008). Our hypothetical scenario described delays in antiepileptic medication and medication benefits in terms of seizure frequency (Figure 5.1). Epilepsy was selected for the condition as the health benefits of medication could be quantified in terms of number of events (reduction in seizures). The scenario was unfamiliar to the cohort (currently receiving antihypertensive medication). It was therefore assumed that the decision was unfamiliar and based on time and potential health benefits, rather than connotations to their actual medications and current health. This provided a time preference rate for 'health' within the context of medications. We did not check if the hypertensive patients had epilepsy, we assumed that the study population was without experience of the condition, but were likely to appreciate the impact of seizures.

Figure 5.1 Example of time preference question

Time Preference

We would like you to imagine that you have been diagnosed with epilepsy. You have seizures (fits) that occur 20 times per year, and which seriously affect your usual activities.

Imagine you start a medicine **ONE YEAR** from now

that will reduce your seizures from 20 to:

12 times per year

If you do not start the medicine for **FOUR YEARS** from now

What is the maximum number of seizures per year that would still make this medicine worthwhile?

<drop-down menu 13:0>

The questionnaire included 4-items that varied in terms of time delay and benefit (seizure reduction) for the medication in year one (Table 5.1). The baseline scenario was experience of 20 seizures per year (Marson et al., 2007). This represented a realistic scenario from which the reduction in seizures at the two time points would generate time preference rates within the range of 0.01 to 0.36, which are the limits in most literature. The first time point was one year into the future, rather than today, due to the inflated effect of immediate health benefit. Two different scenarios were used to represent health benefit at 1 year) to provide multiple observations per delay to increase the stability of estimate (reduction in seizures from 20 to 12, or 20 to 8. Two difference time delays were selected to test if associations between adherence and time preference were sensitive to the length of delay. Delays of 3 and 6 years were considered appropriate for a population likely to be around 60 years of age and would ensure comparison with findings from other UK studies (Cairns & van der Pol, 2000).

Table 5.1 Parameters of the time preference items

Nearest scenario (years)	Seizure reduction	Furthest scenario (years)	Delay	Time preference rate range
1	20 to 12	4	3 years	-0.04 to 0.36
1	20 to 12	7	6 years	-0.02 to 0.17
1	20 to 8	4	3 Years	-0.03 to 0.19
1	20 to 8	7	3 Years	-0.01 to 0.09

5.4.2.2 Nonadherence to medications and other variables

Self-reported nonadherence was measured using the validated 4-item Morisky Medication Adherence Scale (Morisky et al., 2008). Respondents were classified as being nonadherent by responding "yes" to one of 4-items that made specific reference to high blood pressure medication:

- Do you ever forget to take your high blood pressure medicine?
- Are you careless at times about taking your high blood pressure medicine?
- Sometimes if you feel worse when you take your high blood pressure medicine do you stop taking it?
- When you feel better, do you sometimes stop taking your high blood pressure medicine?

The survey also contained a battery of questions to capture a range of demographic, clinical, psychosocial and sociocognitive measures (Appendix 4.1).

Models derived from sociocognitive and self-regulation theory and their component concepts (e.g., attitudes, perceived behavioural control from the Theory of Planned Behaviour; illness perceptions etc.) have been shown to predict a wide range of health related behaviour, including medication adherence. It was postulated that these models, and/or their individual components may explain time preference for health. Variable selection was informed by theoretical and empirical literature from behavioural and medical sciences, pertaining to medicines taking behaviour (Chapter 2; Holmes et al., 2014).

5.4.3 Data analysis

5.4.3.1 Time preference elicitation

Estimation of time preference rates assumed a discounted utility model and were derived as follows:-

$$\rho = \left(\frac{20 - x}{20 - n}\right)^{\frac{1}{v-s}} - 1$$

Where: ρ = time preference rate (annual discount rate)

20 = number of seizures before starting medication

x = Respondents answer i.e. seizure reduction for later medication

n = Number of seizures with earlier medication (i.e. 12 or 8)

v = years in future for delayed medication (i.e. 4 or 7)

s = years in future for earlier medication (i.e. 1 year)

Appendix 5.1 provides details of the time preference rates for each value of 'x'.

5.4.3.2 Time preference analysis

In the primary analysis, mean time preference rates for the 3-year delay and 6-year delay were calculated for a pooled (all countries) dataset and then for each individual country. Cross-country comparisons of zero and negative time preference rates were conducted using descriptive statistics (counts, chi-square).

5.4.3.3 Association between time preference and nonadherence

The association between time preference rates and nonadherence was assessed using students two-sample t-test with equal variance (i.e. adherent and non-adherent), for each individual country. The mean difference between time preference rates for adherent and nonadherent respondents were calculated for each country and 95% confidence intervals (95% CI) were estimated using bootstrap replications.

5.4.3.4 Determinants of time preference

We conducted a secondary analysis of potential associations between demographic, clinical, psychosocial and sociocognitive variables and time preference, for both the 3-year and 6-year delay. Independent variables were initially tested univariately using chi-square and t-tests as appropriate to the variables. Continuous variables with a correlation coefficient of >0.7 were removed due to multicollinearity concerns. Independent variables reaching $p<0.05$ in univariate analysis were entered into linear regressions with time preference as the dependent variable, for both 3-year and 6-year delay, for each country. Multilevel regressions of the pooled data set (all countries), with time preference as the dependent variable were then performed to account for both within-country and between country variance, in two separate analyses for both the 3-year and 6-year delay. Independent variables were selected if they were significant ($p<0.05$) in univariate analysis of the entire data set. Non-contributory variables were then iteratively removed using backwards elimination of those with the highest p-value until $p<0.1$ for all coefficients in the regression. The attribution of country to the observed variance of time preference was derived by the variance partition coefficient (Goldstien et al., 2002).

The data were coded in SPSS (version 19; IBM Corporation, Armonk, NY) and analysed in STATA (version 10; StataCorp LP, College Station, TX). Data on nonadherence were

complete; however, missing data on time preference and other demographic, psychosocial, and sociocognitive outcomes were presumed to be missing at random and were imputed using the methods described by Plumpton et al. (2016). Imputed data were used for all analyses with the exception of demographic variables and descriptive statistics of zero and negative time preferences, for which complete case data were used. Demographic data were analysed using counts, means, and chi-square or ANOVAs to look at cross country comparisons.

5.5 Results

5.5.1 Participants

2639 respondents from 11 countries completed the questionnaire; however, the analysis was restricted to 2272 from Austria, Belgium, England, Germany, Greece, Hungary, The Netherlands, and Wales. Responses from France (n=11), Portugal (n=33) were not used due to small sample sizes, and responses from Poland (n=323) were based on a different, incompatible version of the time preference questionnaire. Respondent characteristics are presented in Table 5.2. Self-reported nonadherence was 42.1% for the pooled sample (all countries), this ranged from 24.1% in The Netherlands to 70.3% in Hungary. There were statistically significant differences across all countries in terms of demographics, health indicators, and medicines use. There were also statistically significant differences in psychosocial factors across countries, with the exception of treatment control (p=0.186) (Table 5.3). The self-reported number of medicines prescribed was highly correlated with the number of units of medicine administered per day and number of items on prescription; to avoid potential multicollinearity we only used number of medicines in the univariate and multivariate regressions analyses.

Table 5.2 Demographics and characteristics of respondents (1 of 2)

Explanatory variable	Country (no. of respondents)																F / χ sq (df) p-value
	Austria (323)		Belgium (180)		England (323)		Germany (274)		Greece (289)		Hungary (323)		The Netherlands (237)		Wales (323)		
Mean Age (95% CI)	60.2 (58.8-61.5)		57.31 (55.6-59.1)		59.57 (58.5-60.7)		56.78 (55.4-58.2)		63.88 (62.6-65.2)		58.24 (56.8-59.7)		58.25 (57.0-59.5)		61.05 (59.9-62.2)		11.13 (7) 0.000
Sex: Female	145	(44.9)	64	(35.6)	141	(43.7)	154	(56.2)	173	(59.9)	179	(55.4)	115	(48.5)	119	(36.8)	61.80 (7) 0.000
Education: Secondary only	120	(38.2)	6	(3.3)	110	(34.3)	51	(18.7)	148	(52.3)	253	(78.8)	7	(3.0)	98	(30.4)	528.56 (7) 0.0000
Marital status: Married	209	(66.1)	134	(74.4)	241	(74.6)	184	(67.6)	187	(65.2)	234	(72.9)	186	(78.8)	258	(80.1)	32.45 (7) 0.000
Student / In employment	119	(37.4)	98	(54.4)	166	(51.4)	150	(55.1)	119	(41.5)	124	(38.6)	151	(64.0)	143	(44.3)	66.16 (7) 0.000
Income source: wages or salaries	93	(32.5)	76	(55.1)	125	(49.4)	115	(58.7)	85	(33.3)	154	(51.7)	94	(62.3)	121	(43.8)	75.89 (7) 0.000
Household income: Low	96	(32.7)	10	(7.3)	65	(25.4)	85	(43.1)	119	(46.9)	88	(28.9)	22	(14.9)	79	(28.3)	297.46
Medium	103	(35.0)	13	(9.5)	73	(28.5)	59	(29.9)	81	(31.9)	78	(25.6)	32	(21.6)	74	(26.5)	(21)
High	57	(19.4)	92	(67.2)	96	(37.5)	32	(16.2)	29	(11.4)	60	(19.7)	71	(48.0)	93	(33.3)	0.000
Not willing to provide	38	(12.9)	22	(16.1)	22	(8.6)	21	(10.7)	25	(9.8)	79	(25.9)	23	(15.5)	33	(11.8)	
Income perception: Comfortable	65	(21.9)	59	(43.7)	118	(45.6)	38	(19.4)	17	(6.7)	30	(10.0)	67	(44.7)	113	(40.6)	408.41
Coping	141	(47.5)	54	(40.0)	84	(32.4)	107	(54.6)	91	(36.0)	104	(34.6)	56	(37.3)	105	(37.8)	(21)
Difficult	54	(18.2)	13	(9.6)	45	(17.4)	38	(19.4)	136	(53.8)	102	(33.9)	13	(8.7)	47	(16.9)	0.000
Not willing to provide	37	(12.5)	9	(6.7)	12	(4.6)	13	(6.6)	9	(3.6)	65	(21.6)	14	(9.3)	13	(4.7)	
Borrowing income: Difficult	122	(41.4)	69	(50.0)	97	(37.6)	101	(51.3)	176	(69.3)	105	(35.0)	60	(40.5)	98	(35.1)	247.89
Neither difficult nor easy	85	(28.8)	24	(17.4)	51	(19.8)	50	(25.4)	41	(16.1)	60	(20.0)	36	(24.3)	70	(25.1)	(21)
Easy	38	(12.9)	24	(17.4)	87	(33.7)	24	(12.2)	20	(7.9)	33	(11.0)	30	(20.3)	81	(29.0)	0.000
Not willing to provide	50	(16.9)	21	(15.2)	23	(8.9)	22	(11.2)	17	(6.7)	102	(34.0)	22	(14.9)	30	(10.8)	

Table 5.2 Demographics and characteristics of respondents (2 of 2)

Health status: Poor	23	(7.2)	4	(2.2)	10	(3.1)	6	(2.2)	0	(0.0)	26	(8.1)	5	(2.1)	13	(4.0)	246.13
Fair	96	(29.9)	25	(14.0)	53	(16.4)	84	(30.7)	93	(32.3)	128	(39.8)	49	(20.9)	51	(15.8)	(7)
Good	128	(39.9)	77	(43.3)	123	(38.1)	140	(51.1)	140	(48.6)	132	(41.0)	112	(47.7)	116	(36.0)	0.000
Very Good	74	(23.1)	72	(40.4)	137	(42.4)	44	(16.1)	55	(19.1)	36	(11.2)	69	(29.4)	142	(44.1)	
Mean number of medical conditions	2.84		2.29		2.28		2.13		2.85		2.85		2.08		2.42		12.18 (7)
(95% CI)	(2.59-3.08)		(2.10-2.47)		(2.15-2.42)		(1.97-2.30)		(2.64-3.06)		(2.68-3.02)		(1.93-2.24)		(2.26-2.57)		0.000
Mean units of medicines per day	5.51		3.78		4.93		3.92		5.06		7.44		3.94		4.97		22.06 (7)
(95% CI)	(4.95-6.07)		(3.33-4.23)		(4.45-5.40)		(3.56-4.27)		(4.57-5.54)		(6.90-7.98)		(3.49-4.38)		(4.45-5.49)		0.000
Most frequently dosed medicine: once daily	114	(35.6)	123	(69.5)	224	(69.3)	100	(36.6)	51	(17.8)	54	(16.8)	157	(66.8)	241	(74.6)	528.97
Twice daily	110	(34.4)	35	(19.8)	63	(19.5)	129	(47.3)	112	(39.2)	155	(48.1)	56	(23.8)	47	(14.6)	(7)
≥ Thrice daily	96	(30.0)	19	(10.7)	36	(11.1)	44	(16.1)	123	(43.0)	113	(35.1)	22	(9.4)	35	(10.8)	0.000
Morisky: Respondents self-reporting as being non-adherent	109	(33.7)	70	(38.9)	134	(41.5)	91	(33.2)	145	(50.2)	227	(70.3)	57	(24.1)	123	(38.1)	165.72 (7) 0.000
MARS Mean score	23.29		23.75		23.41		23.52		22.10		23.00		23.90		23.53		15.56 (7)
(95% CI)	(23.0-23.6)		(23.5-24.0)		(23.2-23.7)		(23.3-23.8)		(21.7-22.5)		(22.7-23.3)		(23.6-24.2)		(23.3-23.8)		0.000

Responses from France (n=11), Portugal (n=33) and Poland (n=323) were not used in the analysis, due to n<100 and version consistency with the time preference items (different in Poland).

Table 5.3 Psychosocial characteristics of respondents (1 of 2)

	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Wales	F / χ sq (df)
Dispositional optimism	15.4	14.7	15.0	15.2	13.6	14.8	15.0	15.1	3.83 (7)
Optimism	(15.0-15.8)	(14.1-15.3)	(14.4-15.6)	(14.8-15.7)	(13.0-14.3)	(14.4-15.3)	(14.3-15.6)	(14.5-15.8)	P=0.000
Beliefs about medicines	19.1	18.1	17.6	17.6	19.8	19.3	16.3	18.2	18.95 (7)
Necessity	(18.6-19.6)	(17.5-18.7)	(17.1-18.1)	(17.1-18.2)	(19.4-20.3)	(18.8-19.7)	(15.7-16.9)	(17.8-18.6)	P=0.000
Concern about illness	15.5	14.2	15.3	15.9	19.5	16.0	13.6	15.5	28.96 (7)
	(15.0-16.1)	(13.4-15.0)	(14.7-15.8)	(15.2-16.6)	(18.9-20.1)	(15.5-16.6)	(12.9-14.3)	(14.9-16.1)	P=0.000
Theory of planned behaviour	28.0	28.3	28.6	27.7	28.7	28.3	28.7	26.9	5.61 (7)
Attitudes	(27.5-28.6)	(27.7-28.8)	(28.1-29.1)	(27.0-28.4)	(28.3-29.2)	(27.8-28.8)	(28.2-29.3)	(26.5-27.3)	P=0.000
Subjective norms	13.3	13.5	13.5	13.0	11.4	13.5	13.1	13.6	19.29 (7)
	(12.9-13.6)	(13.1-13.9)	(13.3-13.8)	(12.6-13.4)	(11.0-11.9)	(13.3-13.7)	(12.7-13.5)	(13.3-13.8)	P=0.000
Barriers	2.1	2.5	2.2	1.9	3.2	3.1	2.4	2.3	33.55 (7)
	(1.9-2.3)	(2.3-2.7)	(2.1-2.4)	(1.7-2.0)	(3.1-3.4)	(3.0-3.3)	(2.1-2.6)	(2.1-2.4)	P=0.000
Facilitators	8.2	9.5	10.3	7.5	12.0	11.4	8.9	10.6	61.59 (7)
	(7.8-8.7)	(9.0-10.0)	(10.0-10.6)	(7.0-8.0)	(11.6-12.3)	(11.1-11.8)	(8.4-9.4)	(10.2-10.9)	P=0.000
Intention	9.2	9.3	9.4	9.4	9.0	8.7	9.1	9.4	8.36 (7)
	(9.0-9.4)	(9.1-9.5)	(9.3-9.6)	(9.2-9.6)	(8.9-9.2)	(8.6-8.9)	(8.8-9.3)	(9.3-9.6)	P=0.000
Self-efficacy	7.6	7.1	7.5	7.7	6.9	7.4	8.1	7.8	6.98 (7)
	(7.3-7.8)	(6.7-7.4)	(7.2-7.7)	(7.4-8.0)	(6.6-7.2)	(7.1-7.6)	(7.8-8.4)	(7.6-8.1)	P=0.000
BRIGHT	0.4	0.3	0.3	0.4	0.8	0.6	0.2	0.4	28.75 (7)
Barriers	(0.3-0.5)	(0.2-0.4)	(0.3-0.4)	(0.3-0.4)	(0.7-0.9)	(0.6-0.7)	(0.2-0.3)	(0.3-0.4)	P=0.000
Social support	3.2	3.8	2.8	1.8	8.1	4.8	1.5	3.4	36.13 (7)
	(2.7-3.7)	(2.9-4.6)	(2.2-3.4)	(1.4-2.2)	(7.1-9.1)	(4.2-5.4)	(1.1-1.9)	(2.8-4.1)	
Illness representations	5.0	3.4	2.7	4.0	6.2	5.6	3.4	3.2	46.53 (7)
Illness consequences	(4.7-5.4)	(2.9-3.8)	(2.4-3.0)	(3.6-4.3)	(5.8-6.5)	(5.2-5.9)	(2.9-3.8)	(2.9-3.6)	P=0.000
Timeline	8.8	9.0	9.3	9.4	9.1	8.8	9.4	9.3	5.35 (7)
	(8.5-9.0)	(8.7-9.4)	(9.1-9.5)	(9.2-9.6)	(8.9-9.2)	(8.6-9.0)	(9.2-9.6)	(9.1-9.5)	P=0.000
Personal control	6.1	6.3	5.7	5.9	7.0	7.1	6.7	5.6	12.03 (7)
	(5.7-6.4)	(5.8-6.7)	(5.4-6.1)	(5.5-6.3)	(6.7-7.2)	(6.8-7.4)	(6.3-7.1)	(5.3-6.0)	P=0.000
Treatment control	8.0	8.2	7.8	7.6	8.1	7.8	7.9	7.9	1.44 (7)
	(7.7-8.2)	(7.9-8.5)	(7.5-8.0)	(7.3-7.9)	(7.9-8.3)	(7.6-8.1)	(7.6-8.2)	(7.6-8.2)	P=0.186
Illness identity	5.1	3.5	3.1	4.4	4.1	4.7	3.5	3.4	16.86 (7)
	(4.7-5.4)	(3.0-3.9)	(2.8-3.5)	(4.1-4.8)	(3.8-4.4)	(4.4-5.1)	(3.0-3.9)	(3.0-3.7)	P=0.000
Concern about illness	5.6	4.7	5.1	5.9	6.5	5.8	4.5	5.4	10.12 (7)
	(5.2-5.9)	(4.3-5.2)	(4.7-5.4)	(5.5-6.3)	(6.1-6.8)	(5.5-6.1)	(4.0-4.9)	(5.0-5.7)	P=0.000
Illness coherence	7.4	7.8	7.7	7.0	6.7	8.4	8.4	7.9	15.59 (7)
	(7.1-7.7)	(7.4-8.1)	(7.4-8.0)	(6.6-7.4)	(6.5-7.0)	(8.2-8.6)	(8.0-8.7)	(7.6-8.1)	P=0.000
Emotional representations	4.1	3.3	3.2	4.0	6.1	4.4	2.9	3.6	25.29 (7)
	(3.7-4.4)	(2.8-3.8)	(2.8-3.5)	(3.6-4.5)	(5.7-6.4)	(4.1-4.7)	(2.5-3.4)	(3.2-4.0)	P=0.000

Table 5.3 Psychosocial characteristics of respondents (2 of 2)

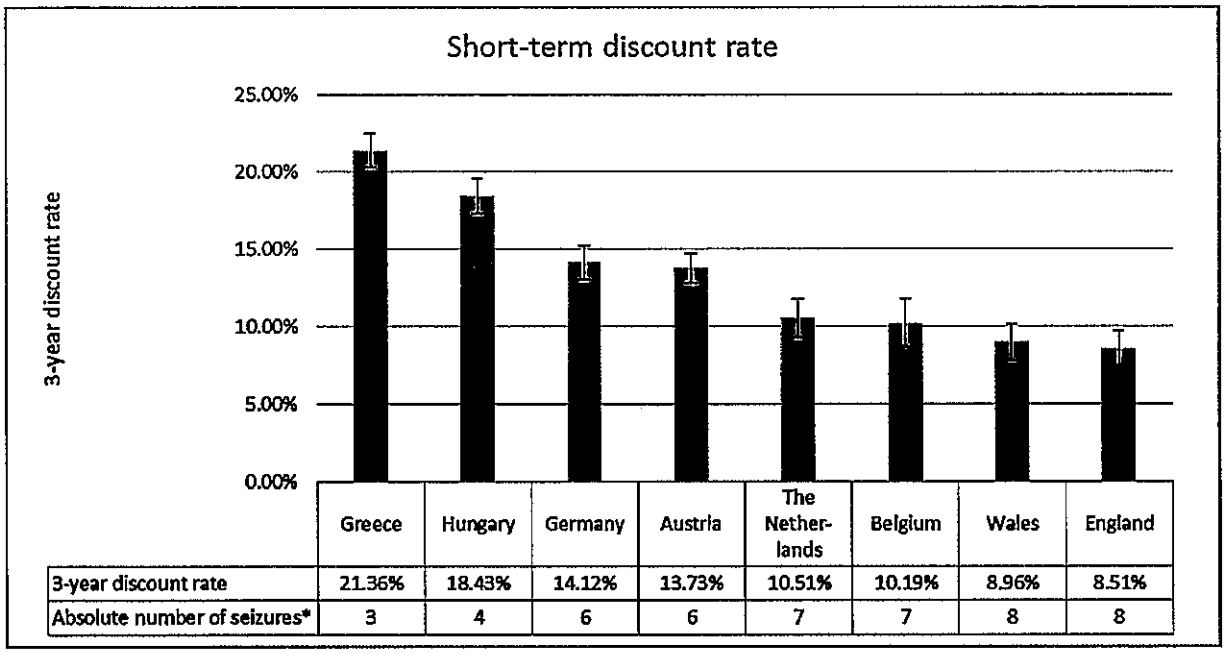
Evaluation of healthcare									
Lead health care practitioner: GP/Family doctor	163.0	123.0	207.0	172.0	65.0	136.0	82.0	222.0	320.95 (7) P=0.000
Sex of lead health care practitioner: Female	114.0	50.0	133.0	82.0	54.0	162.0	80.0	124.0	74.58 (7)
Satisfaction with practitioner	67.6 (66.1-69.2)	67.2 (65.5-68.9)	68.2 (66.3-70.1)	64.1 (62.2-66.0)	62.0 (60.5-63.5)	79.0 (77.9-80.0)	64.1 (61.9-66.3)	68.5 (66.7-70.3)	42.39 (7) P=0.000
Satisfaction with practice	24.2 (23.6-24.8)	23.7 (22.8-24.6)	21.1 (20.4-21.8)	23.3 (22.6-24.0)	17.7 (16.9-18.4)	25.8 (25.4-26.2)	23.1 (22.4-23.9)	20.9 (20.2-21.7)	59.73 (7) P=0.000

5.5.2 Time preference rates

The mean time preference rate for the 3-year delay was 13.37% for the pooled sample (all countries) (range 8.51% England to 21.4% Greece). The mean time preference rate for 6-year delay was 6.66% for the pooled sample (range 4.01% England to 9.77% Greece). In a scenario of starting with 20 seizures per year, where the 1-year delay reduced seizures from 20 to 10, the mean implied time preference rates represent a reduction from 20 to 6 for both the 3-year delay and the 6-year delay. This indicates that respondents would require the medication to prevent an additional four seizures to compensate for the delay. Mean time preference rates were significantly different between countries ($p<0.01$) (Figures 5.2 & 5.3). The 3-year delay led to consistently higher rates than the 6-year delay across all countries ($p<0.05$).

The count of individuals who had negative time preferences was significantly different between countries ($\chi^2(7)$ 43.44, $p<0.001$). The percentage of respondents with a negative time preference in the scenario of a 3-year delay, ranged from 3.7% in Greece to 14.7% in England. Similarly for the 6-year delay the range was 2.7% in Greece to 15.5% in England. The count of zero time preferences was also significantly different between countries ($\chi^2(7)$ 92.25, $p<0.001$). The percentage of respondents who were indifferent (time preference of zero) for the 3-year delay ranged from 2.2% in Greece to 22.7% in Wales; and from 2.0% in Greece to 20.1% in Wales for the 6-year delay.

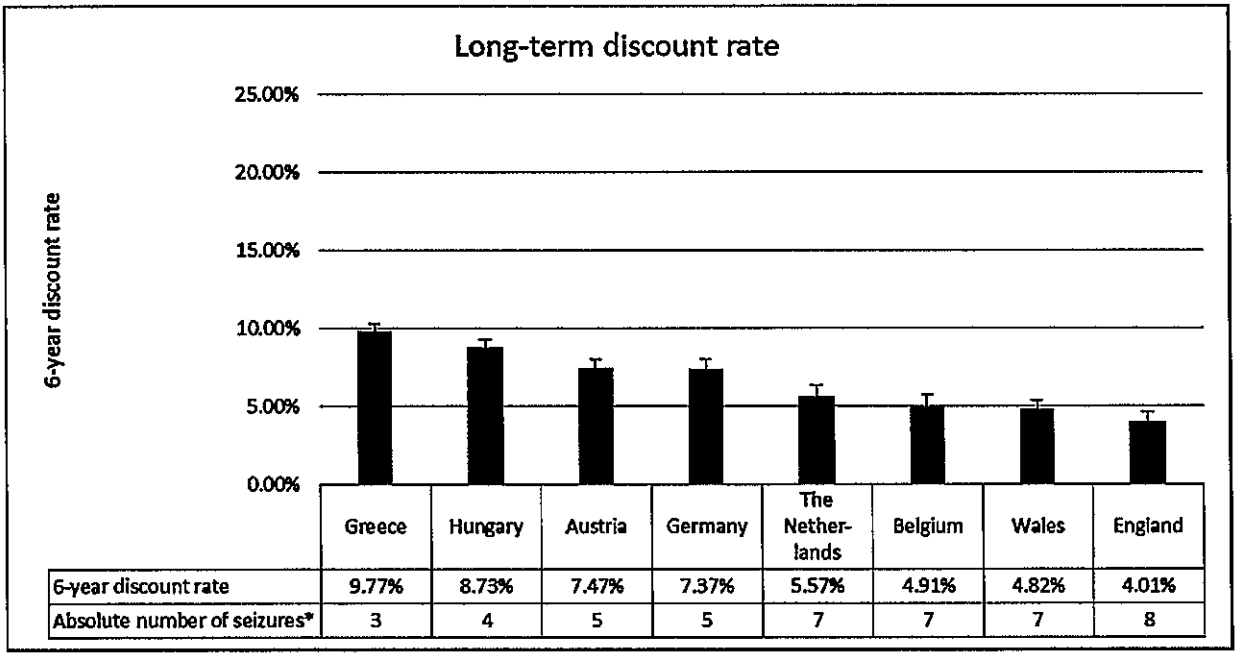
Figure 5.2 Time preference rates for the 3-year delay by country



	Greece	Hungary	Germany	Austria	The Nether-lands	Belgium	Wales	England
3-year discount rate	21.36%	18.43%	14.12%	13.73%	10.51%	10.19%	8.96%	8.51%
Absolute number of seizures*	3	4	6	6	7	7	8	8

*Based on a scenario of starting with 20 seizures per year. Treatment X starts one-year from now and reduced your seizures from 20 to 10. Treatment Y starts 4 (or 7 years). The absolute number of seizures in the maximum number of seizures per year that would make the wait for Treatment Y worthwhile.

Figure 5.3 Time preference rates for the 6-year delay by country



	Greece	Hungary	Austria	Germany	The Nether-lands	Belgium	Wales	England
6-year discount rate	9.77%	8.73%	7.47%	7.37%	5.57%	4.91%	4.82%	4.01%
Absolute number of seizures*	3	4	5	5	7	7	7	8

*Based on a scenario of starting with 20 seizures per year. Treatment X starts one-year from now and reduced your seizures from 20 to 10. Treatment Y starts 4 (or 7 years). The absolute number of seizures in the maximum number of seizures per year that would make the wait for Treatment Y worthwhile.

5.5.3 Time preference and nonadherence

The association between time preference and nonadherence to medication for the pooled sample (all countries) was statistically significant and in the anticipated direction for both 3-year (p=0.01) and 6-year delays (p=0.02). The mean time preference rate for the 3-year delay in the nonadherent group (14.2%, 95%CI 13.5 to 14.9) was higher than for the adherent group (12.8%, 95%CI 12.2 to 13.4) (p=0.003). Similarly, the mean time preference for the 6-year delay in the nonadherent group (7.0%, 95%CI 6.6 to 7.3) was higher than for the adherent group (6.4%, 95%CI 6.1 to 6.7) (p=0.017).

The association between nonadherence and time preference was statistically significant in two of the eight countries; however, this was not in the anticipated direction. In The Netherlands, time preference rates for the 3-year delay were 3.7% higher (p=0.006) in the adherent group (11.4%; 95% CI 10.0 to 12.8) than in the nonadherent group (7.7%; 95% CI 5.3 to 10.1). Similarly the time preference rates for the 6-year delay were 1.8% higher (p=0.008) in the adherent group (6.0%; 95% CI 5.2 to 6.8) than in the nonadherent group (4.2%; 95% CI 2.8 to 5.5). In terms of seizures, this difference between the adherent and nonadherent groups was the equivalent of one additional seizure prevented for the 3-year delay and two additional seizures prevented for the 6-year delay (in a scenario of starting with 20 seizures per year, where the 1-year delay reduced seizures from 20 to 10). Time preference rates for the 6-year delay in Germany were also significantly higher (p=0.048) in the adherent group (14.9%; 95% CI 13.6 to 16.1) than the nonadherent group (12.6%; 95% CI 10.5 to 14.7); but the difference between groups did not reach statistical significance for the 3-year delay (p=0.095). Both the adherent and nonadherent time preferences rates for the 6-year delay in Germany require the later medication to cause remission (20 to 0 for 6-year delay).

The association between nonadherence and time preference (3-year and 6-year delay) was in the anticipated direction (lower time preference rates associated with adherence because individuals place a higher value on future benefits of adherence) in Austria, Belgium, England, Greece (6-year only) and Wales, however these results did not reach statistical significance ($p>0.05$). Figures 5.4 & 5.5 illustrates the mean difference in time preference between adherent and nonadherent respondents by country. The full results are available in Appendix 5.2.

5.5.4 Determinants of time preference: linear regression by country

Variables entered in to the regressions of time preference rates for the 3-year delay explained between 2.85% (Wales) and 18.48% (Hungary) of the variance in time preference rates (Table 5.4). Individuals receiving care from someone other than their GP (lead practitioner) were associated with higher discount rates in both Belgium and Greece. Medicines frequency and patient perceptions of length of time their illness would continue for (illness timeline) were each significant in two countries, but the direction of the association was inconsistent.

Variables entered in to the regressions of time preference rates for the 6-year delay explained 4.32% (Wales) and 16.28% (Hungary) of the variance in time preference rates (Table 5.5). None of the explanatory variables qualified for a regression of 6-year discount rates in Belgium. No single independent variable was a significant predictor of 6-year discount rates in more than one country.

Figure 5.4 Mean difference (bars indicate 95% confidence interval for the difference in means) in time preference rate for the 3-year delay between adherent and non-adherent groups by country

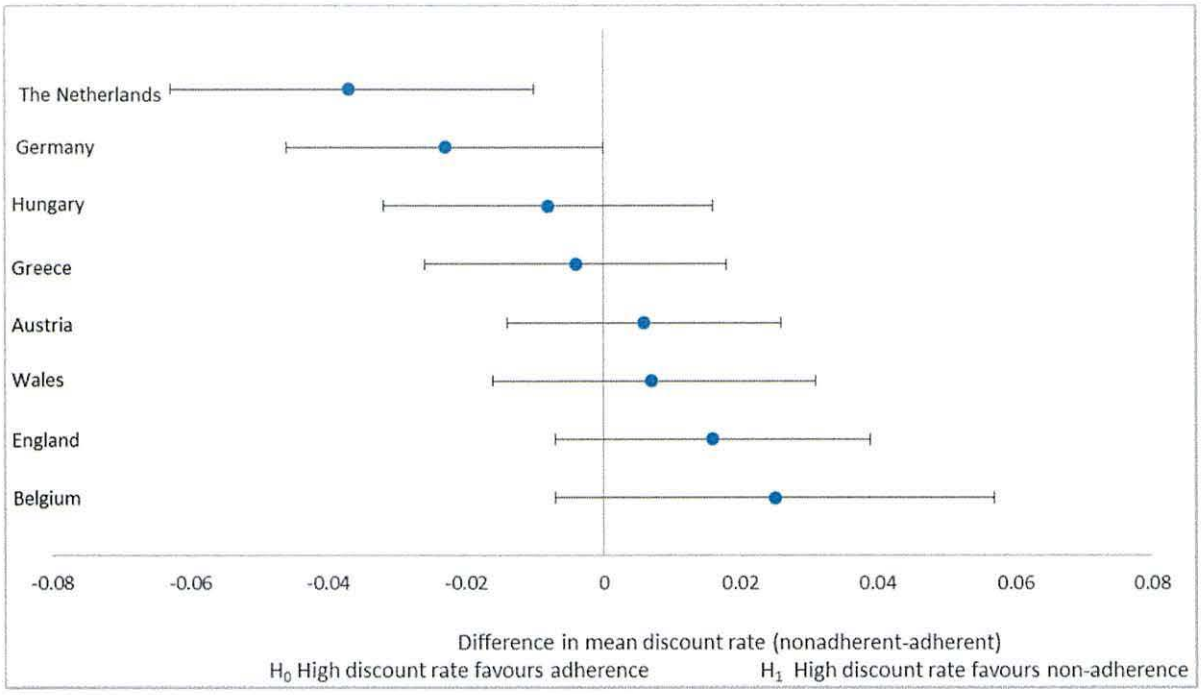
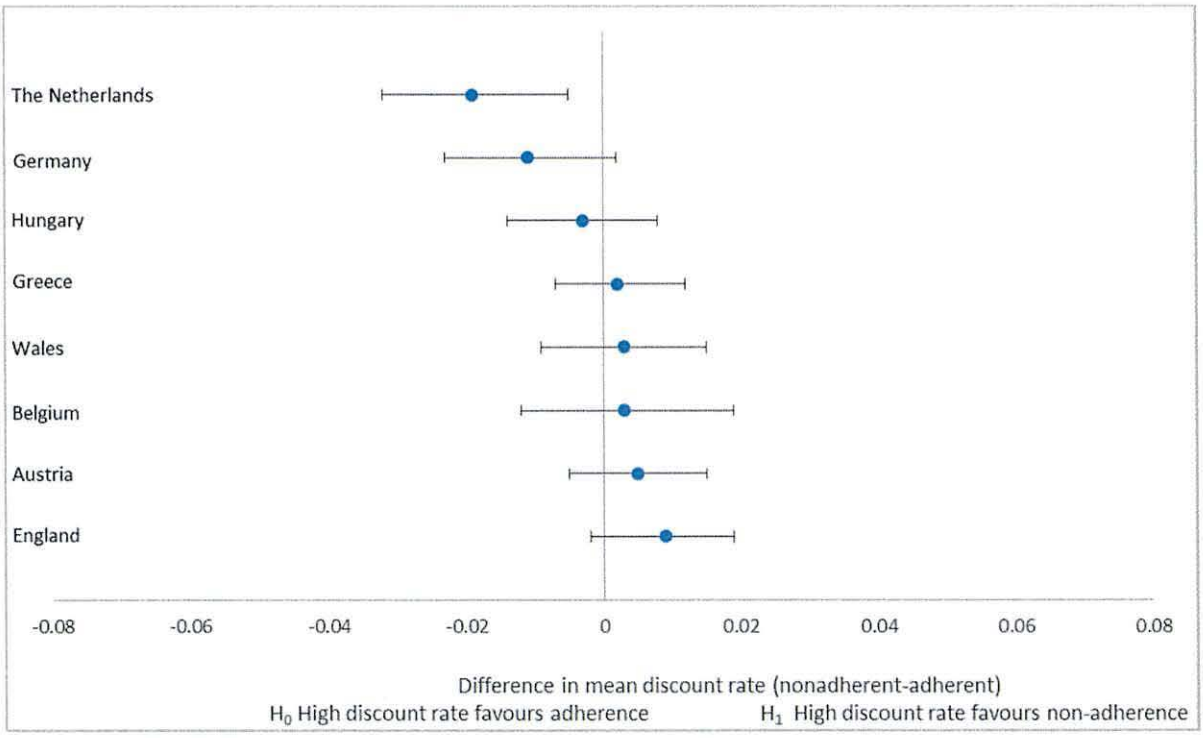


Figure 5.5 Mean difference in time preference rate for the 6-year delay between adherent and non-adherent groups by country



H1: Patients with lower time preference rate may be more adherence to medication for chronic conditions because they place a higher value on future benefits

Table 5.4 Summary of linear regression model using time preference rates for the 3-year delay as the dependent variable: β coefficient (95% CIs) (1 of 3)

	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Wales
Age	*not entered*	-0.13 (-0.26-0.00) P=0.04	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-0.12 (-0.25-0.01) P=0.06
Marital status	*not entered*	*not entered*	*not entered*	*not entered*	-4.91 (-7.22--2.60) P=0.00	*not entered*	*not entered*	*not entered*
Employment	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-0.87 (-3.56-1.81) P=0.52
Morisky non-adherence	*not entered*	*not entered*	*not entered*	-1.93 (-4.22-0.37) P=0.10	*not entered*	*not entered*	-3.08 (-5.86--0.30) P=0.03	*not entered*
MARS adherence	*not entered*	*not entered*	*not entered*	*not entered*	0.37 (0.04-0.70) P=0.03	*not entered*	*not entered*	*not entered*
Dosing frequency ≥ Thrice daily	*not entered*	*not entered*	*not entered*	-0.99 (-3.37-1.40) -3.93 (-7.11--0.76) P=0.05	3.72 (0.61-6.82) 1.02 (-2.39-4.44) P=0.02	*not entered*	-2.42 (-5.13-0.29) -4.54 (-8.37--0.71) P=0.03	*not entered*
Health status: Fair Good Excellent	*not entered*	-9.64 (-20.76-1.48) -8.01 (-18.63-2.61) -7.40 (-18.12-3.32) P=0.36	*not entered*	*not entered*	2.55 (0.09-5.01) 0.88 (-2.57-4.32) P=0.10	-1.16 (-5.41-3.08) 0.60 (-3.80-5.01) 1.68 (-3.71-7.07 P=0.44	*not entered*	*not entered*
Necessity	*not entered*	*not entered*	*not entered*	*not entered*	0.26 (-0.07-0.60) P=0.12	0.01 (-0.29-0.30) P=0.96	*not entered*	*not entered*
Concern	*not entered*	*not entered*	*not entered*	0.30 (0.09-0.52) P=0.01	*not entered*	*not entered*	*not entered*	*not entered*
Subjective norm	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	0.97 (0.37-1.56) P=0.00	*not entered*	*not entered*

Table 5.4 Summary of linear regression model using time preference rates for the 3-year delay as the dependent variable: β coefficient (95% CIs) (2 of 3)

	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Wales
Barriers	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-0.78 (-1.66-0.10) P=0.08	*not entered*
Self-efficacy	*not entered*	*not entered*	-0.57 (-1.09–-0.06) P=0.03	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Lead practitioner	*not entered*	4.26 (0.19-8.32) P=0.04	*not entered*	*not entered*	*not entered*	2.50 (0.12-4.88) P=0.04	*not entered*	*not entered*
Illness consequences	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	(0.42 P=0.07) -0.03-0.87	*not entered*	*not entered*
Timeline	*not entered*	*not entered*	-0.76 (-1.47–-0.05) P=0.04	*not entered*	0.76 (0.04-1.49) P=0.04	*not entered*	*not entered*	*not entered*
Concern about illness	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	0.43 (0.01-0.86) P=0.04	*not entered*	*not entered*
Income source	*not entered*	*not entered*	-3.54 (-5.87–-1.20) P=0.00	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Total income: Medium High Not willing to provide	-1.14 (-3.52-1.24) -1.57 (-4.58-1.45) 2.01 (-1.77-5.79) P=0.23	*not entered*	*not entered*	*not entered*	1.00 (-1.65-3.66) -3.16 (-6.92-0.59) 1.30 (-2.48-5.07) P=0.18	*not entered*	*not entered*	*not entered*

Table 5.4 Summary of linear regression model using time preference rates for the 3-year delay as the dependent variable: β coefficient (95% CIs) (3 of 3)

	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Wales
Income perception: coping	4.00 (1.43-6.57)	*not entered*	*not entered*	*not entered*	*not entered*	2.97 (-0.98-6.92)	2.85 (0.23-5.47)	*not entered*
Difficult	2.33 (-1.00-5.66					3.80 (-0.41-8.01)	2.27 (-2.57-7.12)	
Not willing to provide	-0.32 (-4.19-3.56) P=0.00					2.43 (-2.40-7.27) P=0.35	1.47 (-2.74-5.69) P=0.32	
Borrow income: neither difficult nor easy	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-3.75 (-6.93--0.57)	*not entered*	*not entered*
Easy						-1.15 (-5.24-2.94)		
Not willing to provide						0.75 (-2.74-4.24) P=0.07		
Constant	11.90 (8.99-14.82) P=0.00	24.68 (12.45-36.91) P=0.00	21.77 (14.23-29.31) P=0.00	11.03 (7.35-14.71) P=0.00	0.74 (-10.26-11.74) P=0.89	-3.11 (-14.26-8.05) P=0.58	12.65 (9.87-15.43) P=0.00	16.91 (9.74-24.09) P=0.00
R-squared	6.50	8.15	6.87	6.56	17.79	18.48	11.85	2.85
Adjusted R-squared	4.72	5.51	5.99	5.17	14.52	14.77	9.15	2.24

not entered = independent variable did not reach statistical significance in univariate analysis (p>0.05)

Table 5.5 Summary of linear regression model using time preference rates for the 6-year delay as the dependent variable: β coefficient (95% CIs) (1 of 3)

	Austria	England	Germany	Greece	Hungary	The Netherlands	Wales
Age	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-0.07 (-0.13--0.01) P=0.03
Marital status	*not entered*	*not entered*	*not entered*	-1.57 (-2.58--0.57) P=0.00	*not entered*	*not entered*	*not entered*
Employment	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-0.08 (-1.45-1.29) P=0.91
Medicines units	-0.19 (-0.29--0.10) P=0.00	*not entered*	-0.09 (-0.32-0.15) P=0.47	*not entered*	*not entered*	*not entered*	*not entered*
Morisky non-adherence	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-1.56 (-3.01-0.10) P=0.04	*not entered*
Dosing frequency ≥ Thrice daily	*not entered*	*not entered*	-0.47 (-1.78-0.84) -2.20 (-4.25--0.15) P=0.10	1.02 (-0.34-2.37) -0.26 (-1.75-1.24) P=0.07	*not entered*	-1.91 (-3.32-0.49) -1.96 (-3.94-0.02) P=0.01	*not entered*
Health status: Fair Good Excellent	*not entered*	*not entered*	*not entered*	*not entered*	-0.60 (-2.58-1.38) 0.12 (-1.94-2.19) 0.69 (-1.85-3.23) P=0.49	*not entered*	*not entered*
Necessity	*not entered*	*not entered*	*not entered*	0.16 (0.00-0.32) P=0.05	0.01 (-0.13-0.15) P=0.86	*not entered*	*not entered*
Concern	0.10 (0.00-0.19) P=0.06	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Subjective norm	*not entered*	*not entered*	*not entered*	0.14 (-0.01-0.29) P=0.07	0.40 (0.12-0.69) P=0.01	*not entered*	*not entered*

Table 5.5 Summary of linear regression model using time preference rates for the 6-year delay as the dependent variable: β coefficient (95% CIs) (2 of 3)

	Austria	England	Germany	Greece	Hungary	The Netherlands	Wales
Barriers	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	-0.43 (-0.87-0.02) P=0.06	*not entered*
Intention	*not entered*	-0.45 (-0.93-0.02) P=0.06	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Lead practitioner	*not entered*	*not entered*	*not entered*	*not entered*	1.12 (0.02-2.21) P=0.05	*not entered*	*not entered*
Illness consequences	*not entered*	*not entered*	*not entered*	*not entered*	0.17 (-0.04-0.39) P=0.11	*not entered*	*not entered*
Timeline	*not entered*	-0.29 (-0.61-0.03) P=0.07	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Concern about illness	*not entered*	*not entered*	*not entered*	*not entered*	0.21 (0.00-0.41) P=0.05	*not entered*	*not entered*
Income source	*not entered*	-1.20 (-2.27–0.14) P=0.03	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*
Total income: Medium High Not willing to provide	-0.43 (-1.65-0.79) -0.83 (-2.38-0.72) 0.61 (-1.36-2.58) P=0.50	*not entered*	*not entered*	*not entered*	*not entered*	*not entered*	0.24 (-1.34-1.81) 1.01 (-0.52-2.55) 0.98 (-1.01-2.96) P=0.54
Income perception: coping Difficult Not willing to provide	1.66 (0.33-3.00) 1.79 (0.03-3.55) 0.67 (-1.49-2.84) P=0.09	*not entered*	*not entered*	*not entered*	1.10 (-0.79-2.98) 1.48 (-0.52-3.48) 0.83 (-1.47-3.12) P=0.52	1.28 (-0.12-2.68) 1.63 (-0.72-3.98) 0.88 (-1.31-3.07) P=0.33	*not entered*

Table 5.5 Summary of linear regression model using time preference rates for the 6-year delay as the dependent variable: β coefficient (95% CIs) (3 of 3)

	Austria	England	Germany	Greece	Hungary	The Netherlands	Wales
Borrow income: neither difficult nor easy	*not entered*	*not entered*	*not entered*	*not entered*	-1.64 (-3.15–0.14)	*not entered*	*not entered*
Easy					-0.36 (-2.22-1.50)		
Not willing to provide					0.35 (-1.27-1.98) P=0.10		
Constant	6.10 (3.90-8.30) P=0.00	11.59 (6.21-16.97) P=0.00	8.28(7.18-9.38) P=0.00	5.75 (2.62-8.89) P=0.00	-0.39 (-5.71-4.92) P=0.88	6.84 (5.47-8.21) P=0.00	8.63 (4.88-12.39) P=0.00
R-squared	10.06	5.86	4.32	8.67	16.28	13.38	4.62
Adjusted R-squared	7.76	4.98	3.26	7.06	12.47	10.73	3.11

not entered = independent variable did not reach statistical significance in univariate analysis (p>0.05)

5.5.5 Determinants of time preference: multilevel multivariate analysis

The multilevel model for 3-year delay identified lower number of medical conditions, 'comfortable' income perception, 'difficulty' borrowing income, and high illness consequences (your illness severely affects your life) as being significantly associated with higher time preference rates. The multilevel model for 6-year delay identified 'difficulty' borrowing income, being female, and high concerns about illness as being significantly associated with higher time preference rates. Approximately 40% of the variance was attributable to differences between countries in both cases (Table 5.6)

5.6 Discussion

The association between nonadherence and time preference rates was insubstantial. Whilst the pooled analysis of all countries indicated statistical significance in the anticipated direction, with lower time preference rates associated with adherence to medications, there was substantial variation when analysed by country. Only two of the eight countries showed a significant association and in these cases, higher time preference rates were associated with adherence to medications. It is therefore unclear if the valuation a patient places on immediate versus future costs and benefits does have an influence on their decision to adhere to medication. Higher time preference rates were found to be associated with several factors including: country, being female, number of medication conditions, more comfortable perception of income, difficulty in borrowing income, high concerns about illness, and high perceived consequences of illness.

Table 5.6 Summary of multilevel regression models for time preferences rates

	Time preference rates 3-year delay			Time preference rates 6-year delay		
	B coefficient	95% CI	P	B coefficient	95% CI	P
Sex				-0.41*	-0.79--0.02	0.039
Number of medical conditions	-0.22	-0.49-0.04	0.093			
Illness consequences	0.23†	0.08-0.38	0.002			
Concern about illness				0.11†	0.04-0.17	0.002
Income perception: coping	1.22	0.14-2.29	0.069			
Difficult	1.55	0.21-2.89				
Not willing to provide	0.21	-1.48-1.91				
Borrow income: neither difficult nor easy	0.34*	-0.77-1.46	0.049	0.07	-0.46-0.61	0.087
Easy	0.86*	-0.39-2.10		0.44	-0.15-1.04	
Not willing to provide	1.96*	0.51-3.41		0.72	0.07-1.36	
Constant	11.44‡	8.44-14.44	0.000	6.00‡	4.61-7.39	0.000
Random effect parameters	Variance	95% CI		Variance	95% CI	
Between country variance (σ_u^2)	0.20	0.15-0.26		0.14	0.11-0.18	
Within-country variance (σ_e^2)	0.30	0.30-0.31		0.21	0.21-0.21	
% variance attributable to differences between countries	0.40	0.34-0.45		0.39	0.34-0.45	

Notes. CI, confidence interval. *p<0.05, †p<0.01, ‡p<0.001 Variance partition coefficient, VPC = σu2/(σu2+ σe2). Full model specification. Short-term: sex, education, number of medical conditions, number of different medicines, Morisky, MARS, dosing frequency, health status, necessity, concerns about medicine, normative beliefs, facilitators, intention, prescriber of medicines, barriers (averaged as one less collected in Wales), social support, illness consequences, personal control, identity, concern about illness, illness coherence, emotional representations, total income, income perception, ease of borrowing. Long-term: sex, education, Morisky, dosing frequency, health status, necessity, concerns about medicine, barriers (theory of planned behaviour), prescriber of medicines, barriers (averaged as one less collected in Wales), illness consequences, identity, concern about illness, emotional representations, total income, income perception, ease of borrowing.

5.6.1 Comparison to other studies

Previously published evidence on time preference and nonadherence is also mixed, and whilst studies report associations in the anticipated direction (low time preference rates associated with adherence), the strength of this association is relatively weak. Chapman et al. (2001) report a study of 128 community dwelling older adults receiving treatment for hypertension in the US. They examined the association between five measures of adherence to antihypertensive medication (self-report specific, self-report summary, pill count, blood pressure at interview, blood pressure at doctors visit) and two measures of time preference (health - using a scenario tailored to heart disease and monetary time

preference, and money). Only one of the ten potential correlations was significant and that relationship was weak (time preference for health and pill count $r=0.21$, $p<0.05$). Axon et al. (2009) surveyed 422 adults with hypertension and using a marginal effects model, found that a 1% increase in time preference rate increased the likelihood patients would not follow doctors' treatment plans by 1.6% ($p=0.05$). This was based on stated likelihood rather than measured behaviour. In a more recent example, Brant & Dickenson (2013) found a weak relationship in a small online survey of 47 students with persistent asthma. They also found that low financial time preference was a statistically significant predictor of self-reported adherence to medication ($p=0.03$), together with feelings of embarrassment and concern about medication, and risk preference; however, the contribution of time preference was relatively small. It therefore appears that there is limited evidence on the association between time preference rates and adherence and where there is a statistically significant association the magnitude of this relationship is often small. Reasons for this may include heterogeneity in methods (i.e., use of different hypothetical scenarios or techniques to elicit preferences); study populations (i.e., participants, conditions and medications); and, adherence measurement / definition.

Our study elicited time preference rates aligned with those in reviews of the published literature of time preference for health (Cairns & van der Pol, 2000; Mahboub-Ahari et al., 2014; Olsen, 1993; Cropper et al., 1991; Enemark et al., 1998). Cairns & van der Pol (2000) estimated a marginal time preference in a UK-wide sample (TEMPUS) to be 6.1% for their own health, which compares to our mean rate in England of 6.3% and mean rate in Wales of 6.9%. Cairns & van der Pol (2000) also summarised the empirical time preference literature in health and report on several studies with discount rates similar to our mean time preference rate of 13.4% for the 3-year delay and of 6.7% for the 6-year delay. Olsen (1993) reported mean estimates that ranged from 6.6% to 23.3% for delays of 3 and 6 years elicited from general public ($n=250$) and health planners ($n=77$) in scenarios of ill-health and saving

lives. Cropper et al. (1991) reported mean estimates that ranged from 2.7% to 8.6% for 6 year delay elicited from the general public (n=1600) in scenarios of saving lives. More recently, Mahboub-Ahari et al. (2014) performed a meta-analysis of private time preference rates from 5 studies, with time spans ranging as wide as 2 to 20 years, and estimated the discount rate to be 5.6% (95% CI 0.038 to 0.074). This is significantly lower than our mean rate of 10.0% which may be attributable to differences in time preference elicitation (experimental design, hypothetical scenarios, benefits and time delays) and heterogeneity in study populations.

The highest time preference rates were identified in Greece. In comparison with the lowest rates, the time preference rates for the 3-year delay were 21% in Greece compared to 9% in England; and the time preference rates for the 6-year delay were 10% in Greece compared to 4% in England. This suggests that respondents in Greece are not as risk adverse as their European counterparts. Whilst no prior evidence on time preference rates for medication adherence across countries was identified, evidence on other risk-taking behaviours such as smoking may offer some explanation. Greece has higher smoking rates than the other countries included in the analysis (Bogdanovica et al., 2011). There is also evidence of higher use of antibiotics (Adriaenssens et al., 2011), which may be associated with preferences for immediate treatment.

We found evidence of both negative and zero time preferences, with significant variation between countries. Negative time preferences are assumed to be based on eliminating dread (Loewenstein & Prelac, 1991) i.e. reducing the wait for ill health for example, even if immediate negative experience is for a longer period. In the scenario of medications, a negative time preference or a time preference of zero may reflect individuals' beliefs about medications or an aversion to taking medication. van der Pol & Cairns (2000) report a range

of 16% to 62% of respondents having zero time preference rates, and 3% to 39% having negative time preference rates. This is comparable with our cross-country ranges of for negative rates.

There was substantial between- and within-country variation in what predicts time preference, which may be explained by the significant between and within-country variation in patient demographic and sociocognitive factors reported. We found no previously published studies that had explored the influence of country on time preference, however, we assume that the between country variation may be attributable to cultural differences and associated differences in risk perception. Although any differences were revealed between countries, sex was the only personal demographic to have a significant influence on time preference in the multivariate model. Evidence on the difference in time preference between males and females varies, with the majority of studies reporting no significant relationship (Olsen, 1993; Cropper 1992; West, 2003; Robberstad 2005). Johannesson & Johansson (1997), however, also found that females have a higher discount rate than males, consistent with our findings. Income perception and ability to borrow income were both significant social demographic predictors in the multivariate model. This is consistent with the findings of Robberstad (2005); however, other studies have found no relationship (Cropper 1991, 1992; Johannesson & Johansson, 1997). Our findings that perceptions of illness consequences and concerns about illness were amongst the psychosocial predictors of time preference are novel and as such, there is no existing evidence to compare.

5.6.2 Strengths and limitations

To our knowledge, this is the first multinational study of time preference to test: (i) the association of time preference and adherence to medications; and, (ii) to test such a wide range of potential determinants of time preference including psychosocial and sociocognitive factors. Several different survey methods have been used to derive health time preference including open ended items (Cairns & van der Pol, 2000), discrete choice experiments (van der Pol & Cairns, 2001), and time trade-off techniques (Dolan & Gudex, 1995). This study used established open-ended methods for eliciting time preference rates and reported comparable findings. As evidence suggests that individuals' time preferences are a function of the period of delay as well as the starting point (Cairns & van der Pol, 1997), we used similar starting point and delays as previous health studies of time preference.

There were a number of limitations. Firstly, patients self-selected to participate in the study and we must therefore acknowledge the risk of selection bias which may influence the results insofar as only individuals who showed an interested in participating in the research completed the survey. This may reduce the external validity of our findings. There were also variations in recruitment methods between countries (Chapter 3). Secondly, we acknowledge that the time preference questions were cognitively challenging and the length of the survey may have led to some degree of fatigue. The time preference items were positioned on the 18th screen of 27 and we therefore anticipated that respondents would be involved with the survey and able to engage with the task. Thirdly, the hypothetical scenario used to elicit time preference was not based on the disease the cohort were receiving treatment for and we did not collect information on whether the respondents had epilepsy (the condition used in the scenarios), we are therefore unable to explore the influence of the condition. Fourthly, there are several models of intertemporal choice available for time preference analysis (Carins & van der Pol, 1997); we derived time preference rates using a standard discounted utility model (van der Pol & Cairns, 2008). Our choice of model was

consistent with the methodology of the open-ended methods applied. Further work is necessary on the most appropriate intertemporal choice model when considering the association between time preference and adherence to medications.

5.6.3 Meaning of the study: possible explanations and implications for clinicians and policymakers

We found limited evidence on the association between time preference and adherence to medications. However we found demographic, clinic, psychosocial and sociocognitive factors that influence individuals' time preference that may increase the possibilities for tailoring theory-based interventions aimed at improving other health-related behaviours. For example, we found that on average, females had a higher discount rate than males; therefore, an intervention that provides information on the long-term consequences of their behaviour (e.g. poor diet may cause cardiovascular disease) may have little impact on short-term decision making of females.

5.6.4 Recommendations / unanswered questions and future research

The findings of our study suggest that further methodological research is necessary on the impact of familiarity with hypothetical scenario on the elicitation of time preference rates and the most appropriate intertemporal choice model. It would also be of interest to consider a future longitudinal study of adherence to medication, as this study used a cross-sectional self-report measure of adherence that did not consider persistence with medications. Our focus was on time preference for health, however, further research into time preference in the context of different decision making e.g. financial may provide more information on time and risk perception by country. Horowitz and Carson (1990) found different discount rates for different types of risk.

5.6.5 Conclusions

The findings of our analysis of time preference rates and adherence to medication suggest a weak relationship that varies by country. Consideration of time preference when assessing patients' medication taking behaviour may be of limited use. Evidence on the association between time preference and demographic, clinical, psychosocial, and sociocognitive variables is of interest for future health research using time preference theory.

5.7 Candidates contribution

EAFH (the candidate) designed the survey and protocol (alongside co-authors and the ABC team), designed the time preference survey instrument, gained research governance approval in the UK, managed data collection and recruiting pharmacists in Wales. Catrin Plumpton managed and imputed the data. EAFH (the candidate) analysed the responses, interpreted the results with DH and VM, and drafted the manuscript. DH, VM (supervisors) and CP revised the manuscript for intellectual content. EAFH (the candidate) finalised the manuscript.

Chapter 6

Discrete choice experiment of preferences for antiepileptic medications

6.1 Preface

Chapter 4 presented a generic stated preference discrete choice experiment of persistence with medication and found that patients trade harms and benefits in their decision to persist with medication. The results of the discrete choice experiment were applied to a case study of treatment for ulcerative colitis; to illustrate the probability of persistence with the four most commonly dispensed 5-aminosalicylates in primary care in England.

In a more specific application of stated preference methods, this Chapter presents a stated preference DCE specifically designed to explore how patients with epilepsy trade the harms and benefits of antiepileptic medications. Epilepsy is the most common serious neurological condition, affecting around 350,000 adults in England (NICE, 2012). The most frequently used treatment for the management of epilepsy is antiepileptic medications. Most patients given a diagnosis of epilepsy receive treatment with antiepileptic medication, and between 60-70% of them will then achieve remission from seizures (Cockerell et al., 1995). Around 30-40%, however, will continue to have seizures and experience the consequences of a chronic disabling and stigmatising condition (Jacoby & Baker, 2008). The type of antiepileptic medication prescribed will depend on several factors including type of seizures, age and sex, other medical conditions, concurrent medications, and patient preferences. Evidence from clinical trials indicates that the effectiveness and adverse event profile of these drugs varies by drug and indication (e.g. seizure type). Patients may be prescribed more than one drug, which can increase the risk of adverse events. Achieving remission may therefore come at the cost of adverse medication effects, including common dose-related effects, rare but potentially life-threatening events and long-term effects. A third of people treated for epilepsy are women with the potential to become pregnant; and a growing body of evidence shows their offspring are at increased risk of congenital abnormalities and neuro-developmental problems (Maedor et al., 2011). Further considerations for medication preferences therefore includes teratogenic risk i.e. women with the potential to become pregnant are advised against certain antiepileptic medications due to the increased risk of foetal abnormality.

The SANAD trial, commissioned by the Health Technology Assessment Programme of NHS Research and Development, was the largest UK trial to compare standard and new AEDs.

Arm A compared drugs for partial onset epilepsy (characterised by impaired awareness and responsiveness): carbamazepine, gabapentin, lamotrigine, oxcarbazepine and topiramate, in patients for whom carbamazepine was considered the optimum first-line treatment when compared to valproate (Marson et al. 2007). Arm B compared drugs for patients with generalised or unclassified epilepsy (e.g. tonic clonic seizures characterised by loss of consciousness, muscle stiffening/jerking): valproate, lamotrigine, and topiramate, in patients for whom valproate was considered the optimum first-line treatment when compared to carbamazepine (Marson et al. 2007). The results suggested that sodium valproate should be the drug of choice in generalised and unclassifiable epilepsies, and lamotrigine in focal epilepsies. The results also showed variation in the adverse event profile of each of these medications, for example risk of depression with valproate used to treat patients with generalised or unclassified epilepsy was reported as 0.8%, compared to 2.64% with lamotrigine. When considering patients with partial onset seizures, the risk of depression ranged from 2.23 with carbamazepine to 6.7 with topiramate.

This study combines patient preference data elicited by the discrete choice experiment with actual clinical trial data to determine the utility and probability of uptake of five antiepileptic medications. The DCE described here and the time preference exercise described in Chapter 7 are part of the same survey of patients with epilepsy. This project involved a team of researchers from Bangor University (the candidate and supervisor), The University of Liverpool, and Epilepsy Action (see 6.7 Candidates contribution). Dr. Adele Ring (co-investigator) co-ordinated research governance approvals and collected the qualitative data using an interview schedule designed by EAFH (the candidate).

6.2 Abstract

Background: The decision to adhere to antiepileptic medication involves careful consideration of the potential benefits and harms, yet relatively little is known about the outcomes patients themselves consider important. Understanding patients' preferences and how these differ by patient group increases the possibilities for prescribing to be optimised.

Objectives: (i) to identify outcomes (benefits, harms, life impacts) of antiepileptic medication that patients consider important; (ii) to elicit preferences for these outcomes; (iii) to investigate if perceptions of acceptable trade-offs between benefits and harms differ across different subgroups; (iv) to apply patient preferences to the results of a clinical trial to elicit the utility and probability of uptake of five antiepileptic medications.

Methods: Web-based survey, containing discrete choice experiments (DCEs) to elicit preferences of three pre-defined groups of adults with epilepsy: (i) recently diagnosed epilepsy, (ii) established epilepsy, (iii) women with potential to become pregnant. The DCEs contained five attributes, with two levels, defined using: semi-structured interviews with patients, a focus group with antiepileptic medication prescribers, and clinical trial data. Each used the same fractional factorial design, folded into eight binary choices that asked respondents: Which medication would you prefer to take? The two versions had four attributes in common: remission, fewer seizures, depression, memory problems. The fifth attribute was aggression for recent and established patients, and risk of foetal abnormality for women with potential to become pregnant. Target sample size was 750 respondents, recruited via the Epilepsy Action website. Data was analysed in STATA using a random effects logit model.

Results: 56 patients and 8 prescribing physicians participated in the qualitative phase of the study to determine the most important outcomes of antiepileptic medication. 414 patients with epilepsy (105 women with potential to become pregnant) completed the survey. All attributes were significant and in the expected direction ($p<0.05$). Patients were willing to reduce the chance of remission by 4.02 percentage points (95% CI 3.20, 5.11) for a 1 percentage point reduction in aggression, 3.34 percentage points (95% CI 2.53, 4.35) for a 1 percentage point reduction in poor memory, and 3.34 percentage points (95% CI 2.56, 4.19) for a 1 percentage point reduction in depression. Women with the potential to become pregnant were willing to reduce the chance of remission by 4.96 percentage points (95% CI 4.13, 6.30) for a 1 percentage point reduction in the risk of foetal abnormality, 2.98 percentage points (95% CI 2.21, 3.85) for a 1 percentage point reduction in poor memory, and 1.80 percentage points (95% CI 1.13, 2.66) for a 1 percentage point reduction in depression.

Conclusion: Exploring what patients with epilepsy consider important for measuring antiepileptic medication effectiveness will ensure clinical services are focus on patient-defined needs and that future research is designed to assess appropriate patient-defined outcomes.

6.3 Introduction

Epilepsy is the most common serious neurological condition, affecting around 350,000 adults in England (NICE, 2012). The most frequently used treatment for the management of epilepsy is antiepileptic medications. Decisions concerning which medication to prescribe are primarily based on their effectiveness for seizure control, balanced against their potential to cause harm (adverse drug reactions) (Perucca & Tomson, 2011; Marson et al., 2007). Treatment decisions are therefore complex, but relatively little is known about what patients with epilepsy consider important outcomes of treatment, and how this influences their preferences for one medication over another. It is also likely that these preferences differ by patient group, with some placing greater value on avoiding certain outcomes than others e.g. recently diagnosed male versus women with potential to become pregnant with an established diagnosis.

The ultimate goal of antiepileptic medication is seizure freedom; however, whether this is achieved may be influenced by patients' reasons for preferring one medication to another. Evidence on treatment choices in the US suggests seizure control, fewer adverse events, convenient dosing regimens, and cost are areas of high priority for patients with epilepsy and that there are inter-individual differences in the level of concern about adverse events (Fisher et al., 2000). Prescribing decisions based on efficacy alone may therefore be misaligned with patients' preferences, as the decision to start or continue with treatment is weighted against other factors such as perceived or actual harms and/ or costs. The result of prescribing decisions not meeting patients' preferences may be nonadherence, which is associated with worse patient outcomes (Faught et al., 2012; Williams et al., 2006) and increased health care costs (Davis et al., 2008; Faught et al., 2009). Identification of the harms and benefits that patients perceive to be most important, and recognising the relationship between them, increases the possibilities for medicines optimisation; that is, ensuring patients the right patients get the right medicine at the right time (NICE, 2015). This should lead to prescribing that meets with patient satisfaction whilst achieving optimal

treatment outcome and reduced healthcare costs. Understanding how preferences differ by patient group also helps to inform medication choices within more focused interventions, such as the choice of antiepileptic medication in preconception counselling for women with epilepsy to reduce adverse pregnancy outcomes.

There are various methods of eliciting preferences for healthcare (Ryan et al., 2001). Previous research assessing antiepileptic medications has used ranking exercises (Fisher et al., 2000) and discrete choice experiments (Lloyd et al., 2005; Manjunath et al., 2012; Powell et al., 2015). Discrete choice experiments (DCEs) are a survey method to measure patients' preferences for goods (including healthcare services, interventions, medicines), that can be used in the absence of any data on revealed (actual) preferences (de Bekker-Grob, 2012). Respondents choose between hypothetical but realistic alternatives, described in terms of a number of attributes (e.g. adverse events), each characterised by specific levels (e.g. frequency of adverse events). This allows for the estimation of the relative importance of each attribute, assessment of any tradeoffs between attributes (e.g. seizure freedom versus adverse event), and of respondents' total satisfaction (utility) with the medication (Ryan & Farrar, 2000; de Bekker-Grob, 2012). This method assumes respondents have rational preferences and choose the alternative that maximises their utility. An advantage of DCEs is that they go beyond the remit of simple ranking tasks and provide information on willingness to exchange one characteristic of a medication for another. This is of particular interest when considering risk benefit decisions (Mt-Isa et al., 2014), such as the choice of antiepileptic medication.

In a previous application of DCEs to antiepileptic medication, Lloyd et al. (2005) estimated the importance of adverse events compared with seizure control for 148 patients with epilepsy in the UK, and found that patients were willing to give up additional seizure control for reductions in weight gain, and risks of rash, concentration loss, hair loss and sickness. Similarly, Manjunath et al. (2012) measured preferences for add-on medications for 263 adults in the US, comparing the importance of attributes for seizure frequency to 'short term' adverse events (sleepiness, dizziness, headache, nausea, tremor, double or blurred vision, and skin rash) and 'long term' adverse events (fatigue, moodiness, confusion or memory problems). Patients with epilepsy considered seizure reduction to be their highest priority when ranked against the reduction or elimination of adverse events. More recently, in a more specific application, Powell et al. (2015) elicited the preferences for carbamazepine of 82 patients in the UK, patients were willing to reduce the chance of remission in exchange

for a risk reduction of memory problems, skin rash, and rare but severe, adverse drug reaction (ADR).

In the present study, we aimed to inform decision-making around antiepileptic medication prescribing by soliciting the views of patients with epilepsy on what they consider important. Specific objectives were to: (i) identify outcomes (benefits, harms, life-impacts) of antiepileptic medication that patients consider important; (ii) elicit preferences for these outcomes; and, (iii) investigate if perceptions of acceptable trade-offs between benefits and harms differ across different subgroups. We planned to investigate preferences using a DCE across three pre-defined subgroups: (i) patients with a recent diagnosis; (ii) patients with an established diagnosis; and (iii) women with potential to become pregnant. A further objective of the study was to apply the results of the DCE to clinical trial data to determine which of five commonly prescribed antiepileptic medication maximised utility.

6.4 Methods

Discrete choice experiments require several stages of development: identifying the attributes, assigning levels, experimental design, collecting data, and data analysis. The first stage, identification of the attributes, is a critical stage that requires a thorough methodology (Coast et al., 2011). As such, we split our study into two phases. Firstly, we conducted a qualitative study involving interviews and ranking exercises with patients and physicians to ensure we identified the most important and plausible outcomes of antiepileptic medications. Secondly, we conducted a larger-scale survey containing a DCE study to elicit patient preferences for these outcomes.

Ethical approval was granted by the NHS National Research Ethics Service (Reference Number: 11/NW/0191).

6.4.1 Phase one: qualitative study

Patient interviews

Adults aged 18 years or over, treated at one of three major epilepsy centres across England (Birmingham, Liverpool, and Manchester) or responding to an advertisement circulated to

members of the charity Epilepsy Action, with no other long-term health conditions were eligible for inclusion in the study. People were excluded if they had learning difficulties sufficient to make required tasks unreasonable, were non-English speakers, currently participating in other research, or unable to provide informed consent.

The sample was stratified into three groups: adults with a recent diagnosis (at least 3-months but no longer than 12-months), adults with an established diagnosis (more than 12-months), and women with potential to become pregnant, defined by age (18-50 years). The time frame for recent diagnosis was restricted to a minimum of 3 months to ensure the research did not distress patients in the wake of a new diagnosis, to ensure patients had time to judge whether treatment was beneficial or not, and to meet the practical requirements of identifying and approaching patients within ethical requirements. The sample size was a maximum of 60 patients, with the aim of recruiting up to 20 patients from each group for representation. Interviews were comprised of two parts: Part A was participant generated to elicit patients' experiences of epilepsy and its impact on their everyday lives; Part B was topic-guided to ascertain and rank treatments for, and outcomes relating to antiepileptic medications. We used the ranking exercise on treatment outcomes within Part B to inform selection of attributes for the DCE. Our target sample size for this purpose was 10 ranking exercises per subgroup and 5 cognitive interviews to ascertain the face validity of the DCE survey, including comprehension of the probability of events.

Participants were invited to complete a structured ranking exercise requiring them to:

- Consider a pre-defined list of 2 benefits of antiepileptic medications (e.g. reduction in seizure frequency), add any they considered to be missing, then choose their top 2 and rank them in order of importance.
- Consider a pre-defined list of 12 potential harms of antiepileptic medications (e.g. skin rash), add any they considered to be missing, then choose their top 4 and rank them in order of importance.
- Consider a pre-defined list of 11 potential life-impacts of antiepileptic medications (e.g. negative impacts on relationships with family and friends), add any they considered to be missing, then choose their top 4 and rank them in order of importance.
- Consider the 10 outcomes they had selected (2 benefits, 4 harms, and 4 life impacts), choose their top 4 and rank them in order of importance.

Weighted scores were assigned to the outcomes ranked in this final exercise that were summed and standardised for all individuals in each subgroup. Appendix 6.1 details the interview schedule. The list of benefits, harms and life impacts were taken from clinical trial data (Marson et al., 2007) and validated outcome measures (Baker et al., 1995; Mulhern et al., 2012).

Once we reached the target sample size of 10 ranking exercises per group, we used a cognitive interview schedule (Appendix 6.2) to assess the face validity of the DCE (presentation of attributes and levels), and to gather opinion on how the outcomes of medications (identified as important in the ranking exercises) should be presented in the DCE. We presented the respondents with show cards detailing the different medication outcomes and asked them to describe what they thought the card was explaining. The interviewer used a series of prompts to ascertain whether the respondent understood the information presented to them and to explore the preferred format for presenting binary choice tasks. If respondents asked for clarification on how to interpret risk, the interviewer schedule contained a standard response to ensure consistent examples and information for all participants.

Interviews were conducted in the patient's own home, lasted 2 hours on average, and consent was requested to audio-tape record the interview for subsequent transcription. The ranking exercise used show cards and the results were recorded in a workbook by the researcher.

Focus group with physicians

Physicians responsible for prescribing antiepileptic medications to adults with epilepsy at the Walton Centre NHS Foundation Trust (specialist neurology secondary and tertiary care referral centre, UK) were invited by e-mail to attend a one-hour focus group meeting. The focus group was facilitated by the researcher designing the DCE (EAFH / the candidate). Participants were required to complete the ranking exercise previously completed with patients (described above) and then participate in semi-structured discussions of their views and preferences. Participants were encouraged to share their practical experience of discussing treatment outcomes with patients; and, in particular their distinction between "adverse events" and "life-impacts" of medication. Following this discussion, participants

were asked to individually record the frequency and severity at which an adverse event becomes a 'clinically important adverse event' that requires a change in treatment. The purpose of this exercise was to ensure parity between descriptions of attributes in the DCE and the levels, which were based on 'clinically important adverse event' data from clinical trials. Prescribers were also asked for feedback on potential formats for the patient DCE and the presentation of the attributes and levels. Discussions were audio tape recorded and ranking results were noted in workbooks that were self-completed during the session (Appendix 6.3). One participant could not attend the group but completed the workbook. The group discussion lasted one hour. Participants were asked if they would like to be re-contacted to comment on the draft DCE.

6.4.2 Phase two: discrete choice experiment

DCE Attribute and level selection

The findings of the ranking exercises and focus group informed the attribute selection. We selected the top five outcomes considered plausible medication outcomes by prescribers. This ensured that the attributes were realistic; insofar as they could be traded in the decision to take a medication or change to an alternative, (i.e. the attributes were pertinent to the prescribing decision). The findings of the three predefined subgroups were analysed separately, however the early diagnosis and established diagnosis groups selected resulted in the same attributes (in different orders, but same five). We therefore designed two versions of the DCE: DCE 1: Patients with epilepsy, excluding women with the potential to become pregnant; and, DCE 2: Women with potential to become pregnant; both with the potential to analyse association between preference and time since diagnosis.

DCE 1 had the following five attributes: remission of seizures, reduction in seizure frequency, memory problems, depression, and, anger/aggression. DCE 2 contained foetal abnormality, and four attributes in common with DCE1: remission of seizures, reduction in seizure frequency, memory problems, and depression. Attribute names were presented down the left-hand side of the binary choice and accompanied by a short description. The descriptions were from the focus group findings on 'clinically important adverse event' that require a change in treatment.

Each attribute was assigned two levels identified using clinical trial data (Marson et al., 2007). The levels were the probabilities of event and the range reflected the variance in estimates reported for six antiepileptic medications. We opted to use a single clinical trial as this was the largest epilepsy trial, had a UK perspective, and we had access to patient level data that enabled us to calculate seizure reduction. We presented the levels as frequencies in the questionnaire (1 in X chance or risk) and supplemented with pictograms that used a traffic light colour coding for positive and negative effects. The levels for foetal abnormality reflected data on risks reported on the Epilepsy Action website at the time of the survey. Table 6.1 provides details of the attributes and levels.

Experimental design

As both versions of the DCE had five attributes each with two levels, a full factorial design (that included all possible combinations) would yield 32 antiepileptic medication profiles. In order to keep the task manageable we adopted a fractional factorial design from a published design catalogue (Hahn & Shapiro, 1996) that contained eight profiles. The profiles were converted into "Medication A", then we generated eight binary choices by making systematic changes to the levels used for "Medication A" to form "Medication B" (Street & Burgress, 2007). The DCE consisted of eight binary choice scenarios (Figure 6.1) in which the respondents were asked: Which medication would you prefer to take?

Patient DCE survey

Adults self-reporting as being aged 18 or over and diagnosed with epilepsy by a doctor were eligible to complete the survey. Respondents were required to consent to participate in the study before they accessed the survey, there was no reward for their time, but we did provide details of the potential benefits of the findings. Exclusion criteria were an inability to read/complete web-based or postal questionnaires. Recruitment was via Epilepsy Action (social media, members magazine, local services newsletter, e-forums and newsletters, website home page), an advertisement in local press, and posters in 113 NHS outpatient clinics across England & Wales. The survey was hosted by the Epilepsy Action website and available via a link to an anonymous online service (Snap Surveys, London, UK) between June 2013 and October 2013. Those preferring to complete a hard copy were asked to contact Epilepsy Action.

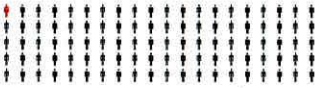
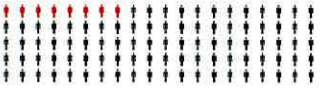
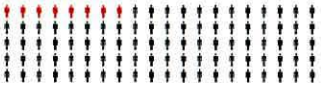
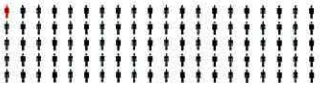
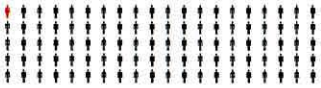
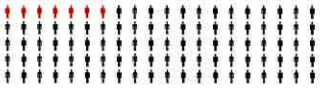
Table 6.1 Attributes and levels of the discrete choice experiments

DCE Attribute	Description (prior to choice questions)	DCE Levels (coding)	Rationale: Standardised rank scores from preliminary study and clinical trial data used to inform levels	
Seizures Stop *One year after starting this medication* **Fewer seizures** *One year after starting this medication*	The chance of responding well: - Seizures stop - Fewer seizures	5 in 10 people (0.5) 3 in 10 people (0.3) 3 in 10 people (0.3) 1 in 10 people (0.1	**Reduction in seizures:** Early:24.00, Est: 22.31 Women*: 25.00, Prescribers: 36.90	SANAD trial raw data on seizure frequency (Arm A) (Marson 2007)
Memory problems *These problems frequently affect activities of daily life* **Depression** *A feeling of low mood that often affects activities of daily life* **Feelings of aggression** *This can be verbal or physical and often affects relationships and activities of daily life*	The risk of side effects. - Memory problems - Depression - Feelings of aggression (not women*) These side-effects^ would be so severe that you would need to change to a different antiepileptic medication	1 in 100 people (0.01) 7 in 100 people (0.07) 1 in 100 people (0.01) 8 in 100 people (0.08) 1 in 100 people (0.01) 8 in 100 people (0.08)	**Problems with memory:** Early:12.22, Est: 6.92 Women*: 1.00, Prescribers: 15.95 **Depression:** Early:10.00, Est: 0.77, Women*: 2.22, Prescribers: 14.75 **Aggression:** Early: 16.00, Est: 0.00 Prescribers: 10.95	Marson (2007) clinically important adverse events.
Harm to your foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ* (Women* ONLY)	Finally, we will also give you information on the risk of harm to the foetus if you get pregnant whilst taking this medication:- This may cause problems, such as spinda-bifida, a hole in the heart, and a cleft palate (where the roof of the mouth is not correctly joined). This may also cause neurodevelopment problems, such as poor memory, poor language and social skills, and low IQ.	2 in 100 pregnant women (0.02) 9 in 100 pregnant women (0.09)	**Foetal abnormality:** Women*: 5.00	Epilepsy Action website

*Women with potential to become pregnant (those who responded "yes" to: "Is there any chance, however remote, that you may become pregnant in the future?")
^ "side-effects" used to describe adverse events, as per findings of our qualitative study.

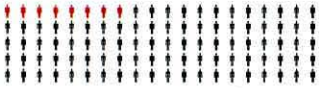
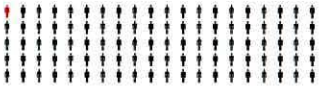
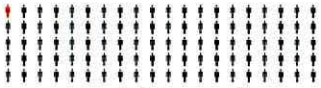
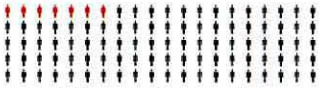
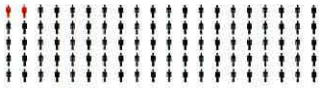
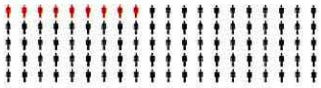
Figure 6.1 Examples of a binary choice question for DCE 1 and DCE 2

DCE: Version 1 for patients with a recent or established diagnosis (excluding women with potential to become pregnant)

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 1 in 100 people experience feelings of aggression	 8 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems

Which medication would you prefer to take? ☐ ☐

DCE: Version 2 for women with potential to become pregnant only

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth - such as spina-bifida or low IQ*	 2 in 100 pregnant women experience foetal harm	 9 in 100 pregnant women experience foetal harm

Which medication would you prefer to take? ☐ ☐

The survey contained 126 items across 6 sections (with the DCE being one section with up to 9 items) (Appendix 6.4). Estimated completion time was 30 minutes. Target sample size was 63 completed DCE responses, based on each main effect level of interest being represented across the design at least 500 times (Orme, 2010). Respondents were directed to DCE 1 or DCE 2 via a series of filter questions. A random sample of 25% were directed to an independent study designed to compare patients' and physicians' preferences for pharmacogenetic testing prior treatment with carbamazepine. Whilst all DCE surveys were hosted on the same platform, the design and analysis of the carbamazepine study was independent of DCEs described in this chapter, and as so it is reported elsewhere (Powell et al., 2015; Appendix 6.5).

We piloted the survey on a convenience sample of Epilepsy Action staff and volunteers, clinical and academic research staff, physicians who agreed to be re-contacted after the focus group, and members of our scientific advisory group. The link to the survey was e-mailed to 55 people, 31 returned comments. Following the pilot, we reordered the questions, reformatted the item to elicit peoples' time preference (reported elsewhere, Chapter 7), and changed the selection criteria for women with potential to become pregnant. Originally, women with potential to become pregnant were defined using filters on sex and age (18 to 50), however, the pilot identified that this strategy was over inclusive and that pregnancy related attributes would not be applicable to all women in this category. The new filter was a single question that asked, "Is there any chance, however remote, that you may become pregnant in the future?"

6.4.3 Statistical Analysis

Results of the DCE were analysed in STATA (version 10; StataCorp LP, College Station, TX) using a random effects logit model that allowed for repeated observations from the same respondent:

DCE 1 $U = \beta_0 + \beta_1 STOP + \beta_2 FEWER + \beta_3 DEPRESSION + \beta_4 MEMORY + \beta_5 ANGER + \varepsilon$

DCE 2 $U = \beta_0 + \beta_1 STOP + \beta_2 FEWER + \beta_3 DEPRESSION + \beta_4 MEMORY + \beta_5 FOETAL + \varepsilon$

U = utility derived by individual

β_0 = constant term

β_I = estimated coefficient for each attribute (variable)

ε = error term

These regressions estimate the importance of attributes (significance and magnitude) and the direction of effect. All attributes were included in the analysis as continuous linear variables. The coefficients from the regression were used to calculate the rate at which respondents were willing to give up a unit change in one attribute in exchange for a unit change in another attribute, while maintaining the same utility (marginal rate of substitution [MRS]). Confidence intervals (95%) were determined using 1000 bootstrap replications. All analyses were conducted in STATA 10.

To test the validity of the DCE we identified a potentially dominant choice in which medication A was superior in all but one attribute (higher chance of remission, lower risk of memory problems, depression, and, anger / aggression; but, higher frequency of seizures). We assumed that patients who selected the alternative (Medicine B) for his choice did not understand the task (or had lexicographic preference, which may be attributable to left or right hand bias) and consequently analysed the DCE with and without these respondents. This was done by comparing the confidence intervals of all the coefficients in the regression to ascertain if there were statistically significant differences.

Subgroup analyses were conducted using log likelihood (LL) ratio tests of the base case regression and models comprising pre-specified subgroups (of n≥30) were performed at a 5% level of significance. The LL of the base case regression was compared to the sum of the LL from the subgroup model, using a 5% level of significance with Bonferroni correction, and the appropriate degrees of freedom (5 for binary subgroups). If the subgroup model was significantly different, we calculated the MRS for each category (e.g. male and female) within the subgroup. A maximum of 8 subgroups were specified *a priori* (age, sex (DCE 1 only), time since diagnosis, time since last seizure, experience of memory problems, experience of depression, experience of aggression (DCE 1 only) or pregnancy concerns (DCE 2 only).

6.4.4 Estimating the probability of uptake using clinical event data

The coefficients derived from DCE (stated preference data) where combined with clinical parameters (actual clinical event data) to estimate the probability of uptake for five antiepileptic medications: carbamazepine (CBZ), gabapentin (GAB), lamotrigine (LTG), oxcarbazepine (OXC), and topiramate (TPM). Adverse event data for each of the attributes, used to describe hypothetical medication A and B in the DCE, were taken from the SANAD trial that compared standard and new antiepileptic medications. We multiplied frequency of event for each medication (seizure outcomes, seizure reduction, depression, memory problems and aggression) by the βcoefficient of the corresponding attribute, to obtain weighted coefficients. The sum of the weighted coefficients provided an estimate of patient utility for each medication. The probability of uptake of each medication was then calculated using the exponential of the total utilities (e.g., exponential of the utility for CBZ divided by the sum of the exponential of the utilities for the four alternatives.

6.5 Results

6.5.1 Ranking exercises and focus group

One-hundred and twenty-nine patients were approached across three clinical sites. Sixty-two (48%) registered their interest in taking part, 5 subsequently declined, contact was lost with 1 person and 56 consented to audio-recorded interview. 41 participants completed the ranking exercises to inform the DCE (10 recent, 13 established, 18 women with potential to become pregnant) Table 6.2. The remaining 15 participated in cognitive interviews to

assess the face validity of the DCE (presentation of attributes and levels). Eight of the ten prescribing physicians agreed to participate in the focus group. One physician completed the workbook remotely but did not attend the group discussion.

Table 6.2 Patient ranking exercise sample characteristics

	Recent diagnosis	Established diagnosis	Women of childbearing age
N	10	13	18
Mean Age	46	39	35
Male	100%	92%	0%

Stratification of women with potential to become pregnant by age resulted in an exclusively male sample for 'recently' diagnosed. Reduction in seizure frequency was the most highly ranked medication outcome across all groups (standardised-score: women with potential to become pregnant=2.5, recent=2.4, established=2.2). Adults recently diagnosed were most concerned about feelings of aggression (standardised-score: 1.6), depression (standardised-score: 1.1) and ability to work (standardised-score: 0.9). Adults with established epilepsy were most concerned with anger and aggression (standardised-score: 1.15), reduced independence (standardised-score: 1.0), negative impacts on relationships (standardised-score: 0.85), and memory problems (standardised-score: 0.69). Women with potential to become pregnant were concerned about memory problems (standardised-score: 1.22), seizure severity (standardised-score: 1.17), reduced independence (standardised-score: 0.78), and foetal abnormality (standardised-score: 0.5). Table 6.3 presents the results of the ranking exercise. Physicians considered life-impacts (e.g. work, relationships) as consequences of benefits and harms of treatment. We therefore selected the most plausible outcomes on which patients could state their preference to take the medication (i.e. the factors that influenced prescribing).

6.5.2 DCE Results

Recruitment to the survey was over an 18 week period. The press advertisement increased recruitment from 1.9 to 2.9 per day for one week (week 4); and posters in NHS outpatient clinics increased recruitment from 0.57 to 2.00 per day over 4-weeks. Due to the nature of the sampling frame we could not capture data on non responders.

6.5.3 Respondents' characteristics

Four-hundred and fourteen patients with epilepsy consented to the survey. 7 completed the paper version. Four withdrew prior to randomisation and 29 did not start their DCE. 92 patients were redirected to the carbamazepine study (Appendix 6.5). 282 patients were included in the analysis: 9 recently diagnosed, 168 established diagnosis, and 105 women with potential to become pregnant [3 recently diagnosed]. Sample characteristics are described in Table 6.4.

Table 6.3 Results of the ranking exercises, presented as standardised weighed rank scores^

Outcome		Women of Childbearing Age	Patient Recent Diagnosis	Patient Established Diagnosis	HCP treating Patient Recent Diagnosis	HCP treating Patient Established Diagnosis
*Seizure Frequency	B	2.50	2.40	2.23	3.75	3.63
*Memory Problems	AE	1.22	0.10	0.69	1.56	1.63
*Depression	AE	0.22	1.10	0.08	1.35	1.60
*Foetal Abnormality	AE	0.50				
*Anger & aggression	AE	0.22	1.60	1.15	1.06	1.13
Ability to work in paid employment	LI	0.44	0.90	0.31	0.73	0.73
Independence	LI	0.78	0.80	1.00	0.54	0.54
Relationships with family and/or friends	LI	0.28	0.30	0.85	0.81	0.56
Seizure severity	B	1.17	0.30	0.62		
Personal control	LI	0.56	0.30	0.54		
Hopes & plans for the future	LI	0.44	0.50	0.69		
Social life and activities	LI	0.11	0.50	0.23		
Worry about having a seizure	LI	0.33	0.60	0.38		
*Headache	AE		0.10		0.19	0.19
Problems with everyday memory and/or concentration	LI	0.44	0.10			
Sleepiness & drowsiness	AE	0.06	0.40	0.23		
Extent to which other people treat you like an inferior person	LI	0.22		0.23		
Difficulty concentrating	AE	0.06				
Weight gain	AE	0.22				
Skin rash	AE	0.17		0.15		
Dizziness	AE					
Makes you feel more negative about yourself	LI	0.11				
Nervousness and/or agitation	AE	0.06				
Tiredness	AE	0.06				

^Standardised score = [(count_rank1*4)+(count_rank2*3)+(count_rank3*2)+(count_rank4)/n] Max=4
*Used in focus group ranking exercise
B = Benefit AE = Adverse Event LI = Life Impact

The median age of respondents was 37 years, 54% were female. Approximately half were living with a partner, wife or husband (51%). Ninety-five percent of respondents described themselves as white British. Over half (56%) were in employment or education. 97% of the respondents were taking antiepileptic medications, 45% of whom had experienced changes to their antiepileptic medications in the past three months. The most common change was to dose (36%), 69% of changes were for lack of seizure control (69%). Over half of the sample that experienced a recent change in antiepileptic medication were classified as non-adherent using the Morisky self-reported nonadherence measure. Approximately 30% of respondents had experienced one or more of the adverse events described in the DCEs.

Table 6.4 DCE Patient characteristics

	DCE 1 Recent & established diagnosis		DCE 2 Women with potential to become pregnant*	
	n	%(range)	n	%()
Demographics				
Age (median)	45	(18-79)	29	(18-55)
Female	95	54%	105	100%
White British	140	94%	86	98%
Live alone	28	19%	6	7%
Employed	70	47%	63	70%
Time since diagnosis				
Over 10 years	127	72%	62	59%
Seizure types				
Focal	56	36%	41	42%
Complex focal	70	45%	45	46%
Absences	64	41%	47	48%
Tonic clonic	102	65%	73	75%
Time since last seizure				
Less than 1 month	88	56%	50	51%
Seizure frequency compared to 1 year ago				
Increased	39	25%	17	17%
Constant	69	44%	50	51%
Decreased	49	31%	31	32%
Antiepileptic medication changes past 3mths				
No change	85	56%	51	54%
Change reason seizures	44	66%	31	74%
Change reason adverse events**	19	28%	15	37%
Change reason remission	5	7%	2	5%
Change and self-reported nonadherence	37	54%	24	57%
Experience of adverse events				
Aggression	16	23%	n/a	n/a
Depression	16	23%	17	39%
Memory Problems	23	33%	14	34%
Change antiepileptic medication due to pregnancy concern	n/a	n/a	31	32%

*Women with potential to become pregnant (those who responded "yes" to: "Is there any chance, however remote, that you may become pregnant in the future?")
**Described in questionnaire as "side-effects"

Patients' Preferences

All five attributes were significant and in the expected direction. Overall goodness of fit of the models were good (DCE1: pseudo-R2 value 0.2722 ; model $\chi 2$ p-value <0.001; DCE2: pseudo-R2 value 0.3406 ; model $\chi 2$ p-value 0.00). The results of DCE 1 (excluding women with potential to become pregnant) are presented in Table 6.5. All else being equal the odds of a patient preferring an antiepileptic medication increased by 3 % for every 1% increase in remission, increased by 1 % for every 1% increase in reduction in seizures, decreased by 10 % for every 1% increase in depression, decreased by 10 % for every 1% increase in memory problems, and decreased by 12 % for every 1% increase in aggression.

The results of DCE 2 (women with potential to become pregnant) are presented in Table 6.6. All else being equal, the odds of a women (with potential to become pregnant) preferring an antiepileptic medication increased by 5 % for every 1% increase in remission, decreased by 8 % for every 1% increase in depression, decreased by 13 % for every1% increase in memory problems, decreased by 21% for every 1% increase in foetal abnormality if you get pregnant whilst taking this medication. The chance of fewer seizures was non-significant for women with potential to become pregnant.

6.5.4 Trading outcomes

Patients were willing to accept a percentage point reduction in the chance of 12-month remission from seizures in exchange for a reduction in the risk of adverse events. Patients with a recent or established diagnosis were willing to reduce the chance of remission by 4.0 percentage points (95% CI 3.2, 5.1) for a 1 percentage point reduction in aggression, 3.3 percentage points (95% CI 2.5, 4.4) for a 1 percentage point reduction in poor memory, and 3.3 percentage points (95% CI 2.6, 4.2) for a 1 percentage point reduction in depression. Women with the potential to become pregnant were willing to reduce the chance of remission by 5.0 percentage points (95% CI 4.1, 6.3) for a 1 percentage point reduction in the risk of foetal abnormality, 3.0 percentage points (95% CI 2.2, 3.9) for a 1 percentage point reduction in poor memory, and 1.8 percentage points (95% CI 1.1, 2.7) for a 1 percentage point reduction in depression (Summary in Table 6.7).

Table 6.5 Random effects logit regression model and marginal rates of substitution (MRS) – DCE 1 (exc. Women with potential to become pregnant)

					Remission		Fewer seizures		Depression		Memory		Aggression	
Attribute	Coef.	P value	95% CI	Odds Ratio	MRS	95% CI	MRS	95% CI	MRS	95% CI	MRS	95% CI	MRS	95% CI
Remission	-0.033	0.000	0.031 to 0.048	1.03	1.00		3.62	1.82 to 12.80	-0.31	-0.39 to -0.24	-0.30	-0.39 to -0.23	-0.25	-0.31 to -0.20
Fewer seizures	-0.009	0.010	0.003 to 0.019	1.01	0.28	0.08 to 0.54	1.00		-0.09	-0.16 to -0.02	-0.08	-0.15 to -0.02	-0.07	-0.13 to -0.02
Depression	0.108	0.000	-0.154 to -0.104	0.90	-3.27	-4.19 to -2.56-	-11.83		1.00		0.98	0.77 to 1.26	0.81	0.66 to 0.99
Memory Problems	0.111	0.000	-0.159 to -0.103	0.90	-3.34	4.35 to -2.53	-12.09	-41.16 to -6.47	1.02	0.79 to 1.29	1.00		0.83	0.66 to 1.03
Aggression	0.133	0.000	-0.182 to -0.132	0.88	-4.02	-5.11 to -3.20	-14.55	-49.49 to -7.66	1.23	1.00 to 1.50	1.20	0.97 to 1.52	1.00	
Constant			-0.191 to 0.123	0.97										

Number of obs = 1339

Number of groups = 177

Average obs per group = 7.6

Wald chi2(5) = 321.27
Log likelihood = -674.71

Table 6.6 Random effects logit regression model and marginal rates of substitution (MRS) – Women with potential to become pregnant

					Remission		Fewer seizures		Depression		Memory		Foetal Abnormality	
	Coef.	P value	95% CI	Odds Ratio	MRS	95% CI	MRS	95% CI	MRS	95% CI	MRS	95% CI	MRS	95% CI
Remission	0.047	0.000	0.038 to 0.070	1.05	1.00		-22.25	-116.30 to 101.73	-0.56	-0.88 to -0.38	-0.34	-0.45 to -0.26	-0.20	-0.24 to -0.16
Fewer seizures	-0.002	0.685	-0.013 to 0.009	1.00	-0.05	-0.25 to 0.19	1.00		0.03	-0.12 to 0.13	0.02	-0.06 to 0.10	0.01	-0.04 to 0.05
Depression	-0.084	0.000	-0.125 to -0.063	0.92	-1.80	-2.66 to -1.13	40.09	-195.27 to 150.85	1.00		0.60	0.37 to 0.95	0.36	0.23 to 0.49
Memory Problems	-0.139	0.000	-0.212 to -0.109	0.87	-2.98	-3.85 to -2.21	66.37	-324.98 to 314.17	1.66	1.05 to 2.68	1.00		0.60	0.45 to 0.74
Foetal Abnormality	-0.231	0.000	-0.315 to -0.213	0.79	-4.96	-6.30 to -4.13	110.32	-566.57 to 498.80	2.75	2.05 to 4.27	1.66	1.34 to 2.23	1.00	
Constant	0.474	0.000	0.248 to 0.924											
Number of obs =790														
Number of groups =103														
Average obs per group = 7.7														
Wald chi2(5) =														
Log likelihood =														

Table 6.7 Summary of patients' marginal rates of substitution between remission and adverse events

Adverse event	Chance of remission willing to forgo (%)		
	DCE 1	DCE 2 (Women*	
Depression	3.27%	1.80%	For a 1% risk reduction in depression
Memory Problems	3.34%	2.98%	For a 1% risk reduction in memory problems
Aggression	4.02%	n/a	For a 1% risk reduction in aggression
Foetal Abnormality	n/a	4.96%	For a 1% risk reduction in foetal abnormality
*Women with potential to become pregnant (those who responded "yes" to: "Is there any chance, however remote, that you may become pregnant in the future?")			

6.5.5 Subgroup analysis

Within the recent and established diagnosis sample, four subgroups qualified for analysis (n≥30 per group), namely age, sex, time since diagnosis and self-reported adherence. Log likelihood ratio tests for sex (within DCE 1) indicated the base case model was statistically different from the model comparing the two subgroups (p=0.015). Marginal rates of substitution indicated that males tended to be willing to forgo a higher chance of remission for a 1 percentage point reduction in depression (female -2.70 [95% CI -3.83 to -1.99] versus male -4.45 [95% CI -7.34 to -2.98]), memory problems (female-2.54 [95% CI -3.60 to -1.71] versus male -4.90 [95% CI -7.95 to -3.25]) and aggression (female -3.29 [95% CI -4.42 to -2.45] versus male -5.38 [95% CI -8.49 to -3.85]), however, these results were not statistically significant (p<0.05). Subgroup analyses results are presented in detail in Appendix 6.6.

Three subgroups qualified for analysis within DCE 2, namely age, time since diagnosis and experience of pregnancy concerns. Log likelihood ratio tests for experience of pregnancy concerns indicated the base case model was statistically different from regressions comparing the two subgroups (p=0.010). Marginal rates of substitution indicated that women who had experience of pregnancy concerns (answered yes to: have you ever stopped or changed your antiepileptic medication because of concerns about your pregnancy?) tended to be willing to forgo a higher chance of remission for a reduction in depression (experience -3.07 [-15.59 to -0.15] versus no experience -1.34 [-2.11 to -0.26]), memory problems (experience -5.36 [-22.98 to -2.05] versus no experience -2.72 [-3.37 to -

2.01]) and foetal abnormality(experience -10.48 [-49.02 to -3.51] versus no experience -3.77 [-4.69 to -3.00]), however, these results were not statistically significant ($p<0.05$).

6.5.6 Probability of antiepileptic medication uptake and implications for clinical trials

Combining adverse event data from clinical trial data with the preference coefficients elicited by the DCE showed that the probability of a patient with focal epilepsy from DCE 1 preferring to take one of the five antiepileptic medications, in descending order was: oxcarbazepine (0.29), carbamazepine (0.25), lamotrigine (0.22), gabapentin (0.15), topiramate (0.08) (Table 6.8).

Table 6.8 Probability of patients with epilepsy choosing to take one of five antiepileptic medications compared in the SANAD trial

		N Events (in 100)					Weighted Coefficients				
Attribute	Coef.	CBZ	GAB	LTG	OXC	TPM	CBZ	GAB	LTG	OXC	TPM
Remission	-0.033	41	28	35	37	40	1.345	0.931	1.173	1.234	1.317
Fewer seizures	-0.009	24	24	23	28	21	0.223	0.222	0.208	0.253	0.188
Depression	0.108	4	5	5	3	8	-0.401	-0.516	-0.572	-0.361	-0.830
Memory Problems	0.111	5	6	3	6	7	-0.585	-0.645	-0.380	-0.685	-0.761
Aggression	0.133	3	2	3	1	6	-0.422	-0.318	-0.422	-0.127	-0.845
						Utility	0.160	-0.326	0.006	0.315	-0.931
						Probability	0.252	0.155	0.216	0.294	0.085
						Preference weighted rank	2	4	3	1	5

Note. carbamazepine (CBZ), gabapentin (GAB), lamotrigine (LTG), oxcarbazepine (GAB), topiramate (TPM)

6.6 Discussion

Seizure freedom was the most important medication outcome across all patient groups and physicians. The ranking exercise found that patients also prioritised adverse events and life impacts. Among patient groups, there was overlap in what was considered important, but priorities differed. Adults with a recent diagnosis were most concerned about feelings of aggression, depression and then their ability to work. Whereas, adults with an established diagnosis were most concerned about their ability to work, negative impacts on relationships, and then memory problems. Women with potential to become pregnant considered reduced independence, feeling in control, and risk of foetal abnormality to be most important. Focus group physicians ranked memory problems, depression, anger and aggression as the most important adverse events; they considered life-impacts (e.g. work, relationships) as consequences of benefits and harms of treatment. The results of the discrete choice experiments found that patients were willing to forgo an increase in chance of remission in exchange for a reduction in the risk of adverse events. Patients were therefore indicating a stronger aversion to risk of adverse events than to seizures, which represents a new perspective for consideration in the treatment of epilepsy. When patient preferences were analysed alongside actual event data from a clinical trial the majority of patients were most likely to choose oxcarbazepine or carbamazepine, over lamotrigine, gabapentin, or topiramate.

To our knowledge this is the first study to consider preference of different groups of patients for antiepileptic medications. Whilst simple ranking exercises can be used to ascertain the outcomes of treatment that are most important, the application of the DCEs (a multi-attribute choice based task) represents a robust theory-based method to elicit preferences. This enables a direct comparison of changes in the 'value' of treatment in terms of the reduction of seizures against the 'value' of a reduction in the risk of adverse events associated with this treatment. DCEs are consistent with Lancaster's theory of consumer demand which contends that preferences and utility are derived from the underlying attributes of goods, rather than actual goods per se (Lancaster, 1966). This method provides more information not only about the order of preferences, but their relative importance and trade-offs between these outcomes (Ryan et al., 2008). Furthermore, the findings of these stated preferences have been used alongside actual event data from the SANAD trial in order to provide more information on the application of preference utilities and potential implication of the findings.

Our systematic approach to the design of the DCE encompasses the views of both patients and physicians at appropriate stages. The study used a systematic and rigorous approach to ascertaining the attributes and levels that involved both patients and prescribers. A key feature of any DCE is that the attributes and levels are plausible (Coast et al. 2010; Ryan et al., 2008). The focus group with physicians ensured the findings of the ranking exercise could be applied DCE in a way that was clinically meaningful. Whilst patients considered life impacts of high importance, physicians perceived these as consequences of benefits or adverse events e.g. anger and aggression leading to problems with relationships. Levels assigned to the salient attributes were derived from actual event data. Furthermore, attribute labels and descriptions were based on the threshold at which physicians would define these events. Thus we ensured a consistent link between what was important to patients and what would be considered by the physician in the decision to change an antiepileptic medication; whilst also ensuring we could apply stated preference data to actual clinical data. Our methodology therefore enabled the results to be put into a meaningful context.

A systematic review conducted by Harrison et al. (2014) found that DCE studies have been generally poor at reporting methodology supporting the explanation of risk and the validity of risk communication. To our strength, however, our DCE was the robust application of cognitive interviews and survey piloting to ensure face validity and optimal comprehension of probability of events and the requirements of the actual choice task. Involving both patients and physicians in this stage was consistent with our aim of ensuring the hypothetical task was as synonymous as possible to decision making in practice.

However, there were a number of limitations to our analysis. Firstly, patients self-selected to the complete the survey. It is therefore more likely that we have encountered selection bias and collected the views of patients more actively interested in expressing their views about their medicine taking, which potentially reduces the external validity of our findings. Secondly, we acknowledge that choice tasks can be cognitively challenging, however, our extensive qualitative work to define the experiment should minimise the extent of this. We also acknowledge that this was a long survey; the DCE was placed at the beginning of the questionnaire to reduce burden and fatigue. Thirdly, a caveat of the DCE is that preferences are estimated with uncertainty, and responses vary depending upon an individual patients' situation and preferences. We can only assume the five attributes selected are pertinent to all respondents. Revealed preference studies would be required to verify the findings. Finally, our estimates of the probability of uptake for five antiepileptic medications involved

DCE 1 only. The preference coefficients were therefore estimated by a sample that excluded women with potential to become pregnant.

In a published application of DCE elicit preferences for antiepileptic medications, Lloyd et al. (2005) used a DCE to elicit the importance of adverse events compared with seizure control for patients with epilepsy in the UK (also recruited by Epilepsy Action but using a postal questionnaire) and found that patients preferred antiepileptic medications with less severe adverse events, greater control and least cost. Manjunath et al. (2012) included attributes for seizure frequency and, among others, 'short term' adverse events (sleepiness, dizziness, headache, nausea, tremor, double or blurred vision and skin rash) and 'long term' adverse events (fatigue, moodiness, confusion or memory problems). The findings of these DCEs are not directly comparable to our study, as with the exception of an attribute representing remission the presentation of harms in all three studies differs. When comparing methods, however, Manjunath et al. (2012) excluded 70 of the 263 patients from the analysis because they had no variation in their responses to the trade-off question (i.e. always chose A or B) (Manjunath et al., 2012) and suggest that this may be because most patients seizures were well controlled and patients were satisfied with current treatment. This, however, could also be explained by the relevance of attributes to patients and their comprehension of the task. Phase one of our study was designed to ensure the utility function being estimated represented important attributes and that respondents would trade choices (comprehended and engaged in the task).

In application to clinical trial data from the SANAD trial of new versus existing antiepileptic medication (described in section 6.1), our estimation of probability of uptake highlights the need to consider patient preferences for the harms and benefits of treatment, alongside the objective of seizure freedom. If we assumed patients preferred the drug with the highest chance of remission at one year, without consideration of other attributes, the most preferred medication would be carbamazepine, followed by oxcarbazepine, topiramate, lamotrigine, then gabapentin. If, however, we take a multiattribute approach and consider five important outcomes weighted in terms of both patient preference and probability of event (based on the data in Table 6.8), the rank order of the medications is estimated to be as follows: oxcarbazepine, followed by carbamazepine, lamotrigine, gabapentin, then topiramate. This suggests that whilst carbamazepine is likely to be the most effective treatment (as ranked by clinical trial evidence), oxcarbazepine is most likely to maximise the patient's utility (as weighted by patient preferences across five outcomes). This suggests that patients consider

outcomes beyond those measured as primary endpoints within trials in their decision to adhere to medication. Failure to consider the outcomes that patients prioritise in their decision to adhere may have consequences of poor clinical outcome (Cramer et al., 2003; Faught, 2012; Williams et al., 2006) and increased healthcare costs (Faught, 2009; Nasseh et al., 2012; Sokol et al., 2005). Furthermore, if utility is not maximised and patients become nonadherent, the effectiveness of the medication (used to rank the medications in clinical trials) is unlikely to be fully recognised.

The findings of this study suggest that antiepileptic medication prescribing based primarily on their effectiveness for controlling seizures, may be suboptimal in terms of patient utility. Treatment decisions were complex with patients valuing a range of treatment outcomes and demonstrating willingness to trade improvements in benefit for reductions in risk of adverse events. This has implications for the implementation of findings from clinical trials in which antiepileptic medications are recommended based on efficacy. Preferences also differed by group, reinforcing the need for patient-centred care and interventions to maximise adherence to medications and thus optimal health outcome.

The next step in this study is to ascertain the point at which outcomes are equivalent. This information could be used to determine minimally important differences to inform trial design. To date, minimally important differences are usually arbitrary figures from a clinical perspective. Inclusion of the patient perspective could lead to more patient focused research that would be more beneficial in practice.

Further research into (i) the link between preferences for harms and benefits and adherence to antiepileptic medications; and, (ii) our understanding of patient behaviour in terms of medication preferences and adherence is warranted. It would be of interest to explore the factors that determines preferences for antiepileptic medication. Here we found differences between the preferences of three patient groups, and it is also likely that there are further clinical, demographic, psychosocial, and sociocogntive factors driving preferences.

Achieving seizure control and minimising side effects of antiepileptic medications are both important for living well with epilepsy. Health care that is responsive to individual need is central to the effective management of epilepsy. The importance of remission from seizures was consistent. However, rankings of unfavourable medication outcomes varied by sub-

group. Healthcare professionals described life-impacts as a consequence of clinical benefits and clinically important adverse events. The results of the DCE indicate that patients place a higher value on reduction in harm than improvements in benefit, and that when put into the context of actual event rates this has consequences for their overall preference different antiepileptic medications. Exploring what patients with epilepsy consider important for measuring antiepileptic medication effectiveness will ensure clinical services are focus on patient-defined needs and that future research is designed to assess appropriate patient-defined outcomes.

6.7 Candidates contribution

DH (supervisor) and co-investigators on the RfPB grant conceived the study. EAFH (the candidate) designed the survey and protocol, designed qualitative interviews to inform the discrete choice experiment, designed the discrete choice experiment, managed survey data collection in collaboration with Epilepsy Action, analysed the responses. AR (co-investigator) co-ordinated research governance approvals and collected the qualitative data using an interview schedule designed by EAFH (the candidate). EAFH (the candidate) interpreted the results of the DCE, alongside DH. EAFH (the candidate) and Catrin Plumpton analysed and interpreted the stated preference in the context of the clinical data. EAFH (the candidate) drafted the manuscript. DH (supervisor) and AM (principal investigator) revised the manuscript for intellectual content. EAFH (the candidate) finalised the manuscript. The study scientific advisory group provided valuable feedback throughout this research.

Chapter 7

Influence of disease familiarity on implied time preferences for seizure frequency reduction

7.1 Preface

Chapter 5 presented a large empirical analysis of time preference, across several countries, including England and Wales. Within this analysis, time preference rates were estimated for a sample of adult patients currently taking antihypertensive medication(s), using a hypothetical scenario of taking an antiepileptic medication to control seizures. We repeated the same time preference exercise, using the same hypothetical scenario of taking medication to control seizures, in the survey of adult patients diagnosed with epilepsy reported in Chapter 6.

In the original time preference analysis (Chapter 5) epilepsy was selected for the condition as the health benefits of medication could be quantified in terms of number of events (reduction in seizures). The scenario was unfamiliar to the cohort (currently receiving antihypertensive medication). It was therefore assumed that the decision was unfamiliar and based on time and potential health benefits, rather than connotations to their actual medications and current health. This provided a time preference rate for 'health' within the context of medications. We did not check if the hypertensive patients had epilepsy, we assumed that the study population was without experience of the condition, but were likely to appreciate the impact of seizures. This subsequent analysis (Chapter 7) will compare the time preference rates of people with hypertension, identified in Chapter 5 (for England and Wales only), with the time preference rates derived from the sample of people with epilepsy. The objective of this exercise is to test whether familiarity with condition used in a hypothetical scenarios to elicit time preference influences the implied time preference rate. This represents one of only a few studies to explore the influence of familiarity with condition on implied time preference rates. The findings may have implications for both the predictive value of Time Preference theory and time preference rates used to discount health benefits in the economic evaluation of new medicines.

7.2 Abstract

Background: Time preference is the increase in magnitude of a future outcome needed to offset a given delay (Maital & Maital, 1978). Time preference rates can be estimated using stated preference techniques that rely on hypothetical scenarios (Cairns 2001). Relevance and experience of the condition described in the hypothetical scenario used within a time preference exercise may have an influence on estimated implied time preference rates. Scenarios that are more familiar may lead to higher estimates (Chapman et al., 1999).

Objectives: To test the association between time preference rates and diagnosis of condition used in the scenario to elicit time preference rates.

Methods: Data from two empirical surveys that estimated time preference using a scenario of delays in starting antiepileptic medication and reduction in seizure frequency were compared for samples of: (i) hypertensive adult patients in England or Wales; and, (ii) UK patients with epilepsy. Time preference rates were elicited using a 4-item questionnaire based on the same hypothetical scenario, to provide estimates for a 3-year and a 6-year delay. The questionnaires were contained within two independent online surveys. Patients were matched using propensity scoring based on, age, sex, and employment status. Significant associations between time preference rate and condition (sample) were assessed using a two-sample t-test with equal variances. Linear regression was used to test associations between time preference and age, sex, employment status and condition, using the propensity score matched sample for both the 3-year and the 6-year delay.

Results: 512 patients with hypertension and 311 patients with epilepsy were included in the analysis. There were significant differences between samples in terms of age ($p<0.001$), sex ($p<0.001$) and employment status ($p=0.001$). Matching data using propensity scoring significantly reduced bias. Mean time preference rates for the 3-year delay were significantly higher for patients with the condition (Epilepsy= 0.21 [95% CI 0.20 to 0.22]) than for patients not known to have the condition (Hypertension= 0.08 [95% CI 0.05 to 0.12]) ($p<0.001$). Similarly, mean time preference rates for the 6 year delay were significantly higher for patients with the condition (Epilepsy=0.012 (0.11 to 0.112 than for patients not known to have the condition (Hypertension=0.04 (0.03 to 0.06) ($p<0.001$). Age, sex, employment status and condition explained 38.4% of the variance in time preference rates for the 3-year delay, with condition being significantly associated with higher time preference rates. Higher time preference rates were also significantly associated with patients with epilepsy ($p<0.001$) and unemployment ($p=0.004$), explaining 56% of variability in the scenario of 6-year delay. Familiarity with condition explained 38.2% of time preference for the 3-year delay and 53.2% of time preference for the 6-year delay

Conclusions: Evidence on the association between experience of the condition described in the hypothetical scenario and estimated time preference rates suggests people with experience of condition have higher time preference. This may be exaggerated by differences in methods (matching versus choice task) and the use of a scenario that incorporates full health (0 seizures = remission).

7.3 Introduction

As previously stated (Chapter 5), time preference rates can be derived using two broad approaches: revealed preference and stated preference methods (Cairns 2002). Revealed preference methods are based on actual behaviour, and analyse observed intertemporal choices, whereas, stated preference techniques model hypothetical scenarios. Whilst there is an acceptance of stated preference methods to elicit time preferences for health (Cairns 2002), there is considerable variation in time preference rates elicited using this method that may be attributed to several factors. These include the time preference domain e.g. health or money (Lawless et al., 2013; West et al., 2003); the choice of hypothetical scenario within the domain (Chapman et al., 1999; Redelmeier & Heller 1993); and, the method used to elicit time preference (van der Pol & Cairns, 2008).

Intertemporal choice is a fundamental decision in many aspects of an individual's everyday life, spanning several domains, such as health, money and the environment (Lawless et al., 2013). Empirical evidence suggests significant differences between time preferences for money and health (Cairns 1992; Chapman & Elstein, 1995; Chapman 1996; Cairns & van der Pol, 1997). The direction of the findings are inconclusive, however, with higher time preference rates for money than for health in some studies (Cairns 1992), and higher rates for health over money in others (Cairns 1994). In a more recent, direct comparison of health and money, West et al. (2003) found significantly lower time preference rates for health related scenarios than for financial related scenarios. Empirical evidence, however, remains mixed with reports of individuals discounting health more heavily than other goods. It is difficult to draw robust conclusions due to differences in the methods used and the time delay for which the time preference rate is estimated. Within the health domain, there are also differences in time preference rates for lives saved versus health states (Olsen et al., 1993); and across different health states. For example, Redelmeier & Heller (1993) compared three conditions and found that mean time preference rates were significantly lower for blindness than colostomy or depression.

One explanation for differences in time preference (across and within health states) is familiarity with decision (Chapman et al., 1999). When eliciting time preference for health, participants are typically required to imagine a health state, and choose between future outcomes related to that hypothetical health state. Whereas, in financial scenarios, participants are seldom required to imagine a situation different to their own, and make a decision that is similar to many everyday decisions (Chapman et al., 1999). Similarly, scenarios pertaining to a familiar health state require less imagination and may reflect recognisable decisions. Chapman et al. (1999) suggested that domain independence (e.g., difference between time preference rates for money and health) may not be due to the differences in the commodity, rather the level of familiarity.

Stated preference surveys ask respondents to trade between current (or near) and future outcomes (Fuchs 1982). Several different survey methods have been used to derive time preferences for health including open-ended (Cairns & van der Pol, 2000) and closed ended methods (Chapman et al., 2001). Closed ended methods, also referred to as choice tasks (Cairns 2001), include discrete choice experiments (DCE) (van der Pol & Cairns, 2001) and time trade-off techniques (Dolan & Gudex, 1995). These methods require the respondent to choose between two levels of future benefit (Cropper et al., 1992). Open-ended methods, also known as matching techniques (Carins 2001), ask the respondent to specify the level of future benefit that would make a delay worthwhile (Cairns 1994, West et al., 2003). In this format, they are required to 'fill in the blank' (Fredrick 2006). The open-ended method has the advantage of estimating individual time preference rates; whereas some closed methods (e.g., DCE) can only derive a group estimate. In a meta-analysis of time preference rates, Percoco & Nijkamp (2009) found that experimental design was significantly associated with the individual time preference estimates derived. van der Pol & Cairns (2008) also compared the open and closed methods of eliciting time preferences for health and found closed methods elicited significantly lower mean time preference rates.

Chapter 5 presented a study of the association between time preference and adherence to medication. The study used the open method based of time preference elicitation. The hypothetical scenario was delays in antiepileptic medication and seizure frequency. The study population were people with hypertension. The scenario may therefore be unfamiliar to the patients, although we could not exclude the possibility that some participants may have had epilepsy. The aim of the present study is to perform a secondary analysis to investigate how experience of the condition used in hypothetical questions to elicit time preference

influences the implied rate of time preference. The hypothesis was that patients who were familiar with the scenario (confirmed diagnosis of epilepsy) would place a higher value on immediate benefit and would therefore have higher time preference rates than people not known to have epilepsy.

7.4 Method

This study used patient level data from two online surveys: (1) a multinational cross-sectional survey of adherence to antihypertensive medication (Appendix 3.1), and, (2) a survey of preferences for antiepileptic medication (Appendix 6.5). To make the samples more comparable, we restricted our sample of hypertensive patients to those recruited from England and Wales. Both surveys were accessed via UK websites. Table 7.1 summarises the survey procedure and administration for both samples.

Table 7.1 Comparison of survey procedure and administration

	Sample 1 – Unfamiliar	Sample 2 – Familiar
Condition	Hypertension	Epilepsy
Recruitment	Recruitment was via advertisements placed in community pharmacies. Advertisements were also placed in local press in England and Wales.	Recruitment was via the charity Epilepsy Action (social media, members magazine, local services newsletter, e-forums and newsletters, website home page), and advertisement in local press (Daily Post, July 2012), and posters in NHS outpatient clinics (n=113, October 2013).
Survey inclusion criteria	Self-reporting as: being 18 years or older, diagnosed by a doctor as having hypertension that lasted at least 3 months, currently prescribed antihypertensive medication, and personally responsible for administering their medication.	Self-reporting as being 18 years or older, and diagnosed by a doctor as having epilepsy.
Survey host	The survey was hosted by SurveyMonkey. Responses were restricted to one per Internet Protocol Address.	The survey was hosted by the Epilepsy Action website and available via a link to an anonymous online service (SNAP) between June 2013 and October 2013.
Total length of survey	The survey contains 135 items with an estimated completion time of 30 minutes.	The survey contained 126 items with an estimated completion time of 30 minutes.
Target sample size	Target sample size was 323 each for England and Wales, assuming 30% non-adherence with the Morisky measure on non-adherence and one-sided 5% level of significance.	Target sample size 189 based on 63 responses to each of 3 discrete choice experiments [Orme 2010], which were the primary outcome measures within this survey.

7.4.1 Outcome measures

The primary outcome measure for this secondary analysis was time preference rate. We collected this for both a 3-year and 6-year delay. The analysis also considered demographics common to both surveys: age, sex and employment status. We used a dichotomous categorisation of "in employment or student" versus "unemployed or retired".

7.4.2 Time preference elicitation method

Both surveys used the same scenario to elicit time preference; however, we customised the format of the questions following two individual pilot studies (Figure 7.1). We started with an open-ended format that asked the respondent to specify the level of future benefit (reduction in seizures) that would make a delay worthwhile. In the original version, we asked respondents to specify the actual number i.e. fill in a blank box. Following a pilot study with research staff involved with the hypertension study, the questionnaire was modified to include a drop-down menu from which respondents could select the future level of benefit that would make the delay worthwhile. The drop down menu included a plausible range of potential values that allowed for the estimation of both positive and negative time preferences. This was the final version used in the hypertension survey (Chapter 5). When the opportunity arose to replicate the time preference survey in our epilepsy project, we piloted version one (hypertension) (Appendix 7.1) with our Epilepsy research team, which included the charity Epilepsy Action and associated volunteers. The hypertension version needed to be adapted (e.g., no longer 'imagine you have epilepsy') and was considered cognitively challenging. We edited the introduction to the task and adapted the response format. We replaced the drop down menu with a series of binary choices, in which the respondent chose between the earlier medication and the later medication. A fixed description of the earlier medication was used throughout the task (*Treatment X starts in 1 year's time and reduces your seizures from 20 to 12*). Whereas the description of the later medication increased in a stepwise manner in each choice set (i.e., *Treatment Y starts in 4 years' time and reduces your seizures from 20 to 0* ... 20 to 1 etc.). Both surveys contained 4-items. We profiled two time delays, 3-years (1 year and 4 years from now) and 6 years (1 year and 7 years from now); and two levels of benefit for the nearest medication (20 to 12 and 20 to 8).

Figure 7.1 Example of time preference question

Hypertension version

Time Preference

We would like you to imagine that you have been diagnosed with epilepsy. You have seizures (fits) that occur 20 times per year, and which seriously affect your usual activities.

Imagine you start a medicine **ONE YEAR** from now

that will reduce your seizures from 20 to:

12 times per year

If you do not start the medicine for **FOUR YEARS** from now

What is the maximum number of seizures per year that would still make this medicine worthwhile?

[redacted]

Epilepsy version

Time Preference

Imagine you have 20 seizures per year. You have to choose between two alternative treatment options X or Y. They vary in terms of when they start and how effective they are at reducing seizures. Everything else about them is the same.

You have to wait longer for treatment Y. You cannot have both treatments. In the years you are waiting for either treatment to start, you continue to have 20 seizures per year.

Q1. Which treatment would you prefer?

☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 12
[redacted]
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 0
[redacted]

Q2. Which treatment would you prefer?
☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 12
[redacted]
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 1
[redacted]

[redacted] *if respondent selects Treatment Y the exercise continues to Q14.*

Q14. Which treatment would you prefer?
☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 12
[redacted]
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 13
[redacted]

7.4.3 Data analysis

Patient responses were included if they had at least one mean time preference rate (3-year or 6-year). Demographic data were presented and analysed using counts, means, and chi-square or ANOVAs to test differences between samples (hypertension / epilepsy). The data were coded in SPSS (version one; IBM Corporation, Armonk, NY) and analysed in STATA (version one; StataCorp LP, College Station, TX).

Propensity score matching

As the data were from two independent samples, we matched the data using a statistical technique known as propensity score matching. The propensity score match allowed for estimation of time preference rates across the whole data set by accounting for the covariates that may predict time preference rates, in order to increase confidence in the result. Respondents were matched on age, sex, and employment status, using caliper matching in STATA. Selection of covariates was supported by evidence that suggests higher time preference rates are associated with older age (Cairns 1994; Johannesson & Johansson, 1997; Olsen 1993) and being female (Chapter 5). Tests of association were conducted on the matched data.

7.4.3.1 Time preference elicitation

Estimation of time preference rates assumed a discounted utility model and were derived as follows:-

$$\rho = \left(\frac{20 - x}{20 - n}\right)^{\frac{1}{v-s}} - 1$$

Where: ρ = time preference rate (annual discount rate)

20 = number of seizures before starting medication

x = number of seizures with the later medication (respondents answer)

n = number of seizures with earlier medication (i.e. 12 or 8)

v = years in future for delayed medication (i.e. 4 or 7)

s = years in future for earlier medication (i.e. 1 year)

Appendix 5.1 provides details of the time preference rates for each value of 'x'. The value of 'x' is the respondent's answer selected from the drop-down menu in version one (hypertension). In version two (epilepsy) this is the number of seizures experienced with 'Treatment Y' in the question preceding the respondent selecting 'Treatment X'. The options for Treatment Y started with 20 to 0, which represents the highest positive time preference obtainable with this exercise. All items allowed for zero and negative time preferences.

7.4.3.2 Base case time preference analysis

In the base case analysis, mean time preference rates for the 3-year delay and 6-year delay were calculated for each sample: epilepsy and hypertension. The difference between time preference rates and condition was assessed using Students two-sample t-test with equal variance. Comparisons of negative and maximum positive time preference rates between conditions were conducted using counts and chi-square to test differences between samples. We conducted a multivariate linear regression of time preferences, for both the 3-year and 6-year delays, using age, sex, employment and condition as explanatory variables. We estimated the contribution of condition by comparing regression models with and without this variable (differences in R-squared).

7.4.3.3 Scenario analysis

Chapter 6 found that patients with epilepsy have strong significant preferences for remission and consider remission to be more important than reduction in the number of seizures. As such, familiarity with condition may reduce engagement with the task i.e. people with epilepsy would select 0 seizures regardless of the other attributes in the scenario (time delays and benefits of medication at one year). A scenario analysis was conducted to test if the association between time preference and condition remained when preferences for remission were eliminated. This was accomplished by trimming the data to exclude respondents who answered 20 to 0 seizures. We conducted separate analyses for the 3-year and 6-year delays.

7.5 Results

Time preference data were available for 825 patients (512 with hypertension, 313 with epilepsy). There were statistically significant differences between samples in terms of age, sex and employment status (each $p \leq 0.001$). The median age of the epilepsy sample (37 years) was significantly lower than that of the hypertensive sample (61 years); more females

completed the epilepsy survey; and, fewer patients with hypertension were employed. Matching the data by propensity scoring significantly reduced bias in age (91.7%), sex (96.9%) and employment status (93.9%) of respondents (Table 7.2). Two patients with epilepsy did not have data on all matching variables; and, 27 patients from hypertension and 1 patient from epilepsy were unsupported following matching and therefore carried zero weight in the matched analysis.

Table 7.2 Demographics of unmatched and propensity matched samples

	Unmatched sample (base case)				Propensity matched sample				
	Hypertension N=512	Epilepsy N=311	Bias	t-test p- value	Hypertension N=485	Epilepsy N=310	Bias	t-test p- value	% reduct bias
Age Mean	59.94	39.03	-176.70	<0.001	40.73	38.98	-14.80	0.085	91.70
Gender Proportion male	0.60	0.29	-66.20	<0.001	0.28	0.29	2.00	0.789	96.90
Employment Proportion unemployed or retired	0.50	0.38	-23.40	0.001	0.39	0.38	-1.40	0.856	93.90

Based on the matched samples, the mean time preference rate for the 3-year delay was 0.08 (95% CI 0.05 to 0.12) for patients with hypertension and 0.21 (95% CI 0.20 to 0.22) for patients with epilepsy. In a scenario starting with 20 seizures per year, where the 1-year delay reduces seizures from 20 to 10, patient with epilepsy would require a reduction from 20 to 3 if they had to wait 3-years. Whereas, people with hypertension would require a reduction from 20 to 8.

The mean time preference rate for the 6-year delay was 0.04 (95% CI 0.03 to 0.06) for patients with hypertension and 0.12 (95% CI 0.11 to 0.12) for patients with epilepsy. Time preference rates for the 3-year and 6-year delays were in the expected direction, with the 3-year rate being consistently higher than 6-year rate. Mean time preference rates were significantly different between conditions ($p<0.001$) (Table 7.3).

The percentage of respondents with a negative time preference in the scenario of a 3-year delay, ranged from 6.4% of patients with epilepsy to 10.2% of patients with hypertension, and similarly for the 6-year delay (6.4% to 11.9%). In contrast, the count of patients that had the maximum positive time preference (reduction of seizures from 20 to 0 for the latter

medication), was significantly higher for patients with epilepsy than for patients with hypertension: 30.4% compared to 1.7% for the 3-year delay (p<0.001), and 43.3% compared to 5.8% for the 6-year delay (p<0.001).

Table 7.3 Mean time preference rates by condition for 3-year and 6-year delay.

	Hypertension		Epilepsy			
Propensity matched sample	Mean (95% CI)	N	Mean (95% CI)	N	p-value	F
3-year delay	0.084 (0.051-0.116)	485	0.211 (0.203-0.219)	310	0.0000	56.17
6-year delay	0.042 (0.027-0.057)	487	0.116 (0.114-0.119)	308	0.0000	89.74

The direction of the coefficients in the regressions were in the expected directions (higher time preference rates were associated with older patients, males, unemployment and patients with epilepsy) but the majority did not reach statistical significance. Higher time preference rates for the 3-year delay were significantly associated with familiarity of condition (p<0.001) (Table 7.4). Similarly, higher time preference rates for the 6-year delay were significantly associated with familiarity of condition (p<0.001) and also unemployment (p=0.004) (Table 7.5). Familiarity with condition explained 38.2% of time preference for the 3-year delay and 53.2% of time preference for the 6-year delay.

Table 7.4 Summary of linear regression model using time preference rates for the 3-year delay as the dependent variable

Propensity matched sample	β coefficient	(95% CIs)		p-value
Age	0.001	0.000	0.002	0.183
Sex	-0.005	-0.029	0.019	0.665
Employment	-0.005	-0.041	0.030	0.770
Condition	0.128	0.094	0.162	0.000
Constant	0.057	-0.017	0.130	0.129
N=795				
R-squared = 0.384				

Table 7.5 Summary of linear regression model using time preference rates for the 6-year delay as the dependent variable

Propensity matched sample	β coefficient	(95% CIs)		p-value
Age	0.000	0.000	0.001	0.050
Sex	-0.002	-0.012	0.008	0.700
Employment	-0.018	-0.031	-0.006	0.004
Condition	0.075	0.060	0.089	0.000
Constant	0.033	0.002	0.064	0.036
N=795				
R-squared = 0.560				

7.5.1 Scenario analysis

The significant differences between time preference and condition remained when preferences for remission were eliminated from the matched sample. Mean time preference decreased to 0.16 (95% CI 0.14 to 0.17) for patients with epilepsy, and 0.08 (95% CI 0.05 to 0.11) for patients with hypertension, for the 3-year delay ($p<0.001$). Similarly, the association between time preference and condition also remained when preferences for remission were eliminated for the 6-year delay. Time preference rates for the 6-year delay were 0.03 (95% CI 0.02 to 0.05) for patients with hypertension and 0.07 (95% CI 0.06 to 0.08) for patients with epilepsy ($p<0.001$).

Multivariate regressions for scenario analysis were similar to the base case for the 3-year (Table 7.6) and 6-year delays (Table 7.7). Familiarity with condition explained 16.2% of time preference for the 3-year delay and 8.5% of time preference for the 6-year delay. Whilst the proportion explained was lower, the significant association was robust to elimination of strong preferences with remission; which suggests that time preference rates are consistently associated with familiarity of condition.

Table 7.6 Summary of linear regression model using trimmed time preference rates for the 3-year delay as the dependent variable (excluding maximum positive [remission] rates)

Propensity matched sample	β coefficient	(95% CIs)		p-value
Age	0.001	-0.001	0.003	0.368
Sex	-0.009	-0.042	0.023	0.578
Employment	-0.010	-0.065	0.045	0.726
Condition	0.080	0.043	0.117	0.000
Constant	0.052	-0.046	0.149	0.298
N=565				
R-squared = 0.167				

Table 7.7 Summary of linear regression model using trimmed time preference rates for the 6-year delay as the dependent variable (excluding maximum positive [remission] rates)

Propensity matched sample	β coefficient	(95% CIs)		p-value
Age	0.001	0.001	0.001	0.023
Sex	-0.001	-0.017	0.014	0.871
Employment	-0.026	-0.043	-0.008	0.005
Condition	0.033	0.016	0.050	0.000
Constant	0.015	-0.023	0.052	0.439
N=475				
R-squared = 0.189				

7.6 Discussion

Familiarity with the condition described in the hypothetical scenario used within a time preference exercise resulted in significantly higher implied time preference rates for both 3-year and 6-year delays. When controlling for demographic variables, experience of a condition makes the largest and most significant contribution to time preference rates. Distributions of time preference rate were different between samples who are familiar and unfamiliar with the condition, but the significant association between higher time preference and familiarity of condition were maintained when data excluded the possibility of seizure remission.

The regressions showed that higher time preference rates for the 6-year delay were associated with unemployed patients. We found no previous evidence on association between employment status and time preference for health, but the literature on education suggests that students may be future orientated and therefore have lower time preference rates (van der Pol 2011). This consistent with the interpretation of our employment variable, which was categorised as "in employment or student" versus "unemployed or retired". We found no association between time preference and age or sex.

Our findings of a negative time preference rate in more than a tenth of patients with hypertension who would be willing to wait longer for a less effective medication (e.g. wait 4 years for a medication that reduces seizures from 20 to 13; rather than waiting 1 year for a medication that reduces seizures from 20 to 12) may reflect unfamiliarity with the routine of taking antiepileptic medication, a lack of understating or knowledge on the effectiveness of antiepileptic medication, differences in illness perceptions, beliefs, and concerns about medicines (Horne et al., 2013).

In contrast, the count of patients that had the maximum positive time preference was significantly higher for patients with epilepsy. This rate was derived by the selecting a seizure reduction of 20 to 0 for the latter medication, which in effect profiles a scenario of achieving remission in 4 (or 7) years' time. The fact that 30 to 43% of patients with epilepsy chose this option is unsurprising as people with the condition (currently experiencing seizures) are more likely to want to reach remission. The inclusion of this as a possible outcome may have limited the sensitivity of the measure (see limitations), however, the scenario using trimmed data suggests that the association between time preference rates and familiarity of condition is robust to elimination of this option.

7.6.1 Comparison with other studies

The actual discounts rates derived in this study ranged from 0.04 (hypertension 6-year delay) to 0.21 per annum (epilepsy 3-year delay). Cairns & van der Pol (2000) estimated the marginal time preference in a UK-wide sample and found the median implied discount rates were 0.06 for health, which is more comparable with our sample of hypertensive patients. All of our estimates were higher than the 0.035 per annum, published in the he Green Book (HM Treasury 2003) and recommended for discounting of costs and benefits in appraisal and evaluation for Central Government.

In a comparable study of time preference decision making about treatments for migraine and Crohn's disease, Chapman and Nelson (1999) found no consistent effect of familiarity for two patient groups (familiar and unfamiliar with scenario) with symptomatic conditions. Our findings suggest that there are differences between our scenario and populations, however, we can only explain the differences one direction (we do not have data on time preferences for antihypertensive medication). If we consider the hypothesis that differences between health-related and finance-related scenarios are due to familiarity with decision-making, and scenarios involving money are more familiar than scenarios involving health. The results of our study compare favourably with West et al. (2003) who found significantly lower time preference rates for health-related scenarios than in finance-related scenarios.

In a meta-analysis of 44 experimental and field studies, Percoco & Nijkamp (2009), found that experimental design, such as scenario, layout and decision task, has an important impact on the estimate of time preference rates. They concluded that the lack of a consensus on the methodology to elicit individual time preference rates represents a

conceptual flaw in the literature. They recommend caution in using estimates from the empirical literature as proxy values for the discounting of future costs in evaluations and projects. Some of the differences in time preference rates between our two study populations may be attributable to differences in methods. van der Pol & Cairns (2008) compared the open and closed methods of eliciting time preferences found that the closed ended method (a discrete choice experiment) elicited statistically significantly lower mean implied time preference rates than the open ended method. The results showed that for a 5-year delay using hypothetical scenario involving one's own health, the mean implied time preference rate was 0.110 (95% CI 0.084 to 0.136) for the open-ended method (n=891) and 0.031 (95% CI 0.018 to 0.043) for the closed ended method (n=3071) ($p<0.05$). Whereas our findings show significantly higher mean implied time preference rates elicited using a closed method (epilepsy version), compared to an open method (hypertension version). We do not have data to compare individual responses using both methods.

7.6.2 Implications

The findings of this study have implications for the selection of scenarios when designing a time preference survey in health. We selected epileptic seizures in the first instance (for the hypertension survey) as we needed a condition in which the health benefits of medication could be quantified in terms of number of events (reduction in seizures). We assumed that the study population was without experience of the condition, but were likely to appreciate the impact of seizures. The focus was therefore on time and potential health benefits, rather than connotations to their actual medication and current health. This provided a time preference rate for 'health' that was most relevant to our original research question regarding associations between time preference and adherence to medications (see Chapter 5).

7.6.3 Strengths and limitations

The strengths and limitations of the two individual surveys are discussed elsewhere (Chapter 3 and Chapter 6). There are several strengths to this piece of research. Firstly, the study used robust methods in the comparison of the time preference values elicited from two separate surveys. Secondly, the surveys were customised for each patient population, using pilot studies. Thirdly, efforts were made to improve the comparability of the independent samples by use of propensity scoring which reduced bias by over 90% of all matched variables. Finally, a scenario analysis provided an assessment of the impact of 'remission' in the hypothetical scenario used to elicit time preference. This was informed by evidence on

patient preferences for medication in terms of chance of remission and chance of fewer seizures reported in Chapter 6. There were, however, a number of limitations to this analysis. Firstly, we did not have data on experience of epilepsy for patients in the hypertension sample. Based on the prevalence of epilepsy in the UK (1 in 103) (Epilepsy Action, nd), and the size of our hypertension sample, we would expect approximately 5 patients with hypertension to also have epilepsy. Secondly, we used two different methods for eliciting time preference, open ended and closed ended. Finally, the surveys were web-based which may have restricted access for some people, and relied on self-report of diagnosis and unconfirmed by health professional or records.

7.6.4 Future research directions

The influence of familiarity of condition used in hypothetical scenarios is a key issue for the estimation, generalisability and validity of time preference rates. Further research is recommended on the association between time preference rates and: different domains, i.e., health and money in terms of familiarity hypothesis; different scenarios; and different methods. Prospectively designed studies involving cognitive interviewing comparison with revealed preferences is required to validate the estimates derived from stated preference surveys.

7.6.5 Conclusion

Evidence on the association between experience of the condition described in the hypothetical scenario and estimated time preference rates suggests people with experience of condition have higher time preference. This indicated that they are less willing to wait for a more effective treatment, because they know the impact of seizures on their health, and thus placed a high value on the more immediate health gain. This may be exaggerated by the use of scenario that incorporates remission; and, the framing of the question / experimental design.

7.7 Candidates contribution

EAFH (the candidate) and DH conceived the study. The candidate's contribution to the associated surveys is detailed Chapter 3 and Chapter 6. EAFH (the candidate) designed the epilepsy survey and protocol, designed the time preference survey instrument, gained research governance approval, managed data collection in collaboration with Epilepsy Action, analysed the responses, interpreted the results, and drafted the manuscript; under the supervision of DH. DH, VM (supervisors) and Catrin Plumpton were involved in the data analysis and interpretation, and revised the manuscript for intellectual content. EAFH (the candidate) finalised the manuscript.

Chapter 8

Discussion and Conclusion

8.1 Summary / statement of principal findings

This thesis has explored determinants of adherence to medication with a specific focus on the application of health psychology and behavioural economic theories. The application of health psychology models found association between adherence and individual components of models within sociocognitive and self-regulation frameworks. Of notable interest was the finding that the value of existing theoretical frameworks increased with consideration of distal variables and proximal control beliefs, such as self-efficacy. The application of behavioural economic models showed that the random utility framework provides a useful way to explain persistence with medications, but there is weak evidence on association between adherence and time preference. Components of health psychology theories were associated with persistence, measured using random utility theory; and, time preference rates, and derived using the discounted utility model. Concurrent assessment of models increased explanatory power and enabled simultaneous assessment of multiple determinants of adherence (e.g., patient-level and therapy-related level).

The answers to the seven research questions have been summarised below:

Chapter 2 addressed Research question 1:

What do theoretical models of behaviour contribute to our understanding of adherence to medications? What empirical evidence exists and what is the quality of this evidence?

A systematic review of 20 years of empirical research found sociocognitive, and self-regulation theories contribute to our understanding of adherence to medications. Within the sociocognitive framework, there is empirical evidence that subordinate health beliefs model and individual components within (perceived barriers, perceived susceptibility) are significant predictors of adherence to medication. Within the self-regulation framework, there is empirical evidence of treatment beliefs (necessity beliefs and medication concerns) predicting adherence to medication. Most notable is the contribution of self-efficacy as a proximal determinant of adherence in both frameworks. Sixty-seven studies were included in the review, often only single components of models explained the variance in adherence, and the variance explained was limited.

Chapter 3 addressed Research question 2:

What is the association between self-reported nonadherence to hypertensive medication and country, demographic, clinical and psychosocial factors?

A multinational cross-sectional survey of self-reported nonadherence to antihypertensive medications (n=2595) found lower age, lower level of self-efficacy, and components of models within the self-regulation (respondents' perceptions of their illness) were associated with nonadherence, measured on the Morisky Medication Adherence Scale, across several countries. A multilevel, multivariate analysis found that males, younger age, being employed, low number of medicines, high dosing frequency, difficulty borrowing money, low self-efficacy, components of models within sociocognitive theory (high normative beliefs, high perceived barriers), and, components of models within self-regulation theory (low personal control, low concern about illness), are significantly associated with nonadherence. Country differences explained 11% of the variance in nonadherence.

Chapter 4 addressed Research question 3:

Which attributes of medications do patients consider important in their decision to persist? How are trade-offs between medications affected by psychosocial and sociocognitive factors? How can empirical evidence on stated preferences be linked to actual clinical event data?

A stated preference discrete choice analysis found that medicine characteristics of treatment benefit, harms (common mild adverse drug reaction, rare but potentially life threatening ADR) and convenience (dose frequency) have a statistically significant effect on stated persistence with medication. Trade-offs between these medicine characteristics were significantly associated with sex, employment, education, marital status, MARS adherence, self-efficacy, components of models within sociocognitive theory (Theory or Planned Behaviour (TPB) intention, TPB norm, TPB barriers), and, components of models within self-regulation theory (illness consequences, treatment control, illness concern, beliefs about medicines). A case study of ulcerative colitis illustrated how empirical evidence on stated preference to persist could be linked to actual clinical data, by weighting the results of the DCE utility function against clinical event data for four alternative medications. The

probability of persistence for each medication was sensitive to changes in sociocognitive factors. Components of the theory of planned behaviour had greatest influence on probability of persistence with 5-aminosalicylic acid medications for ulcerative colitis.

Chapter 5 addressed Research question 4:

What is the association between self-reported nonadherence to hypertensive medication and time preference for health benefits? What is the association between time preference rates and country, demographic, clinical and psychosocial factors?

The association between nonadherence and time preference rates was insubstantial. Whilst the pooled result reached statistical significance in the anticipated direction, with lower time preference rates associated with adherence to medications, there was substantial variation by country. Only two of the eight countries showed a significant association and in these cases, higher time preference rates were associated with adherence to medications.

A multilevel multivariate analysis of the time preference rates for the 3-year delay found, low number of medication conditions, more comfortable income perception, difficult to borrow income, and components of models within self-regulation theory (high illness consequences) were significant determinants of higher time preference rates. Time preference rates for the 6-year delay were significantly associated with, difficulty to borrow income, being female, and, components of models within self-regulation theory (high concerns about illness). Country differences explained 40% of the variance in time preference for both the 3-year and 6-year delay.

Chapter 6 addressed Research question 5:

How do people with epilepsy trade harms and benefits of antiepileptic medications? Does this vary by patient group? How do patient preferences for antiepileptic medications compare with recommendations based on clinical efficacy?

Qualitative interviews with patients with epilepsy (n=56) and a focus group with prescribing clinicians (n=8) found the characteristics that women with potential to become pregnant consider in their decision to take antiepileptic medications are different to the rest of the patient population. Two distinct discrete choice experiments of patients with epilepsy (n=177) and women with the potential to become pregnant (n=103) both found that patients were willing to forgo an increase in chance of remission in exchange for a reduction in the risk of adverse events (i.e. place a higher value on reduction in harms than improvements in treatment benefit). There were also within patient group variations. Models accounting for sex (DCE 1) and pregnancy concern (DCE 2) were significantly different; however, differences in trading behaviour did not reach statistical significance.

Empirical evidence from the DCE was linked to actual clinical data, by weighting the results of the DCE utility function against event data from a recent clinical trial of five antiepileptic medications. We found the rank order of the five drugs based on clinical efficacy (results of the clinical trial) to be inconsistent with the rank order of the five drugs based on the utility model (combined with DCE data).

Chapter 7 addressed Research question 6:

Are the time preference rates derived from hypothetical scenarios influenced by familiarity with the condition used?

Time preference rates, derived using a scenario of antiepileptic medication and seizure frequency, were significantly different for patients with epilepsy compared to patients not known to have epilepsy, for both 3 and 6-year delay. Mean time preference rates for the 3-year delay were significantly higher for patients with the condition than for patients not known to have the condition for both the 3-year and 6-year delay. Condition was the only significant predictor of the 3-year delay, where having epilepsy was associated with higher time preference rates. The same association was found for the 6-year delay, together with unemployment. Familiarity with condition explained 38.2% of time preference for the 3-year delay and 53.2% of time preference for the 6-year delay.

Chapter 8 addressed Research question 7:

How can the behavioural theories be consolidated to provide a theoretical basis for the development and assessment of adherence enhancing interventions?

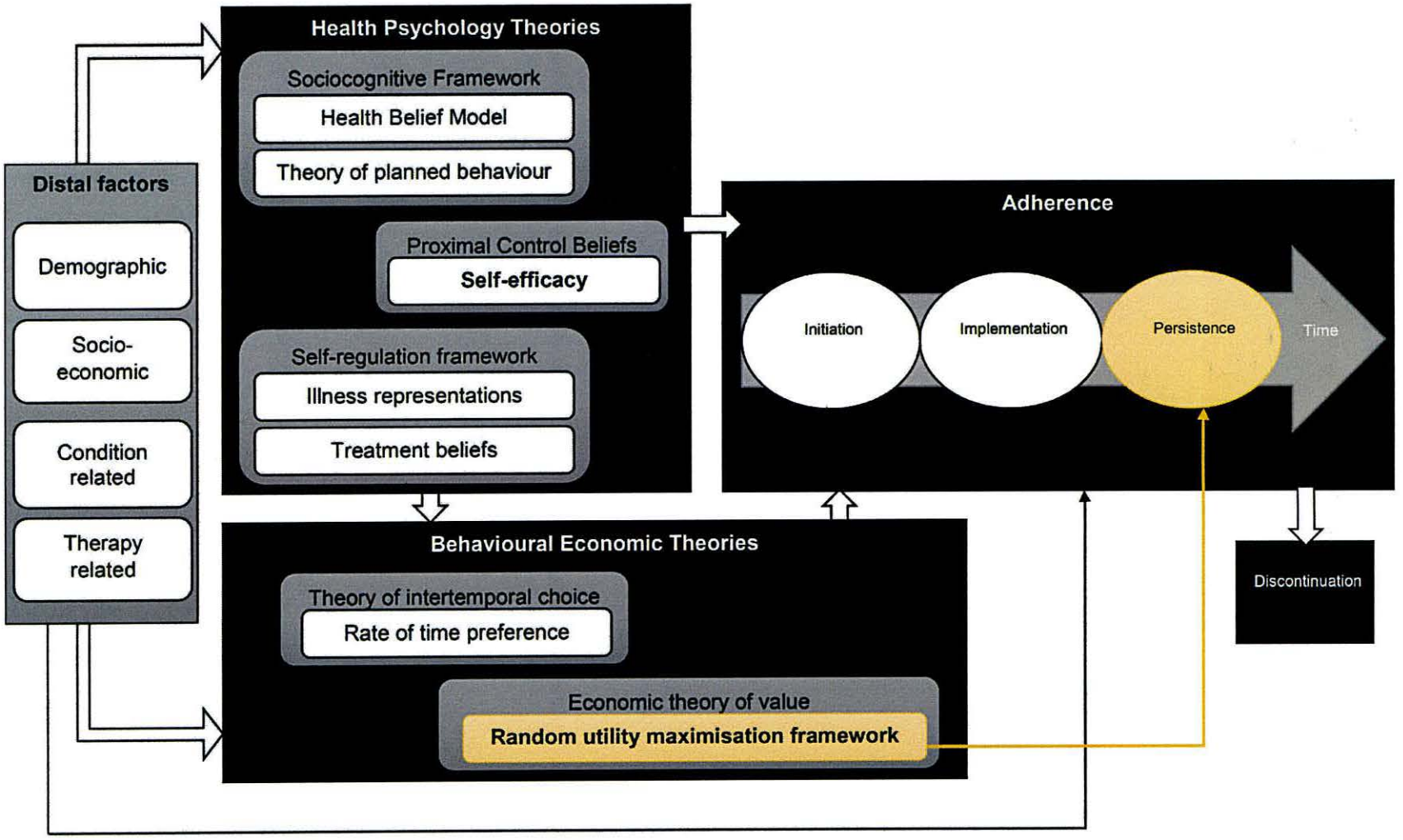
Figure 8.1 illustrates how the models applied in this thesis can be consolidated into a multidisciplinary, multi-factorial framework. The level of evidence for each theoretical framework, subordinate models, and individual component, is summarised in Table 8.1. This table highlights the multidisciplinary approach to this PhD and the strength of concurrent assessment of behavioural theories. Evidence of a range of health psychology and behavioural economic explanatory variables has been consistently classified, which is rarely the case in research within and between health psychology and behavioural economics. The application of theory has been to both explain adherence to medication, and to explain persistence with medication. The evidence presented was gathered using a variety of robust primary and secondary research, including a systematic review, cross-sectional surveys, and secondary data analysis. This provides a potential foundation for the development of more integrated theory and/or the development and assessment of adherence enhancing interventions.

8.1.1 Contribution to behavioural economics and health psychology

The conceptual model of health psychology and behavioural economic theories associated with adherence behaviour (Figure 8.1) represents a unique contribution to the study of behaviour economics. Firstly, the model contains the first link, to our knowledge, between health psychology models and behavioural economic theories. This link is based on the concurrent assessment of multidisciplinary frameworks (Chapter 4), thus highlighting the potential for models from health psychology to add to the predictive value of behavioural economic models, and vice-versa. The model also distinguishes behaviour at different stages in the process of adherence (i.e. random utility theory applied directly to the study of persistence), thus highlighting the possibility that certain behavioural models may have value at different stages of the process of adherence (e.g. initiation, implementation, and discontinuation).

The health psychology literature has several examples of models that explain health related behaviour within and across theoretical frameworks. The conceptual model of health psychology and behavioural economic theories associated with adherence behaviour (Figure 8.1) postulated in this thesis, represents an advancement in both the multidisciplinary application of these models, and perspectives on the measurement of adherence behaviour. Firstly, the combination and concurrent assessment of both health psychology and behavioural economics increases the capacity of targets for intervention, which may be from a person-based or medicines-based approach. Secondly, this thesis recognises adherence to medication as a distinct adherence behaviour, with three quantifiable stages: initiation, implementation, and discontinuation. This is an important advancement in the field of health psychology and adherence research where the definition and measurement of adherence is often inconsistent (Chapter 2). Furthermore, there has been a tendency to combine evidence from heterogeneous adherence behaviours (e.g. medication adherence, exercise adherence) which may compromise predictive value of models, with respect to which stage of the process they are most informative (e.g. initiation, implementation and discontinuation). The presentation of adherence in these stages within the conceptual model, and the concurrent analysis of behavioural economic theories and psychosocial theories in the context of persistence, illustrates the need for more specific assessment of the stages of medication adherence, from a multidisciplinary perspective, in future studies.

Figure 8.1. Conceptual model of health psychology and behavioural economic theories associated with adherence behaviour



Note. Yellow = theory informing adherence measurement i.e. stated preference to persist

Table 8.1: Summary of thesis evidence: associations between adherence to medication and demographic, clinical, psychosocial and sociocognitive factors, presented by theory, framework, model and individual component (*p ≤ 0.05; ** p ≤ 0.01)

	Systematic Review	Multinational survey of adherence				Time preference analysis	
	Chapter 2	Chapter 3		Chapter 4	Chapter 5	Chapter 5	
Explanatory variables	Significant association Measured n/N[1]	Significant association with Morisky in at least one country[2]	Significant association with Morisky in multilevel (country) model	Significant association with persistence in DCE analysis	Significant difference between adherent/nonadherent using Morisky t-test[3]	Significant association with 3-year delay in multilevel model	Significant association with 6-year delay in multilevel model
Demographics							
Age		*	**				*
Sex			*	*			
Employment		**	*	**			
Education				**			
Marital status				*			
Socioeconomic							
Income source		*					
Borrow money		**	**			*	
Therapy related							
Number of tablets		*					
Number of medicines		*	**				
Dosing frequency		**	**				
Proximal control beliefs							
Self-efficacy	17/19	**	**	**			
Sociocognitive Theory							
Theory of planned behaviour (TPB)							
TPB: Intention	2/5			*			
TPB: Beliefs	1/4		*	**			
TPB: Barriers	11/17	*		**			
Barriers (BRIGHT)		*	**				
Self-regulation Theory							
Illness representations							
IPQ: Consequences	1/6	*		*		**	
IPQ: Personal control	2/6	*	**				
IPQ: Treatment control	1/3			**			
IPQ: Illness concern			**	*			**
IPQ: Illness coherence		**					
Treatment beliefs							
BMQ: Concerns	7/8			*			
Time preference for health[3]							
Time preference rate 3-year delay					**		
Time preference rate 6-year delay					*		

Note. [1]n number of studies reporting a statistically significant (p ≤ 0.05) association with adherence; N number of studies that entered independent variable into the final regression model (results entered as counts because of heterogeneity between populations, study design, and outcomes). [2]Highest significance level reported in any single country. Shaded cells = not considered in analysis. [3]Excluding Poland due to differences in time preference questionnaire.

8.2 Comparison with other studies

The empirical evidence reported within this thesis makes a valuable contribution to the literature (Holmes et al., *forthcoming;* Holmes et al., 2014; Morrison et al., 2015). The findings of the literature review (Chapter 2) are comparable with other research in this field. Zeber et al., (2013) published a systematic review that focused on one stage of adherence, initiation. Their review included five sociocognitive studies, and found medication beliefs, knowledge and trust to be associated with initiation. Our paper (Holmes et al., 2014, Chapter 2) considered a broader range of theoretical models, and as such was able compare the performance of models from several theoretical frameworks and draw important conclusions on the value of distal variables and control beliefs.

The findings of the multinational survey of determinants to medications (Chapter 3) make new and improved contributions to evidence of association between adherence and theory based determinants, as reviewed in Chapter 2 (Bane et al., 2006; Hekler et al., 2008; Roh 2005; Ross et al., 2004). Based on the criteria used to judge the quality of studies included in the literature review (described in Chapter 2, Table 2.1) our survey scores 29/100; it would therefore rank 4th out of the top 50 cross-sectional studies conducted in the past 20 years, and would be the highest ranked study of adherence to antihypertensive medication. Previous studies have tended to look at single models, or at best single frameworks; and reported data from a single country.

When comparing the results of the literature review and our empirical analysis of predictors of nonadherence, a notable finding was that the association between beliefs about medicine and adherence was not statistically significant in the primary analysis (multivariate by country and multilevel). Findings of the literature review (Chapter 2) found strong evidence of association between adherence and medication beliefs (10/11 studies reached statistical significance). The statistically significant association between high concerns about medicines and intentional nonadherence suggests that patients who have concerns about their medicines (e.g. worries, long-term effects, dependency on medicines, etc.) are more likely to deliberately stop taking their high blood pressure medicines.

Evidence from both the literature review (Chapter 2) and the survey (Chapter 3) supports the need for a multifaceted approach to improving adherence to medication (Sabate 2003); and, builds on the evidence of the importance of self-efficacy (DiMatteo et al., 2012; O'Carroll et al., 2011). In a meta-analysis of adherence enhancing interventions in studies using electronically complied drug dosing histories, Demonceau et al., (2013) found that electronic monitoring feedback and congnitive-educational interventions are potentially effective approaches to enhancing patient adherence. A Cochrane review of strategies for improving adherence to antiepileptic medication including 6 studies found behavioural modification (such as intensive reminders) had more positive effects on adherence than cognitive / educational interventions; and (Al-aqeel & Al-sabhan, 2011). The link between improvements in adherence and improvements in health outcome, however, remains weak, with few studies of interventions reporting improvements in both (Nieuwlaat et al., 2014). Recent evidence continues to suggest the need for complex interventions that increase knowledge and are delivered within specific disease populations (Conn et al., 2016). This thesis provides an understanding for why such interventions are more likely to lead to an effective change in behaviour; and a framework from which to develop more theory based testing of strategies to improve adherence.

The use of the random utility framework in this thesis (Chapter 4) provides further evidence to support the use of this theory to analyse persistence, as proposed by (Lamiraud & Geoffard, 2007). The concurrent assessment of utility and theory led factors, represents a new multidisciplinary perspective of this approach that may prove informative to health psychologists and behavioural economist alike. Shingler et al., (2014) developed a theoretical model of treatment preferences, adherence and outcomes for patients with cancer. Their model, was based on a literature review, and considered patient preference as a variable grouped under behavioural factors. This thesis represents a more empirical application of preference elicitation informed by economic theory, which provides a framework for analysis of the influence of alternative behavioural factors on preferences, as opposed to considering them within a broad indistinguishable category. On a fundamental level the DCE study in Chapter 4 also contributes to evidence on preferences for medication attributes such as lower dose frequency and reduced risk of mild adverse reactions improving adherence (Mohamed et al. 2015; Stone et al., 2004). A recent study identified strategies that help patients cope with adverse medication events or formulate the desired treatment outcomes, as targets for adherence enhancing interventions (Zomahoun et al., 2015), our findings in Chapter 4 concur with this suggestion.

This thesis also contributes to the literature on patient preferences for antiepileptic medications (Manjunath et al., 2012, Lloyd et al., 2005), whilst adding the new dimension of considering utility maximisation alongside health maximisation (the most efficacious treatment) (Chapter 6). This study adds to the literature on preferences for medications (e.g., examples within de Bekker-Grob et al., 2012; Clark et al., 2014) and more specifically the literature on stated preferences for antiepileptic medications (Lloyd et al. 2005; Manjunath et al. 2012). The directions of preferences for harms and benefits of treatments were comparable; and, the extension of this method to estimate the utility and probability of uptake of antiepileptic medications represents an advancement in this field. The methods used the DCE of preferences for antiepileptic medication represent a robust application of this method, particularly the use of qualitative research to inform attribute selection (Coast et al., 2012) and the communication of risk (Harrison et al., 2014).

This thesis contributes to the time preference literature from both an empirical (Chapter 5) and methodological perspective (Chapter 7). The study of associations between time preference and medication adherence add to the limited evidence base (Axon et al. 2009, Chapman et al. 2001) and concur with a weak relationship between adherence and time preference. Time preference rates elicited in both Chapter 5 and Chapter 7, however, are comparable with published estimates of time preference rates for health for a UK-wide sample (Cairns & van der Pol 2000). Chapter 7 also represents a contribution to the era of a multidisciplinary approach to examining intertemporal choice (Loewesnstien et al. 2003). Whilst the analysis of familiarity of scenario provides evidence on the influence of elicitation methods; which is also gaining considerable recognition in the time preference literature (van der Pol & Cairns, 2008; Percoco & Nijkamp, 2009).

Finally, the suggestion of a multidisciplinary framework is a first step towards consolidation of models to further our understanding of adherence to medication. The classification of theory throughout this thesis, with a view to maximising the potential for informing behaviour change intervention, represents an application of suggestions by Michie and colleagues (Stavri & Michie, 2012; Michie & Johnston, 2012; and Michie et al., 2015); whose development of the taxonomy of behaviour change techniques progressed and was published during the writing of this thesis. This improves the potential for this work to inform future work that may be more patient group or condition specific (such as Shingler et al., 2014, development of a theoretical model in oncology).

Loewenstien (2003) commented on the differences in fundamental approach of economists and psychologists; arguing that psychology is predominantly empirical based, comprising multiple theories tested against further observations; whereas economics is more theory based, leaning towards single theories with subsequent empirical application. Whilst each discipline may differ in terminology, assumptions, and research methods, this thesis has highlighted some common ground that could enhance understanding of diverse aspects of theories from each discipline.

Most notably, consider the relationship between stated preferences as explored in random utility theory (behavioural economics) and intention, examined in the Theory of planned behaviour (health psychology). Psychologists recognise that although some people may develop an intention to change their health behaviour, this may not result in actual action i.e. an intention to persist with medication, does not guarantee the patient will continue taking their medication. This discrepancy is known as the "intention–behaviour gap" (Sheeran 2002). From an economics perspective, this gap corresponds to the difference between stated and revealed preferences. Revealed preferences are based on actual behaviour, whereby economists analyse observed choices; whereas, stated preference techniques model hypothetical scenarios and assume this as a proxy for actual behaviour. Whilst economists traditionally prefer revealed preference data, opportunities to acquire observed data on actual choices in health care, are often limited (e.g. future health unknown, future products and policies in development, cross-sectional survey design), thus there is an acceptance of stated preference methods. To date there is limited stated preference data on adherence to medication (Holmes et al., 2016, Lamiraud & Geoffard, 2007; Mohamed at al., 2015; Stone et al., 2004) and no revealed preference studies to validate these findings. Psychologists, however, have sought to identify further variables that may explain the intention-behaviour gap, that may also be targets for adherence enhancing intervention; these include self-efficacy (Bandura 1992, 1997) and implementation intentions (Gollwitzer & Sheeran, 2006). Furthermore, models such as The Transtheoretical Model (Prochaska et al., 1994) and The Health Action Process Approach (HAPA) (Schwarzer, 2001) propose to link intention with behaviour. The literature review in Chapter 2 identified no empirical evidence of the application of these models to medication adherence, however, this thesis contains significant empirical evidence of the role of self-efficacy in predicting medication adherence (summarised across individual studies/chapters in Figure 8.2).

The awareness of the gap between intended and actual behaviour highlights the benefits of a multidisciplinary approach to understanding adherence to medication. Within this thesis random utility theory has been used to explain how preferences for medication characteristics can influence persistence, whilst consideration of psychosocial variables provides evidence on factors that may also contribute. Future research should also consider the recognition of the intention-behaviour gap by psychologists – and associated frameworks – as theoretical foundations for further examination of potential differences between stated and revealed preferences.

8.3 Implications

This thesis provides empirical evidence on determinants of nonadherence that could be targeted for interventions with a view to modifying behaviour (Chapters 2-5). A further stage of behavioural change research is now necessary to develop and evaluate potential interventions, however, we can go some way to assuming that a theoretical foundation is more likely to lead to interventions that are tailored to patients' needs, address the most appropriate aspects of adherence management, and lead to higher rates of adherence. Furthermore, consideration of models that reach beyond health outcomes (e.g. the utility model) may lead to higher rates of adherence to the 'most appropriate' medication (Chapter 4). Thus resulting, not only in higher rates of adherence, but also medicines optimisation. In the long-term, improving medication adherence and achieving medicines optimisation has implications of improved health and wellbeing, more effective disease management, and increased patient safety. In return, this should lead to a reduction in healthcare resource use (including a reduction in medicines waste) and a reduction in costs.

The findings of this thesis have a number of specific implications for adherence research, research methods and clinical practice.

8.3.1 Implications for adherence research

- *Behavioural models help to explain nonadherence and could inform research into determinants of adherence, but further behaviour change research is required.*

This thesis identified several behavioural models that explain a proportion of the variance in nonadherence. Targeting variables within these models, which are amenable to change, may modify adherence behaviour. However, determining associations between nonadherence and components of behavioural models does not necessarily mean that adherence enhancing interventions designed to modify these components will lead to improved adherence and health outcome. A further stage of behaviour change research and adequate implementation is still required. This thesis builds on a body of evidence suggesting that improvements in self-efficacy lead to improvements in adherence (DiMatteo et al. 2013; O'Carroll et al. 2011)

- *Application of multiple or extended models may better explain adherence to medications.*

The application of single existing behavioural models may limit the potential to explain adherence to medications and inform the development of adherence enhancing interventions. The findings of the systematic review (Chapter 2) suggest that application of multiple or extended models improve predictions and that consideration of different populations within the same treatment area, or along the illness trajectory, yield different results. The empirical evidence in Chapters 3-5 adds to this, as we see multiple theoretical models predicting adherence and persistence with mediation.

Furthermore, a significant finding of this research suggests that the predictive value of existing theoretical frameworks is increased by consideration of distal variables and proximal control beliefs (e.g. self-efficacy) (Chapter 2 and Chapter 3). Consolidation of existing models of behaviour change has the potential to increase predictive utility and inform new conceptual models/theory. Figure 8.2 summarised the empirical evidence and illustrated where the strength of the evidence lies. Interpretation of these findings, in terms of behaviour, requires an appreciation of the various processes that comprise adherence to medications, and acknowledgement that adherence to medications may be intentional or unintentional.

8.3.2 Implications for research methods

- *The findings of this thesis support the notion that variable selection should be theory driven rather than data driven and be determined a priori.*

The findings of the systematic review (Chapters 2) and the survey of determinants of nonadherence (Chapters 3) indicated that determinants of nonadherence go beyond demographic and clinical variables that are often easily measures and readily available. Traditionally, variable selection in the clinical literature has leaned towards availability, rather than theoretical reasons; this may have limited value in the development of strategies to modify behaviour and improve adherence. Behavioural theories postulate a range of factors as determinants of behaviour and attempt to explain why behaviours differ (and hence, how they can change). Considering what influences behaviour, and how we can change behaviour, is likely to be more effective than looking at ad hoc associations.

- *Attention to definition of adherence and measurement techniques used is required for interpretation of findings. Furthermore, classification of the theoretical frameworks used to identify potential determinants of adherence should also be adhered to, in order to increase the quality and generalisability of findings.*

The systematic review reported in Chapter 2 found the quality of existing research to be suboptimal, reporting a mean quality assessment score of 36% based on adherence measurement, sample size and study design. Studies were heterogeneous in terms of adherence measurement and inconsistent in their definition of adherence as behaviour. The research highlighted the difficulties in synthesising evidence from existing literature, recognition that meta-analysis of heterogeneous behavioural research is inappropriate was a key strength of the review. This caps the hierarchy of evidence available in this field. Zeber et al. (2013) also stressed the methodological challenges of synthesising findings from empirical adherence studies, in discussion of their review of determinants of initiation of medication.

Efforts to understand adherence behaviour should clearly define the process of interest and measure it accordingly. Chapter 1 provided details of a new taxonomy for adherence to medications, defined by three processes: initiation, implementation and discontinuation. Practice and implementation of adherence research needs to be more explicit and transparent; and the use of a consistent definition of adherence to medications with

appropriate measurement techniques are necessary for future research. The empirical research illustrates how determinants of nonadherence differ according to the measures used e.g. Morisky results for nonadherence (binary variable) versus MARS measures of adherence (continuous variable) (Chapter 3). We also distinguished between intentional and unintentional behaviour (nonadherence). Consolidation of models will require appreciation of the dynamic 'process' of adherence and the variations/flaws within existing research.

Furthermore, adoption of a taxonomy for adherence and a classification system for behavioural theories may lead to less heterogeneity and more capacity to combine findings and strengthen the evidence base on the explanatory side. The findings of behavioural research should be categorised to maximise their use for development and assessment of adherence enhancing interventions. The use of theoretical frameworks to identify determinants of nonadherence has implications for the development and testing of adherence enhancing interventions, insofar as it increases the potential to combine evidence and provides a framework for the assessment of behaviour change research (Michie et al., 2015).

- *Involvement of prescribers in the selection of attributes and levels, for a patient directed DCE, has potential to increase the plausibility of scenarios*

Our systematic approach to the design of the DCE in Chapter 6 encompassed the views of both patients and prescribers at appropriate stages. The focus group with prescribers ensured the findings of the ranking exercise informed the DCE in a way that was clinically meaningful. For example, the descriptions of the attributes were based on the frequency and severity at which prescribers considered the attribute to be 'clinically meaningful' – this represented the point at which they would the stop medication and prescribe an alternative medication. Which in turn, was the definition used for the event data used to attach salient levels, and to model probability of uptake in the secondary analysis. This ensured a consistent link between the properties of patients, factors that influenced prescribing, and patient level data used to model the implications of patient preferences.

- *Probability of persistence with different medications can be achieved by combining stated preference and clinical trial data.*

In the absence of revealed data on persistence, stated preference techniques can be used to measure preferences for medications. Chapter 4 and Chapter 6 provided empirical

examples of the use of stated preference discrete choice experiments to elicit preferences for medications that were linked to real clinical data to estimate the utility and probability of persistence with, and initiation of, actual medications. Furthermore, Chapter 4 used concurrent assessment of demographic, clinical, psychosocial, and sociocognitive factors to assess potential influences on these preferences (see below).

- *Time preference rates are sensitive to familiarity of the hypothetical scenario used to elicit them.*

Discount rates used in economic evaluation may be misaligned with the rate at which patients actually discount future costs and benefit for health. In Chapter 5 we found evidence that time preference rates elicited using a scenario of delays in antiepileptic medication and seizure reduction, elicited higher discount rates than are currently recommended for economic evaluation. In Chapter 7 we found that the results are sensitive to familiarity of the condition used in the scenario (here epilepsy). Furthermore, this research explored if differences in experimental design explain some of the variance in time preference rates. The lack of a consensus on the methodology to elicit individual time preference rates represents a conceptual flaw in the literature (Percoco & Nijkamp, 2009). The analysis used the discounted utility model, however the data suggests the hyperbolic discount function may have been more appropriate but there was insufficient data to fit this model, and we can therefore only conclude that there are significant differences in time preference rates for the 3-year and 6-year delay.

8.3.3 Implications for prescribing / clinical practice

- *Patients trade harms and benefits in their decision to persist with a medication and the utility derived from medications may be modified directly or indirectly. Different patient groups have different preferences, which has implications for prescribing practice.*

The results of the discrete choice experiment in Chapter 4 illustrated how people have preferences for the attributes of a medication, that directly influence probability of persistence. Via concurrent assessment of preferences and other demographic and behavioural factors, this research proved that utility could also be increased indirectly, by targeting modifiable factors for intervention

It is important that prescribers are aware that different patient groups trade different harms and benefits for medications. For example, Chapter 6 demonstrated that women with the potential to become pregnant have different preferences for medication than the wider epilepsy population. The specific consideration of the risk of foetal abnormality could potentially lead to discontinuation of therapy. Explicit consideration of how preferences for outcomes weight the decision to persist (both within and between patients groups) could lead to patient-level considerations being used in both research and practice.

- *Patient preferences should be considered alongside clinical efficacy in the decision to prescribe medication.*

Chapter 7 found that prioritisation of antiepileptic medication on the basis of clinical efficacy does not reflect patient preferences. Prescribing based on the basis of clinical efficacy alone (health maximisation), and not utility maximisation, may lead to suboptimal prescribing. Patients should be involved in their prescribing and their preferences for medication attributes should be considered, alongside clinical effectiveness.

8.4 Strengths and limitations

This thesis has addressed questions on the association between medication adherence and theory driven factors, using a range of research methods including a systematic literature, four studies using primary data collection and analysis, and a study using secondary analysis of previously analysed primary data. In doing so, it makes several unique contributions to existing knowledge and literature on adherence to medications.

- Chapter 2 provides the first systematic review to consider multiple theoretical frameworks in a single narrative analysis.
- Chapter 3 reports on the first multinational study to test the combined contribution of demographic, clinical, psychosocial, sociocognitive and economic factors simultaneously across several countries to determine associations with adherence to medications. Variable selection was based on the findings of the systematic review in Chapter 2 to ensure a robust theoretical framework for analysis.

- Chapter 4 presents the first multinational assessment of the decision to persist with medication, and is the first study to test the influence of psychosocial and sociocognitive characteristics on preferences within a discrete choice experiment analysis.
- Chapter 5 is the first multinational analysis of time preferences for health, described using a scenario of medication delay / benefits.
- Chapter 6 is the first study to combine stated preferences for antiepileptic medications with clinical trial data in order to model the influence of probability of outcome/event on utility and probability of uptake.
- Chapter 7 is one of very few studies to test the influence of familiarity on scenarios used in stated preference surveys. Few studies to date have questioned the influence of scenario on the elicitation and comparison of time preference rates for health.

There are several notable strengths to this PhD. Firstly, variable selection for the empirical research were informed by a robust systematic literature review, conducted according to the methods of the Centre for Reviews and Dissemination (2008) and reported according to the PRISMA statement (Liberati et al., 2009). The review focused on the highest quality evidence and acknowledged that meta-analysis was inappropriate for the broad range of studies included in the review. Most studies identified were cross-sectional, which cannot accommodate dynamic theoretical propositions, capture the entire process of adherence, or make inferences concerning causality of effect.

Secondly, this thesis considered multiple theoretical frameworks from both health psychology and behavioural economics. The application of several behavioural models across multiple empirical studies has been systematic and followed a consistent classification system. The format of identifying explanatory factors as individual components of subordinate models within broader theoretical frameworks has provided a clear and consistent evaluation of empirical evidence. This has also allowed for a more complex analysis of multiple models.

Thirdly, this thesis has involved the concurrent assessment of multiple theories within and across disciplines. The systematic review reported in Chapter 2 tested multiple frameworks. The novelty and key strength of the survey in Chapter 3 was the range of theoretically informed factors tested concurrently in a large multinational sample. Then, the discrete

choice experiment in Chapter 4 represented an application of behavioural economic theory that included a concurrent analysis of the influence of factors derived from health psychology models, again using a large multinational sample. The selection of psychosocial and sociocognitive factors tested alongside the DCE attributes was guided by theory and based on empirical evidence. Evidence from multiple paradigms increases the possibilities for interventions that could be person or medicine based, and represents a unique contribution to the health economics literature.

Finally, a significant strength of this PhD is the progression of methods within and between projects. Within Chapter 4 the results of the primary data analysis were combined with secondary data, in a retrospective case study of 5-ASAs for ulcerative colitis to illustrate how hypothetical preference data could be combined with clinical event data to estimate utility and probability of uptake across a sample of 'real' medications. Subsequently, I built on this experience, and implemented the same methodology in a new epilepsy project. The DCE in Chapter 6, was specifically designed to elicit preferences for harms and benefits of five 'real' antiepileptic medications, with a prospective analysis plan to analyse how patient preferences influences utility and probability of uptake of these specific medications using patient level data from a large UK clinical trial. Similarly, there was progression in the methods used for the selection of attributes and levels for the discrete choice experiments. The DCE in Chapter 4 used a scenario of a nonspecific medication, to explore a broad range of factors that influence persistence with medication. We used previously actionable attributes and based the descriptions on the terminology used by the European Medicines Agency, therefore relevant to the multinational sample. The epilepsy project reported in Chapter 6, later provided the opportunity to employ a more robust methodology in which we used qualitative research and ranking exercises with several stakeholders to ensure precise specification of the utility function and a more plausible decision scenario. Within both studies we gave considerable attention to the communication of risk, however, the latter project provided an opportunity to test and improve the face validity of the experiments using cognitive interviews. Harrison et al., (2014) reported that DCE studies are generally poor at reporting the methodology supporting the communication of risk, in comparison to studies contained in this review the study rates highly. In comparison with other studies, the epilepsy DCE had a high level of completion and low levels of nontrading behaviour (<1%), which would indicate participants engaged with the task. Manjunath et al., (2012) reported higher levels of nontrading behaviour (27%) by a relatively comparable sample of patients with epilepsy (n=263, mean age 42 years, 56% female) completing an online DCE of preferences for antiepileptic medication.

The systematic review in Chapter 2 also provided insight into the quality of existing empirical research and contributed to the design the empirical survey of determinants of adherence to hypertension using health psychology theories. Compromises had to be made on the basis of pragmatism, budget and time; therefore a longitudinal analysis was not possible. The cross-sectional survey, however, represented an improved application of these methods, compared to other empirical studies of adherence to antihypertensive medication identified in Chapter 2.

There are several limitations to this PhD. Firstly, heterogeneity between existing evidence limited the potential for meta-analysis and a definitive conclusion on the predictive value of behavioural models in the prediction of nonadherence to medication.

Secondly, the primary evidence is from a cross-sectional study that used a self-report measure of adherence. This imposes limitations on the applications of models, particularly when using self-regulatory components - as the models are not static and the theory assumes dynamic changes over time. Both surveys were self-administered, with self-reported inclusion criteria and measures. The use of web-based surveys may have led to selection bias. Studies investigating patients who are willing to participate in research may miss people who do not seek, or have dropped out of healthcare, which may introduce sampling bias and limits generalisability to the least adherent patients. Both surveys were also long and had tasks within them that were cognitively challenging, such as the time preference questionnaire and the discrete choice experiments, that involved interpreting multiple risks. There was inevitable missing data in the surveys, this was imputed for the large adherence survey, however the epilepsy analysis was on complete cases only.

Thirdly, the PhD comprises data from heterogeneous samples. The systematic review reported data with no restriction on condition, the adherence survey sampled people with hypertension, the results of the DCE of persistence were modelled on data for ulcerative colitis, and the second study was of patients with epilepsy. Evidence on 3-month persistence for both symptomatic and asymptomatic conditions ranges between 57% and 78% for 5-ASAs (Kane et al., 2009; Lachaine 2013); and between 59% and 75% for antihypertensive medication (Vrijens et al., 2008; Xu et al., 2013). 12-month persistence ranges are also relatively comparable. In both cases persistence also varies within medication class (Xu et

al., 2013; Lachaine et el., 2013). This evidence suggests that persistence data trend towards similar levels, regardless of disease type.

Fourthly, the research relied heavily on stated preference analysis, and as with any stated preference methods there will be a degree of uncertainty as to whether hypothetical decisions match what would happen in real life. Revealed preference studies are required to validate this data.

Finally, the research was conducted within the limitations of two larger funded projects. I was employed as the research fellow in health economics on both projects and was restricted by the funding outline. A pragmatic approach was necessary to complete the research within specified time frames. The projects also involved working with a larger, international, team of researchers, which brought associated challenges and complexities in the implementation of the research methods.

8.5 Future research directions

The implications discussed in section 8.3 outline areas that warrant further examination.

Overall, the importance of a theoretical foundation from which to develop, assess, and implement strategies to improve adherence has been highlighted throughout this thesis. There is vast potential for the development of both simple, and complex, adherence enhancing interventions with the potential to improve adherence and health outcomes, whilst reducing healthcare resource use and costs. The findings of this thesis have potential to inform the next stage in behavioural research which would be studies of behaviour change techniques and the assessment of such interventions.

Further theoretical research is also necessary to test the association between individual components of behavioural models and nonadherence at every point in the process e.g. initiation, implementation, and persistence. This will reduce gaps in the evidence base for the whole behaviour (process of adherence) and maximise the potential for existing or

consolidated behavioural models to explain why patients are nonadherent, in the context of frameworks that could explain and help modify this behaviour.

Future research from both a theory and behaviour change perspective will benefit from the use of agreed taxonomies, the availability of more robust adherence measurement techniques, and overall should build on the development of better practice that is emerging in this field (Vrijens et al. 2012; Michie et al. 2015).

8.6 Conclusion

Behavioural theories have potential to explain why behaviours differ within and between individuals, with the goal of designing interventions to change the prevalence of such behaviours and produce improvements in individual and population health. This thesis identified several theories from the disciplines of health psychology and behavioural economics, and applied them to the study of adherence to medications. Applications of models based on health psychology theory proved useful at explaining adherence to medications; however, no individual theory explained more than a limited amount of the variability in adherence. Application of economic theory provided a novel insight to potential reasons for nonadherence and enabled a multidisciplinary exploration of what influences persistence. The empirical investigation considered differences between countries and differences in patient populations, which illustrate the need for a tailored approach to adherence research. Consolidation of behavioural models may provide a strengthened theoretical basis for the development and assessment of adherence enhancing interventions that could promote sustainable behaviour change in clinical practice.

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Appendices

Appendix 1.1: Taxonomy for describing adherence to medications

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., ... & Matyjaszczyk, M. (2012). A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*, *73*(5), 691-705.

Appendix 2.1: Search strategy example: MEDLINE via Pubmed

1. patient compliance [Majr]
2. treatment Refusal [Majr]
3. #1 OR #2
4. pharmaceutic*
5. prescript*
6. medicat*
7. medicament
8. medicine
9. medicines
10. drug
11. drugs
12. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. theory
14. theories
15. model
16. models
17. #13 OR #14 OR #15 OR #16
18. medication adherence report
19. MARS
20. Medication adherence questionnaire
21. Morisky
22. illness perception questionnaire
23. IPQ
24. brief illness perception questionnaire
25. brief IPQ
26. beliefs about medicines questionnaire
27. BMQ
28. theory of planned behaviour
29. TPB

30. beliefs and behaviours questionnaire
31. BBQ
32. health belief* model
33. HBM
34. life orientation test
35. LOT
36. life orientation test-revised
37. LOT-R
38. optimis*
39. self regulation theory
40. self regulation model
41. implementation intentions
42. perceived control
43. attitudes beliefs
44. subjective norm*
45. perceived behavioural control
46. motivation
47. necessity concerns
48. psychodynamic
49. cognitive behavi*
50. transtheoretical model
51. precede-proceed model
52. common-sense model
53. theory of reasoned action
54. purposeful action theory
55. social cognitive theory
56. self-efficacy
57. protection motivation theory
58. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57

59. psycholog*

60. #58 OR #59

61. #3 AND #12 AND #17 AND #60

62. Limits : Animals, All infant : birth-23 months, All child : 0-18 years

63. 61 NOT 62

Appendix 2.2: List of studies included in the systematic review

List 1: In study number order [#] = number in Table 2.2 & Table 2.4

List 2: In alphabetical order [#] = number in Table 2.2 & Table 2.4

A2.2.1: List 1: In study number order [#] = number in Table 2.2 & Table 2.4

1. Gonzalez, J. S., Penedo, F. J., Llabre, M. M., Durán, R. E., Antoni, M. H., Schneiderman, N., & Horne, R. (2007). Physical symptoms, beliefs about medications, negative mood, and long-term HIV medication adherence. *Annals of behavioural Medicine*, *34*(1), 46-55. **[1]**
2. Weaver, K. E., Llabre, M. M., Durán, R. E., Antoni, M. H., Ironson, G., Penedo, F. J., & Schneiderman, N. (2005). A stress and coping model of medication adherence and viral load in HIV-positive men and women on highly active antiretroviral therapy (HAART). *Health Psychology*, *24*(4), 385. **[2]**
3. Halkitis, P. N., & Palamar, J. (2008). A mediation model to explain HIV antiretroviral adherence among gay and bisexual men. *Journal of gay & lesbian social services*, *19*(1), 35-55. **[3]**
4. Lynam, I. A. N., Catley, D., Goggin, K., Rabinowitz, J. L., Gerkovich, M. M., Williams, K., & Wright, J. (2009). Autonomous regulation and locus of control as predictors of antiretroviral medication adherence. *Journal of health Psychology*, *14*(4), 578-586. **[4]**
5. Barclay, T. R., Hinkin, C. H., Castellon, S. A., Mason, K. I., Reinhard, M. J., Marion, S. D., ... & Durvasula, R. S. (2007). Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. *Health Psychology*, *26*(1), 40. **[5]**
6. Stilley, C. S., Sereika, S., Muldoon, M. F., Ryan, C. M., & Dunbar-Jacob, J. (2004). Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. *Annals of behavioural Medicine*, *27*(2), 117-124. **[6]**
7. Schmitz, J. M., Sayre, S. L., Stotts, A. L., Rothfleisch, J., & Mooney, M. E. (2005). Medication compliance during a smoking cessation clinical trial: a brief intervention using MEMS feedback. *Journal of behavioural medicine*, *28*(2), 139-147. **[7]**
8. Apter, A. J., Boston, R. C., George, M., Norfleet, A. L., Tenhave, T., Coyne, J. C., ... & Feldman, H. I. (2003). Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *Journal of Allergy and Clinical Immunology*, *111*(6), 1219-1226. **[8]**

9. Cohen, N. L., Ross, E. C., Bagby, R. M., Farvolden, P., & Kennedy, S. H. (2004). The 5-factor model of personality and antidepressant medication compliance. *Canadian Journal of Psychiatry*, 49, 106–13. **[9]**
10. Brus, H., van de Laar, M., Taal, E., Rasker, J., & Wiegman, O. (1999). Determinants of compliance with medication in patients with rheumatoid arthritis: the importance of self-efficacy expectations. *Patient education and counseling*, *36*(1), 57-64. **[10]**
11. Abraham, C., Clift, S., & Grabowski, P. (1999). Cognitive predictors of adherence to malaria prophylaxis regimens on return from a malarious region: a prospective study. *Social science & medicine*, *48*(11), 1641-1654. **[11]**
12. Simoni, J. M., Frick, P. A., & Huang, B. (2006). A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy. *Health Psychology*, *25*(1), 74. **[12]**
13. Williams, G. C., Rodin, G. C., Ryan, R. M., Grolnick, W. S., & Deci, E. L. (1998). Autonomous regulation and long-term medication adherence in adult outpatients. *Health Psychology*, *17*(3), 269. **[13]**
14. Lim, W. S., Low, H. N., Chan, S. P., Chen, H. N., Ding, Y. Y., & Tan, T. L. (2004). Impact of a pharmacist consult clinic on a hospital-based geriatric outpatient clinic in Singapore. *Annals-Academy of Medicine Singapore*, *33*(2), 220-227. **[14]**
15. Farquharson, L., Noble, L. M., Barker, C., & Behrens, R. H. (2004). Health beliefs and communication in the travel clinic consultation as predictors of adherence to malaria chemoprophylaxis. *British journal of health psychology*, *9*(2), 201-217. **[15]**
16. Fraser, C., Morgante, L., Hadjimichael, O., & Vollmer, T. (2004). A Prospective Study of Adherence to Glatiramer Acetate in Individuals with Multiple Sclerosis*. *Journal of Neuroscience Nursing*, *36*(3), 120-hyhen. **[16]**
17. Turner, A. P., Kivlahan, D. R., Sloan, A. P., & Haselkorn, J. K. (2007). Predicting ongoing adherence to disease modifying therapies in multiple sclerosis: utility of the health beliefs model. *Multiple Sclerosis*, *13*(9), 1146-1152. **[17]**
18. Rudman, L. A., Hope Gonzales, M., & Borgida, E. (1999). Mishandling the Gift of Life: Noncompliance in Renal Transplant Patients1. *Journal of Applied Social Psychology*, *29*(4), 834-851. **[18]**
19. George, J., & Shalansky, S. J. (2007). Predictors of refill non-adherence in patients with heart failure. *British journal of clinical pharmacology*, *63*(4), 488-493. **[19]**
20. Chisholm, M. A., Williamson, G. M., Lance, C. E., & Mulloy, L. L. (2007). Predicting adherence to immunosuppressant therapy: a prospective analysis of the theory of planned behaviour. *Nephrology Dialysis Transplantation*, *22*(8), 2339-2348. **[20]**

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24. Greenstein, S., & Siegal, B. (1998). Compliance and Noncompliance in Patients with a Functioning Renal Transplant: A Multicenter Study1, 2. *Transplantation*, *66*(12), 1718-1726. **[24]**

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26. Byrne, M., Walsh, J., & Murphy, A. W. (2005). Secondary prevention of coronary heart disease: patient beliefs and health-related behaviour. *Journal of psychosomatic research*, *58*(5), 403-415. **[26]**

27. De Smet, B. D., Erickson, S. R., & Kirking, D. M. (2006). Self-reported adherence in patients with asthma. *Annals of Pharmacotherapy*, *40*(3), 414-420. **[27]**

28. Johnson, M. O., Elliott, T. R., Neilands, T. B., Morin, S. F., & Chesney, M. A. (2006). A social problem-solving model of adherence to HIV medications. *Health Psychology*, *25*(3), 355. **[28]**

29. Ross, S., Walker, A., & MacLeod, M. J. (2004). Patient compliance in hypertension: role of illness perceptions and treatment beliefs. *Journal of human hypertension*, *18*(9), 607-613. **[29]**

30. Chao, J., Nau, D. P., Aikens, J. E., & Taylor, S. D. (2005). The mediating role of health beliefs in the relationship between depressive symptoms and medication adherence in persons with diabetes. *Research in Social and administrative Pharmacy*, *1*(4), 508-525. **[30]**

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32. Youssef, R. M., & Moubarak, I. I. (2002). Patterns and determinants of treatment compliance among hypertensive patients. *East Mediterranean Health Journal*, 8, 579–92. **[32]**

33. Chen, S. L., Tsai, J. C., & Lee, W. L. (2009). The impact of illness perception on adherence to therapeutic regimens of patients with hypertension in Taiwan. *Journal of Clinical Nursing*, *18*(15), 2234-2244. **[33]**

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36. Brown, C. M., & Segal, R. (1996). The effects of health and treatment perceptions on the use of prescribed medication and home remedies among African American and white American hypertensives. *Social science & medicine*, *43*(6), 903-917. **[36]**

37. Clatworthy, J., Bowskill, R., Parham, R., Rank, T., Scott, J., & Horne, R. (2009). Understanding medication nonadherence in bipolar disorders using a Necessity-Concerns Framework. *Journal of Affective Disorders*, *116*(1), 51-55. **[37]**

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51. Mann, D. M., Ponieman, D., Leventhal, H., & Halm, E. A. (2009). Predictors of adherence to diabetes medications: the role of disease and medication beliefs. *Journal of behavioural medicine*, *32*(3), 278-284. **[51]**

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54. Bane, C., Hughe, C. M., & McElnay, J. C. (2006). Determinants of medication adherence in hypertensive patients: an application of self-efficacy and the Theory of Planned Behaviour. *International Journal of Pharmacy Practice*, *14*(3), 197-204. **[54]**

55. Atkinson, J. S., Nilsson Schönnesson, L., Williams, M. L., & Timpson, S. C. (2008). Associations among correlates of schedule adherence to antiretroviral therapy (ART): A path analysis of a sample of crack cocaine using sexually active African–Americans with HIV infection. *AIDS care*, *20*(2), 253-262. **[55]**

56. Holstad, M. K. M., Pace, J. C., De, A. K., & Ura, D. R. (2006). Factors associated with adherence to antiretroviral therapy. *Journal of the Association of Nurses in AIDS Care*, *17*(2), 4-15. **[56]**

57. Schmid-Mohler, G., Thut, M. P., Wüthrich, R. P., Denhaerynck, K., & De Geest, S. (2010). Non-adherence to immunosuppressive medication in renal transplant recipients within the scope of the integrative model of behavioural prediction: a cross-sectional study. *Clinical transplantation*, *24*(2), 213-222. **[57]**

58. Hekler, E. B., Lambert, J., Leventhal, E., Leventhal, H., Jahn, E., & Contrada, R. J. (2008). Commonsense illness beliefs, adherence behaviours, and hypertension control among African Americans. *Journal of behavioural medicine*, *31*(5), 391-400. **[58]**

59. Horne, R., & Weinman, J. (2002). Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining nonadherence to preventer medication. *Psychology and Health*, *17*(1), 17-32. **[59]**

60. Starace, F., Massa, A., Amico, K. R., & Fisher, J. D. (2006). Adherence to antiretroviral therapy: an empirical test of the information-motivation- behavioural skills model. *Health Psychology*, *25*(2), 153. **[60]**

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65. Fraser, C., Hadjimichael, O., & Vollmer, T. (2003). Predictors of Adherence to Glatiramer Acetate Therapy in Individuals with Self-Reported Progressive Forms of Multiple Sclerosis*. *Journal of Neuroscience Nursing*, *35*(3), 163-170. **[65]**

66. Christensen, A. J., & Smith, T. W. (1995). Personality and patient adherence: correlates of the five-factor model in renal dialysis. *Journal of behavioural medicine*, *18*(3), 305-313. **[66]**

67. Budd, R. J., Hughes, I. C., & Smith, J. A. (1996). Health beliefs and compliance with antipsychotic medication. *British Journal of Clinical Psychology*, *35*(3), 393-397. **[67]**

A2.2.2 List 2: In alphabetical order [#] = number in Table 2.2 & Table 2.4

Abraham, C., Clift, S., & Grabowski, P. (1999). Cognitive predictors of adherence to malaria prophylaxis regimens on return from a malarious region: a prospective study. *Social science & medicine*, *48*(11), 1641-1654. **[11]**

Amico, K. R., Toro-Alfonso, J., & Fisher, J. D. (2005). An empirical test of the information, motivation and behavioural skills model of antiretroviral therapy adherence. *AIDS care*, *17*(6), 661-673. **[44]**

Apter, A. J., Boston, R. C., George, M., Norfleet, A. L., Tenhave, T., Coyne, J. C., ... & Feldman, H. I. (2003). Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *Journal of Allergy and Clinical Immunology*, *111*(6), 1219-1226. **[8]**

Atkinson, J. S., Nilsson Schönnesson, L., Williams, M. L., & Timpson, S. C. (2008). Associations among correlates of schedule adherence to antiretroviral therapy (ART): A path analysis of a sample of crack cocaine using sexually active African–Americans with HIV infection. *AIDS care*, *20*(2), 253-262. **[55]**

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Appendix 3.1: Research Governance

Project details
Grant Agreement number:
223477, Funding Scheme: Collaborative Project
Project's coordinator:
Przemyslaw Kardas, PhD, Associate Professor, Medical University of Lodz
Tel: +48678 72 10, Fax: (+48 42) 631 93 60, E-mail: family@umed.lodz.pl

National research teams

Austria
Lorenz Auer-Hackenberg, Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna.
Univ. Lekt. Dr. Heimo Lagler, Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna.
Ass. Prof. Priv. Doz. Dr. Michael Ramharter, Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna.
Ethics reference: 590/2011

Belgium
Fabienne Dobbels, Katholieke Universiteit Leuven, Leuven, Belgium
Todd Ruppar, Katholieke Universiteit Leuven, Leuven, Belgium
Kaat Siebens, Katholieke Universiteit Leuven, Leuven, Belgium
Sabina De Geest, Katholieke Universiteit Leuven, Leuven, Belgium
Ethics reference: B322201110621

England
Wendy Clyne, Keele University,Keele,
Comfort Mshelia, Leeds University, Leeds, UK
Sarah McLachlan, Keele University,Keele,UK
Ethics reference: 10/WNo01/57

France
Fabrice Baton, Kappa Santé, Charlotte Drochon, Kappa Santé, Nathalie Texier, Kappa Santé, Dr. Eric Van Ganse
University of Lyon.

Germany
Sabine Breiholz, Drug Commission of German Pharmacists (AMK).
Dr. med. Lilian Krist, Institute for Social Medicine, Epidemiology and Health Economics, Charité University Medical Centre, Berlin.
Dr. med. Falk Müller-Riemenschneider, Institute for Social Medicine, Epidemiology and Health Economics, Charité University Medical Centre, Berlin.
Ethics reference: EA1/133/11

Greece
Dr. Dimitra Gennimata, Department of Public and Administrative Health, National School of Public Health, Athens.
Dr. Koula Merakou, Department of Public and Administrative Health, National School of Public Health, Athens.

Hungary
Berend, Dóra, Health Marketing Research Centre, Marketing and Media Institute, Corvinus University, Budapest.
Prof. Dr. Kiss István, President, Hungarian Society of Hypertension.
Dr. Simon Judit, Health Marketing Research Centre, Marketing and Media Institute, Corvinus University, Budapest.
Ethics reference: 20457/2011-EKU(663/PI/11),

Netherlands
Jan Hermsen, Netherlands Institute for Health Services Research, Utrecht.
Dr. Liset van Dijk, Netherlands Institute for Health Services Research, Utrecht.

Portugal
Dr. Luis Caldeira, National Authority of Medicines and Health Products (INFARMED), Lisbon.
Frederico Saraiva, National Authority of Medicines and Health Products (INFARMED), Lisbon.

Poland
Przemyslaw Kardas, PhD, Associate Professor, Medical University of Lodz
Michal Matyjaszczyk, Medical University of Lodz, Lodz, Poland
Pawel Lewek, Medical University of Lodz, Lodz, Poland
Ethics reference: OKB 03.2010

Wales
Prof. Dyfrig Hughes, Bangor University, Bangor UK.
Prof. Val Morrison, Bangor University, Bangor UK.
Emily Fargher, Bangor University, Bangor UK.
Ethics reference: 10/WNo01/57

Appendix 3.2: ABC Survey (Version 5.1 08/12/10_English)

ABC Survey Screen 1: Participant information, displayed on institutional host web site

ABC Project: A Survey on Medicines Use
Participant Information

Researchers from Bangor and Keele Universities are working with colleagues throughout Europe, to investigate what influences whether people take their tablets. Taking part in this study involves completing an online questionnaire on one occasion only. The results of this survey will provide valuable information to develop ways of helping patients take their tablets appropriately. We hope that you will take part.

AM I ELIGIBLE?
If you are 18 years of age or over, and have been diagnosed by a doctor as having high blood pressure, then you may be eligible.

WHAT IS INVOLVED?
We would like you to complete the questionnaire that follows. Most questions can be answered by simply ticking the box alongside the answer that applies to you. It should take about 30 minutes. There are no 'right' or 'wrong' answers; answer truthfully with what you feel best describes you, your opinions, and your actions. Your opinions are very valuable to us. We ask that you complete all the questions asked. However, your participation is voluntary and you may withdraw from the survey at any stage, for any reason.

CONFIDENTIALITY
All the information that you provide will be strictly CONFIDENTIAL and seen only by the research team. You will not be asked to provide your name or any other identifiable information. Taking part in the study will not affect any of the treatment you receive. Neither your doctor nor your pharmacist will know you have completed the survey.

FUNDING
The 'ABC project' has been funded by the European Commission to assess patients' use of medicines across several countries in Europe.

MORE INFORMATION
If you would like to know anything more about the survey, or should you have any questions or concerns, please do not hesitate to contact us.

E-mail: ABC@bangor.ac.uk / ABC@keele.ac.uk
Telephone: 01248 38 2709 / 01782 734 794

Thank you for taking time to read this information.

☐ If you would like to take part in the survey please tick this box to confirm that you have read and understood the participant information

>>Next>>

ABC Survey Screen 2: Eligibility filter, first screen hosted by Survey Monkey.

Introductory Questions

Please begin by completing the questions below.

After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. Are you over 18 years old?

☐ Yes

☐ No

2. Have you been diagnosed by your doctor as having high blood pressure (hypertension) that has lasted at least 3 months?

☐ Yes

☐ No

3. Are you currently prescribed medication for high blood pressure (hypertension)?

☐ Yes

☐ No

***4. Have you ever been diagnosed with:**

☐ Diabetes

☐ Psoriasis

☐ Psychiatric condition

☐ Liver dysfunction

5. Are you independent in medicines taking?

☐ Yes, I am independent and self-responsible for taking my medicines

☐ No, another person takes care of administration of my medicines

6. Are you living in a nursing home or similar facility?

☐ Yes

☐ No

>>NEXT>>

ABC Survey Screen 3: Demographics

Questions About You

First, we would like to ask you questions about yourself. After answering the questions, go to the next screen by clicking the NEXT button at the bottom.

1. Please select the country of your residence

<<drop-down list of all countries involved in the survey>>

2. Are you ...?

☐ Female ☐ Male

3. How old were you on your last birthday?

☐☐

4. What is the first part of your postcode?

☐☐☐☐

5. What is the highest level of education you have achieved?

☐ Primary

☐ Secondary

☐ Higher education

6. Marital status:

☐ Single

☐ Married / In a civil partnership

☐ Separated

☐ Divorced

☐ Widowed

7. Employment status:

☐ Working full time

☐ Working part time

☐ Unemployed

☐ Retired

☐ Student

☐ On sick leave (lasting longer than 7 days)

☐ Others (including unpaid work

>>NEXT>>

ABC Survey Screen 4: Medicines Use

Your Use of Medicines Today

1. How many medical conditions are you currently receiving prescribed medication for?

☐

2. Thinking of today, how many different medicines have you been prescribed to take each day? (please enter the number)

☐

3. Thinking of today, how many units of medicines (eg. tablets) have you been prescribed to take each day? (please enter number)

☐

4. How many times a day you are supposed to take your medicines?

☐ Once a day

☐ Two times a day

☐ Three times a day

☐ Four or more times a day

>>NEXT>>

ABC Survey Screen 5: Health status

Your Health

1. In general, would you say your health is...? (tick one)

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

>>NEXT>>

ABC Survey Screen 6: Affordability

Your Prescriptions

The next questions ask you about both the number of prescriptions and items which a doctor or other health professional may have prescribed for you.

A prescription is the sheet of paper you were issued with. A prescription may include more than one item (individual medicine). For example, if you received a prescription listing two medicines, the total number of items is two.

1. As far as you can remember, during the last four weeks, how many items (individual medicines) have you been prescribed?

☐

2. Do you currently pay for prescribed medicines?

☐ No: I have full exemption

☐ Yes: I pay a prescription charge

☐ Yes: I pay the full cost of the medicine

3. Do you ever feel that you have to think about how much money you have available to spend when you obtain medicines?

☐ Yes ☐ No

4. Please indicate which of the statements below applies to you:

a) If I am worried about money I take less of a medicine to make it last longer

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

b) I have to leave getting my prescription dispensed until I get paid

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

c) If I have a number of different items on my prescription, I don't get them all dispensed, because I can't afford them all at once

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

d) I have in the past borrowed money to pay for prescription medicines

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

e) Knowing that I will not be able to afford the prescription stops me from going to see my doctor

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

f) I ask my general practitioner / family doctor to supply a longer supply of my medicine to help me when I haven't got enough money

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

>>NEXT>>

ABC Survey Screen 7: Medicines Adherence (primary outcome measure) – 4-item Morisky Questionnaire

You indicated that you are taking medicines for high blood pressure. People have identified several issues regarding their medicines-taking behaviour and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your long-term illness medicine.

1. Do you ever forget to take your high blood pressure medicine?

☐ Yes

☐ No

2. Are you careless at times about taking your high blood pressure medicine?

☐ Yes

☐ No

3. Sometimes if you feel worse when you take your high blood pressure medicine do you stop taking it?

☐ Yes

☐ No

4. When you feel better, do you sometimes stop taking your high blood pressure medicine?

☐ Yes

☐ No

>>NEXT>>

ABC Survey Screen 8: Medicines Adherence (secondary outcome measures) – MARS_5

Questions About Taking Your Medicines

- Many people find a way of using their medicines that suits them.
- This may differ from the instructions on the label or from what their doctor has said.
- We would like to ask you a few questions about how you use your medicines.

Here are some ways in which people have said that they use their medicines.

For each of the statements, please tick the dot which best applies to you.

Your own way of using your medicines:

1. I forget to take them

☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

2. I alter the dose

☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

3. I stop taking them for a while

☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

4. I decide to miss out a dose ☐

☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

5. I take less than instructed

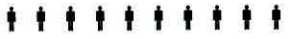
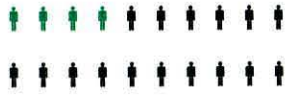
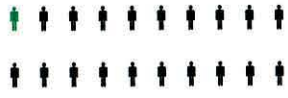
☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

>>NEXT>>

ABC Survey Screen 9-17: Discrete choice experiment

Your Preferences

We would like you to imagine that you have been prescribed a **new** medicine that you should continue taking until your doctor advises otherwise. In the following questions the characteristics of two alternative medicines will be described to you, please indicate which medicine you would be most likely to continue taking, 'Medicine A or Medicine B'.

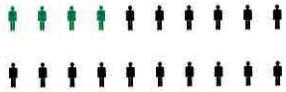
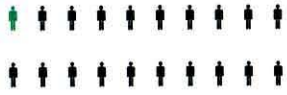
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	5 in 10 	1 in 10 
Number of times you need to take the medicine	Once a day	Twice a day
Treatment benefits	4 in 20 	1 in 20 
Potentially life-threatening side-effects	Uncommon: 1 person in 100	Very Rare: 1 person in 10,000

1. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 10: Discrete choice experiment cont.

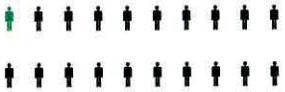
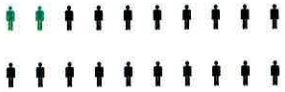
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	1 in 10 	3 in 10 
Number of times you need to take the medicine	Twice a day	Four times a day
Treatment benefits	4 in 20 	1 in 20 
Potentially life-threatening side-effects	Rare: 1 person in 1,000	Uncommon: 1 person in 100

2. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 11: Discrete choice experiment cont.

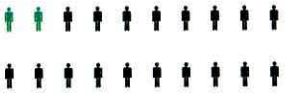
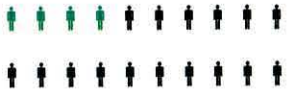
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	1 in 10 	3 in 10 
Number of times you need to take the medicine	Once a day	Twice a day
Treatment benefits	1 in 20 	2 in 20 
Potentially life-threatening side-effects	Very Rare: 1 person in 10,000	Rare: 1 person in 1,000

3. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 12: Discrete choice experiment cont.

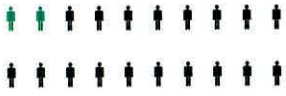
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	3 in 10 	5 in 10 
Number of times you need to take the medicine	Once a day	Twice a day
Treatment benefits	2 in 20 	4 in 20 
Potentially life-threatening side-effects	Rare: 1 person in 1,000	Uncommon: 1 person in 100

4. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 13: Discrete choice experiment cont.

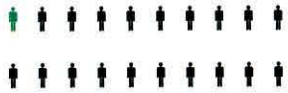
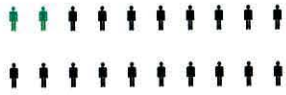
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	3 in 10 	5 in 10 
Number of times you need to take the medicine	Twice a day	Four times a day
Treatment benefits	1 in 20 	2 in 20 
Potentially life-threatening side-effects	Uncommon: 1 person in 100	Very Rare: 1 person in 10,000

5. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 14: Discrete choice experiment cont.

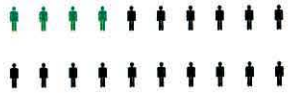
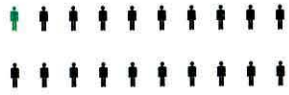
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	5 in 10 	1 in 10 
Number of times you need to take the medicine	Four times a day	Once a day
Treatment benefits	1 in 20 	2 in 20 
Potentially life-threatening side-effects	Rare: 1 person in 1,000	Uncommon: 1 person in 100

6. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 15: Discrete choice experiment cont.

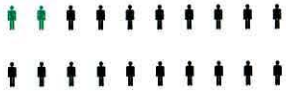
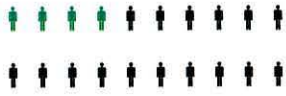
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	3 in 10 	5 in 10 
Number of times you need to take the medicine	Four times a day	Once a day
Treatment benefits	4 in 20 	1 in 20 
Potentially life-threatening side-effects	Very Rare: 1 person in 10,000	Rare: 1 person in 1,000

7. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 16: Discrete choice experiment cont.

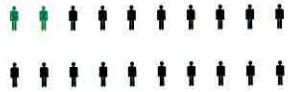
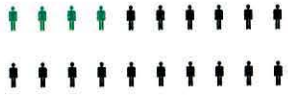
	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	5 in 10 	1 in 10 
Number of times you need to take the medicine	Twice a day	Four times a day
Treatment benefits	2 in 20 	4 in 20 
Potentially life-threatening side-effects	Very Rare: 1 person in 10,000	Rare: 1 person in 1,000

8. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screen 17: Discrete choice experiment cont.

	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	1 in 10 	3 in 10 
Number of times you need to take the medicine	Four times a day	Once a day
Treatment benefits	2 in 20 	4 in 20 
Potentially life-threatening side-effects	Uncommon: 1 person in 100	Very Rare: 1 person in 10,000

9. Which medicine would you be most likely to continue taking?

☐ A ☐ B

>>NEXT>>

ABC Survey Screens 18a-d: Time Preference Questionnaire

Time Preference

We would like you to imagine that you have been diagnosed with epilepsy. You have seizures (fits) that occur 20 times per year, and which seriously affect your usual activities.

Imagine you start a medicine **ONE YEAR** from now

that will reduce your seizures from 20 to:

12 times per year

If you do not start the medicine for **FOUR YEARS** from now

What is the maximum number of seizures per year that would still make this medicine worthwhile?

>>>NEXT>>>

ABC Survey Screens 18b: Time Preference Questionnaire (cont)

Imagine you start a medicine **ONE YEAR** from now

that will reduce your seizures from 20 to:

12 times per year

If you do not start the medicine for **SEVEN YEARS** from now

What is the maximum number of seizures per year that would still make this medicine worthwhile?

>>>NEXT>>>

ABC Survey Screens 18c: Time Preference Questionnaire (cont)

Imagine you start a medicine **ONE YEAR** from now

that will reduce your seizures from 20 to:

8 times per year

If you do not start the medicine for **FOUR YEARS** from now

What is the maximum number of seizures per year that would still make this medicine worthwhile?

>>>NEXT>>>

ABC Survey Screens 18d: Time Preference Questionnaire (cont)

Imagine you start a medicine **ONE YEAR** from now

that will reduce your seizures from 20 to:

8 times per year

If you do not start the medicine for **SEVEN YEARS** from now

What is the maximum number of seizures per year that would still make this medicine worthwhile?

>>>NEXT>>>

ABC Survey Screen 19: LOT-R

These questions are about you. Try not to let your response to one statement influence your responses to other statements.

There are no "correct" or "incorrect" answers. Answer according to your own feelings, rather than how you think other people might answer.

1. In uncertain times, I usually expect the best.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

2. It's easy for me to relax.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

3. If something can go wrong for me, it will.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

4. I'm always optimistic about my future.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

5. I enjoy my friends a lot.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

6. It's important for me to keep busy.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

7. I hardly ever expect things to go my way.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

8. I don't get upset too easily.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

9. I rarely count on good things happening to me.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

10. Overall, I expect more good things to happen to me than bad.

☐ I agree a lot; ☐ I agree a little; ☐ I neither agree nor disagree; ☐ I disagree a little; ☐ I disagree a lot

>>NEXT>>

ABC Survey Screen 20 BMQ_S11

Your Views About Medicines Prescribed For You19. BMQ

We would like to ask you about your personal views about medicines prescribed for you.

These are statements other people have made about their medicines.

Please show how much you agree or disagree with them by clicking on the appropriate dot.

There are no right or wrong answers. We are interested in your personal views.

Views about MEDICINES PRESCRIBED FOR YOU:

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

1. My health, at present, depends on these medicines

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

2. Having to take these medicines worries me

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

3. My life would be impossible without these medicines

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

4. I sometimes worry about long-term effects of these medicines

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

5. Without these medicines I would be very ill

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

6. These medicines are a mystery to me

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

7. My health in the future will depend on these medicines

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

8. These medicines disrupt my life

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

9. I sometimes worry about becoming too dependent on these medicines

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

10. These medicines protect me from becoming worse ☐

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

11. These medicines give me unpleasant side effects ☐

☐Strongly Agree ☐Agree ☐Uncertain ☐Disagree ☐Strongly Disagree

>>>NEXT>>

ABC Survey Screen 21: Theory of Planned Behaviour questionnaire

Your Beliefs About Taking Your Medicines

We would like to know your beliefs about taking your medicines.

Please show how much you agree or disagree with each statement by clicking on the appropriate dot.

□I agree a lot; □I agree a little; □ I neither agree or disagree; □ I disagree a little; □ I disagree a lot

1. If I were to take my medicines regularly.....

.....they would help me to stay well

.....they would reduce my chances of developing complications from my illness

.....they would keep the cause of my illness under control

.....they would keep my symptoms under control □

.....they would help me avoid needing further treatment

.....they would cause me unpleasant side effects (e.g. feeling sick or bloated)

.....they would lead to me gaining weight

2. My doctor or nurse would approve of me taking my medicines regularly

3. My wife/husband/partner would approve of me taking my medicines regularly

4. Members of my family or close relatives would approve of me taking my medicines regularly

5. Changes to my daily routine would make it more difficult for me to take my medicines regularly

6. Having a regular review with the healthcare professional would make it easier for me to take my medicines regularly

7. Keeping to a regular routine and being disciplined would make it easier for me to take my medicines regularly

8. It is likely that I will take my medicines regularly

9. I intend to take my medicines regularly

10. Putting out my tablets in a box would make it easier for me to take my medicines regularly

For each of the following questions, please indicate, by placing a tick in the appropriate dot for each question, your level of confidence for each of the following:

☐ Not at all confident; ☐ Somewhat confident; ☐ Very confident; ☐ Extremely confident; ☐ Completely confident

11. Overall, how confident are you that you will always take your medications as prescribed?

12. Overall, how confident are you that you will always take your medications at the prescribed times?

>>NEXT>>

ABC Survey Screen 22: EUROPEP

EUROPEP

General Health Service Use

1. Which of the following is mostly involved in the care of your high blood pressure (hypertension)?

□ Nurse practitioner

□ General practitioner/family physician

□ Specialist/consultant - hospital based

□ Specialist/consultant - private

□ Hospital physician

□ Private practitioner

□ Occupational health physician

□ Pharmacist

□ Other

□ Not applicable

2. What is the gender of the above-mentioned practitioner?

□ Female

□ Male

3. What is your assessment of the healthcare practitioner (referred to above) over the last 12 months with respect to:

1 - Poor 2 3 4 5 - Excellent

1. Making you feel you have time during consultation

2. Showing interest in your personal situation

3. Making it easy for you to tell him or her about your problem

4. Involving you in decisions about your medical care

5. Listening to you □

6. Keeping your records and data confidential

7. Providing quick relief of your symptoms □

8. Helping you to feel well so that you can perform your normal daily activities

9. Thoroughness of the approach to your problems

10. Physical examination of you

11. Offering you services for preventing diseases (e.g. screening, health checks, immunisations)

12. Explaining the purpose of examinations, tests and treatments

13. Telling you enough about your symptoms and/or illness

14. Helping you deal with emotions related to your health status

15. Helping understand why it is important to follow the GP's advice

16. Knowing what has been done or told during previous contacts in the practice

17. Preparing you for what to expect from specialists, hospital care or other care providers

4. What is your assessment of the general practice over the last 12 months with respect to:

18. The helpfulness of the practice staff (other than the doctor) to you

19. Getting an appointment to suit you?

20. Getting through to the practice on the telephone? □

21. Being able to talk to the general practitioner on the telephone □

22. Waiting time in the waiting room? □

23. Providing quick services for urgent health problems?

>>NEXT>>

ABC Survey Screen 23: BRIGHT – Barriers and social support

BRIGHT (Barriers and Social Support)

People give different reasons why it is difficult to take their medicines or to take their medicines on time. Is there anything that you recognize from the problems listed below?

Please provide a response for each statement by clicking on the appropriate dot.

In the past year…

□Never; □ Occasionally; □ Sometimes; □ Frequently; □ All the time; □ Not applicable

1. I ran out of medicines □
2. I was confused about which medicines to take
3. I did not want other people to know that I have a health problem
4. Something disrupted my daily medicine routine (e.g., I was on holiday)
5. I was forgetful
6. I could not afford to buy my medicines
7. I felt depressed or overwhelmed
8. I forgot to take my medicines with me when leaving the house
9. I had too many medicines to take
10. I suffered from the side effects of my medicine.
11. I had to take too many different doses during the day
12. I had problems swallowing the large pills of my medicines
13. I did not like the taste of my medicines
14. I had problems removing the medicines from the package
15. I had problems drinking enough water to swallow the medicines

People from your personal environment can support you to take your medications. The following questions relate to this topic. Please mark the answer which best represents how often you received support from people in your personal environment in the following situations over the past 4 weeks.

In the past 4 weeks...

□ Never; □ Occasionally; □ Sometimes; □ Frequently; □ All the time

16. Was there someone who reminded you to take your medicines?

17. Was there someone who helped you to prepare the medicines?

18. Was there someone who encouraged you to take your medicines correctly?

19. Was there someone who gave practical tips to make it easier for you to take your medicines?

20. Was there someone who adapted his or her own life habits (waking up, schedule...) to make it easier for you to take your medicines?

21. Was there someone who understood the problems or discomfort that resulted from your medicines?

22. Was there someone who reprimanded you because you didn't take your medicines correctly?

>>NEXT>>

ABC Survey Screen 24: The Brief Illness Perception Questionnaire

For the following questions, please tick the number that best corresponds to your views

Brief-IPQ

1. How much does your illness affect your life?

0 - no affect at all 1 2 3 4 5 6 7 8 9 10 – severely affects my life

2. How long do you think your illness will continue?

0 - a very short time 1 2 3 4 5 6 7 8 9 10 - forever

3. How much control do you feel you have over your illness?

0 – absolutely no control 1 2 3 4 5 6 7 8 9 10 – extreme amount of control

4. How much do you think your treatment can help your illness?

0 - not at all 1 2 3 4 5 6 7 8 9 10 – extremely helpful

5. How much do you experience symptoms from your illness?

0 – no symptoms at all 1 2 3 4 5 6 7 8 9 10 – many severe symptoms

6. How concerned are you about your illness?

0 - not at all concerned 1 2 3 4 5 6 7 8 9 10 – extremely concerned

7. How well do you feel you understand your illness?

0 - don't understand at all 1 2 3 4 5 6 7 8 9 10 – understand very clearly

8. How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or

depressed?)

0 - not at all affected emotionally 1 2 3 4 5 6 7 8 9 10 – extremely affected emotionally

9. Please list in rank-order the three most important factors that you believe caused your illness. The most important causes for me:

1.

2.

3.

>>NEXT>>

ABC Survey Screen 25: Antibiotics

Your Use of Antibiotics

Now, we would like to ask you several questions about the ANTIBIOTICS used for short-term conditions. There are no right or wrong answers, please be as honest as possible.

24. ANTIBIOTICS

1. How long has it been since you were prescribed an antibiotic (to be taken orally) last time?

□ Up to 12 months

□ More than one year ago

□ I am currently taking an antibiotic

□ Never

□ Don't remember

2. For how many days you were prescribed that antibiotic?

□□

3. How many times a day you were supposed to take that antibiotic?

□ Once a day

□ Two times a day

□ Three times a day

□ Four or more times a day

□ Don't remember

4. Did you obtain that antibiotic (e.g. from pharmacy)?

□ Yes

□ No

□ Don't remember

5. If you did not obtain that antibiotic from pharmacy, what was the main reason for that?

□ I felt better

□ I was afraid of side effects

□ I was afraid that antibiotic could affect my immunity

□ Cost

□ I did not need it

□ Other

□ Don't remember

□ Not Applicable

6. Did you start the treatment with that antibiotic?

□ Yes

□ No

□ Don't remember

7. If you did not start the treatment with that antibiotic, what was the main reason for that?

□ I felt better

□ I was afraid of side effects

□ I was afraid that antibiotic could affect my immunity

□ To save it for future

□ I did not need it

□ Other

□ Don't remember

>>CONT.>>

ABC Survey Screen 25: Antibiotics [cont.]

8. When taking that antibiotic, have you stopped your treatment before the time scheduled by your doctor?

□ Yes

□ No

□ Don't remember

9. If you stopped your treatment before the time scheduled by your doctor, what was the main reason for that?

□ Forgetfulness

□ I felt better

□ Side effects

□ Cost

□ To save it for future

□Other

□ Don't remem ber

10. When taking this antibiotic, have you skipped or missed one or more doses?

□ Yes

□ No

□ Don't remember

11. If you skipped or missed one or more doses, what was the main reason for that?

□ Forgetfulness

□ I felt better

□ Side effects

□ Cost

□ To save it for future

□ Other

□ Don't remember

>>NEXT>>

ABC Survey Screen 26: Income

The following questions ask you about your income. This information is useful to make sure we have the views of people with different financial circumstances and will help us to compare the results between difference populations.

1. Please consider the income of all household members and any income which may be received by the household as a whole. What is the main source of income in your household?

□ Wages or salaries

□ Income from self-employment (excluding farming)

□ Income from farming

□ Pensions

□ Unemployment/redundancy benefit

□ Any other social benefits or grants

□Income from investment, savings, insurance or property

□ Income from other sources

□ Don't know

□ Not willing to provide

2. What is your household's total income, after tax and compulsory deductions, from all sources? Please mark the letter corresponding to your answer. If you don't know the exact figure, please give an estimate.

	Approximate WEEKLY	Approximate MONTHLY	Approximate ANNUAL		
J	Less than £164	Less than £715	Less than £8,550	J	
R	£164 to under £220	£715 to under £960	£8,550 to under £11,470	R	
C	£220 to under £275	£960 to under £1,200	£11,470 to £14,440	C	
M	£275 to under £333	£1,200 to under £1,450	£14,440 to under £17,360	M	
F	£333 to under £405	£1,450 to under £1,760	£17,360 to under £21,120	F	
S	£405 to under £492	£1,760 to under £2,140	£21,120 to under £25,650	S	
K	£492 to under £592	£2,140 to under £2,570	£25,650 to under £30,870	K	
P	£592 to under £730	£2,570 to under £3,170	£30,870 to under £38,060	P	
D	£730 to under £961	£3,170 to under £4,180	£38,060 to under £50,110	D	
H	£961 or more	£4,180 or more	£50,110 or more	H	

□ Not willing to provide

3. Which of the following descriptions comes closest to how you feel about your household's income at present?

□ Living comfortably on present income

□ Coping on present income

□ Finding it difficult on present income

□ Finding it very difficult on present income

□ Not willing to provide

4. If for some reason you were in serious financial difficulties and had to borrow money to make ends meet, how difficult or easy would that be?

□ Very difficult

□ Quite difficult

□ Neither easy nor difficult

□ Quite easy

□Very easy

□Not willing to provide

>>NEXT>>

ABC Survey Screen 27: The final A3.1: ABC Survey Screen – Thank you and contact information

THANK YOU!

We would like to thank you very much for completing this survey.

If you have any questions, please do not hesitate to e-mail us:

ABCprojectPatientSurvey@gmail.com

To learn more about the ABC Project, please visit www.ABCproject.eu

The ABC Project Team

Appendix 4.1: Psychosocial measures used in the exploratory analysis of the Discrete Choice Experiment (DCE)

Psychological theory, model, variable	Number of items {score}	Item description	Scoring scale
Sociocognitive theory:			
Theory of Planned Behaviour			
Subjective norms	3-items {3-15}	1. My doctor or nurse would approve of me taking my medicines regularly 2. My wife/husband/partner would approve of me taking my medicines regularly 3. Members of my family or close relatives would approve of me taking my medicines regularly	5-point Likert scale: I agree a lot {5} I agree a little I neither agree or disagree I disagree a little I disagree a lot {1}
Barriers	1-items {3-15}	1. Changes to my daily routine would make it more difficult for me to take my medicines regularly	
Intention	2-items {2-10}	1. It is likely that I will take my medicines regularly 2. I intend to take my medicines regularly	
Self-efficacy	2-items {2-10}	1. Overall, how confident are you that you will always take your medications as prescribed? 2. Overall, how confident are you that you will always take your medications at the prescribed times?	5-point Likert scale: Not at all confident {1} Somewhat confident Very confident Extremely confident Completely confident {5}
BRIGHT Environmental Constraints / Facilitators			
Social support	7-items {0-35}	1. Was there someone who reminded you to take your medicines? 2. Was there someone who helped you to prepare the medicines? 3. Was there someone who encouraged you to take your medicines correctly? 4. Was there someone who gave practical tips to make it easier for you to take your medicines? 5. Was there someone who adapted his or her own life habits (waking up, schedule…) to make it easier for you to take your medicines? 6. Was there someone who understood the problems or discomfort that resulted from your medicines? 7. Was there someone who reprimanded you because you didn't take your medicines correctly?	5-point Likert scale: In the past 4 weeks … Never {0} Occasionally Sometimes Frequently All the time {4}

Psychological theory, model, variable	Number of items {score}	Item description	Scoring scale
BRIGHT Barriers	15-items {0-75}	1. I ran out of medicines 2. I was confused about which medicines to take 3. I did not want other people to know that I have a health problem 4. Something disrupted my daily medicine routine (e.g., I was on holiday) 5. I was forgetful 6. I could not afford to buy my medicines 7. I felt depressed or overwhelmed 8. I forgot to take my medicines with me when leaving the house 9. I had too many medicines to take 10. I suffered from the side effects of my medicine. 11. I had to take too many different doses during the day 12. I had problems swallowing the large pills of my medicines 13. I did not like the taste of my medicines 14. I had problems removing the medicines from the package 15. I had problems drinking enough water to swallow the medicines	5-point Likert scale: In the past year … Never {0} Occasionally Sometimes Frequently All the time {4}
Self-regulation theory: Illness Representations			
Illness consequences	1-item {0-10}	1. How much does your illness affect your life?	{0} - no affect at all {1 2 3 4 5 6 7 8 9} {10} - severely affects my life
Personal control	1-item {0-10}	1. How much control do you feel you have over your illness?	{0} - absolutely no control {1 2 3 4 5 6 7 8 9} {10} - extreme amount of control
Treatment control	1-item {0-10}	1. How much do you think your treatment can help your illness?	{0} - not at all {1 2 3 4 5 6 7 8 9} {10} - extremely helpful
Illness concern	1-item {0-10}	1. How concerned are you about your illness?	{0} - not at all concerned {1 2 3 4 5 6 7 8 9} {10} - extremely concerned
Treatment Beliefs			

Psychological theory, model, variable	Number of items {score}	Item description	Scoring scale
Necessity of medicine	5-items {5-25}	1. My health, at present, depends on these medicines 2. My life would be impossible without these medicines 3. Without these medicines I would be very ill 4. My health in the future will depend on these medicines 5. These medicines protect me from becoming worse	5-point Likert scale: Strongly Agree {5} Agree Uncertain Disagree Strongly Disagree {1}
Concerns about medicine	6-items {6-30}	1. Having to take these medicines worries me 2. I sometimes worry about long-term effects of these medicines 3. These medicines are a mystery to me 4. These medicines disrupt my life 5. I sometimes worry about becoming too dependent on these medicines 6. These medicines give me unpleasant side effects	5-point Likert scale: Strongly Agree {5} Agree Uncertain Disagree Strongly Disagree {1}

Appendix 5.1: Details of questions and time preference rates

Question	Nearest scenario		Furthest scenario		Time preference rate
	Years	Seizures	Years	Seizures (respondents answer)	
1	1	12	4	0	0.3572
1	1	12	4	1	0.3342
1	1	12	4	2	0.3104
1	1	12	4	3	0.2856
1	1	12	4	4	0.2599
1	1	12	4	5	0.2331
1	1	12	4	6	0.2051
1	1	12	4	7	0.1757
1	1	12	4	8	0.1447
1	1	12	4	9	0.1120
1	1	12	4	10	0.0772
1	1	12	4	11	0.0400
1	1	12	4	12	0.0000
1	1	12	4	13	-0.0435
2	1	12	7	0	0.1650
2	1	12	7	1	0.1551
2	1	12	7	2	0.1447
2	1	12	7	3	0.1339
2	1	12	7	4	0.1225
2	1	12	7	5	0.1105
2	1	12	7	6	0.0978
2	1	12	7	7	0.0843
2	1	12	7	8	0.0699
2	1	12	7	9	0.0545
2	1	12	7	10	0.0379
2	1	12	7	11	0.0198
2	1	12	7	12	0.0000
2	1	12	7	13	-0.0220
3	1	8	4	0	0.1856
3	1	8	4	1	0.1655
3	1	8	4	2	0.1447
3	1	8	4	3	0.1231
3	1	8	4	4	0.1006
3	1	8	4	5	0.0772
3	1	8	4	6	0.0527
3	1	8	4	7	0.0270
3	1	8	4	8	0.0000
3	1	8	4	9	-0.0286
4	1	8	7	0	0.0889
4	1	8	7	1	0.0796
4	1	8	7	2	0.0699
4	1	8	7	3	0.0598
4	1	8	7	4	0.0491
4	1	8	7	5	0.0379
4	1	8	7	6	0.0260
4	1	8	7	7	0.0134
4	1	8	7	8	0.0000
4	1	8	7	9	-0.0144

Appendix 5.2: Mean time preference rates by country and by group: adherent / nonadherent

	Time preference rate for 3-year delay										
	Mean	95%CI	95%CI	Adherent	95%CI	95%CI	Nonadherent	95%CI	95%CI	t^	p-value
Austria	0.137	0.128	0.147	0.135	0.124	0.147	0.142	0.125	0.158	0.810	0.421
Belgium	0.102	0.086	0.118	0.092	0.073	0.111	0.117	0.090	0.145	1.210	0.227
England	0.085	0.073	0.097	0.078	0.063	0.094	0.095	0.077	0.112	1.560	0.121
Germany	0.141	0.130	0.152	0.149	0.136	0.161	0.126	0.105	0.147	-1.990	0.048
Greece	0.214	0.203	0.225	0.216	0.200	0.231	0.212	0.196	0.227	-0.120	0.906
Hungary	0.184	0.173	0.196	0.190	0.170	0.210	0.182	0.168	0.195	-0.630	0.529
The Netherlands	0.105	0.093	0.118	0.114	0.100	0.128	0.077	0.053	0.101	-2.790	0.006
Wales	0.090	0.078	0.102	0.087	0.072	0.101	0.094	0.075	0.114	0.590	0.555
	Time preference rate for 6-year delay										
	Mean	95%CI	95%CI	Adherent	95%CI	95%CI	Nonadherent	95%CI	95%CI	t^	p-value
Austria	0.075	0.070	0.080	0.073	0.067	0.079	0.078	0.070	0.086	1.010	0.312
Belgium	0.049	0.041	0.057	0.048	0.038	0.058	0.051	0.038	0.065	0.430	0.671
England	0.040	0.034	0.046	0.036	0.029	0.044	0.045	0.037	0.054	1.670	0.095
Germany	0.074	0.068	0.080	0.077	0.070	0.084	0.066	0.055	0.077	-1.710	0.089
Greece	0.098	0.093	0.103	0.096	0.089	0.104	0.099	0.092	0.106	0.470	0.635
Hungary	0.087	0.082	0.093	0.089	0.080	0.099	0.086	0.080	0.093	-0.530	0.596
The Netherlands	0.056	0.048	0.063	0.060	0.052	0.068	0.042	0.028	0.055	-2.680	0.008
Wales	0.048	0.043	0.054	0.047	0.040	0.054	0.050	0.041	0.059	0.510	0.611

^ students two-sample t-test with equal variance (i.e. adherent and non-adherent), for each individual country

Appendix 6.1: Example of interview schedule and workbook for the ranking exercise conducted with women with an established diagnosis of epilepsy

PART B – Ranking Exercise

[NB: Dealing with dual choice when ranking: *If items are equally ranked it is of interest to explore why. If the items are considered to have the same meaning, record them as the same rank by listing them on the same line, separated with a "/". If the items have different meanings but are equally weighted in the respondents mind, ask them if they had to choose just one of the two which would it be? The one they choose takes the higher ranking in the booklet. If they cannot choose, amend the ranking in the booklet e.g. 1,2,3,4 becomes 1,2,2,4 if the second and third items are different but are considered equal].*

In this part of the interview, we would like you to think about the benefits, side-effects and outcomes of AED treatment. Then we will go onto discuss other possible treatments.

B.1

First of all … Thinking about the benefits of AED treatment here are two commonly described benefits. ***[Interviewer gives out separate benefits cards (B1.1)]***

i) Which is the **most important benefit to you?** (whether experienced or not) ***[interviewer record ranking responses on grid at B1.2 in booklet]***
ii) Explain your choice.

B.2

Now we want to ask you to think about possible SEs AEDs. In Part A, you told us that . . . . [*interviewer recap re. any problems/SEs described at A.3]*

Here is a list of ***possible*** side effects that have been described previously by some people with epilepsy ***[interviewer give checklist B2.1]***. Looking at this list:

i) Anything missing (as far as you are concerned) ? What? [**Interviewer enter any self-nominated *AED SEs on grid at B2.2 in booklet*]**
ii) ***[Interviewer give out separate SE cards]*** Pick out up to **4** SE's/problems that concern you most (whether experienced or not; and including any self-nominated)
iii) Place the 4 in order of most concern to least concern [*using ranking cards*] ***[interviewer record ranking responses on grid at B2.3 in booklet]***
iv) Explain your choice/ranking of these 4.

B3

Now we want you to think about aspects of your daily life that may be affected by having epilepsy.

Here *is a sheet* ***with a number of aspects of daily life that PWE have reported [interviewer show checklist B3.1 - Daily Life Impacts Board***]. Looking at this list:

i) Anything missing? what? [**interviewer enter any self-nominated life impacts *on grid at B3.2 in booklet***]

ii) [***interviewer give out separate Daily Life Impacts cards***]. Ask participant: pick out up to **4 aspects of daily life that you would hope to see the most improvement in as a result of taking AED. [*interviewer record responses on grid in at B3.3 booklet]***

iii) Explain choice.

B.4

[INTERVIEWER to refer to B2.3 and extract the 4 relevant AED SE cards; refer to worksheet B3.3 and extract relevant 4 Daily Impacts cards; give the two medication benefits cards]

Thinking about what you have told me so far, here are the two benefits of AEDs we discussed, here are the four problems/side effects that you consider to be of most concern, and here are the four aspects of daily life that you would hope to see the most improvement in.

i) *So can I now ask you to <u>select your top 4</u> from all of these and then rank them in order of importance?* ***[interviewer record ranked responses on grid at B4 in booklet]***

Patient Preferences and Priorities For Treatment

Interview Workbook – Women
Established Epilepsy CBA

Patient ID:

.....

QUESTION A1

Epilepsy History

Seizure Frequency

A1.1

In the last year, how many seizures have you had altogether?

None.....☐

One only.....☐

2-3.....☐

4-5.....☐

6-9.....☐

10 or more....☐

A1.2

How long ago did you have your last (most recent) seizure?

Within the last week.....☐

Within the last month.....☐

More than 1 month but less than 3 months ago.....☐

More than 3 months but less than 6 months ago.....☐

More than 6 months ago.....☐

A1.3

What types of seizures do you have?

Tonic-clonic (grand mal) only.....☐

Tonic-clonic (grand mal) and other types....☐

Other types only.....☐

QUESTION A2

Current AED Treatment Status

A2.1

Are you currently taking any drugs to control your seizures?

Yes ..... ☐

No ..... ☐

IF YES,

A2.2

How many drugs do you take?

One only ..... ☐

Two ..... ☐

Three ..... ☐

Four or Five ..... ☐

A2.3

Which of the following are you taking?

Carbamazepine or Tegretol ..... ☐

Phenytoin or Epanutin ..... ☐

Phenobarbitone or Prominal ..... ☐

Sodium valproate or Epilim ..... ☐

Lamotrigine or Lamictal ..... ☐

Gabapentin or Neurontin ..... ☐

Topiramate or Topamax ..... ☐

Oxcarbazepine or Trileptal ..... ☐

Levetiracetam or Keppra ..... ☐

Pregabalin or Lyrica ..... ☐

Other (please write in) ..... ☐

QUESTION A3

Seizure Control

A3.1

Thinking about your own epilepsy how well does your antiepileptic drug treatment control your seizures?

Not at all										Completely
0	1	2	3	4	5	6	7	8	9	10

Exercise B1

AED Benefits cards

B1.1

Reduction in seizure

Reduction in seizure

AED Benefit(s) Ranking

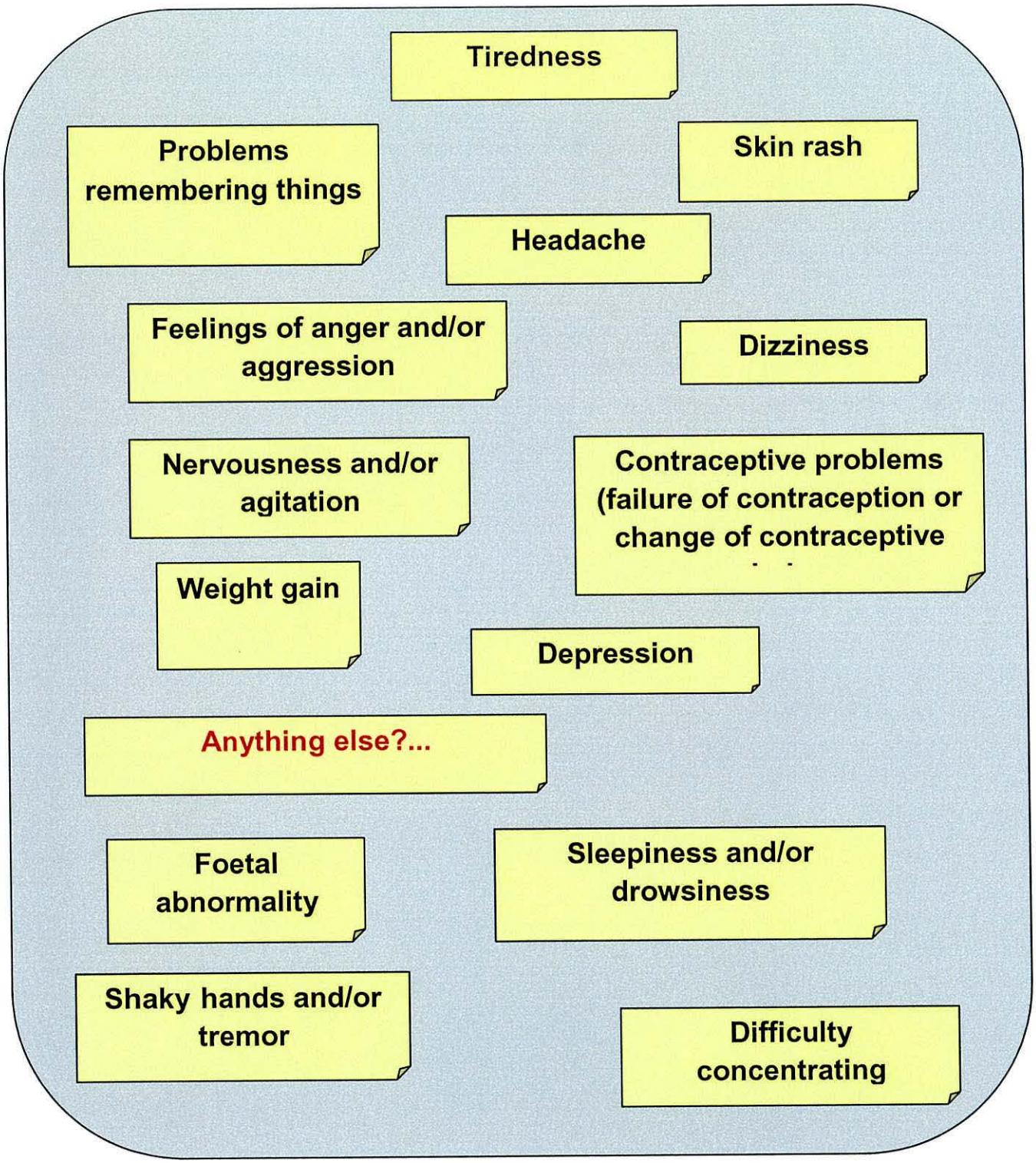
B1.2

Most important benefit

1	
2	

Exercise B2

AED Side Effects Board - B2.1



Patient Self-nominated Missing Side Effect(s)

B2.2

AED Side Effects Ranking

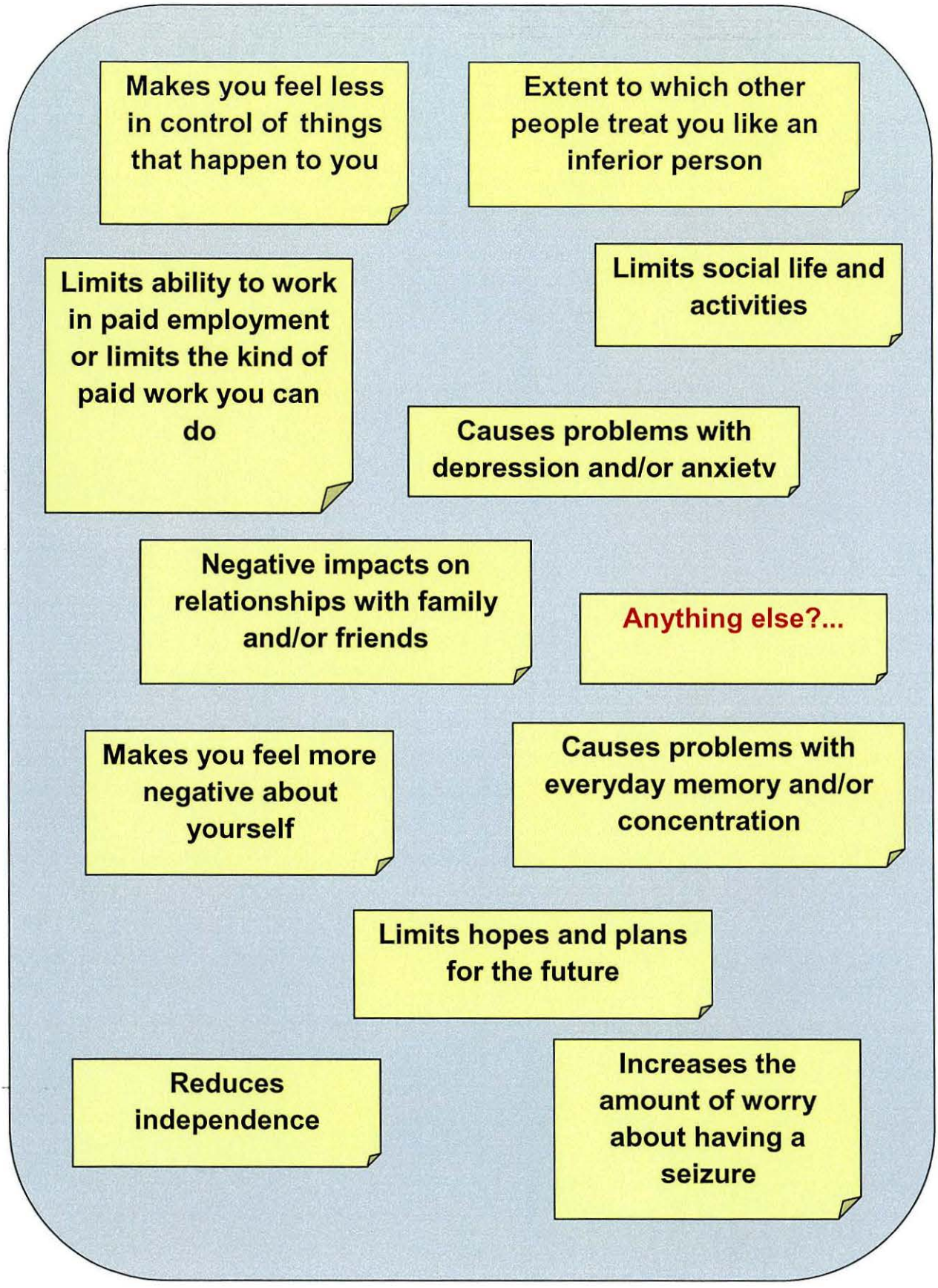
B2.3

Rank: (1) 'most' to (4) 'least' troublesome.

1	
2	
3	
4	

Exercise B3

Life Impacts Board - B3.1



Patient self-nominated Missing Daily Life Impact(s)

B3.2

Daily Life Impact(s) Cards

B3.3

Daily life impacts: Select up to 4 impacts most improved (reduction of impact) due to AED treatment

Exercise B4

Overall - Top 4 attributes

Rank: (1) 'most' to (4) 'least' important

1	
2	
3	
4	

Appendix 6.2: Example of cognitive interview schedule and workbook for the ranking exercise conducted with people with established epilepsy

PART B INTERVIEW SCHEDULE: STAGE 2

This part of the interview is about Antiepileptic drug treatment. We would like your opinion on how the outcomes of drug treatment should be described in a survey for people with epilepsy.

Outcomes of drug treatment include:-

- Benefits, for example, the drug may stop seizures happening, and;
- Side-effects, for example the drug may cause headaches.

They may also include:

- Impacts on daily life, for example how much control you feel you have over the things that happen to you.

I am going to show you some cards that describe different outcomes of drug treatment.

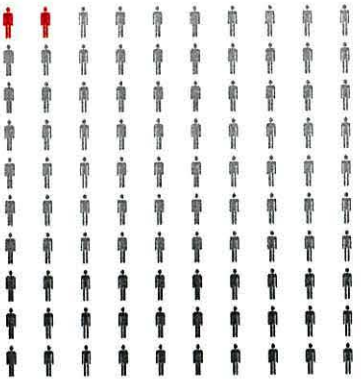
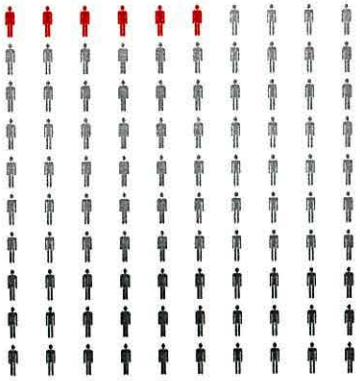
Then I would like you to describe to me **what YOU think the card is explaining**.

<Place cards in front of the interviewee one at a time>

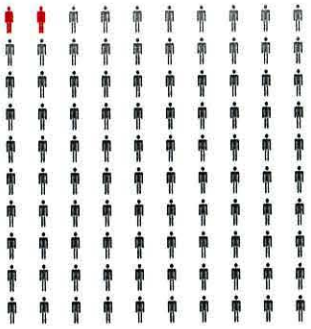
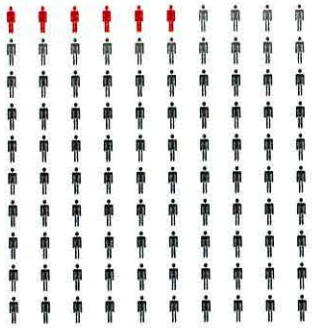
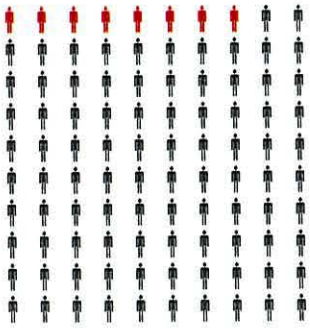
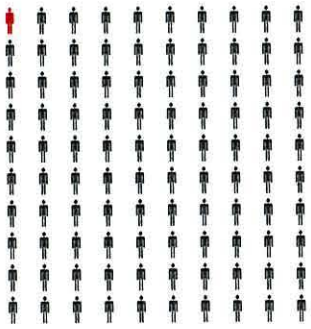
Possible prompts / options for framing the question:-

- Could I ask you to tell me what your understanding is, of what is being presented on this card?
- Can you tell me what is being presented for Drug A?
- Can you tell me what is being presented for Drug B?
- Is it clear how they differ?
- What is your understanding of *<insert attribute label>* as it is presented here?
- So, what do you think the card is describing?
- Do you think the information here *<point to box below Drug A or Drug B>* explains this outcome *<point to attribute label>*?
- Do you think the information could be presented differently?

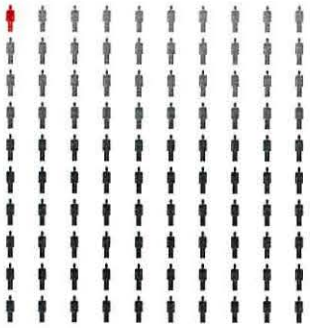
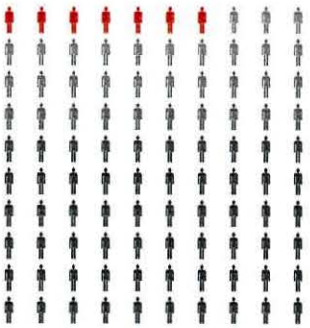
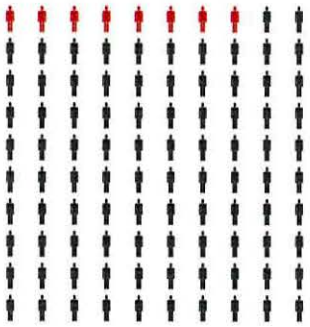
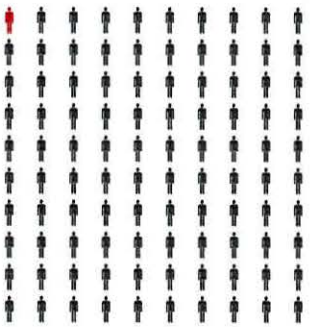
Notes are provided for the interviewer on explaining risk – should the interviewee request clarification when discussing cards. Card E should only be shown to WOCBA and should be used if judged appropriate following the 'gate-keeping' questions in Part A.

	Drug A	Drug B
Headache	 2 in 100 people	 6 in 100 people

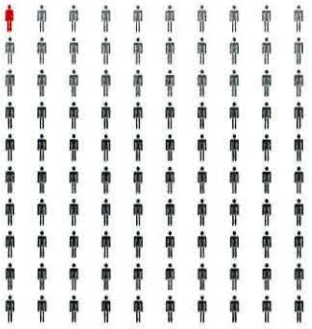
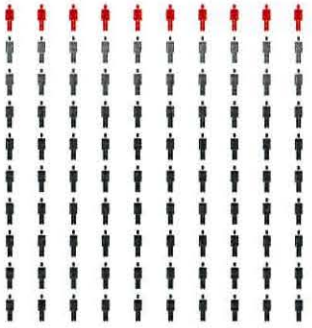
CARD A

	Drug A	Drug B
Headache	 2 in 100 people	 6 in 100 people
Feelings of aggression	 8 in 100 people	 1 in 100 people

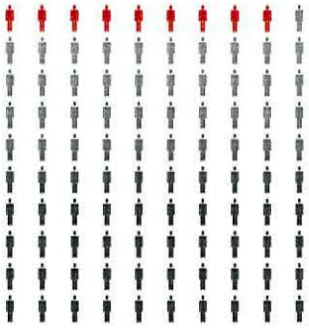
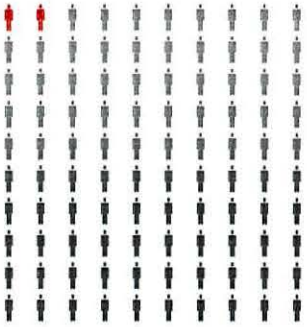
CARD B

	Drug A	Drug B
Memory problems	 1 in 100 people	 7 in 100 people
Depression	 8 in 100 people	 1 in 100 people

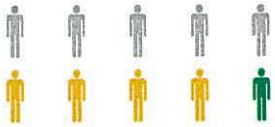
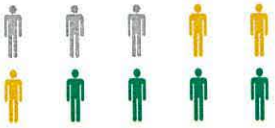
CARD C

	Drug A	Drug B
Allergic rash	 1 in 100 people	 10 in 100 people
Potentially life-threatening side-effects	**UNCOMMON** 1 in 5,000 people	**RARE** 1 in 10,000 people

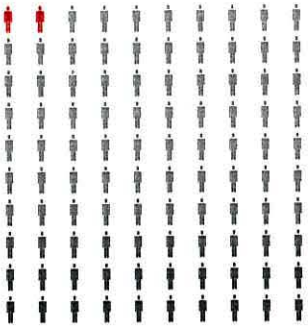
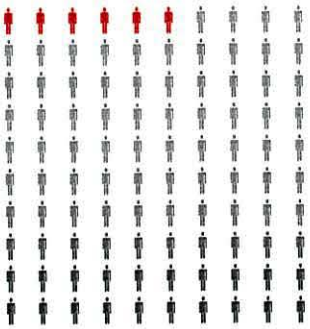
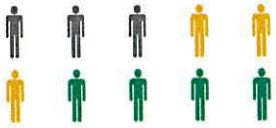
CARD D

	Drug A	Drug B
Harm to foetus if you get pregnant whilst taking this drug	 9 in 100 pregnancies	 2 in 100 pregnancies

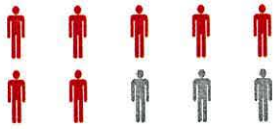
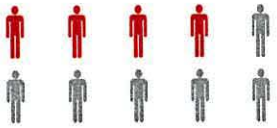
CARD E

	Drug A	Drug B
Number of seizures	After one year of starting Drug A:  5 in 10 people have no change 4 in 10 people have half as many 1 in 10 people have no seizures	After one year of starting Drug B:  3 in 10 people have no change 3 in 10 people have half as many 4 in 10 people have no seizures

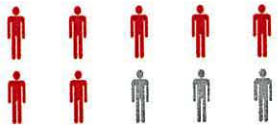
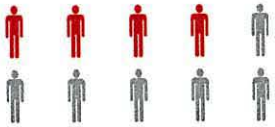
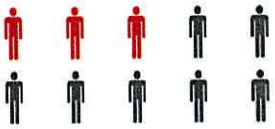
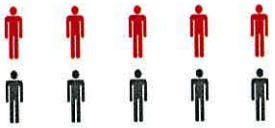
CARD F

	Drug A	Drug B
Headache	 2 in 100 people	 6 in 100 people
Number of seizures	After one year of starting Drug A:  5 in 10 people have <u>no change</u> 4 in 10 people have <u>half as many</u> 1 in 10 people have <u>no seizures</u>	After one year of starting Drug B:  3 in 10 people have <u>no change</u> 3 in 10 people have <u>half as many</u> 4 in 10 people have <u>no seizures</u>

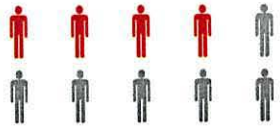
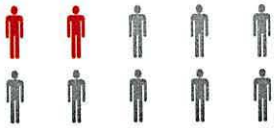
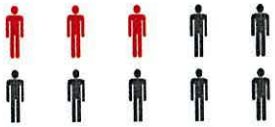
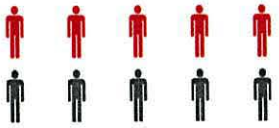
CARD G

	Drug A	Drug B
Usual activities e.g. work, study, housework family or leisure activities (inc. driving)	 7 in 10 people have some problems, or are unable to perform, their usual activities	 4 in 10 people have some problems, or are unable to perform, their usual activities

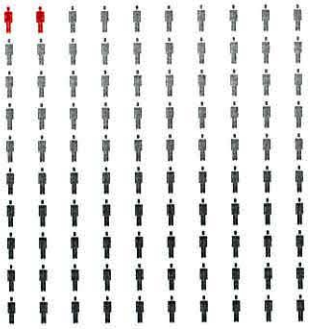
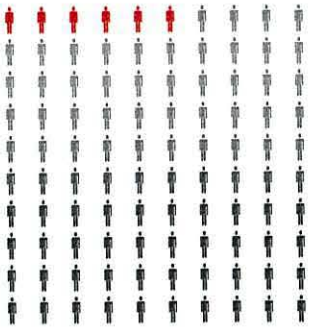
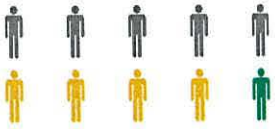
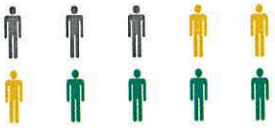
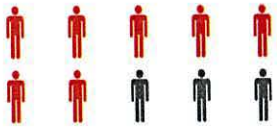
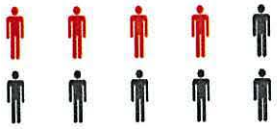
CARD H

	Drug A	Drug B
Usual activities e.g. work, study, housework family or leisure activities (inc. driving)	 7 in 10 people have some problems, or are unable to perform, their usual activities	 4 in 10 people have some problems, or are unable to perform, their usual activities
Concentration	 3 in 10 people have serious problems concentrating for more than a short period of time	 5 in 10 people have serious problems concentrating for more than a short period of time

CARD I

	Drug A	Drug B
Control	 4 in 10 people feel they have little or no control over things that happen to them	 2 in 10 people feel they have little or no control over things that happen to them
Stigma	 3 in 10 people feel some people treat them like an inferior person	 5 in 10 people feel some people treat them like an inferior person

CARD J

	Drug A	Drug B
Headache	 2 in 100 people have experienced headache whilst taking this drug	 6 in 100 people have experienced headache whilst taking this drug
Number of seizures	After one year of starting Drug A:  5 in 10 people have no change 4 in 10 people have half as many 1 in 10 people have no seizures	After one year of starting Drug B:  3 in 10 people have no change 3 in 10 people have half as many 4 in 10 people have no seizures
Usual activities e.g. work, study, housework family or leisure activities (inc. driving)	 7 in 10 people have some problems, or are unable to perform, their usual activities	 4 in 10 people have some problems, or are unable to perform, their usual activities

CARD K

Notes on explaining risk:-

All probabilities are presented in terms of X in 10 or X in 100. This is consistent with drug patient information leaflets. If the respondent enquires, or prefers percentages, they can be explained to them as follows:-

The notes given below should ONLY be used if the interviewee requests clarification – and should only be used after they have attempted to answer the question: ***What do you think this card is explaining?***

Number of seizures (card A):-
2 in 10 is a 20% chance
3 in 10 is a 30% chance
4 in 10 is a 40% chance
5 in 10 is a 50% chance

Higher chance (number of %) means it is more likely to happen.
Lower chance (number or % means it is less likely to happen.

Higher chance (number or %) is better for no seizures, because this means you are more likely to go 12-months with no seizures.
Lower chance (number or %) is better for no change, because this means you are more likely to have some improvement.

Side effects (cards B-F):-
1 in 100 people is a 1% risk of the side-effect
2 in 100 people is a 2% risk of the side-effect
6 in 100 people is a 6% risk of the side-effect
7 in 100 people is a 7% risk of the side-effect
8 in 100 people is an 8% risk of the side-effect

Lower risk (number or %) is better.

Adverse drug reaction (card G):-
1 in 5,000 people is 0.0002%
1 in 10,000 people is 0.0001%

Rare is better than uncommon.

Appendix 6.3: Focus group work book, completed by participants

The Walton Centre NHS
NHS Foundation Trust

Research for Patient Benefit Programme (RfPB)

Defining patient preferences and priorities for treatment options and outcomes in epilepsy

Principal Investigator: Prof. A Marson

Focus Group

Facilitator: Emily Fargher, Research Fellow

Centre for Health Economics & Medicines Evaluation

Bangor University

Introduction

Aims and Objectives of the Study

1. To identify which healthcare interventions are considered important by people with epilepsy and how different patient subgroups prioritise different interventions.

2. To identify which outcomes of healthcare interventions are considered important by people with epilepsy, and how the different patient subgroups prioritise different outcomes.

3. To identify views and definitions of equivalence for outcomes used in clinical trials among people with epilepsy, and to investigate perceptions of acceptable trade-offs between benefits and harm across the different subgroups.

Two linked studies have been designed to utilise a range of research methods. Semi-structured individual interviews with patients and focus group discussions are being used to explore views, understandings, experiences, and interpretations of treatment options, outcomes and preferences.

Interviews with patients have provided a short-list of outcomes of Antiepileptic drug treatments that are important to patients; today's focus group aims to review these findings to ensure the study is clinically meaningful, consistent with prescribing practice, and can be related to clinical trial data.

A large-scale survey, involving discrete choice methodology, will then allow examination of whether the views and preferences of the few are supported by those of the many; and to quantify the relative weightings given to these by a larger and more inclusive stakeholder group.

Which is the most important outcome of AED treatment?

	Early Onset Diagnosis < 1 year	Established Diagnosis ≥ 1 year
Reduction in seizure frequency	☐	☐
Reduction in seizure severity	☐	☐

Anything missing?

Please list any benefits that are missing and may be of greater importance:

Which medication would you be most likely to continue taking?

	Drug A	Drug B
Number of seizures	After one year of starting Drug A:  5 in 10 people have no change 4 in 10 people have half as many 1 in 10 people have no seizures	After one year of starting Drug B:  3 in 10 people have no change 3 in 10 people have half as many 4 in 10 people have no seizures

Comments:

Rank patient reported side-effects in order of most concern (1) to least concern (4)

	Early Onset Diagnosis < 1 year	Established Diagnosis ≥ 1 year
Feelings of aggression	☐	☐
Depression	☐	☐
Memory problems	☐	☐
Headache	☐	☐

Anything missing?

Please list any side-effects that are missing and may be of greater concern:

Describe the frequency and severity at which the following patient reported side-effects are considered:

"Clinically Important Adverse Events"

(Reasons for stopping or switching treatment)

Feelings of aggression

Depression

Memory problems

Headache

Rank patient reported life-impacts in order of most concern (1) to least concern (4)

(When considering stopping or switching treatment)

	Early Onset Diagnosis < 1 year	Established Diagnosis ≥ 1 year
Limits ability to work in paid employment or kind of paid work you can do	☐	☐
Negative impacts on relationships with family and/or friends	☐	☐
Makes you feel less in control of the things that happen to you	☐	☐
Reduces independence	☐	☐
Limits hope and plans for the future	☐	☐

Select the level at which patient reported life-impacts would contribute to a decision to stop or switch treatment:

Limits ability to work in paid employment or kind of paid work you can do
☐ No problems performing usual activities
☐ Some problems performing usual activities
☐ Unable to perform usual activities
☐ *This would not influence prescribing*

Negative impacts on relationships with family and/or friends
☐ Relationships are somewhat worse
☐ Relationships are very much worse
☐ *This would not influence prescribing*

Makes you feel less in control of the things that happen to you
☐ You feel you have some control over things that happen to you
☐ You feel that you have little control over things that happen to you
☐ You feel you have no control over things that happen to you
☐ *This would not influence prescribing*

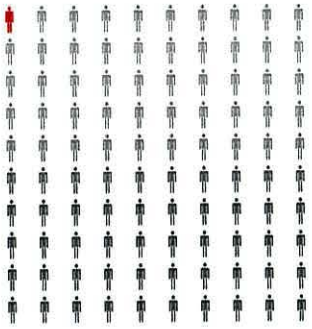
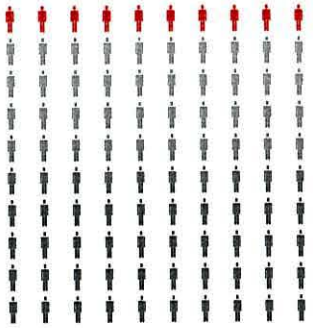
Reduces independence
☐ Your level of independence is somewhat worse
☐ Your level of independence is very much worse
☐ *This would not influence prescribing*

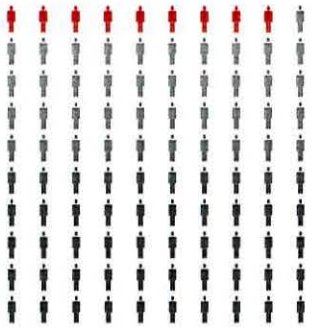
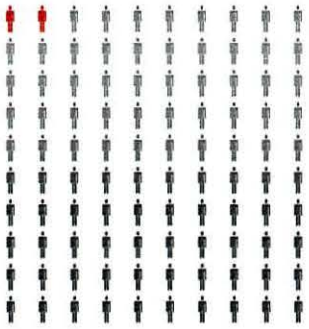
Rank top 5 outcomes

	Early Onset Diagnosis < 1 year	Established Diagnosis ≥ 1 year
Seizure reduction	☐	☐
Feelings of aggression	☐	☐
Depression	☐	☐
Memory problems	☐	☐
Headache	☐	☐
Limits ability to work in paid employment or kind of paid work you can do	☐	☐
Negative impacts on relationships with family and/or friends	☐	☐
Makes you feel less in control of the things that happen to you	☐	☐
Reduces independence	☐	☐
Limits hope and plans for the future	☐	☐

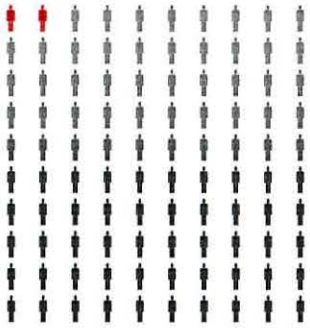
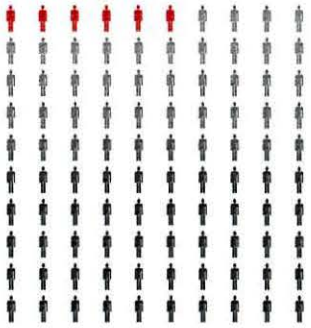
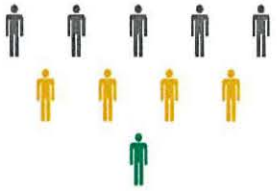
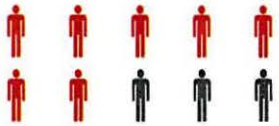
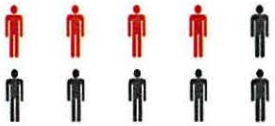
Please indicate (✓) where you have experienced the most common interactions:

	Side-effects and Benefits of AED Treatment				
	Feeling of aggression	Depression	Memory problems	Headache	Seizure frequency
Limits ability to work in paid employment or kind of paid work you can do					
Negative impacts on relationships with family and/or friends					
Makes you feel less in control of the things that happen to you					
Reduces independence					
Limits hope and plans for the future					

	Drug A	Drug B
Allergic Rash	 1 in 100 people	 10 in 100 people
Potentially life-threatening side-effects	**UNCOMMON** 1 in 5,000 people	**RARE** 1 in 10,000 people

	Drug A	Drug B
Harm to foetus if you get pregnant whilst taking this drug	 9 in 100 pregnancies	 2 in 100 pregnancies

Which medication would you be most likely to continue taking?

	Drug A	Drug B
Headache	 2 in 100 people have experienced headache whilst taking this drug	 6 in 100 people have experienced headache whilst taking this drug
Number of seizures	After one year of starting Drug A:  5 in 10 people have no change 4 in 10 people have half as many 1 in 10 people have no seizures	After one year of starting Drug B:  3 in 10 people have no change 3 in 10 people have half as many 4 in 10 people have no seizures
Usual activities e.g. work, study, housework family or leisure activities (inc. driving)	 7 in 10 people have some problems, or are unable to perform, their usual activities	 4 in 10 people have some problems, or are unable to perform, their usual activities

Many thanks for taking the time to support this research project. Your views and experiences are most appreciated.

✂- - - - - - - - - ----------

Defining patient preferences and priorities for treatment options and outcomes in epilepsy

Principal Investigator: Prof. A Marson

Please provide your e-mail address below if you are happy to be contacted in the future:-

☐ I am willing to provide feedback on the design of the patient questionnaire

☐ I would like to receive a summary of the findings

E-mail:

Appendix 6.4: Epilepsy Survey

Participant Information Sheet

Epilepsy Action Survey

Which treatment would you prefer?

Epilepsy Action is working with researchers from the University of Liverpool and Bangor University UK on a new research project. The project aims to find out which treatments for epilepsy you would like to be available.

What is the purpose of this study?

For most people with epilepsy, treatment for their seizures involves taking anti-epileptic medication. However, a number of other treatment options are becoming increasingly available. We know very little about what people with epilepsy themselves consider important in terms of the management of their condition. For example, we know very little about how people with epilepsy decide whether or not a treatment is beneficial for them, or not. In this study, we want to try to understand better what people with epilepsy consider important, both in terms of possible treatment options and the results of those treatments.

The information that people provide as part of this study will help to ensure that healthcare services in the future include treatment options and results that people with epilepsy themselves have identified as important.

When will this study be recruiting?

People with epilepsy are invited to complete this questionnaire between May and September 2013.

Who can take part?

If you are 18 years of age or over, and a doctor has told you that you have epilepsy, then you can take part in the survey.

What do I have to do if I am interested in taking part?

Taking part in this study involves completing an online questionnaire on one occasion only. You will answer most questions by ticking the box alongside the answer that applies to you. It should take about 20 minutes. There are no 'right' or 'wrong' answers; you should answer with what you feel best describes you, your opinions, and your actions. Your opinions are very valuable to us. We ask that you complete all the questions asked.

If you would prefer to complete a paper copy of the questionnaire, please contact Margaret Rawnsley (details below). She will post you a questionnaire and a pre-paid envelope to return it.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If having read this information you are not interested in taking part in this study then you do not need to do anything and we would like to take this opportunity to thank you for your time. Please be assured that your participation is voluntary and that you are free to withdraw at any time, without giving any reason, and without your care or legal rights being affected.

What are the possible disadvantages and risks of taking part?

There are no physical risks associated with taking part in the survey. Taking part in the study will not affect any of the treatment you receive. Neither your doctor nor your pharmacist will know you have completed the survey.

What are the possible benefits of taking part?

There are not likely to be any immediate benefits for you, if you choose to take part in the survey, although you may appreciate being given the opportunity to express your personal views and opinions. However, the information we get will improve understanding about what people with epilepsy consider important, both with regard to possible treatment options and the outcomes of those treatments.

Will my taking part in this study be kept confidential?

All information collected about you will be kept strictly confidential and seen only by the research team. We will not ask you to provide your name or any other identifiable information.

What will happen to the results of the research study?

Once the data collection is complete, data analysis and report writing will begin. We hope to complete this work by the end of 2013. If you would like a copy of the results, please let us know and we will ensure that you receive one.

Who is funding the study?

This study is being funded by The National Institute for Health Research, which is part of the Department of Health.

Who has reviewed the study?

This study has been reviewed and received approval from NRES Research Ethics Committee North West - Preston [REC reference: 11/NW/0191] and the University of Liverpool.

Who is conducting the research?

The study is a collaboration between Epilepsy Action and academic researchers at the University of Liverpool and Bangor University. Professor Tony Marson from Liverpool University and The Walton Centre for Neurology and Neurosurgery is the principal investigator and the clinical lead investigator. Professor Ann Jacoby at Liverpool University is the lead investigator.

More Information

If you have any questions or concerns, or would like more information about the project, please do not hesitate to contact Margaret Rawnsley at Epilepsy Action.

E-mail:- *mrawnsley@epilepsy.org.uk*

Telephone:- *01213 210 8800*

Thank you for reading this information.

Interested?

☐ **If you would like to take part in the survey, please tick this box to confirm that you have read and understood the participant information on this page.**

Introduction:

1. How old are you? . . . . . years

2. Are you?

Female	☐ → go to Q3
Male	☐ → go to Q5

3. Is there any possibility, however remote, that you might become pregnant in the future?

Yes	☐ → go to Q4
No	☐ → go to Q5

4. For how long have you had epilepsy?

Less than 4 months	☐ → go to Page 13, Part 1 Q17
4-12 months	☐ → go to Page 13, Part 1 Q17
1-5 years	☐ → go to Page 13, Part 1 Q17
6- 10 years	☐ → go to Page 13, Part 1 Q17
More than 10 years	☐ → go to Page 13, Part 1 Q17

5. For how long have you had epilepsy?

Less than 4 months	☐ → go to Page 4, Part 1 Q1
4-12 months	☐ → go to Page 4, Part 1 Q1
1-5 years	☐→ go to Page 4, Part 1 Q1
6-10 years	☐→ go to Page 4, Part 1 Q1
More than 10 years	☐→ go to Page 4, Part 1 Q1

PART 1 - Q1

Which anti-epileptic medication would you prefer?

This part of the questionnaire will help us to find out which anti-epileptic medications people would prefer to take.

We would like you to imagine you have the choice between two medications. Medication A and Medication B. We will give you the same information about each medication.

The chance of responding well:-

- Seizures stop
- Fewer seizures

The risk of severe side effects:-

- Feelings of aggression
- Depression
- Memory problems

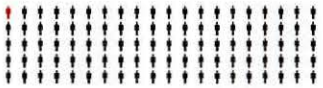
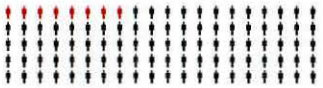
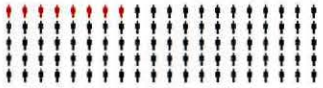
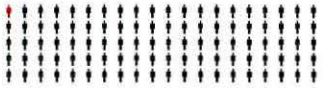
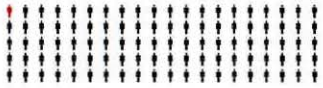
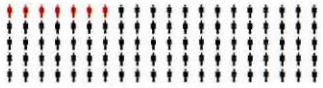
These side effects would be so severe that you would need to change to a different anti-epileptic medication.

We will then ask you **"Which medication would you prefer to take?"**

There are **eight choices**. Each time you should select either Medication A or Medication B. Medication A and Medication will be different in every question.

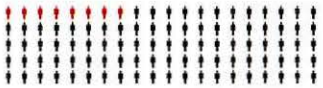
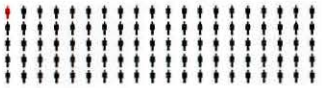
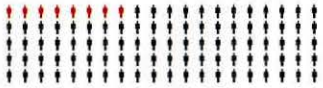
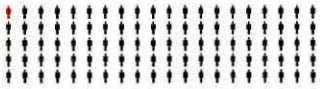
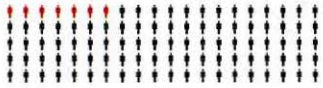
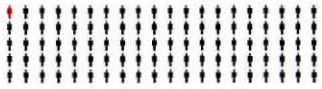
Please try to answer every question. There are no right or wrong answers. We are interested in your views.

(Part 1 Q1-8) Choice 1 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 1 in 100 people experience feelings of aggression	 8 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems

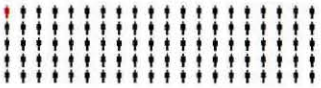
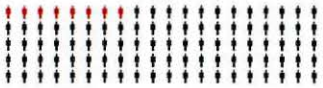
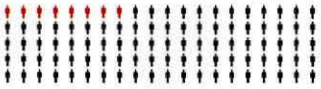
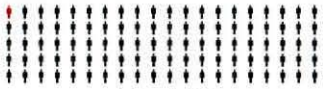
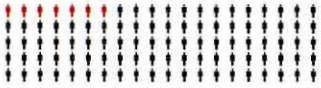
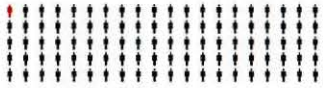
Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 2 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 8 in 100 people experience feelings of aggression	 1 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems

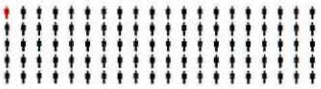
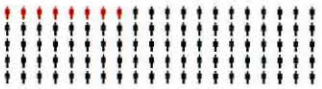
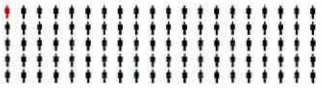
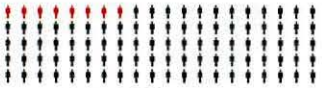
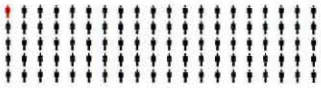
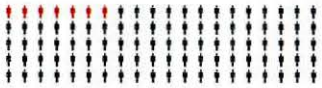
Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 3 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 1 in 100 people experience feelings of aggression	 8 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems

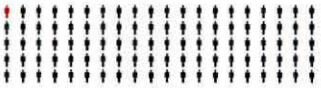
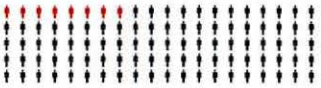
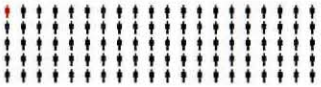
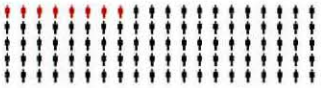
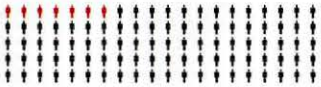
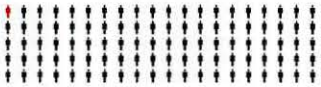
Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 4 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 1 in 100 people experience feelings of aggression	 8 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems

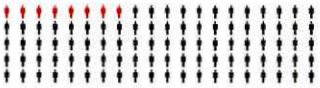
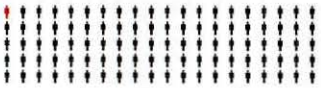
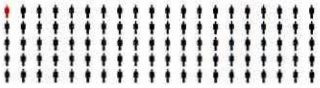
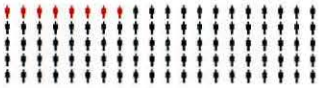
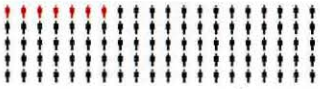
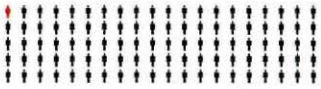
Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 5 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 1 in 100 people experience feelings of aggression	 8 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems

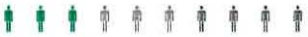
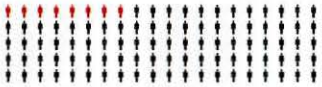
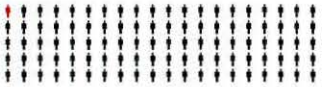
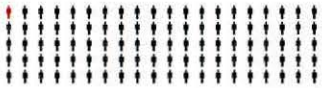
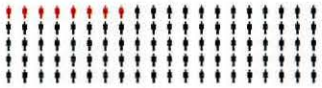
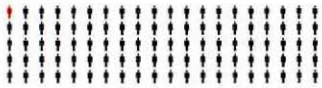
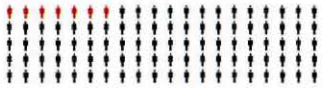
Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 6 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 8 in 100 people experience feelings of aggression	 1 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems

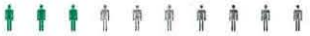
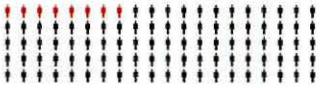
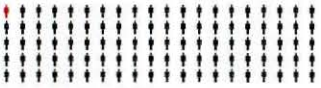
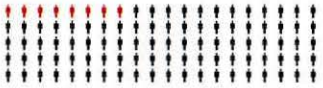
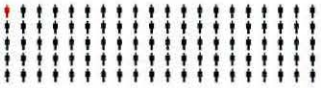
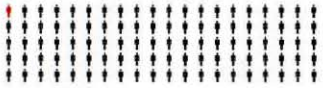
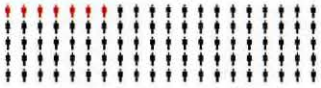
Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 7 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 8 in 100 people experience feelings of aggression	 1 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems

Which medication would you prefer to take? ☐ ☐

(Part 1 Q1-8) Choice 8 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Feelings of Aggression *This can be verbal or physical and often affects relationships and activities of daily life*	 8 in 100 people experience feelings of aggression	 1 in 100 people experience feelings of aggression
Depression *A feeling of low mood which often affects activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems
Which medication would you prefer to take?	☐	☐

Now go to Part 2 on Page 22

PART 1 (17-24)

Which medication would you prefer?

This part of the questionnaire will help us to find out which anti-epileptic medications people would prefer to take.

We would like you to imagine you have the choice between two medications. Medication A and Medication B. We will give you the same information about each medication.

The chance of responding well:-

- Seizures stop
- Experience fewer seizures

The risk of severe side effects:-

- Depression
- Memory problems

The side effects listed would be so severe that you would need to change to a different anti-epileptic medication.

Finally, we will also give you information on the risk of harm to the foetus if you get pregnant whilst taking this medication:-

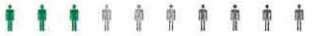
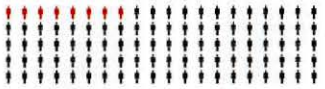
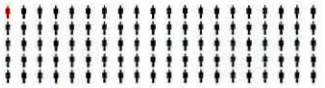
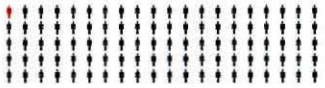
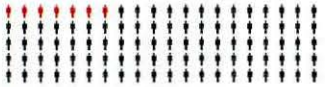
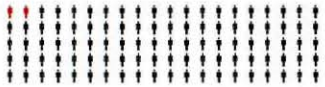
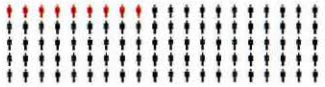
- This may cause birth problems, such as spina-bifida, a hole in the heart, and a cleft palate (where the roof of the mouth is not correctly joined). This may also cause neurodevelopment problems, such as poor memory, poor language and social skills, and low IQ.

We will then ask you **"Which medication would you prefer to take?"**

There are **eight choices**. Each time you should select either Medication A or Medication B. Medication A and Medication will be different in every question.

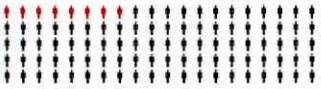
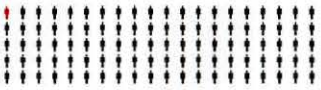
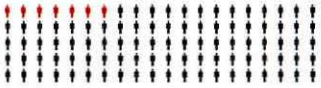
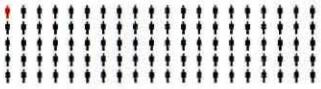
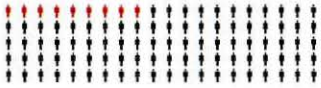
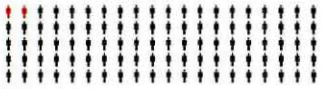
Please try to answer every question. There are no right or wrong answers. We are interested in your views.

(Part 1 Q17-24) Choice 1 of 8: Which medication would you prefer? Tick A or B

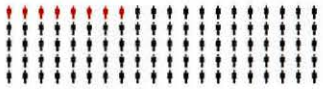
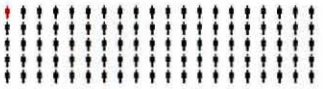
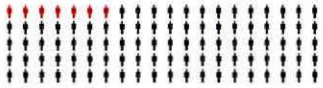
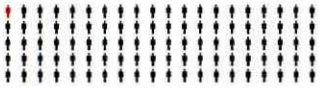
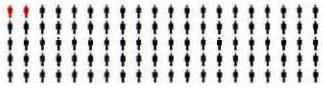
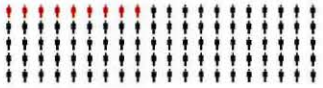
	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth - such as spina-bifida or low IQ*	 2 in 100 pregnant women experience foetal harm	 9 in 100 pregnant women experience foetal harm

Which medication would you prefer to take? ☐ ☐

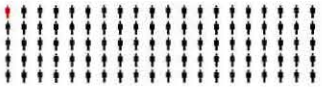
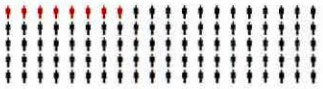
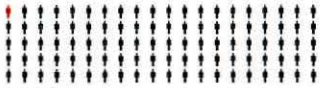
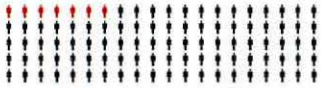
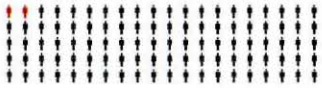
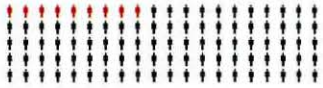
(Part 1 Q17-24) Choice 2 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 9 in 100 pregnant women experience foetal harm	 2 in 100 pregnant women experience foetal harm
Which medication would you prefer to take?	☐	☐

(Part 1 Q17-24) Choice 3 of 8: Which medication would you prefer? Tick A or B

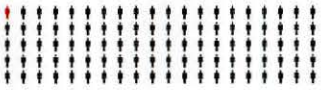
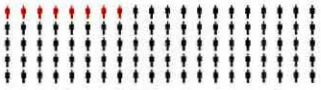
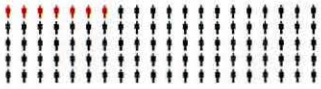
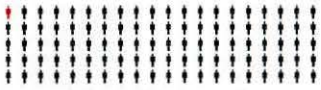
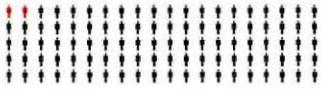
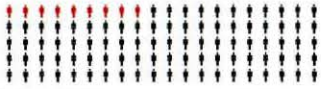
	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 2 in 100 pregnant women experience foetal harm	 9 in 100 pregnant women experience foetal harm
Which medication would you prefer to take?	☐	☐

(Part 1 Q17-24) Choice 4 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 2 in 100 pregnant women experience foetal harm	 9 in 100 pregnant women experience foetal harm

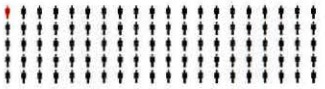
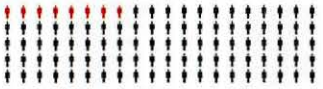
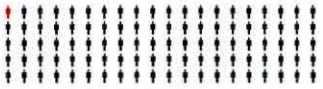
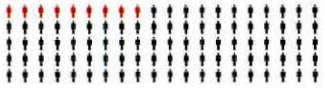
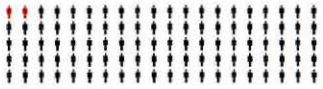
Which medication would you prefer to take? ☐ ☐

(Part 1 Q17-24) Choice 5 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 2 in 100 pregnant women experience foetal harm	 9 in 100 pregnant women experience foetal harm

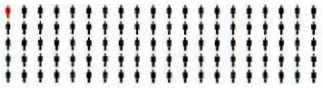
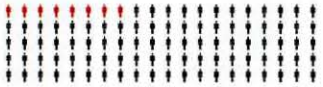
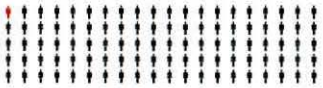
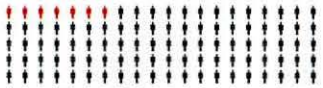
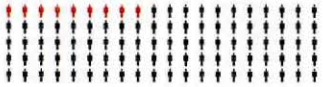
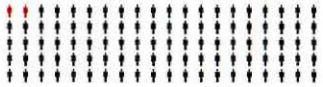
Which medication would you prefer to take? ☐ ☐

(Part 1 Q17-24) Choice 6 of 8: Which medication would you prefer? Tick A or B

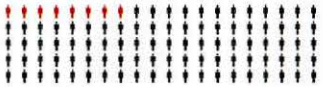
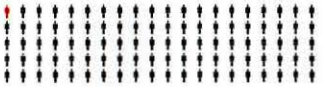
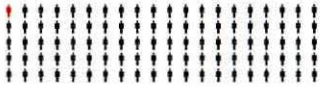
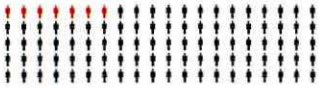
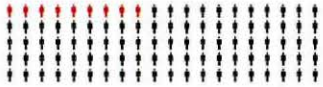
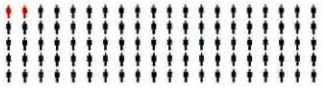
	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 5 in 10 people seizures stop	 3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 7 in 100 people experience memory problems	 1 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 9 in 100 pregnant women experience foetal harm	 2 in 100 pregnant women risk foetal harm

Which medication would you prefer to take? ☐ ☐

(Part 1 Q17-24) Choice 7 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 1 in 10 people experience fewer seizures	 3 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 1 in 100 experience depression	 8 in 100 people experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 9 in 100 pregnant women experience foetal harm	 2 in 100 pregnant women experience foetal harm
Which medication would you prefer to take?	☐	☐

(Part 1 Q17-24) Choice 8 of 8: Which medication would you prefer? Tick A or B

	MEDICATION A	MEDICATION B
Seizures Stop *One year after starting this medication*	 3 in 10 people seizures stop	 5 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	 3 in 10 people experience fewer seizures	 1 in 10 people experience fewer seizures
Depression *This low mood frequently affect activities of daily life*	 8 in 100 people experience depression	 1 in 100 experience depression
Memory Problems *These problems frequently affect activities of daily life*	 1 in 100 people experience memory problems	 7 in 100 people experience memory problems
Harm to foetus if you get pregnant whilst taking this medication *Causing problems from birth – such as spina-bifida or low IQ*	 9 in 100 pregnant women experience foetal harm	 2 in 100 pregnant women experience foetal harm
Which medication would you prefer to take?	☐	☐

Q25. Have you ever stopped or changed your anti-epileptic medication because of concerns about pregnancy?

☐ Yes

☐ No

Now go to Part 2 on Page 22

PART 2: You and your medication

1. What type or types of seizure do you have?

   ☐ Seizures where I am aware of what is happening (such as focal seizures)

   ☐ Seizures where I am confused or only partially aware (such as complex focal seizures)

   ☐ Seizures where I briefly lose consciousness (such as absences, tonic, atonic seizures)

   ☐ Seizures where I lose consciousness and jerk or convulse (such as tonic clonic seizures)

2. How long since your last seizure? (Please tick one option)

   ☐ Less than a week

   ☐ Less than a month

   ☐ Less than 6 months

   ☐ Less than a year

   ☐ I have had no seizures for over a year (I don't have seizures any more)

3. Compared to one year ago are your seizures:-

   ☐ More often

   ☐ Less often

   ☐ About the same

4. Over the **past three months**, have you taken any antiepileptic medication to help control your seizures?

   ☐ Yes → go to Q4.1

   ☐ No → go to Q5

   4.1. Has there been any change in the type or amount of your antiepileptic medication in the **past three months? (please tick all that apply)**

   ☐ No, no change in medication →go to Q5

   ☐ Yes, medication dose increased/decreased →go to Q4.2

   ☐ Yes, changed from one type of medication to another → go to Q4.2

   ☐ Yes, started taking an additional medication → go to Q4.2

   ☐ Yes, changed to fewer types of medication →go to Q4.2

   ☐ Yes, stopped medication altogether → go to Q4.2

4.2. Did you change or stop because: **(please tick all that apply)**

☐ The medication you were on did not control your seizures well enough

☐ The medication caused unpleasant side-effects

☐ You were no longer having seizures

☐ Some other reason

5. Do you ever forget to take your anti-epileptic medication?
   ☐ Yes

   ☐ No

6. Do you ever have problems remembering to take your anti-epileptic medication?
   ☐ Yes

   ☐ No

7. When you feel better, do you sometimes stop taking your anti-epileptic medication do you stop taking it?
   ☐ Yes

   ☐ No

8. Sometimes, if you feel worse when you take your anti-epileptic medication, do you stop taking it?
   ☐ Yes

   ☐ No

9. Have you ever had to change or stop your anti-epileptic medication due to:-
   ☐ Feelings of aggression (verbal or physical)

   ☐ Depression

   ☐ Memory problems

10. Have you ever taken a medication called carbamazepine to treat your epilepsy? (*also known as carbamazepine modified release, Tegretol, Carbagen SR, Tegretol Prolonged Release*)

    ☐ Yes →go to Q11

    ☐ No →go to Part 3

11. Have you ever had one of the following side-effects with carbamazepine? (tick all that apply)

☐ Yes – Skin rash - Itchy red rash that may have been on your upper body

☐ Yes - Very severe skin reaction - hot, painful patches on the skin, which may have blistered, and required treatment in hospital

☐ No

Now go to Part 3

<<Part 3 not included in this thesis>>

Now go to Part 4

Part 4: Background Information

1. Who do you live with at home? (please tick all that apply)
   - ☐ With your husband/wife, partner, or family
   - ☐ With your children
   - ☐ With your parents
   - ☐ With a brother or sister
   - ☐ With some other person
   - ☐ No one - I live alone

2. Which of the following best describes your current work status?
   - ☐ Employee in full-time job (30 hours or more per week)
   - ☐ Employee in part-time job (less than 30 hours per week)
   - ☐ Self-employed - full or part time
   - ☐ Government-supported training
   - ☐ Unemployed and available for work
   - ☐ Wholly retired from work
   - ☐ Full-time education at school, college or university
   - ☐ Looking after home/family
   - ☐ Permanently sick/disabled
   - ☐ Doing something else

3. Choose one option that best describes your ethnic group
   - ☐ White →go to part 5
   - ☐ Mixed / Multiple ethnic groups →go to Q3.1
   - ☐ Asian / Asian British →Q3.3
   - ☐ Black / African / Caribbean / Black British →go to part 5
   - ☐ Other ethnic group →go to part 5

3.1. Choose one option that best describes your ethnic background
   - ☐ White and Black Caribbean →go to part 5
   - ☐ White and Black African →go to part 5
   - ☐ White and Asian →Q3.2
   - ☐ Any other Mixed / Multiple ethnic background→go to part 5How would you describe your <u>parents</u> ethnic backgrounds (tick all that apply)
   - ☐ White
   - ☐ Bangladeshi
   - ☐ Chinese
   - ☐ Indian
   - ☐ Japanese
   - ☐ Pakistani
   - ☐ Thai
   - ☐ Other Asian background

3.2. Choose one option that best describes your ethic background
   - ☐ Bangladeshi
   - ☐ Chinese
   - ☐ Indian
   - ☐ Japanese
   - ☐ Pakistani
   - ☐ Thai
   - ☐ Other Asian background

Now go to Part 5

PART 5: Time Preference

Imagine you have 20 seizures per year. You have to choose between two alternative treatment options X or Y. They vary in terms of when they start and how effective they are at reducing seizures. Everything else about them is the same.

You have to wait longer for treatment Y. You cannot have both treatments. In the years you are waiting for either treatment to start, you continue to have 20 seizures per year.

Q1. Which treatment would you prefer?

1. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 0** → go to Q2

2. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 1** → go to Q3

3. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 2** → go to Q4

4. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 3** → go to Q5

5. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 4** → go to Q6

6. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 5** → go to Q7

7. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 6** → go to Q8

8. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 7** → go to Q9

9. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
   ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 8** → go to Q10

10. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
    ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 9** → go to Q11

11. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
    ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 10** → go to Q12

12. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
    ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 11** → go to Q13

13. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
    ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 12** → go to Q14

14. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q15
    ☐ Treatment Y starts in **4 years** time and reduces your seizures from **20 to 13** → go to Q15

15. Now imagine Treatment Y starts in 7 years time. Which treatment would you prefer?

☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 0** → go to Q16

16. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 1** → go to Q17

17. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 2** → go to Q18

18. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 3** → go to Q19

19. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 4** → go to Q20

20. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 5** → go to Q21

21. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 6** → go to Q22

22. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 7** → go to Q23

23. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 8** → go to Q24

24. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 9** → go to Q25

25. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 10** → go to Q26

26. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 11** → go to Q27

27. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 12** → go to Q28

28. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 12** → go to Q29
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 13** → go to Q29

29. Now imagine Treatment X reduces your seizures from 20 to 8. Which treatment would you prefer?

☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 0 → go to Q30

30. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 1 → go to Q31

31. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 2 → go to Q32

32. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 3 → go to Q33

33. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 4 → go to Q34

34. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 5 → go to Q35

35. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 6 → go to Q36

36. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 7 → go to Q37

37. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 8 → go to Q38

38. ☐ Treatment X starts in 1 years time and reduces your seizures from 20 to 8 → go to Q39
☐ Treatment Y starts in 4 years time and reduces your seizures from 20 to 9 → go to Q39

39. Now imagine Treatment Y starts in 7 years time. Which treatment would you prefer?

☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from 20 to 0 → go to Q40

40. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 1** → go to Q41

41. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 2** → go toQ42

42. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 3** → go toQ43

43. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 4** → go to Q46

44. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 5** → go to Q44

45. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 6** → go to Q45

46. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 7** → go to Q46

47. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8** → END
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 8** → go toQ47

48. ☐ Treatment X starts in **1 years** time and reduces your seizures from **20 to 8**
☐ Treatment Y starts in **7 years** time and reduces your seizures from **20 to 9**

Thank-you

We would like to thank you for taking the time to complete this questionnaire.

For more information on this project, please contact Margaret Rawnsley at Epilepsy Action by calling 0113 210 8800 or e-mailing mrawnsley@epileps.org.uk

Appendix 6.5: Powell et al. (2015)

Powell, G., Holmes, E. A., Plumpton, C. O., Ring, A., Baker, G. A., Jacoby, A., ... & Hughes, D. A. (2015). Pharmacogenetic testing prior to carbamazepine treatment of epilepsy: patients' and physicians' preferences for testing and service delivery. *British journal of clinical pharmacology*,*80*(5), 1149-1159.

Appendix 6.6: Subgroup analysis of Epilepsy DCE

	n[1]	P value		n[1]	P value
Age > 45 years	90		Age >29 years	49	
Age ≤ 45 years	87	0.232	Age≤ 29 years	54	0.045
Sex male	82				
Sex female	95	0.015*			
Time since diagnosis >10 years	127		Time since diagnosis >10 years	62	
Time since diagnosis ≤10 years	49	0.130	Time since diagnosis ≤10 years	40	0.607
Self-reported adherence	32				
Self-reported nonadherence	37	0.044			
			Pregnancy concerns experience	31	
			Pregnancy concerns no experience	66	0.010*
* Statistically significant at p<0.010 (adjusted for multiple comparisons). [1]n≥30 per subgroup based on central limit theorem.					

Female and Male Patients' marginal rates of substitution between remission and adverse events

Adverse event	Chance of remission willing to forgo (%)		
	Female	Male	
Depression	-2.70 [-3.83 to -1.99]	-4.45 [-7.34 to -2.98]	For a 1% risk reduction in depression
Memory Problems	-2.54 [-3.60 to -1.71]	-4.90 [-7.95 to -3.25]	For a 1% risk reduction in memory problems
Aggression	-3.29 [-4.42 to -2.45]	-5.38 [-8.49 to -3.85]	For a 1% risk reduction in aggression

Confidence intervals overlap – differences are statistically non-significant.

Women (with potential to become pregnant) marginal rates of substitution between remission and adverse events by experience of pregnancy concerns

Adverse event	Chance of remission willing to forgo (%)		
	Female	Male	
Depression	-3.07 [-15.59 to -0.15]	-1.34 [-2.11 to -0.26]	For a 1% risk reduction in depression
Memory Problems	-5.36 [-22.98 to -2.05]	-2.72 [-3.37 to -2.01]	For a 1% risk reduction in memory problems
Foetal Abnormality	-10.48 [-49.02 to -3.51]	-3.77 [-4.69 to -3.00]	For a 1% risk reduction in foetal abnormality if you get pregnant

Confidence intervals overlap – differences are statistically non-significant.