Economic Evaluation of Alcohol Treatments

Linking drinking patterns, alcohol consequences and cost effectiveness of alcohol treatments

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Abstract

The negative individual and social impacts of alcohol consumption raise a considerable policy interest surrounding alcohol treatment. Economic evaluations help on the allocation of scarce health care resources, but these have been inadequately conducted in the alcohol field.

This thesis builds up a taxonomy of alcohol-related consequences that should be included in economic evaluations of alcohol treatment and uses this taxonomy to critically review the published evidence around the cost effectiveness of alcohol treatments. The review provides a set of recommendations and most of them are pursued throughout the thesis.

An economic model for the cost effectiveness of alcohol treatments is developed. The framework provides the means to conduct economic evaluation while bearing the complexity and challenges of decision making in the field of human behaviour. A link between drinking patterns, health consequences and alcohol treatment effectiveness and cost effectiveness is created. This is a probabilistic lifetime model that uses the cohort simulation approach. The model can be applied to any setting and this is exemplified for a UK-scenario. The methods and data for the generation of UK-specific model inputs are described and used in two model applications. A first application of the model extrapolates the results of a short term randomized controlled trial and provides the expected lifetime costs and outcomes of the treatments compared, by age and gender. A second application compares two alcohol treatments delivered in different countries and to populations very different at baseline. Both case-studies show the importance of time and that only a long-term analysis can capture both short-term alcohol consequences, such as injuries, and long-term consequences, such as most forms of alcohol-related chronic diseases.

Assumptions and implications of the methods and analyses are discussed and recommendations for future research are presented.

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Publications

I have made efforts to disseminate the research presented in this thesis. The following papers have been published and accepted for publication, respectively:

Barbosa C, Godfrey C, Parrott S (2010) Methodological Assessment of Economic Evaluations of Alcohol Treatment. What is missing? *Alcohol and Alcoholism* 45: 53-63.

Barbosa C, Taylor B, Godfrey C, Rehm J, Parrott S, Drummond C (in press) Modelling lifetime QALYs and health care costs from different drinking patterns over time: a modified Markov model. *International Journal of Methods in Psychiatric Research* (accepted for publication on 29/05/09).

Author's declaration

I declare that this thesis is the original work of the author and that none of the material contained in this thesis has previously been submitted for a degree in this, or any other, awarding institution. The research contained in this thesis has been undertaken under the supervision of the Research Advisory Group, as directed by the University of York.

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Chapter 1. Introduction

1.1 Background

Alcohol consumption contributes substantially to the global burden of disease (4% of total mortality and between 4% and 5% of disability adjusted life years) and is of the world's largest avoidable risk factors (Rehm et al., 2009). Europe has a high level of alcohol consumption and the resulting alcohol-related disabilities are the highest in the world (WHO, 2009). A recent analysis of the burden of disease in the European region in 2002 showed that alcohol consumption was causally related to 6.1% of all deaths, 12.3% of all Years of Life Lost (YLL) and 10.7% of all Disability Adjusted Life Years (DALYs) (Rehm et al., 2006c). It is estimated that 23 million Europeans (5% of men, 1% of women) are dependent on alcohol (WHO, 2004). In addition to being a drug of dependence, alcohol is a cause of some 60 different diseases and conditions with short and long term health consequences (Room et al., 2005). A one litre reduction of pure alcohol drunk per adult each year could decrease total mortality in men by 1% in southern and central Europe, and 3% in northern Europe (Anderson and Baumberg, 2006). Alcohol consumption increases the risk of social harms, ranging from social nuisances such as public disorder through to more serious consequences such as marital harm, child abuse, drink-driving accidents, loss of work productivity, serious pre-natal conditions, crime, violence and homicide (Babor et al., 2003).

The physical, psychological and social harms of excessive alcohol use represent an important public health problem and are associated with considerable social costs. These have been estimated for the European Union, United States and Canada to be around €270bn (2003 prices) (Anderson and Baumberg, 2006), USA$185bn (1998 prices) (WHO, 2004), and CAN$14.6bn (2002 prices) (Rehm et al., 2006a), respectively.

Alcohol treatment has the potential to reduce the incidence, progression, and costs of individual health and social complications. There is considerable evidence base on the effectiveness of different alcohol treatments based on short-term drinking and health outcomes (Raistrick et al., 2006; Miller WR and Wilbourne PL, 2002; Heather et al., 2006). Several studies have attempted to summarize this evidence in systematic reviews and/ or meta-analysis of the effectiveness of Brief Interventions (BI) (Kaner et al., 2007; McQueen et al., 2009) and of other psychosocial alcohol treatments, such as Motivational Interviewing (MI) (Burke et al., 2003; Lundahl and Burke, 2009). More intense alcohol approaches have also shown evidence of effect for reducing alcohol-related harm, such as behavioural training for problem drinkers (Walters, 2000) and pharmacological therapies (Mann et al., 2004; Srisurapanont and Jarusuraisin, 2005). However, there are limitations

in evidence synthesis due to the wide range of alcohol treatment outcomes and the lack of standardization when reporting treatment effects (French, 2000). The effects measured have generally related to short-term changes (French, 2000). In addition, evidence synthesis is challenged by the large range of alcohol treatments (Howard, 1993).

While there is evidence on the effectiveness of alcohol treatments there is far less evidence on the cost effectiveness of alcohol treatment (Anderson and Baumberg, 2006; Anderson et al., 2009; Babor et al., 2003; Slattery et al., 2003; Ludbrook, 2004; French, 2000; Godfrey, 1994) and of substance abuse treatment in general (Cartwright, 2000; Godfrey and Parrott, 2000). Decision makers have increased the use of cost effectiveness analysis to inform decisions as to which interventions should be reimbursed from collective funding (Taylor et al., 2004). Research suggests that funding for alcohol treatments has been lacking across many countries (Meara and Frank, 2005). Better quality and weight of evidence about the cost effectiveness as well as the effectiveness of alcohol interventions could be an important aid to those attempting to assess the allocation of scarce health care funds across and within conditions.

The discipline of health economics highlights that health care resources are limited and the health care system is subject to a budget constraint. Economic evaluation techniques provide a valuable framework to allocate resources to the most effective alcohol treatment alternatives. Full economic evaluations are evaluations where the costs and consequences of at least two alternatives are compared. Such evaluations can help decisions on which strategy represents better value for money (Gold *et al.*, 1996b; Drummond *et al.*, 2005c). While there has been a considerable expansion of the quality and quantity of health economic evaluations in many clinical areas, this has not occurred for alcohol treatment and indeed, as reviewed in this thesis, many existing studies lack methodological rigour. The overall aim of this thesis is to explore and develop economic evaluation techniques relevant to alcohol treatment.

1.2 What are economic evaluations?

Full economic evaluations can be classified as Cost Effectiveness Analysis (CEA), Cost Benefit Analysis (CBA) or Cost Utility Analysis (CUA). The three analytical approaches are distinguished based on the way health benefits associated with alternative interventions under comparison are measured and valued (Drummond et al., 2005b; Tsuchiya and Williams, 2001). In a CEA, costs are related to a single, common effect that may differ in magnitude between the alternative programmes, for example drinks consumed per day. However, natural units pose numerous problems related to standardization and comparability. This is because different studies may report different units and the same units can also have different interpretations. Furthermore, interventions may have several

health outcomes that are not all captured in a single natural unit of effect. Many studies use abstinence as the outcome of the analysis. However, do abstinence-based measures capture all the health effects of alcohol treatment? Would a reduction in alcohol consumption have no value? Previous reviews showed that most of the economic studies in the addiction field report natural effectiveness estimates as the outcome measure of treatment (French, 2000; Homer *et al.*, 2008; Popovici *et al.*, 2008). The problem is that to make decisions on the allocation of scarce resources between competing treatments outcomes should be comparable and a single outcome measure should be used. This single outcome measure can be obtained with the other two types of economic evaluation: CBA and CUA.

CBA requires the monetary valuation of health benefits and reports a net monetary gain (or loss) or a cost/benefit ratio. It overcomes the problem of different outcome measures or comparing programmes with multiple outcomes as everything is measured in monetary terms (Godfrey, 1994). Even though several evaluations of alcohol treatment have claimed to be a CBA (French, 2000), in fact few would be classified as such because they have not attempted to value health benefits in monetary terms presenting ratios of the costs of programmes to non-health outcomes (for example, future health care costs). The philosophical foundation of CBA lays in principles of welfare economics where the relevant source of values are individual consumers (Drummond et al., 2005c). Using techniques of Willingness to Pay (WTP) the CBA framework can quantify a wide range of effects. CBA is broader in scope and so it can inform resource allocation decisions both within and between sectors of the economy. However, this does not come without problems (Drummond and Stoddart, 1995).

A CUA uses measures that reflect the value individuals put on their health, called utilities. Quality Adjusted Life Years (QALYs) are a widely used measure of health benefits used in CUA that incorporates mortality and morbidity estimates in a single index. Generic measures of Health-Related Quality of Life (HRQoL), such as QALYs, are extremely useful for a decision maker because the outcome measure is comparable across conditions and interventions.

Cost per QALY estimates allow a comparison between different health care interventions that compete for the same pool of funding. However, generic instruments measure a subject's overall HRQoL and might not capture specific individual impacts of alcohol treatment.

While the type of study defines how the individual outcomes of treatment are considered, which other costs and consequences are included in an economic evaluation depend upon the perspective the analyst takes. Two main perspectives can be distinguished, the welfarist perspective and the decision maker perspective. In the welfarist approach individuals are considered to be the best judges of their own welfare (consumer *sovereignty*) (Drummond et al., 2005c) and this perspective

is more in line with a CBA. The decision maker or "extra-welfarist" perspective considers how best to allocate an exiting budget and is more in line with CEA and CUA. Whilst a welfarist perspective has the potential to be wider in terms of the costs and consequences included, the decision maker perspective tends to be much narrower.

1.3 Challenges to economic evaluations of alcohol treatment

The first section of this chapter emphasized the paucity of economic evaluations of alcohol treatment. Why is there a lack of economic evaluations of alcohol treatment? Why is their quality poor?

The apparent lack of development of methodology behind the economic evaluation of alcohol treatments might be related to particular features of research in the alcohol field. The variety of treatment approaches is related to several factors such as, focus on different types of drinkers (less or more severe), delivery in different settings (e.g., hospital, primary care, community, prison), delivery by different types of health personnel (e.g., nurses, family doctors, psychiatrists, psychologists), different treatment intensities (number of contacts, treatment duration, etc.), and different definitions (e.g., what is considered a brief intervention in one study is an extended intervention in another (Drummond et al., 2009)). In addition, alcohol treatment is usually accompanied by other types of health interventions (e.g., psychosocial treatment in addition to a pharmacological treatment) and ancillary services (housing, childcare, etc.).

From an economic perspective many existing studies are not full economic evaluations. Partial economic evaluations are of limited help to decision makers because these do not identify the interventions where investment produces the greatest increase in benefit at least cost (Maynard and Godfrey, 1994). Indeed, many economic studies in the alcohol field are cost-of-illness studies that are concerned with the social costs of alcohol consumption. Cost-offset studies, examining the effect of a specific intervention, are limited to whether the costs of the intervention are offset by health care savings (Holder, 1987; Holder et al., 2000; Reutzel et al., 1987; Holder and Blose, 1992). An intriguing feature of many of these studies is that the individual benefits of treatment are disregarded. The impact of alcohol treatment on quantity and quality of life of the individual drinker is not valued and only the impact on the health care sector and/ or other sectors of economy is valued, therefore assuming that health benefits to patients have a zero value to society.

This is consistent with the *rational addiction model* (Becker and Murphy, 1988), which assumes individuals have taken the potential future health harms into account in their consumption decisions. Such a model, if this assumption about behaviour is valid, would also be in line with the welfarist perspective explained above. However, alcohol drinkers, particularly dependent drinkers, might not

be able to make the best decisions about their own welfare and need help through treatment. In this case, the benefits of alcohol treatment upon the individual drinker should be taken into account, which is the case in other health treatment and economic evaluations where the prime focus is individual outcomes. This assumption about individual behaviour is consistent with the "extra-welfarist" perspective where the objective is to maximize health gains subject to a budget constraint.

The health gains from alcohol treatment encompass physical and psychological individual outcomes which have been taken into account in different ways in previous studies. There is no agreement on a common measure of effect of treatment. For example, studies report different measures of alcohol consumption, such as abstinence and grams per day, or the scores of different questionnaires specific to alcohol problems. This poses a clear problem of comparability between the effects of different treatments and is one of the main challenges in economic evaluations of alcohol treatment. There is also no apparent consensus about the terminology used for definitions in the field. For example, the international literature uses different definitions for "binge drinking" and for "brief interventions". The lack of consistency and standardization in methods in studies of substance abuse interventions has also been described in French (2000) and Popovici et al. (2008).

Alcohol treatments are associated with a wide range of consequences outside the health sector and capturing these in the evaluation of treatment is not easy and has been poorly done in previous studies (French, 2000; Godfrey, 1994). Homer et al. (2008) and French (2000) have noted the importance of taking into account the social impact of alcohol through a broad societal perspective in economic studies. The consequences that fall on society are various, for example criminal activity, road traffic accidents, workplace losses, health care use, and so on. With such a wide range of alcohol-related consequences there is a danger that studies overlap categories of consequences and end up double counting. For example, double counting occurs if health care costs related with a criminal act are taken into account both under criminal activity costs and health care costs.

In a review of the economic benefits of addiction interventions McCollister and French (2003) mentioned that despite the relatively small contribution of changes in health services utilization, in comparison with reduced criminal activity, this outcome domain was the most used in studies that evaluated the social impact of treatment. The authors also pointed out the importance of including criminal activity in economic evaluations as it represented the greatest economic benefit of addiction interventions.

The quality of the research conducted in the field is also compromised by the paucity of economic data collected together with clinical outcomes in studies of high quality, such as Randomized

Controlled Trials (RCT). For this reason costs have been collected retrospectively from various sources. Furthermore, effectiveness estimates of alcohol treatment are based on studies with a short time horizon. This raises another feature in the field which is the temporal relationship between drinking and effects of consumption, particularly an unsafe consumption. Alcohol-related consequences happen in different time periods. While some of the consequences are acute, for example, most forms of injury, other consequences are chronic since most of alcohol-related diseases are the effect of long-term consumption. Alcohol consequences may also be difficult to measure in a prospective study due to an insufficient follow-up time. The extent of these consequences is determined not solely by the amount of alcohol consumed but also by its consumption pattern, i.e. the frequency and setting of drinking over time (Rehm et al., 2009). French (2000), Homer et al. (2008) and Popovici et al. (2008) recognized that alcohol treatment has long-term health and social benefits and mentioned the need for long-term data and modelling techniques.

1.4 Objectives

The discussion above invites a series of objectives for the remainder of this thesis. Economic evaluations of alcohol treatments need to follow more rigorous principles in order to guide policy decisions with confidence and help inform decisions with respect to the allocation of scarce resources. The current literature, reviewed in Chapter 3, contains many inconsistencies in the methods used for the identification, measurement and valuation of costs and consequences relevant to alcohol treatment.

The general objectives of this thesis are:

1) To discuss issues and provide guidance which could increase the rigour employed in economic evaluations of alcohol treatment
2) To explore methods to ensure more consistency in future studies in order to build up the economic evidence base
3) To explore both short and long term drinking outcomes in economic evaluations of alcohol treatment

1.5 Structure of the thesis

The research for this thesis is pursued in three main areas. The first part explores criteria to take forward economic evaluations and looks at the current state of research according to those criteria. The review shows that current research has focused on abstinence-based measures and has

disregarded the long-term effects of alcohol treatments. The second part of the thesis develops an economic evaluation model that studies health consequences, not confined to abstinence, over a long-term horizon. The third part applies the model in one country setting and tests it with two empirical examples. The breakdown of each chapter is as follows.

Chapter 2 explores all alcohol-related consequences that could be identified in an economic analysis of alcohol treatments. A taxonomy of the alcohol-related societal and individual-level consequences is developed. This taxonomy is designed to promote consistency and uniformity in economic evaluations of alcohol treatment and provides a quality assurance guide to previous studies by helping on the clarification of the alcohol-related consequences that have been included and omitted. The taxonomy developed in this chapter is the foundation for the extraction of the methodology in Chapter 3.

In Chapter 3 the existing literature on economic evaluations of alcohol treatment is identified. The methods used for the identification, measurement and valuation of society-level outcomes, individual-level outcomes and input costs are reviewed and appraised. This literature is used to provide a set of recommendations on the conduct of cost effectiveness analyses, most of these recommendations are followed in the remaining of the thesis.

Chapter 4 uses the evidence of Chapters 2 and 3 to inform the design of a decision analytical model that simulates the drinking patterns of a cohort over lifetime. Determining the cost effectiveness and predicting the outcomes of different alcohol treatments requires modelling of the long term consequences of changing drinking patterns. The model of drinking behaviour establishes a link between drinking patterns, health consequences and alcohol treatment effectiveness and cost effectiveness. This is an important contribution to the techniques usually applied where only short term costs and outcomes are analysed.

Chapter 5 explores the generation of country-specific model inputs, with an example of the application of the methods to the UK. These are the inputs required to populate the model that are specific to the setting where the economic evaluation is drawn but independent of the alcohol treatments evaluated. Therefore, the values generated in this chapter can be used for a range of alcohol treatments assessed in the UK.

Chapters 6 and 7 consist of two applications of the Markov model of drinking behaviour developed in Chapter 4. Both case-studies are presented for a UK setting and use the country-specific model inputs calculated in Chapter 5.

Chapter 6 applies the Markov model to the UKATT trial (UKATT Research Team, 2005b, a). The UKATT trial consisted of a cost effectiveness analysis alongside a pragmatic multicentre

randomized trial aimed at comparing the cost effectiveness of Social Behaviour and Network Therapy (SBNT), a new treatment for alcohol problems, with that of the proved Motivational Enhancement Therapy (MET), under real world conditions. The short term trial showed no strong evidence about the effectiveness and cost effectiveness of the two treatments. The Markov model of drinking behaviour assesses the incremental costs, survival and QALYs for MET vs. SBNT over the long term.

Chapter 7 presents a cost effectiveness analysis of a new pharmacological alcohol treatment compared to the current standard of care for the management of problematic drinkers using the model developed in Chapter 4. This second case-study presents important distinguishing features from the first one. Along with the model application and the generation of cost effectiveness results, some analyses are conducted before carrying out the economic evaluation. These analyses involve matching patients' baseline characteristics and allow the comparison of treatment effects taken from two independent RCTs conducted in different countries, with different follow-up periods and with patients significantly different in terms of baseline characteristics.

Both case-studies show the importance of assessing the long-term consequences when examining the cost effectiveness of alcohol treatments. There is a considerable change in the cost effectiveness results as the short-term analysis progresses to a long-term horizon, which provides evidence for the cost effectiveness of alcohol treatments and the need to measure costs and outcomes over a lifetime horizon.

The final chapter, Chapter 8, presents an overview and discussion of the previous chapters. The principal achievements with each of the chapters are summarized and issues arising from this thesis are formed into an agenda for future research.

Chapter 2. Taxonomy of societal and individual alcohol consequences in the Economic Evaluation of Alcohol Treatments

2.1 Rationale for a taxonomy of alcohol consequences

There is considerable methodological heterogeneity in economic evaluations of alcohol treatment. The lack of harmonization in methods and terminology, the variety of alcohol treatment approaches and the complexity and multiplicity of treatment outcomes may have contributed to the slow development of economic analyses of alcohol treatment. A major issue is the identification of alcohol treatment consequences. This task is complex because of the multiple consequences that can be identified and the temporal lag between receiving alcohol treatment and observing changes in alcohol-related consequences. In addition, measuring and valuing consequences such as the impact that alcohol drinking has on friends, victims and families' utility is a challenging endeavour. There is no general agreement in which consequences should be identified, measured and valued in economic evaluations of alcohol treatment (Babor et al., 2003; Ensor and Godfrey, 1993; Lehto, 1997). A recent review of studies that evaluated the economic benefits of interventions noted that several outcome domains have been excluded from previous studies and called for more rigorous methods for performing economic evaluations of addiction interventions (McCollister and French, 2003).

This chapter identifies the consequences of alcohol consumption that should be accounted for in an economic evaluation of psychosocial or pharmacological alcohol treatments and how these consequences can be measured and valued. Economic evaluations also identify the resources used or inputs of the programme evaluated. This does not pose an additional challenge when compared to other health interventions and is not explored further in this chapter. The main objective is to stratify all alcohol-related social and individual consequences into domains and categories. This stratification is built throughout the chapter resulting in a taxonomy of alcohol-consequences. Identification, measurement and valuation methods are presented as these help with the stratification and provide information for the following chapters. The taxonomy built throughout this chapter will be used in Chapter 3 as a framework for the extraction of the methodology that has been used in economic evaluations of alcohol treatment. In addition, the development of this taxonomy will inform the structure of an economic framework for the model developed in Chapter 4.

In economic terms, social consequences are the sum of private and external consequences that can represent a cost or a benefit. Private alcohol consequences are the consequences accruing to the

individuals engaged in the drinking activity while external consequences are consequences of an action by drinker(s) that fall on others. Within alcohol-related consequences this thesis defines *society-level consequences* as the consequences that arise from individuals' drinking behaviour which affect society, including alcohol-related victims and drinkers' families. *Individual-level consequences* are defined as the consequences felt by the drinkers themselves. In this chapter, it is argued that the consequences taken into account in economic evaluations of alcohol treatment depend on two interrelated factors: 1) the theory of consumer behaviour and, 2) the perspective under which these are evaluated.

The taxonomy is designed to be used in economic evaluations of alcohol treatment and therefore the consequences identified are those that represent a cost at the societal and individual-level and that can be reduced by alcohol treatment. By focusing on alcohol treatments this thesis disregards social or individual benefits related with low risk alcohol consumption. Several social benefits of alcohol consumption have been described such as social enhancement and pleasure (Peele and Brodsky, 2000), reduction of the burden in the health care system due to a reduction in Coronary Heart Disease (CHD) and reduction in absence with productivity gains to society due to better physical health and psychosocial adjustment for the individual (Vasse et al., 1998). Individual benefits of moderate alcohol consumption include higher wages (Barrett, 2002; French and Zarkin, 1995; Slater et al., 1999), and individual health benefits due to a reduction in stress levels and lower incidence of CHD (Boffetta and Garfinkel, 1990; Doll et al., 1994; English et al., 1995; Peele and Brodsky, 2000). These benefits are related to a level of consumption that would not require treatment. Alcohol misusers that accept to be treated recognize that their alcohol-related problems supersede the potential benefits of alcohol consumption. In contrast, other policies directed at all drinkers whether having problems or not and involving some coercion, for example, taxation, could be thought of having different individual impacts. For example, the evaluation of population-level interventions, such as prevention and legislation, would need to take into account the impact on the benefits of low risk alcohol consumption.

The social costs of alcohol have been widely described and many studies provide a framework for the identification, measurement and valuation of these costs (Leontaridi, 2003). However, the framework provided has been embedded in cost-of-illness or public finance studies and is not directly extrapolated to cost effectiveness analyses of two or more interventions. Cost-of-illness studies can demonstrate the scale of health problems, but they are limited in determining how resources are to be allocated because they do not measure the individual benefits or compare interventions in terms of their costs and outcomes (Byford et al., 2000; Drummond, 1992; Currie et al., 2000). The taxonomy of alcohol consequences for cost effectiveness analysis of alcohol

treatment combines: 1) the theoretical framework described for social cost studies, as these studies can provide a framework for the cost estimation in economic evaluations (Luce et al., 1996; Rice, 2000), with 2) the framework used in economic evaluations. The stratification developed here prevents double counting as categories that could erroneously be allocated to more than one domain are allocated to a single domain, based on identification, measurement and valuation methods.

The taxonomy of alcohol consequences is designed in two separate steps. In a first step, all alcohol-related consequences are divided between society-level and individual-level and in a second step, within these two groups, consequences are stratified into domains. For each domain, the categories that should be identified in an economic evaluation of alcohol treatment are gradually accumulated. Firstly, in section 2.2 the society-level consequences of alcohol treatment are explored. Secondly, in section 2.3 the individual-level consequences of a treatment-seeking population are depicted. Section 2.4 presents an overview of the factors that determine the extent of consequences that are included in the economic evaluation of alcohol treatments. Finally, section 2.5 presents the taxonomy of alcohol-related consequences in full.

2.2 Society-level consequences

As previously noted, this document classifies society-level consequences as the consequences that arise from individuals' drinking behaviour that affect society, including alcohol-related victims and drinkers' families. It could be questioned whether the consequences imposed by the drinkers upon other members of their own family constitute private consequences at an individual or at a societal level. On the one hand, the drinker might take into account the effects on other family members in deciding his or her extent of substance abuse and then these consequences would be treated under the individual-drinker level consequences domain. On the other hand, the consequences of alcohol misuse upon other people who have had no part in the initial decision should be treated at a societal level. The chosen approach in this thesis is to include consequences to the drinker's family in this section.

Alcohol drinking above safe levels imposes a cost to different spheres of society. Society-level consequences are stratified into the following seven domains, according to where and to whom in society they fall: 1) criminal activity, 2) road traffic accidents, 3) workplace and productivity losses, 4) health-related quality of life, 5) general health care, 6) other specific alcohol treatment and, 7) social services and non-statutory care. Providing treatment for alcohol problems has the potential to reduce these social costs. Therefore, when evaluating the cost effectiveness of alcohol treatments, ideally, all the aforementioned consequences should be analysed. These seven domains are explained in the seven subsections below and at the end of each subsection a summary table is

presented. The summary tables describing each society-level consequence domain are added up at the end to constitute a single table with the full taxonomy of alcohol consequences.

2.2.1 Criminal activity

This subsection outlines the main issues involved with identifying, measuring, and valuing alcohol-related crime consequences.

Identification- Acute alcohol intoxication contributes to crime. The time span between drinking and offences to the criminal justice is short and treatment interventions have the potential to reduce criminal activity in a not too distant period of time. Crime and disorder data in many countries are far from perfect and this contributes to the difficulties researchers may face in identifying and measuring these consequences. Crime data are largely derived from subjective judgements about alcohol's role in affecting behaviour, and it is difficult to be sure that the event would not have occurred, or would have less serious consequences, if the offender had not been drinking. Alcohol can be implicated as a causal factor in crime in two ways: high alcohol intake represents a risk factor in becoming a victim and alcohol is also a potential causal factor in committing a crime (WHO, 2000).

Ensor and Godfrey (1993) argued that while some crimes are drink-specific, such as underage drinking, drunk and incapable, and drink driving, others are linked to alcohol misuse such as property damage, arson, aggression, acquisitive crime and sexual offences. The unequivocal influence of alcohol on offending behaviour can only be determined in those cases for which alcohol consumption is inherent to the offence definition (e.g., drink and disorderly) or, further, if an offender is tested against some objective legal standard (e.g., drink driving) (Tierney and Hobbs, 2003).

There is a great deal of research examining the link between alcohol consumption and various types of crime and disorder. In a Home Office research study (Bennett, 2000) it was shown that a significant proportion of people arrested by the police for a range of offences had been drinking prior to their arrest. Another study found that violent offenders were more likely to be heavy drinkers than demographically matched samples of the population in general (Welte and Miller, 1987). In addition, a high proportion of violent crimes and public order offences are committed by people who have been drinking (Graham and West, 2001).

Measurement- Establishing the link between alcohol consumption and crime activities is not easy and measuring the problems that alcohol drinking rises is not any easier than identifying these problems. There is a significant and positive association between alcohol consumption and rates of violence (Home Office, 2002). However, a causality relation is not as well defined because alcohol

misuse is, to some degree, one of the causes of criminal activity but not the only one. Even when drinking immediately precedes a criminal act, the attribution of alcohol as a casual factor in the crime is not at all clear.

The measurement of the extent of crime usually relies on crime reports or other sources of crime statistics (crime surveys, data from police departments, Closed-Circuit Television (CCTV), incident log databases, etc.), depending on the country and current practices. The allocation of offences to alcohol can be done through a direct approach or an indirect approach (WHO, 2000). For the specific case of alcohol-related crime, the direct approach is used when a connection between alcohol consumption and an offence, offender or victim is established. This approach, due to the subjective judgements behind it, is subject to many uncertainties (WHO, 2000). Using alcohol test data may overestimate the cost findings as those found to have drunk prior to committing an offence may not necessarily commit that offence because of alcohol misuse. Another possibility is using police officers records of whether alcohol was a factor in the arrest which can sometimes be used as an indicator of alcohol-related crime. One can argue that this is a rather "crude" and subjective measure and with lack of reliability as not all offences end up in arrestment. Notifiable offences recorded by the police might not be the best source as they are greatly influenced by the level of enforcement. Additionally, police can only record those crimes that come to their attention and hence the number of recorded offences can be an underestimate of the actual number of offences committed (WHO, 2000). For this reason victim and population surveys are also important to find better estimates. The indirect approach involves making correlations between spatial, temporal and contextual indicators of alcohol consumption and crime and disorder (Tierney and Hobbs, 2003).

According to data availability, two processes for measuring the effect of alcohol treatment on criminal activity within an economic evaluation are suggested: 1) use of patient-level criminal data to compare data before and after the delivery of treatment or, 2) use of national estimates of overall criminal activity and apply Alcohol Attribution Factors (AAFs) for levels of consumption before and after treatment. The former is applicable to economic evaluations conducted alongside a clinical trial with questionnaires addressing crime issues. The latter involves the use of AAFs for the role of alcohol in criminal behaviour which have been presented in some studies, for different levels of alcohol consumption (English et al., 1995; Babor et al., 2003). AAFs are defined as the proportion of all outcomes from a cause, which can be attributable to alcohol, after controlling for the confounding effects of demographic variables and other risk factors (Gordis, 2009). For example, Rehm et al. (2003c) presented global AAFs for injury mortality and morbidity with a specific World Health Organization (WHO) code for violence (W 158). One of the problems with the use of national estimates is that crime data is country-specific and the methods used to record it

vary both between and within countries. Applying attribution factors to estimates of overall criminal activity is not an easy task as the attribution factors are generated for crimes which do not always have the same exact specification as the estimates of overall criminal activity to which they are applied.

Valuation- Estimation of the social costs of crime is an arduous task as costs of a different nature have to be accounted for. In a methodological study, Rajkumar and French (1997) demonstrated a method to estimate all the benefits of avoided crime. The societal costs from criminal acts have also been estimated by other authors (Cohen, 2000; Miller et al., 1996). These valuations include victim costs (medical care, productivity loss, damaged property, quality of life) and also the *opportunity costs* of engaging in a criminal career, i.e. the costs of following a criminal career instead of the next best alternative path.

In an extensive American report (Miller et al., 1996) criminal acts were taken from patient reports, police reports, department of justice reports, department of transportation records or questionnaires delivered to the victims. The Miller et al. (1996) report also presented monetary conversions (monetary value per unit change in outcome) for identified offences.

In order to facilitate the valuation of criminal activity actions for the taxonomy, the types of consequences are divided into those actions taken in anticipation of crime, actions taken as a consequence of crime and actions taken as a response to crime (Leontaridi, 2003). The valuation process is specific to each one of these consequences as presented below.

2.2.1.1 Actions taken in anticipation of crime

This category includes measures that reduce the probability or risk of potential victims becoming one. This involves the ***acquisition of security products*** such as alarms, security lights, security for vehicles, special doors and gates, contract with a security agency, and ***precautionary behaviour*** such as taxis instead of public transport, staying at home after dark and avoidance of dangerous areas (Leontaridi, 2003). Individuals also purchase *insurance policies* to avoid the financial uncertainty from the risk of becoming victims of crime. Insurance consists of a financial transfer from potential victims with insurance to actual victims with insurance and does not alter the resources available to the society. However, resources used in ***insurance administration*** represent an opportunity cost to the economy as they could be used to provide other activities and should be accounted for. For almost all of these actions a monetary valuation can be obtained due to the existence of market prices. Brand and Price (2000) estimated the costs of acquisition of security products and the costs of insurance administration associated with the anticipation of crime. However, the authors did not estimate costs that result from precautionary behaviour.

Actions of precautionary behaviour, might lead to a reduction in the consumption of goods and services by the general population which causes a loss of revenue to local businesses. This component of precautionary behaviour can be valued with the market price of commodities.

Actions taken in anticipation of crime are more broadly the result of *fear of crime*, which has a psychological component that is not captured on the action *per se*. The *fear of crime* will have an impact on the quality of life of the general population and this health component is better valued under the health-related quality of life losses domain. For example, a person that lives in a dangerous neighbourhood might not go out at night for leisure, which eventually translates into a lower quality of life than that of a person that lives in secure area. Dolan and Peasgood (2007) developed a methodology to provide estimates of the costs arising from the anticipation of possible victimisation. They called these costs the costs of *fear of crime*. The authors focused on measuring and valuing health losses arising from *fear of crime* and recognized crime as an important factor affecting quality of life. Therefore, according to measurement and valuation methods, the health component of *fear of crime* is categorized under the health-related quality of life domain below.

The costs discussed are arguably a small subset of the total costs of fear of crime, since they do not include the non-health costs of changes in behaviour and changes in views about society (Dolan and Peasgood, 2007). These latter components have never been measured and are a matter for further research.

2.2.1.2 Actions taken as a consequence of crime

The consequences of crime are various and encompass different domains. Before going into the detail of this subsection, it should be noted that some of the consequences of crime are allocated to a different domain. This enables a more comprehensive stratification of the domains and avoids double counting.

Crime has consequences to other individuals (including drinker's family, households and businesses) and the economy in general. Crime victims may need *victim support*. The psychological and physical impacts of crime on victims and victim's families and friends involve recovery from injuries and shock directly affecting their quality of life. These costs can far outweigh any financial cost. This is further explored under the domain "health-related quality of life" below (subsection 2.2.4).

Other society-level consequences of crime include the *loss on productive output and absenteeism* of the victim due to injuries, or participation in the criminal justice process. This loss on productive output is related to the time lost by the victim and could have otherwise been spent as work or leisure. There is also a loss on productive output due to *victim's premature mortality* from

homicide. These consequences will be further explained in the appropriate domain "workplace and productivity losses" below (subsection 2.2.3).

Crime can also induce an increase in the demand of *health services* by the victims. This impact on health services is further explained in the domain "general health care utilization" below (subsection 2.2.5).

Crime victims may have their ***property damaged*** or ***stolen***. Stolen property represents an unwanted transfer of resources. The costs of stolen property can be shifted from victims to society by means of insurance coverage and government-sponsored reparation programmes. Damaged property involves an opportunity cost of using resources for repairs that could be used somewhere else. The costs involved in the administration process in order to compensate victims from stolen property or for the resources used in damaged items can be used as a monetary value to estimate these losses.

2.2.1.3 Actions taken in response to crime and tackling criminal activities

This category of consequences covers actions taken by the police, ***prosecution*** and ***defence services***, ***courts***[1], and ***prison and probation services***. A monetary value of these actions can be retrieved from government sources, for example the publications from the Home Office (1998) and from HM Treasury (2000) in the UK.

A summary table for the domain of criminal activity depicting all the categories identified above and correspondent variables is presented below (Table 1). When evaluating alcohol treatments, ideally all the presented variables should be identified, measured and valued. It should be stressed again that, in order to avoid double counting, some categories related to criminal activity are allocated to another domain, according to their valuation method. For example, even though victims suffer an impact in their health-related quality of life due to criminal activity, such consequences are accounted for in the domain of "health-related quality of life".

[1] In England, criminal offences are split into three categories: i) triable only on indictment- these are the most serious and always tried in Crown Court; ii) triable-either-way- these offences may be tried either at the Crown or magistrates' court; iii) summary- these offences are triable only at a magistrates' court.

Table 1- Society-level consequences: criminal activity

Building a taxonomy of Alcohol Consequences		
Society Level Consequences		
Criminal activity	Anticipation of crime	Acquisition of security products Precautionary behaviour Insurance administration
	Consequence of crime	Damaged/ stolen property
	Response to crime	Prosecution service Courts Defence Prison and probation services

2.2.2 Road traffic accidents

Identification- Driving over the legal limit of alcohol is considered an offence and is strongly associated with road accidents and road deaths to motor vehicle occupants and to pedestrians. These accidents result in property damage, victims' loss of quality of life, medical care costs, police enforcement, and lost work. The time span between acute alcohol ingestion and drink-driving accidents is short and treatment interventions have the potential to reduce alcohol-related road traffic accidents in a not too distant period of time. A previous review demonstrated the existence of a causal relationship between alcohol and road fatalities and injuries (English et al., 1995). Rehm et al. (2003b) included traffic accidents in the unintentional injury category and presented global AAFs for injury mortality and morbidity due to motor vehicle accidents.

Most European Union countries have a maximum Blood Alcohol Concentration (BAC) allowed for drink-driving, which varies between 0.0 g/L and 0.8 g/L (Anderson and Baumberg, 2006). The current maximum BAC for a driver is 0.8 g/ L in the UK.

Measurement- Road crash data can be used to estimate the number of alcohol-related crashes. Road crash reports may be based on BAC, breathalyser, motor skills test, or just observation. The WHO International Guide for Measuring Alcohol Consumption and Harm (2000) presented a number of different measurement possibilities such as: 1) fatal crashes with positive BAC; 2) alcohol-related crashes based on police reports; 3) night-time crashes; 4) single-vehicle night-time crashes; 6) fatal crashes; 7) roadside surveys and; 8) arrests for driving under the influence. Alternatively, AAFs can be used together with global estimates of road accident data.

Valuation- Drink driving consequences have an impact on the criminal justice system, on lost output due to premature deaths or a serious causality and on the physical and psychological health of accident victims. In order to avoid double counting, the valuation of each one of these consequences is explained under the appropriate domain subsection. Under the criminal justice

system there are costs related to drink driving offences that fall on courts and on prison (see sub section 2.2.1.3 above). This offence also has an impact on the loss of victims productivity due to drink driving premature deaths or absenteeism (see subsection 2.2.3 below) and on the health system through the use of medical care and ambulances (see subsection 2.2.5 below). The health-related quality of life losses involved are the health and emotional impact on accident victims (see subsection 2.2.4 below).

The costs of road traffic accidents that should be identified in an economic evaluation of alcohol treatment are summarized in Table 2 below and these are twofold: the legal costs of dealing with drink driving offences within the criminal justice system and the costs related to property damage from drink and driving accidents. The same argument with respect to the avoidance of double counting, as presented in the above section, prevails. Therefore, for example, the impact these accidents have on victims' productivity is accounted for in the domain of "workplace and productivity losses".

Table 2- Society-level consequences: road traffic accidents

Building a taxonomy for the costs of Alcohol Consequences	
	Society Level Consequences
Road traffic accidents	Legal costs of drink driving offences Property damage from drink and driving accidents

2.2.3 Workplace and productivity losses

Identification- Productivity losses are related to the impact that alcohol misuse has on the workplace and the wider economy. Studies of the relationship between alcohol use or misuse and labour market outcomes suffer from the uncertainty about the causal path between them (Leontaridi, 2003). Alcohol misuse may affect productivity, wages and labour opportunities but problems at work may, in turn, induce heavier drinking.

Measurement and valuation- The methods used for the measurement and valuation of this domain are controversial and have been extensively discussed in the literature, but no consensus has been reached (Drummond et al., 2005c; Gold et al., 1996b; Drummond and McGuire, 2001). Three different mutually exclusive approaches have been suggested for measuring and valuing workplace and productivity losses: the traditional human capital method (Rice and Cooper, 1967), the friction cost method (Koopmanschap et al., 1995) and the incorporation of these costs in quality of life measurements (Gold et al., 1996a). The first is widely used and wages are assumed to be equivalent to the value of an individual's productive worth and used as a monetary conversion. This method usually does not take into account those who are not in the workforce, such as homemakers, retired, students and children. Despite this, a value can be placed on some activities by estimating the cost

of hiring a market replacement for each individual function. In the second, friction cost method, only the time to replace and train a replacement worker is costed and loss of earnings are not valued. This second approach assumes that in an efficiently functioning labour market, there would be no reason for overall levels of employment to change and the social costs of productivity losses would only be the sunk costs of any training required. In flexible, efficiently functioning labour markets there would be a wage at which all those who would like a job would be able to get it. So, one could expect those job places freed by the problematic drinker to be occupied by someone else. However, in reality a net decrease or increase in the number of jobs in the economy cannot be determined a priori. It depends on factors such as labour intensity (concentration of labour versus capital) and the flexibility of alternative use of resources such as employee retraining (Drummond and McGuire, 2001). The third approach is the most controversial in that it is assumed that in valuing their utility loss on normal activities individuals implicitly include their earnings and productivity losses. Overall, there is no economic agreement regarding the methods for inclusion of productivity costs in an economic evaluation. There is some concern relating to double counting when productivity costs are valued in monetary terms, which has to be controlled for when valuation of HRQoL is incorporated in the same analysis. Therefore, when estimating the value of health, individuals should ignore income effects (Drummond et al., 2005c) if one of the two first approaches described above is used for measuring and valuing productivity losses.

For a more clear description of the effects of alcohol misuse in productivity losses these are divided in the following three categories: 1) productivity losses due to morbidity; 2) productivity losses due to mortality; and 3) productivity losses due to criminal careers. There are many inconsistencies in the literature regarding the effect of alcohol in these losses and a review of the evidence is provided below.

2.2.3.1 Productivity losses due to morbidity

The evidence of the relationship between alcohol consumption and productivity losses due to morbidity is mixed. Productivity losses due to morbidity can be the result of absenteeism, reduced employee efficiency, reduced employment and workplace accidents (Leontaridi, 2003). The extent to which alcohol is related to each one of these variables is discussed in the following text.

- Absenteeism

There is some evidence that alcohol misuse encourages drinkers' short and long-term absenteeism (Gill, 1994). The relationship between alcohol misuse and individual drinkers' absenteeism is not clearly established yet. However, the risk of absence attributable to injury has been shown to be related to the amount of alcohol consumed (Head et al., 2002). For this case, there is no time gap

between alcohol drinking and consequences as injuries are usually the result of acute drinking. Several types of alcohol-related unintentional injuries can be identified and these are: falls, drowning, burns, poisonings, motor vehicle accidents (already mentioned in sub section 2.2.2), workplace accidents (covered below), and others. The reviews conducted by Rehm et al. (2003b; 2004) and English et al. (1995) calculated AAFs for these injuries morbidity (and also mortality). Absenteeism is also increased for victims of alcohol-related crime or victims of road accidents and family and close friends of the problem drinker.

Chronic drinking may also affect absenteeism. Many long term diseases are associated with alcohol misuse, some with an AAF of 100%, leading to sickness absence. Sickness absence is reflected in reduced productivity and diverted resources away from their efficient use.

The costs due to absenteeism can be calculated using the human capital method by measuring the number of working days lost due to alcohol misuse/ victimization (usually from the company or workplace reports) and valuing them using the average costs of an employee, after taking into account employer's costs (national insurance contributions, pension contributions, etc.). This method usually assumes that the rates of absenteeism are the same among full and part-time employees. Alternatively, the friction cost method could be used where only the costs during the replacement period are taken into account.

Sickness absence should not be confounded with the time lost due to health care use. This time lost is costed in an economic evaluation of alcohol treatment under individual-level consequences.

- Reduced employee efficiency

Reduced efficiency at the workplace may be the result of a hangover, of health problems associated with alcohol misuse or may be the direct effect of employees being under the influence of alcohol while at work. The productivity of co-workers and managers is affected as well as the morale in the workplace (Ames et al., 1997).

It is extremely difficult to measure the proportion of reduced efficiency due to alcohol misuse and the extent of its effect on society (Gill, 1994). A relationship between alcohol consumption and wage appears to exist but the magnitude of this relationship is not always reported in a consistent way. If a wage reduction is a result of problem alcohol-drinking behaviour of the individual worker, then this reduction would translate to how much society loses in terms of reduced efficiency, and therefore the measurement and valuation problems would be solved. However, this assumes a perfect economy where workers productivity would be assessed and wages regulated accordingly to workers' performance. It is extremely difficult to cost the impact alcohol consumption has on a

reduction in employee efficiency but this is not a reason for not attempting to do so in the economic evaluation of alcohol treatments.

- Reduced employment

There is strong evidence of a negative relationship between problematic alcohol consumption and employment. Mullahy and Sindelar (1996) found that problem drinking reduces employment and increases unemployment. The same results were observed in a more recent study (Terza, 2002). Lower employment probability was also found in a recent study conducted in Finland for an alcohol dependent population (Johansson et al., 2007). The authors of the Finnish study also showed that abstaining does not decrease employment probability and that the underperformance of abstainers in a labour market is due to the fact that some abstainers are ex-drinkers (Johansson et al., 2006). A study conducted in England, using data from the Health Survey England, showed that problem drinking is negatively associated with employment (MacDonald and Shields, 2004). In contrast, the study conducted by Feng et al. (2001) found a positive, albeit insignificant, association between problem drinking and employment.

One possible explanation for problem drinking reducing employment is that dependent workers may find it difficult to cope with demanding tasks. MacDonald and Shields (2004) argued that alcohol misuse may lower performance among heavy and dependent drinkers through a "discouraged worker effect" as it may lead to a lower chance of finding employment and hence to a greater chance of discouragement in the labour market.

Even though the relationship between alcohol drinking and reduced employment is somehow controversial, measuring this relationship and how alcohol treatment impacts it should be attempted in an economic evaluation. The measurement of reduced employment can be done by a cross-sectional or observational study where a probability of working can be retrieved for this specific population. Then the valuation can be done by using the average costs of an employee from the last job she or he had, after taking into account employer's costs (national insurance contributions, pension contributions, etc.).

- Productivity losses due to workplace accidents

Workplace accidents lead to loss of productivity due to absenteeism and also reduced efficiency. While there appears to be clear evidence concerning the relationship between alcohol use and injury in the general population, there are major gaps in knowledge on the relationship between alcohol use and workplace injury. Epidemiological studies in the workplace have not provided conclusive evidence that a strong causal link exists between alcohol use and workplace injuries/accidents

(MacDonald, 1997). There is more information about fatal injuries in the workplace than there is for non-fatal ones.

Cherpitel (1993) conducted a review of hospital Emergency Department (ED) studies and identified only one study that focused on workplace injuries. The identified case-control study showed that only 4% of work-related injuries were associated with alcohol use (Lings et al., 1984). Another study conducted at an ED also concluded that few work injuries (5%) were alcohol-related (Trent, 1991). In contrast, Orozco et al (2005) conducted a study at an ED and found a relatively high number of alcohol-related injuries at workplaces. It might be the case that alcohol-related work injuries are underrepresented due to the study design, where the focus is not specifically on injuries that occur in the workplace.

Most of the other studies are cross-sectional surveys and, in general, they indicate a weak association between alcohol use and non-fatal workplace injuries. Veazie and Smith (2000) found that alcohol dependent workers were not at a higher risk of injury. The same findings were reported in a study conducted by Spicer et al. (2003). In contrast, Dawson (1994) found that the odds of occupational injury increased with the frequency of heavy drinking. It might be that the inconsistency between findings is related to a failure in controlling adequately for occupational differences as some jobs have a much higher risk of accident than others (Holcom et al., 1993).

Despite the different arguments presented in the literature, when evaluating an alcohol treatment the potential for a reduction in workplace injuries should be accounted for. Work injury data can usually be obtained from medical reports. Unit costs can be used to value the health care costs (allocated to "general healthcare" subsection 2.2.5) and productivity losses due to workplace injury can be valued through the human capital approach.

2.2.3.2 Productivity losses due to mortality

The category of productivity loses due to mortality can be informed by two variables: premature death and workplace fatalities.

- Premature death

Alcohol misuse can result in deaths directly related to alcohol or where alcohol is an attribution factor. Productivity losses due to premature deaths are those of the alcohol drinkers and of the victims of alcohol-related offences and drink-driving accidents.

Premature deaths represent a loss of productive output in the economy and should be included in the economic evaluation of alcohol treatment. However, measuring the effect alcohol treatment has in reducing premature mortality is not straightforward due to the lag in time between alcohol drinking

and alcohol-related diseases mortality. This lag in time is not a problem for premature deaths from alcohol-related injury. If the economic evaluation of the specific alcohol treatments evaluated is not informed by a long follow-up study, then alcohol-related mortality from chronic diseases cannot be captured. In addition, a study with a small sample size does not capture all mortality from alcohol-related injuries. Those situations can be overcome by adopting a modelling approach. In a modelling approach, productivity losses due to premature mortality that are avoided by alcohol treatment can be estimated using population data of alcohol-related mortality together with the effect of treatment in alcohol behaviour. The number of alcohol-related deaths can be taken from country-specific mortality statistics. For the cases where alcohol misuse is an attribution factor, attribution factors should be used (Britton and McPherson, 2001).

Productivity losses due to premature deaths can be valued in terms of the discounted present value of the sum of employment earnings over the estimated life years, through the human capital approach (Mushkin, 1978). This approach undervalues life since it does not take a value of life over and above earnings lost (see sub section 2.2.4 below for "health-related quality of life consequences"). To avoid death or sickness, people would be willing to pay much more than simply their lost future earnings. A WTP approach would certainly produce higher estimates for productivity losses due to mortality. Just as the human capital approach, the WTP is a method broadly used to assign money values to health outcomes. This method involves asking respondents about the contingency of an actual market existing for a programme or health benefit and to reveal the maximum they would be willing to pay for such programme or benefit (Drummond et al., 2005c).

The need to value life has arisen in other public sectors such as transport and environment. Methods of WTP have their foundation in transport cost benefit analysis (Drummond et al., 2005c) For example, the money value of a statistical life, i.e. the value of life in uncertain conditions, has been calculated by Jones-Lee et al. (1985) in the context of road safety. In Great Britain, the Department of Transport uses the Value of Preventing a Fatality (VPF) for the estimation of the values of road causalities and accidents prevention. It uses the WTP approach for valuing human costs and also includes lost output, and medical and ambulance costs. The value of prevention of a fatality has been put between £750,000 to £1,250,000 in 1997 prices (Department of Transport, 2007). The Health and Safety Executive stated: "VPF is often understood to mean that a value is being placed on a life. This is not the case. It is simply another way of saying what people are prepared to pay to secure a certain averaged risk reduction" (Health and Safety Executive, 2001; p 65).

However, WTP methods do not value only productivity losses. The human capital approach is more suitable for this domain as the focus is on the productivity losses due to premature mortality.

- Workplace fatalities

Alcohol use can also contribute to work-related accidents that cause premature mortality. Some studies that examined the role of alcohol in fatal workplace injuries concluded that alcohol contributes to workplace fatalities, such as the Hollo et al. (1993) study and the Driscoll (2003) study. However, just as for workplace morbidity, there is some controversy on the contribution of alcohol to workplace mortality. Measurement and valuation principles follow the same arguments as in "premature death" above.

2.2.3.3 Productivity losses due to criminal careers

The productivity losses incurred due to criminal careers are based on the value of foregone production by persons that follow a criminal life, for example illegal production of alcohol. However, estimating the proportion of drinkers that actually follow a criminal career as a consequence of their consumption is not an easy exercise. Nevertheless, ideally, an attempt to cost this category should be made in an economic evaluation of alcohol treatment.

The categories that should be identified under the domain of workplace and productivity losses, when conducting an economic evaluation of alcohol treatments, are summarized in Table 3.

Table 3- Society-level consequences: workplace and productivity losses

Building a taxonomy for the costs of Alcohol Consequences		
Society Level Consequences		
Workplace and productivity losses	Due to morbidity	Absenteeism Reduced efficiency Reduced employment Workplace accidents
	Due to mortality	Premature death Workplace fatalities
	Due to criminal career	

2.2.4 Health-related quality of life

Identification- Alcohol misuse may cause losses in health-related quality of life[2] and utility at a societal level. HRQoL losses may impact different groups of society and are broken down into the following categories: 1) loss in HRQoL to family and friends due to death or illness of the alcohol misuser or of his/ her victims; 2) loss in HRQoL to the victims of crime or drink-driving accidents; 3) loss in HRQoL to the general population due to fear of crime.

These losses impose a cost to society, in the form of non-physical resources, i.e. they impose costs where the valuation process is different from other costs in terms of the methodology used. Past and also some current studies call these costs "intangible costs". Intangible costs are costs that when reduced do not release production or consumption resources for other uses making it extremely difficult to place a value upon them. So, when HRQoL is reduced or eliminated, it does not yield resources available for other uses, and vice versa. In contrast, tangible costs are the costs, which when reduced, yield resources which are then available to the community for consumption or investment purposes (Single et al., 2001). However, Drummond et al. (2005c) argued that these HRQoL consequences are not "costs" (that is, resources denied to others) and are not strictly intangible as they are measured and valued, through utility or WTP approaches, as explained below. The same point of view is undertaken by Culyer (2005, p. 177) who stated that there are in fact "many quantifying measures of pain, disutility and so on". For these latter reasons, the term "intangible costs" is substituted by "non-physical resources" henceforth in this thesis.

The utility and willingness to pay approaches for measuring and valuing non-physical resources are the ones advocated for an economic evaluation of alcohol treatment.

Measurement- The effect of alcohol misuse on society's physical, mental and social dimensions of well being can be represented by measures of HRQoL. Examples of HRQoL measures are generic preference-based measures and general health profiles (Drummond et al., 2005).

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[2] WHO (2002) defines Quality of Life as a multidimensional concept incorporating individuals' perspective of their position in life after accounting for their cultural settings and with regard to their goals, expectations, standards and concerns.

Generic preference-based measures of health have two components, one is a system for describing health or its impact on quality of life using a standardized descriptive system, and the second is an algorithm for assigning values to each state described by the system. The focus here is on measurement, i.e. the first component of generic preference-based measures. The individual is usually asked to report their own health by using the descriptive system.

Generic preference-based measures include: the Quality of Well-Being (QWB) scale (Kaplan et al., 1995), Rosser Classification of illness states, Index of Health-Related Quality of life, Health Utility Index (HUI) marks one, two and three (HUI1, HUI2 and HUI3) (Torrance et al., 1995), EuroQol 5 Dimensions (EQ-5D) (Williams, 1990), Short Form 6 Dimensions (SF-6D) (Brazier et al., 2002; Brazier et al., 2004)- a derivative of the SF-36 (Ware and Sherbourne, 1992) and the Assessment of Quality of Life (AQoL) (Hawthorne et al., 1999). The EQ-5D (Williams, 1990; Brooks, 1996) is a self-rated descriptive system that comprises 5 dimensions of health (mobility, self-care, usual activities, pain/ discomfort, anxiety/depression) and a five-digit number describing the five-dimensional health status. Each dimension has three possible levels of severity (i.e. no problems, moderate, extreme problems). In total, 243, (3^5), health states can be defined.

Briefly, the methods to measure preference under certainty include the Time Trade-Off (TTO), the Paired Comparison and the Person Trade-Off (PTO) methods. Measuring preference under uncertainty is done through the widely known Standard Gamble (SG) method. Scaling methods such as rating scale, category scaling, visual analogue scale and ratio scale are not choice-based methods (Drummond et al., 2005c)

General health profiles also measure HRQoL and can be applied across different patient populations and in different disease areas. However, usually the scoring for these instruments is not based on preferences of individuals for the various possible outcomes (Drummond et al., 2005c). A well-know general health profile is the SF-36 (Ware and Sherbourne, 1992). The SF-36 health survey is a standardized questionnaire used to assess patient health across eight dimensions. This instrument does not produce a single quality of life score, but rather produces a profile of scores across the different domains of the instrument. So, improvement in different dimensions cannot be compared, neither can different programmes that produce outcomes of different types. However, methods exist to convert the SF-36 score into a single utility index (Brazier et al., 2002).

Another approach is attaching money values to these HRQoL consequences. The methods used for measurement under these circumstances usually include questionnaires or surveys. These techniques are explained in the valuation stage below.

Valuation- Regarding the second component of generic preference-based measures of health, i.e. the valuation process, the scoring of each state is provided by an algorithm based on valuations obtained from a sample of, usually, the general population and using one of the measurement techniques described. These instruments generate preference-based single index scores for each state of health on the scale required to construct QALYs. A QALY represents a common health output measure that captures both changes in morbidity and mortality. QALYs are a measure of health utility with in-built equity criteria in that one QALY is of equal worth for everybody. Quality adjustment factors, used to determine QALYs, are weights usually ranging from 0 to 1. These weights are called utilities and reflect the relative desirability of each health state.

For example, the EQ5D can be scored in a number of ways depending on the method of valuation and source country, but the most widely used to date is the UK York TTO Tariff, which is based on a UK population valuation (Brazier et al., 2007; Kind et al., 1999). The EQ-5D index represents societal preference values for the 243 health states with the state of "perfect health" (11111) being assigned a value of 1 and the state of "death" being assigned a value of 0. Negative values represent states worse than death. Dolan (1995) obtained an index for the UK population by using a large population sample (n = 2997). He used the TTO in the valuation of 42 EQ-5D health states and derived an algorithm for societal preference values of all possible EQ-5D health states

Several alternatives to QALYs have been suggested as Healthy-Years Equivalents (HYEs), Saved-young-life equivalents (SAVEs), and Disability Adjusted Life Years (DALYs). HYEs measure the preferences over the entire path of health states through which the individual would pass, rather than for each state alone. In addition, it measures preferences using a two-stage standard gamble (Mehrez and Gafni, 1993, 1991). The SAVEs approach uses the PTO method in its determination of preferences. In the SAVEs approach each member of society is asked what kinds of trade-offs they would like for others. In contrast, in the QALY approach, people are asked about trade-off they would like for themselves (Drummond et al., 2005c). DALYs are the selected unit used by the WHO. Unlike QALYs, DALYs use age weights that give the highest values to years lived in young adulthood and by doing so the measure adopts a stronger equity position. The disability weight is estimated by a panel of public health experts (Arnesen and Kapiriri, 2004).

Another approach to value these consequences is to attach monetary values to health outcomes and three techniques can be used for doing so: 1) the human capital approach, 2) revealed preferences, and 3) stated preferences of WTP or contingent valuation (Drummond et al., 2005c). There is no internationally agreed method for putting a monetary value on human life.

The human capital approach can be used in two ways: 1) as the sole basis for valuing all aspects of health improvements, and 2) as a method of valuing part of the benefits of health care interventions,

valuing productivity changes only (Drummond et al., 2005c). The loss of productive output has already been taken into account in subsection 2.2.3. The loss of the non-physical value of life is not valued when the human capital approach is used. In addition, the lives of those who are not in the workforce, such as homemakers and the retired are not usually valued with this method. However, there will be a loss of unpaid work as well as the loss of life incurred by these people.

The revealed preference approach is a wage-risk approach based on actual consumer choices. However, estimations are job specific and vary with context. This approach is rather difficult to implement regarding health outcomes valuation. The stated preferences of WTP approach or contingent valuation uses survey methods. In this context, respondents reveal the maximum they would be willing to pay for a reduction in the psychological disturbance that others' alcohol misuse is imposing on them or for a change that reduced the probability of illness or death. The estimates with this method usually overwhelm the estimates by the human capital approach. Lifetime earnings, as calculated by the human capital approach, can be seen as a lower bound to a person's willingness to pay for a decreased risk of death. The WTP approach is extremely important, otherwise premature deaths of those out of the workforce would end up being beneficial to community as this population is consuming more than producing. It also allows taking into account the non-physical consequences of alcohol consumption.

Special attention should be taken in order to avoid double counting. As mentioned above, if productivity losses are measured in monetary terms the analyst should ensure that individuals ignore income effects when asked about their quality of life.

Most of the literature to date has solely included HRQoL of victims. Despite evidence of both stress-related psychological and physical symptoms experienced by family members of substance misusers (Copello et al., 2009), the HRQoL of family and friends of the alcohol misuser has rarely been measured. The HRQoL impact of fear of crime has also not been extensively valued in the literature (Dubourg et al., 2005). Dolan and Peasgood (2007) recommended the use of QALYs to estimate the health losses associated with the fear of crime. This same approach was also used to value the costs of crime to victims in Dolan et al. (2005).

A summary table of health-related quality of life consequences due to alcohol misuse is presented in Table 4. When performing an economic evaluation of alcohol treatment, an attempt should be made to cost all the categories identified under this domain.

Table 4- Society-level consequences: health-related quality of life

Building a taxonomy for the costs of Alcohol Consequences	
Society Level Consequences	
Health-Related Quality of Life (HRQoL)	HRQoL of family and friends of the alcohol misuser HRQoL of victims of crime and drink-driving accidents HRQoL of the general population: fear of crime

2.2.5 General health care

Alcohol misuse is related to a range of health effects which may result in an excess use of healthcare resources compared to the rest of the population (Leontaridi, 2003). In publicly funded health care systems, this presents a considerable societal burden as a significant quantity of medical resources is diverted from other purposes to alcohol-related problems, whilst in private insurance systems such costs could fall on other contributors. There is considerable research into the potential for treatment to reduce future healthcare costs (Holder, 1987; Holder et al., 2000; Holder and Blose, 1992; Parthasarathy et al., 2001; Potamianos et al., 1986; UKATT Research Team, 2005a). Therefore, this should be accounted for in an economic evaluation of alcohol treatment.

Identification- There is strong evidence that the consumption of alcohol is related to a variety of health consequences to the individual drinker and members of society affected by drinking behaviour. These consequences may be attributable to a long-term use of alcohol, as is the case of drinkers' chronic diseases or they can be a short-term effect of drinking alcohol, as is the case of intentional and unintentional injuries. Other consequences are due to both patterns as is the case of suicide and strokes. The strength and, in some cases, the direction of this association (e.g. CHD) varies with the level of consumption and with the drinking pattern, by age and gender (Rehm et al., 2001a).

Some health consequences would not exist if alcohol was not present, i.e. they are totally attributable to alcohol drinking. Examples of these conditions are: alcoholic psychosis, alcohol dependence, alcohol abuse, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic liver cirrhosis, ethanol toxicity, methanol toxicity and other alcohol poisoning. Other health consequences are partly attributable to alcohol abuse, such as: lip cancer, oral cancer, pharyngeal cancer, oesophageal cancer, colon cancer, rectal cancer, hepatic cancer, pancreatic cancer, laryngeal cancer, breast cancer, pellagra, hypertension, ischemic heart disease, cardiac dyrshythmias, heart failure, stroke, oesophageal varices, gastro-oesophageal haem, cholelithisasis, acute pancreatitis, low birth weight, intentional and unintentional injuries (Single et al., 2001). The WHO (2002) identifies alcohol-related unintentional injuries as: motor vehicle accidents (W150),

poisonings (W151), falls (W152), fires (W153), drownings (W154), and other unintentional injuries (W155), and alcohol-related intentional injuries as: self-inflicted injuries (W157), violence (W158), war (W159) and other intentional injuries (W160). The epidemiological contribution of alcohol on injuries and chronic diseases has been reported in widely know studies (Ezzati et al., 2004; Corrao et al., 1999; Corrao et al., 2000).

The previously described domains of alcohol-related crime (section 2.2.1), road traffic accidents (section 2.2.2), workplace accidents (section 2.2.3) and health-related quality of life (section 2.2.4) encompass consequences that lead to an increase in health care utilization.

Measurement- Measuring the events identified above in order to cost general health care utilization due to alcohol consumption is difficult for the same reasons presented above for measuring productivity losses due to mortality. However, the focus here is on morbidity and associated health care costs. In a short-term study those events might not be captured due to the time lag between alcohol drinking and chronic diseases morbidity. In addition, if the sample size is small the probability of capturing the effects of acute exposition to alcohol, as is the case of the injuries described above, is low. Therefore, a modelling approach will help in overcoming some of these problems and the burden on the health care system can be quantified. Within this approach population risk estimates can be applied to individuals' levels of consumption observed before and after alcohol treatment (see Chapter 4). However, obtaining population estimates of the relationship between alcohol drinking and the events that may in turn represent a burden in general health care, is not straightforward.

The probability and severity of adverse health effects of alcohol are strongly related to level of intake, often in a non-linear fashion and situation-dependent. The attributable fractions of alcohol-related morbidity can be determined with a fair degree of confidence from large-scale population-based epidemiological studies establishing the risk of disorders at different levels of consumption (WHO, 2000). Risk functions allow for alcohol diseases risks to be estimated at any level of consumption (Corrao et al., 1999; Corrao et al., 2004; Corrao et al., 2000). However, the determination of AAFs is complicated for those disorders that might relate to consumption in a curvilinear fashion as for coronary heart disease.

The relationship between alcohol consumption and CHD is complex. On the one hand, alcohol consumption at high levels is associated with hypertension, which is a strong risk factor for stroke. On the other hand, at low levels of consumption, alcohol may have a protective effect for stroke, due to its effect on High Density Lipoprotein (HDL) cholesterol, platelet stickiness and other thrombogenic factors. The review conducted by English et al. (1995) showed a J shape for risk of stroke and level of alcohol consumption and this is supported by other studies (Boffetta and

Garfinkel, 1990; Corrao et al., 2000; Doll et al., 1994). However, Rhem et al. (2001a) and Puddey et al. (1999) showed that patterns of drinking influence CHD and so this J relationship is not always verified. In addition, the J-shaped relationship is solely observed in established market economies for age groups (men and women) older than 45 where benefits of light to moderate consumptions on CHD and other ischemic disease categories apply (Rehm et al., 2001b). It should be noted that the population with which this thesis is concerned and to whom alcohol treatment is delivered is drinking at high level and would, therefore, be at the end part of a J-shaped curve where the effects of alcohol are solely detrimental.

There is also some uncertainty about the causal relationship between mental disorders and alcohol misuse. It is not straightforward to develop AAFs for mental disorders and determine which fraction of alcohol health service resources for mental disorder is caused by alcohol abuse.

On the basis of accepted, standard epidemiological criteria (Rothman et al., 2008), alcohol consumption is causally associated with both intentional and unintentional injury. Both the risk of injury and the severity of injury follow a dose-response relation with the amount of alcohol present in the body at the time of injury (Rehm et al., 2003a). AAFs have been calculated for intentional and unintentional injuries (Ezzati et al., 2004; English et al., 1995; Rehm et al., 2003b; Rehm et al., 2003c) and this can be used in order to calculate the costs to the health service due to alcohol-related injuries. A recent study developed a lifetime mortality risk function for alcohol injuries where both the amount of alcohol consumed and patterns of drinking were included (Taylor et al., 2008). Injury morbidity AAFs can be derived by multiplying the mortality AAFs by two thirds for motor vehicle accidents and by four ninths for all other types of injuries (Ezzati et al., 2004).

When costing these consequences in an economic evaluation of alcohol treatment the AAFs can be applied to the number of cases in the country of interest. For a hospital perspective, the number of cases of each alcohol-related problem can be retrieved from data on the main case of hospital admission, according to the coding system used in the country of the study, for example the International Classification of Disease 10^{th} edition (ICD-10) from the WHO (1992) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) from the American Psychiatric Association (1994). Secondary or contributory diagnoses are inconsistently recorded, so the WHO international guide recommends the analyst to focus only on principal diagnoses (WHO, 2000).

Valuation- General health services use may include the following: accident and emergency services; hospital out-patient, inpatient and day patient visits; practice nurse consultations; General Practice (GP) surgery visits; home visits by GP or nurse; occupational therapist contact; individual psychotherapy visit; ambulance services; laboratory services; non-dependency drugs, etc. These services are just an example as they vary between and within countries depending on a range of

factors, such as: current practice, institutional arrangements, setting, legislation, and health system organization, among other factors.

A monetary valuation of alcohol-related consequences on the health care system uses gross or micro- costing methods, depending on the detail of the data available, as explained in Drummond et al. (2005c) and further explored in Chapter 3. Several sources are available to provide, for example, the cost estimates for a unit of health care, such as the cost of a day of inpatient treatment or the cost of a visit to the emergency department. When micro-costing is conducted, data on the type and frequency of medical and psychiatric services consumed can be matched with unit cost estimates to determine health care costs. Unit costs are available in several countries, for example in England the Personal Social Services Research Unit (PSSRU) (Curtis, 2007) can be used. A gross approach is facilitated by the existence of a coding system, like the ICD in the UK, so the level of services can be related to particular health problems. In this case, average costs such as the reference costs provided by the Department of Health in the UK (Department of Health, 2006) with conditions coded in Healthcare Resource Groups (HRG) (The NHS Information Centre, 2007a) can be applied after matching ICD codes to HRG codes. Then, morbidity rates for the specific country can be applied to these health care expenditures in order to get a weighted cost (this is explored further in Chapter 5). A summary table with examples of the general health care costs that can be included in an economic evaluation of alcohol treatment is presented below (Table 5).

Table 5- Society-level consequences: general health care

Building a taxonomy for the costs of Alcohol Consequences	
Society Level Consequences	
General health care	General Health care is specific to setting, current practice and other conditions. The health care resources presented here are other than those related to the inputs of the alcohol treatment under analysis. Examples: accident and emergency services; hospital out-patient, inpatient and day patient visits; practice nurse consultations; GP surgery visits; home visits by GP or nurse; occupational therapist contact; individual psychotherapy visit; ambulance services; laboratory services and; non-dependency drugs.

2.2.6 Other specific alcohol treatment

Identification- This domain relates to specific alcohol treatments uptake, other than the alcohol interventions to which the economic evaluation is drawn. As explained for the domain of general health care utilization, the taxonomy intends to be fully comprehensive, even though the identification of specific alcohol treatments in the analysis will depend on the type of health care financing and other country-specific factors. Some countries have publicly supported clinics that are dedicated to the treatment of alcohol and other substances abuse. In the UK, many of the alcohol treatment services are provided in the voluntary sector and the National Health Service (NHS) provides a very wide range of services being the dominant funder of alcohol services.

Measurement- Many health care systems collect data about the health problems for which patients sought and received treatment. A treatment episode or service received from a health provider can be linked to an alcohol-related diagnosis and attributed to alcohol abuse. The services covered in this domain are specifically delivered to patients with alcohol problems, so the use of AAFs is not required (AAF=1).

Valuation- The valuation process of these health care consequences is the same as the one presented in subsection 2.2.5 above. A monetary valuation of these health care costs is calculated by estimating the specific health expenditure related to the alcohol problem.

A summary table with examples of the specific alcohol treatment costs that can be included in an economic evaluation of alcohol treatment is presented below (Table 6). The provision of alcohol treatment might reduce the uptake of other specific alcohol treatment and for this reason this domain should be considered in the cost effectiveness analysis of alcohol treatments.

Table 6- Society-level consequences: other specific alcohol treatment

Building a taxonomy for the costs of Alcohol Consequences	
Society Level Consequences	
Other specific alcohol treatment	Alcohol treatment is specific to the setting, current practice and other conditions. The specific alcohol treatment uptake is other than the alcohol treatment under analysis. Examples: therapeutic community, hospital detoxification, detoxification in primary care, short and long-term residential treatment, referral to other agencies after treatment, dependency drugs, hospital inpatient for alcohol problems, specialist alcohol clinic advice or counselling.

2.2.7 Social services and non-statutory care

Identification- The societal cost burden due to alcohol consumption expands to an increase in the uptake of social services and non-statutory care. The effect of treatment in this domain depends on the availability of these services in the country where the economic evaluation is being undertaken. Alcohol misuse and its related problems may have an impact on the use of the following services: advisor regarding state benefits and housing issues, social workers interventions, occupational therapists, citizens' advice services, advisors on legal or debt issues, homeless persons' agencies, employment advisors and fire services. These services are examples as their exact definitions vary between and within countries.

Measurement- The use of these services can be measured in the form of number of contacts per cause, which can usually be found in the services' records.

Valuation- In England, for example, there are national sources that provide estimates of the costs for social services, such as the PSSRU (Curtis, 2007). The number of alcohol-related contacts is multiplied by the unit costs in order to get a monetary value for these consequences.

Welfare benefits as a result of alcohol-related sickness represent a financial transfer from, for example, taxpayers to the sick person, and should not be included. However, administration costs involved in these procedures should be taken into account as they could be used to provide other activities.

Alcohol treatment has the potential to reduce alcohol misuse which can have a beneficial impact on the utilization of social services. A summary table with examples of the variables that can be identified under this domain is presented below (Table 7).

Table 7- Society-level consequences: social services and non-statutory care

Building a taxonomy for the costs of Alcohol Consequences	
Society Level Consequences	
Social services and non-statutory care	Social services and non-statutory care are specific to the setting and other conditions. Examples of possible identified variables: advisor regarding state benefits and housing issues, social workers interventions, occupational therapists, citizens' advice services, advisors on legal or debt issues, homeless persons' agencies, employment advisors and fire services, and related administration costs.

Table 8 presents the stratification of all society-level consequences, with the identified domains and correspondent categories and variables.

Table 8- Society-level consequences in the economic evaluation of alcohol treatments

A- Society Level Consequences		
1- Criminal activity	1.1 Anticipation of crime	1.1.1 Acquisition of security products 1.1.2 Precautionary behaviour 1.1.3 Insurance administration *Health impact of fear of crime: included in 4.3*
	1.2 Consequence of crime	1.2.1 Damaged/ stolen property *Productivity losses due to injury: included in 3.1.1 and 3.1.2* *Productivity losses due to premature death: included in 3.2.1* *Psychological impact on family and friends: included in 4.1* *Psychological impact on victims: included in 4.2* *Health services uptake: included in 5*
	1.3 Response to crime	1.3.1 Prosecution service 1.3.2 Courts 1.3.3 Defence 1.3.4 Prison and probation services
2- Road traffic accidents	2.1 Drink driving offences 2.2 Property damage *Productivity losses due to injury: included in 3.1.1 and 3.1.2* *Productivity losses due to premature death: included in 3.2.1* *Psychological impact on family and friends: included in 4.1* *Psychological impact on victims: included in 4.2* *Health services uptake: included in 5*	
3- Workplace and productivity losses	3.1 Due to morbidity	3.1.1 Absenteeism 3.1.2 Reduced efficiency 3.1.3 Reduced employment 3.1.4 Workplace accidents
	3.2 Due to mortality	3.2.1 Premature death 3.2.2 Workplace fatalities
	3.3 Due to criminal career	
4- Health-Related Quality of Life (HRQoL)	4.1 HRQoL of family and friends of the alcohol misuser 4.2 HRQoL of victims of crime and drink-driving accidents 4.3 HRQoL of the general population: fear of crime	
5- General health care utilization	General Health care is specific to setting, current practice and other conditions. The health care resources here identified are other than those related to the inputs of the alcohol treatments under analysis.	
6-Other specific alcohol treatment utilization	Specific alcohol treatment is specific to setting, current practice and other conditions. The specific alcohol treatment uptake is other than the alcohol treatment under analysis.	
7- Social services and non-statutory care	Social services and non-statutory care are specific to setting, and other conditions.	

2.3 Individual-level consequences

Individual-level consequences are the consequences accruing to the individuals engaged in the drinking activity. Alcohol treatment has the potential to reduce these consequences and the costs associated, hence, these should be identified, measured and valued in any economic evaluation of alcohol treatment.

The individual-level effects are part of the effectiveness component of the economic evaluation. The process of valuing individual-level health consequences classifies the type of economic evaluation as CEA, CUA and CBA. Clinicians are generally more interested in measures with clinical relevance, such as a change in alcohol consumption, and therefore may prefer a CEA design. In contrast, health financiers and health policy decision makers are interested in common or general health measures that allow a comparison between different health interventions, favouring the conduct of CBA and CUA.

The following text stratifies the consequences that impose a cost to the individual drinker, with the purpose of designing a taxonomy to be used when evaluating the cost effectiveness of alcohol treatments. The impact of alcohol consumption on the individual drinker is stratified in the following two domains: **health consequences**, and **patients' expenditure**.

2.3.1 Health consequences

The societal and individual-level consequences are conceptually different and, while for the society consequences all categories could be included in the study, for individual-level health consequences in practice only one category should be included. The type of health consequence included defines the type of economic evaluation. For example, if the study uses QALYs as the outcome measure, then it is classified as a CUA. If the health measure is valued in monetary terms, the evaluation is a CBA. CEA uses natural health measures such as alcohol drinks per day. For a matter of presentation all individual-level consequences are presented below and gathered in the taxonomy, even though just one health consequence is generally included depending on the economic study design.

Health consequences are divided for the taxonomy into clinical consequences and HRQoL.

2.3.1.1 Clinical consequences

The category of **clinical consequences** is divided into alcohol consumption, alcohol-related problems, and life expectancy. The commonly used instruments specifically used for classifying clinical consequences do not present the facets of HRQoL instruments

Alcohol consumption is measured by the quantity and/ or frequency of consumption. Different instruments can be used, for example, the Alcohol Problems Questionnaire (APQ) (Drummond, 1990) and the Alcohol Use Disorders Identification Test (AUDIT) questionnaire (Babor et al., 2001) are widely used. Changes in alcohol consumption are frequently used as an outcome measure in cost effectiveness analysis of alcohol treatment.

Specific terminology is used when referring to the level of alcohol consumption. Given that some of these terms will be used in this thesis it is worth providing a description of the different terms and definitions at this point. There is a lack of consensus regarding the definition of, for example, a standard drink, a binge drinking episode, low risk alcohol consumption, hazardous alcohol drinking and harmful alcohol drinking. The concept of "standard drink" differs from country to country and changes over time. In the UK one unit or one standard drink equals 10 millilitres (ml) or approximately 8 grams (g) of pure alcohol (Anderson and Baumberg, 2006), while in the US one standard drink equals 13.6g of ethanol. Conversions between standard drinks are possible as one ml of alcohol contains 0.785g of alcohol (ethanol). According to the WHO (1992), the commonly used term "binge drinking", which means the same as "episodic heavy drinking", reflects a drinking occasion where at least 60g of alcohol are consumed. Three other terms are often used: "low risk", "hazardous" and "harmful" alcohol consumption. Hazardous consumption is defined as a level of consumption or pattern of drinking that increases the risk of developing alcohol-related harm (Babor et al., 2003). Harmful drinking is defined as a pattern of drinking that causes damage to health, either physical or mental, and is introduced in the ICD-10 classification of mental and behavioural disorders as a diagnostic term (WHO, 1992). Low risk alcohol consumption is a level of consumption that carries no risk to health. According to the WHO (1992) definition, "abstinence" is when zero grams of alcohol per day are consumed. Whereas, "relapse" is the opposite of abstinence, meaning any alcohol consumption (Anderson and Baumberg, 2006). Alcohol dependence is a term used when the use of alcohol takes a much higher priority for individuals than other behaviours that once had a greater value. Alcohol dependence is included as a diagnostic entity in the ICD-10 (WHO, 1992).

General consequences of alcohol misuse are captured by the *alcohol-related problems* variable. Alcohol-related problems to the individual drinker can be measured by instruments such as the Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell et al., 1983), AUDIT (Babor et al., 2001), Leeds Dependence Questionnaire (LDQ) (Raistrick et al., 1994), the APQ (Drummond, 1990), or the Alcohol Dependence Scale (ADS) (Skinner and Allen, 1982). Several studies use these questionnaires as a measure of effectiveness of the intervention, where a change in the questionnaire score is monitored.

Life expectancy or life years gained with alcohol treatment is another effectiveness measure that an economic evaluation might adopt. According to the level and pattern of consumption alcohol decreases life expectancy to a higher or lower extent and therefore, treatment can result in Life Years Gained (LYG). Because of the lag in time between treatment and capturing alcohol-specific mortality for alcohol-related diseases or the sample size not being big enough to capture mortality due to injuries, the cost effectiveness analysis needs to adopt modelling techniques. When measures of health-related quality of life are used, life years and morbidity are captured in the domain of "health-related quality of life", below. The use of QALYs and DALYs instead of life years lost means that the assessment includes a valuation of the deterioration in the quality of life.

2.3.1.2 Health-related quality of life

The risk of the most commonly experienced negative social consequences of alcohol such as: getting into a fight, harming home life, work, studies, friendships or social life, increases proportionally to the amount of alcohol consumed (Anderson and Baumberg, 2006). There is also evidence that marriages where there are alcohol problems are more likely to breakdown and to end in divorce (Leonard and Rothbard, 1999; Fu and Goldman, 2000). All these consequences, together with alcohol-related health problems, cause a loss of quality of life to the alcohol misuser that should be included when conducting an economic evaluation of alcohol treatment. By reducing the extent of these consequences, alcohol treatment has the potential to improve drinker's quality of life.

The effect of alcohol misuse on drinkers' physical, mental and social dimensions of well being can be represented by measures of HRQoL that might capture life years and morbidity. This domain is separated in three categories based on HRQoL measures: 1) utility approach, 2) monetary approach and 3) health profile approach.

In the *utility* approach, instruments such as the QWB scale (Kaplan et al., 1995) and EQ-5D (Williams, 1990) generate preference-based single index scores for each state of health. When expressed as a numerical weight on a preference scale, health state preference values can be combined with length of life to calculate preference-based measures such as QALYs. As mentioned, QALY is a generic measure of HRQoL that accounts for both the quantity and quality of life (a more extensive explanation of measurement and valuation in the utility approach has been provided in section 2.2.4). In order to avoid double counting, when participants are asked about health state preferences they should not take into account productivity losses. QALYs have been established as a popular measure of health benefits (Richardson and Manca, 2004). However, the preference-based instruments available to measure HRQoL do not include facets of quality of life related to alcohol consumption making quality of life valuations for individuals with alcohol problems difficult to determine and deriving utility measures might turn to be rather difficult in this field.

Gunther et al. (2007) examined whether the EQ-5D could be used as a valid measure for describing and valuing HRQoL in alcohol dependent individuals. The EQ-5D was compared against a quality of life measure, a utility scale, measures of psychopathology and measures of social functioning. The similarity with some of the measures favoured EQ-5D's validity, however the instrument showed a moderate ceiling effect (Gunther et al., 2007). The authors noted that, despite EQ-5D's validity, more research would be needed in order to conclude on the suitability of this instrument to an alcohol-dependent population. Their results showed that the EQ-5D may not discriminate very well between health states in individuals with alcohol dependence. Nevertheless, two bodies that have issued guidance on the conduct of economic evaluations, the UK National Institute for Health and Clinical Excellence (NICE, 2008) and the US Public Health Service Panel on Cost Effectiveness in Health and Medicine (Gold et al., 1996b), recommend the use of generic QALYs based on a health state classification system with preference weights assigned by the public coupled with a generic preference-based instrument such a the EQ-5D.

The *monetary approach* attaches money values to HRQoL consequences. Three techniques can be used for a monetary valuation: 1) the human capital approach, 2) revealed preferences, and 3) stated preferences of WTP or contingent valuation (Drummond et al., 2005c). Measurement and valuation methods using these techniques are explained in section 2.2.4 above. When using this approach for valuing health consequences, participants should be asked not to take into account productivity losses otherwise there would be a risk of double counting.

The *health profile approach* uses generic instruments that do not produce a single quality of life score, but rather produce a profile of scores. An example is the widely known SF-36 health survey (Ware and Sherbourne, 1992). Some studies assessing HRQoL in individuals with alcohol use disorders have used generic instruments designed to measure a subject's overall HRQoL. A review conducted by Foster et al. (1999) concluded that the HRQoL of alcohol-dependent subjects was very poor when compared to normative populations. Accordingly, other studies reported that the HRQoL of subjects with alcohol use disorders was poor compared to that of a reference population (Foster et al., 1998; McKenna et al., 1996; Romeis et al., 1999; Volk et al., 1997). Foster et al. (2000) reported differences between gender, with women presenting lower HRQoL. .

Foster et al. (2000) also showed that a HRQoL instrument originally designed for cancer patients, the Rotterdam Symptoms Taxonomy (Dehaes et al., 1990), was a useful HRQoL assessment tool in alcohol dependent subjects. Recently, a specific instrument derived from the SF-36 generic scale was developed in order to measure the HRQoL of alcohol-dependent individuals, the AlQoL 9 (Malet et al., 2006). However, these are condition-specific and not generic measures of HRQoL.

They do not provide a comprehensive measure of quality of life and, therefore, cannot be used to compare the cost-effectiveness of programs in different disease areas (Drummond et al., 2005c).

2.3.2 Patients' expenditure

Patients' expenditures related to their alcohol misuse can also be affected by alcohol treatment. These include out of pocket health care costs (other than the treatment specifically analysed in the economic evaluation), expenditure on alcohol, travel and time costs due to other health care use (other than treatment under analysis), higher health insurance premiums and criminal justice related costs (e.g. lawyers fees, penalties and so on). Depending on the perspective of the study these expenditures can be valued or not. Including expenditure on alcohol assumes that any utility from alcohol consumption is null and that, by reducing alcohol consumption as an effect of treatment, drinkers have the opportunity to reallocate their budget to other goods and services that increase their utility. This should be the case for very high levels of consumption or dependence and assumes a dynamic utility function. McCollister and French (2003) stated that from a societal perspective expenditures on alcohol are simply an income transfer from one individual in society to another and therefore do not represent a net benefit or loss. Nevertheless, these expenditures represent a lost opportunity to purchase other goods and for this reason some studies might choose to include them in an economic evaluation (McCollister and French, 2003).

There is strong evidence of a relationship between problem drinking or dependence and *loss of earnings* (Mullahy and Sindelar, 1996; Mullahy and Sindelar, 1991, 1993; French and Zarkin, 1995; MacDonald and Shields, 2004; Terza, 2002). In order to avoid double counting, loss of earnings to the alcohol misuser are considered under society-level consequences (workplace and productivity losses domain).

Alcohol treatment has the potential to reduce alcohol misuse which can have a beneficial impact on the individual-level consequences presented above. A summary table with the individual-level domains that can be accounted for in an economic evaluation of alcohol treatment is presented below (Table 9). It is emphasized that, usually, only one primary outcome from the health consequences domain is considered in an economic analysis. The individual health measure chosen and how it is valued in the analysis classifies the type of economic evaluation as cost effectiveness analysis, cost benefit analysis or cost utility analysis.

Table 9- Individual-level consequences domains

Building a taxonomy for the costs of Alcohol Consequences		
Individual Level Consequences		
1- Health consequences†	1.1- Clinical consequences	1.1.1 Alcohol consumption* 1.1.2 Alcohol-related problems* 1.1.3 Life expectancy*
	1.2- HRQoL	1.2.1 Utility approach** 1.2.2 Monetary approach*** 1.2.3 Health profile approach*
2- Patients' expenditure	2.1 Out of pocket health care costs†† 2.2 Expenditure on alcohol 2.3 Travel and time costs†† 2.4 Higher health insurance premium 2.5 Criminal justice related costs *Loss of earnings: included in society- level consequences*	

*Used in cost effectiveness analysis or in cost benefit analysis if a monetary valuation is attached; **Used in cost utility analysis or in cost benefit analysis if a monetary valuation is attached; ***Used in cost benefit analysis; †Only one outcome is usually used; ††Other than the treatments compared in the economic evaluation.

2.4 The level of consequences in Economic Evaluations

This section discusses the extent to which the identified consequences are accounted for when conducting an economic evaluation of alcohol treatments. It argues that the consequences that are taken into account in economic evaluations of alcohol treatment depend on two interrelated factors: 1) the theory of consumer behaviour and, 2) the perspective under which these are evaluated.

2.4.1 Level of consequences and theory of consumer behaviour

The extent to which individual-level consequences are accounted for is embedded in consumer theory. Three models of addiction are briefly presented: rational addiction, myopic addiction and imperfectly rational addiction models.

Within the theory of consumer rationality, drinking alcohol and incurring its present and future negative consequences is a rational decision as the drinker has full knowledge of the effect of the contemplated addiction (Becker and Murphy, 1988). Under the theory of rational addiction consumers value their own consumption rationally and seek to maximize the value of their consumption subject to various limitations such as income and borrowing power. The rational addiction model asserts that, alcohol use, like other behaviour, forms part of a solution to a global expected lifetime-utility maximisation (Becker and Murphy, 1988). Therefore, the costs incurred by the individual (e.g. private medical treatment, loss of quality and quantity of life, wages loss, drinkers' spending on alcohol, lawyers' fees and defence costs and penalties) are assumed to be offset by the benefits that the consumer obtains from alcohol use, namely pleasure. Under this

model of addiction, alcohol consumption enhances welfare and externalities can be dealt with by suitable government action. The theory of consumer rationality is aligned with a perspective where the individual-level effects are not considered in economic evaluations of alcohol treatment, also called a "welfarist" perspective as explained in the next section.

On the other hand, addictive behaviour seems to violate the assumption of rational consumer behaviour, which is consistent with the models of myopic addiction (Liang et al., 2003). When there are market failures, for example if the consumer has limited information on the adverse effects of consumption or the nature of their alcohol problem, they cannot make rational choices (Godfrey, 2006). Therefore, consumers may not be fully informed or may be misinformed about the consequences their actions will impose on themselves. In this case, the misinformed consumer sustains unperceived costs and this has an effect on the potential range of consequences that are considered. Single et al. (2001) argue that if alcohol problems do not involve rational decisions and in fact the consumer is willing to stop consuming in order to avoid the negative consequences alcohol imposes on him or herself, then all individual negative consequences should be accounted for as these have not been knowingly incurred.

Even if the negative consequences of alcohol have been knowingly incurred, short-run utility maximization does not necessarily imply long-term positive overall benefits from alcohol misuse, which is consistent with an imperfectly rational addiction model (Schelling, 1978) and with a decision-maker perspective. The alcohol demand model presented by Cook and Moore (2000) was specified in the rational-addiction form. However, the authors noted that it would be reasonable that some consumers moderate their drinking in response to expectations concerning effects on employment, family, health status and future schooling (Cook and Moore, 2000). A standard rational addiction model appears inappropriate for the economic evaluation of alcohol treatments where individuals require treatment in order to reduce alcohol drinking and associated problems.

The imperfectly rational addiction model is the approach that better aligns with economic evaluations of alcohol treatment for a treatment-seeking population or a population accepting treatment given that the knowledge of the effect of the contemplated behaviour drives these problematic drinkers to treatment. This is a population that is willing to stop or moderate consumption in order to avoid the negative consequences alcohol imposes on him or herself and needs help for doing so. There are also coercive alcohol treatments such as those related to drink-driving offences. In this case it can be assumed that the alcohol misuser has full knowledge of the associated consequences and a rational addict model might be a better fit. Even though the theoretical predictions of the rational addiction model of Becker and Murphy (1988) have been confirmed empirically (Ferguson, 2000) this has not been tested for a treated population. There is

no right or wrong answer for the best theory to be used in an economic evaluation framework. Overall, if the consequences of alcohol misuse to the drinkers were to be classified as private and not taken into account in economic evaluations, then it must be assumed that drinkers are fully informed, they accept to bear the internal and external costs of consumption and they make rational consumption decisions in light of all the information available to them. In contrast, full information may not be available as to the consequences that alcohol abuse imposes on the drinker, the drinker may not make a rational decision and there may be no mechanism by which the costs that alcohol misuse imposes on the rest of community can be converted into internal costs to be borne by the drinker (Single et al., 2001). A compromise between the rational and myopic addiction models is found under an imperfectly rational addiction model, where alcohol drinkers are willing to reduce or cut their consumption.

There is no consensus in the model of addiction that should be used in economic evaluations of alcohol treatment. It is extremely important that researchers state the theory followed in their analyses as the application of a specific theory depends on the question addressed and who is addressing it and where. This will ultimately determine the costs and consequences included in an economic evaluation. A rational addiction model might be a better fit for private health care systems than public ones. As the following section shows, this is consistent with the general use of a welfarist and decision maker perspectives, for private and public health care systems, respectively.

2.4.2 Level of consequences and perspective of the analysis

The perspective of the analysis influences the types of consequences included in an economic evaluation. A societal perspective is one where all costs and consequences, no matter on whom or where they fall, are included. However, different economic theories suggest modifications to a societal perspective and three different analytical perspectives can be distinguished: 1) the "welfarist" perspective, 2) the "extra-welfarist" perspective and 3) the "decision making approach" (Drummond et al., 2005c).

Welfare economics is concerned with social welfare being comprised of the utilities of each member of society where individuals are the best judges of their own welfare (consumer sovereignty). A Welfarist approach is a conceptually broader perspective based on WTP valuations and potentially includes a wider range of costs and consequences to inform resource allocation decisions both within and between sectors of economy. However, this approach involves a number of assumptions about the rationality and information knowledge of alcohol misusers which may exclude some other effects such as individual-level effects. Welfarists argue that the social consequences of alcohol abuse should only be estimated as net social consequences given that

drinkers' private consequences and their associated costs and benefits are irrelevant to the interests of the community as a whole. Under such approach, individuals are assumed to take into account both the private benefits and costs of an activity when they decide to undertake such activity. The foundation of CBA is in principles of welfare economics where the relevant source of monetary values for programme outcomes are the individual consumers (Drummond et al., 2005c).

The "extrawelfarist" approach aligns the economic evaluation framework with the decision maker. The decision maker or extra-welfarist approaches have a narrower view of the consequences that should be included in the analysis. Decision makers make choices within a constrained budget and the objective of the economic evaluation is different according to different sectors, which determines the consequences that are identified, measured and valued. For example, for a public health care decision maker the main objective is to maximise individual HRQoL constrained by the health care budget. If a study is performed from a health insurer's perspective, this will lead to the exclusion of all costs outside the healthcare sector, and of all costs within the healthcare sector that are not reimbursed by the health insurer (e.g. co-payments) (Oostenbrink et al., 2002). A different approach is used in other areas of public policy. For example, for a criminal justice perspective, individual-level consequences might not be considered. When evaluating criminal justice interventions, the decision maker may only include the impact on criminal justice expenditures, the number of offences, and fear of crime.

Decision makers across the world set different frameworks for the conduct of economic evaluations of health care interventions. Different countries adopt different perspectives (Claxton et al., 2010). In the Netherlands, for example, it is recommended that economic evaluations take a societal perspective and measure health benefits in terms of QALYs (Ziekenfondsraad, 1999), with preferences stated by the general population. The Dutch pharmacoeconomic guidelines stated that "given the social perspective, a representative random sample from the population is the most suitable source of data for the evaluation of the quality of life in utilities" (Ziekenfondsraad, 1999,p 19).

In England and Wales, NICE represents national policy decisions on whether appraised health technologies should or should not be funded by the tax-funded NHS. NICE advocates the use of economic evaluations to make real decisions in health care. It uses the concept of a reference case, which was introduced by the Washington Panel (Gold et al., 1996b), in order to define the methods that should be used in a particular analysis. Under this reference case NICE's perspective on costs is that of the NHS and Personal Social Services and the perspective on outcomes takes into account all health effects on individuals. It also establishes QALYs as the preferred measure of health benefit, elicited through a choice-based method and using a validated generic measure with

population values to describe health states (NICE, 2008). The choice of population values is consistent with the extrawelfarist approach, where priority choices are made within a publicly-funded rather than a free market health care system based on willingness to pay (Godfrey, 2006).

The health service perspective is widely used to assess the relative efficiency of alternative healthcare interventions. However, there has been some criticism to the health system perspective. An economic evaluation with a health system perspective can determine the mix of interventions that maximize health outcomes within a limited health budget. Yet, this does not necessarily maximize the welfare of society (Johannesson, 1995). Byford and Raftery (1998) pointed out two main reasons for the use of a societal perspective instead of a health system one. First, only a societal perspective can detect cost shifting between sectors as the costs and benefits that result from health interventions may be incurred by sectors other than the health service. Second, a narrow perspective does not take into account alternative uses for resources outside the healthcare sector (Byford and Raftery, 1998).

Studies that adopt narrow perspectives may lead to resource allocation decisions that are not optimal and because different perspectives have different objectives there is a potential to allocative inefficiency. However, it should be recognized that it is very difficult to measure all the range of both inputs and consequences of different interventions across all sectors of the economy and a general equilibrium might be not be achieved. This has been observed in a report on the appropriate perspective for health care decisions by Claxton et al. (2010). The authors questioned the application of a societal perspective, especially when a NHS budget fixed by the government needs to be followed and, therefore, the financial transfers between different sectors are beyond the remit of NICE. An extension of NICE's perspective could provide an incentive to price technologies to the point at which the overall benefits, to the NHS and the wider economy, are null, and external benefits would be turned into higher internal NHS costs (Claxton et al., 2010). Nevertheless, wider effects can be considered under NICE's perspective in exceptional circumstances identified by the Department of Health (NICE, 2008). It has been recognized that the simplification of constraints and objectives when analyses are limited to health care technologies may not be appropriate from a wider view (Claxton et al., 2007). With this respect, NICE has issued guidance on public health interventions and national policies (NICE, 2009). Public health interventions are directed at populations or communities rather than specific individuals, as for example a prevention strategy of alcohol abuse targeting the general population. The broad nature of costs and benefits of public health interventions suggests that an intersectoral approach is required in order to identify them (Weatherly et al., 2009). This thesis focuses on alcohol treatment and not on alcohol public health interventions. However, the wider impact of treatment on society makes alcohol treatments a

special health technology that might justify the exceptional account of broader consequences by bodies such as NICE.

The key point is that economic evaluations are explicit about the perspective adopted and are put into the context of the defined goals. The exclusion of items must be made explicit and the impact of their exclusion on the final results should be discussed. The implications of the decision and the generalisability of the results to other jurisdictions also need to be assessed.

The final section gathers the information presented in all sections into a summary taxonomy.

2.5 Taxonomy of alcohol consequences

Sections 2.2 and 2.3 above provide a stratification of societal and individual-level consequences of alcohol consumption into domains and corresponding categories. Section 2.4 shows that the consequences included depend on the theory of consumer behaviour followed and on the perspective of the analysis.

The final taxonomy is built by adding up the tables presented at the end of each domain of the first two sections of this chapter. The stratification presented prevents double counting in a transparent and theoretically consistent way. The perspective of the analysis is also one item that needs to be filled in the taxonomy. The two main components of the final taxonomy are the society-level consequences and the individual-level consequences. All domains and variables can be identified in the analysis, with an exception for the health consequences domain under individual-level consequences. In the health consequences domain only one health measure should be included and this defines the type of economic evaluation. The resulting stratification is presented in Table 10.

A number of factors will influence the set of items of the taxonomy that are included in an economic evaluation. Depending on the perspective of the analysis, some alcohol treatments may not affect all alcohol-related society-level consequences. In a public health care system perspective, for example, any increase in health problems will impose costs that fall in the general population through social insurance schemes or taxes. In this case the domains of "General Health Care" and "Other specific alcohol treatment" are included in the economic evaluation. A societal perspective, where all costs and consequences are included, may be appropriate for broad based policy decisions. For example, those decisions where a shift between different sector budgets must be taken into account.

The taxonomy can be used as a layout for the consequences that should be identified, measured and valued in the economic evaluation of alcohol treatments and a new taxonomy can be completed after the analysis is conducted, in order to appraise the consequences actually included. Data

availability might condition the feasibility of taking into account all the consequences identified at the beginning of the evaluation. The reason for the exclusion of some consequences should be explained in the analysis and the failure to include some of the consequences may encourage further research. The taxonomy enlightens the appraisal of the methods used for the identification, measurement and valuation of society-level and individual-level consequences in economic evaluations of alcohol treatments. Therefore, by detecting the gaps in the inclusion of consequences, the need for better studies with respect to the methods for estimating alcohol-related consequences can be justified.

Table 10- Taxonomy of alcohol consequences in the economic evaluation of alcohol treatments

Alcohol Consequences in an Economic Evaluation of alcohol treatments		
Study/ project ID-	**Perspective-**	
Domains	**Type of economic evaluation**:	
A- Society Level Consequences		
1- Criminal activity	Anticipation of crime	Acquisition of security products Precautionary behaviour Insurance administration
	Consequence of crime	Damaged/ stolen property
	Response to crime	Prosecution service Courts Defence Prison and probation services
2- Road traffic accidents	Drink driving offences	
	Property damage	
3- Workplace and productivity losses	Due to morbidity	Absenteeism Reduced efficiency Reduced employment Workplace accidents
	Due to mortality	Premature death Workplace fatalities
	Due to criminal career	
4- Health-Related Quality of Life (HRQoL)	HRQoL of family and friends of the alcohol misuser HRQoL of victims of crime and drink-driving accidents HRQoL of the general population: fear of crime	
5- General health care	General Health care is specific to setting, current practice and other conditions††	
6-Other specific alcohol treatment	Specific alcohol treatment is specific to setting, current practice and other conditions††	
7- Social services and non-statutory care	Social services and non-statutory care are specific to setting, and other conditions	
B- Individual Level Consequences		
1- Health consequences†	Clinical consequences	Alcohol consumption* Alcohol-related problems* Life expectancy*
	HRQoL	Utility approach** Monetary approach*** Health profile approach*
2- Patients' expenditure	Out of pocket health care cost†† Expenditure on alcohol Travel and time costs†† Higher health insurance premium Criminal justice related costs	

*Used in cost effectiveness analysis or in cost benefit analysis if a monetary valuation is applied; **Used in cost utility analysis or in cost benefit analysis if a monetary valuation is applied; ***Used in cost benefit analysis; †Only one outcome is usually used ††Other than the treatments compared in the economic evaluation.

2.6 Conclusion

This chapter stratifies the alcohol-related consequences that should be addressed in the economic evaluation of psychosocial or pharmacological alcohol treatments. It is an attempt to resolve the inconsistencies in the methodology and reporting of alcohol consequences.

Three main points can be concluded. First, all theoretical considerations behind an economic evaluation should be stated. There is no correct or incorrect theory of consumer behaviour that should be followed nor is there a single perspective. The important issue for the economic evaluation taxonomy is that any assumption is made explicit rather than implicit and researchers must attempt to justify their assumptions and the effect of these assumptions on the evaluation results. Second, many of the aspects stated in the previous point are related with the country of the analysis, and organization of health care services. The concept of opportunity cost, which is extremely important in health economics, depends on the perspective of the analysis. For a health system perspective, the opportunity cost of investing in a healthcare intervention is the health benefits that could have been achieved had the investment occurred for the next best health care alternative. Whilst, for a societal perspective, the opportunity cost of investing in a healthcare intervention is the benefits forgone had the investment occurred for the next best alternative for society. Third, even when a societal perspective is attempted there are problems related to data availability. If consequences are excluded because of the lack of data this might prevent an efficient allocation of resources.

The broad range of alcohol consequences included in the taxonomy can be embedded in a public health concept where treatment will improve the health of the individual drinker and of the population. This guidance will help in the presentation of cost effectiveness evidence to those who need it and treatment integration into the overall policy response to alcohol. The stratification can be used across boundaries. However, a common taxonomy of alcohol-related consequences does not mean that the results of a cost effectiveness analysis can be generalized across settings and countries and such comparisons are only accurate if other factors, such as the setting and population characteristics, remain constant.

To conclude, this chapter brings together the framework applied in social cost studies of alcohol with the theory underlying economic evaluations of health care interventions. This allowed the development of a comprehensive alcohol-related consequences taxonomy which enlightens the harmonization of methods in the alcohol research field. The taxonomy enables the critical appraisal of economic evaluations of alcohol treatments and stimulates development and refinement of economic evaluations in the alcohol field. It will be used in the following chapter where the methods applied in previous full economic evaluations of alcohol treatment are reviewed.

Chapter 3. Review of Economic Evaluations of alcohol treatments

3.1 Objectives of the review

The aim of this chapter is to review the methodology used in published full economic evaluations retrieved through a systematic search of the literature, and offer research recommendations with a view to enhancing the rigour, consistency and harmonization of economic evaluations in the alcohol field. This chapter aims at comparing the studies in terms of the methods used to assess the society-level consequences and the methods used to carry out the analysis of individual-level consequences and costs of the intervention. Accordingly, it is not the review's aim to present any summary measure or provide a qualitative description of the results of the different studies. This methodological review is used to inform the development of an economic model for alcohol treatment in the following chapter. The taxonomy of society and individual-level consequences built in Chapter 2 is used as a framework for the extraction of the methodology used in the studies.

Within health economics only full economic evaluations can help on resource allocation and decision making on which strategy is good value for money (Drummond et al., 2005c; Gold et al., 1996b). A considerable amount of the economic literature of alcohol interventions consists of partial economic evaluations and, even though cost studies provide useful information for a full economic evaluation (Popovici et al., 2008), they do not help in setting priorities in the health care system and are not reviewed here. This methodological review focuses on full economic evaluations as a quality control strategy. The objective is to critically appraise the methods adopted in the best designed economic evaluations of alcohol treatment to date and also use this information for the remainder of the thesis.

This review focuses on:

1. The identification of society and individual-level consequences affected by different types of alcohol treatment
2. The different methods for measurement of the two groups of consequences and their advantages and disadvantages
3. The different methods for valuation of the two groups of consequences and their advantages and disadvantages
4. Identification, measurement and valuation methods used for costing the treatments

Even though costing treatments does not present a challenge in economic evaluations of alcohol treatment these methods are also reviewed here. This is done for a matter of consistency, so that all

items that make part of an economic evaluation are analysed. It also provides information, for the model developed in the upcoming chapter.

The next section presents the methods used for the systematic search, where the selection criteria and search strategy are reported. This is followed by the methods used for the methodology extraction of the selected studies. The following two sections report the results of the systematic search and the results of the methodology extraction. The limitations of the methodological review are then considered. The last section presents a critique of the methodology used in the studies reviewed and suggests recommendations for future practice.

Methods

The following two sections present the methods for the systematic search and for the methodology extraction, respectively.

3.2 Methods for the systematic search

The first step is scoping the primary literature (Appendix 1- Scoping strategy). The literature scoping confirms that no similar comprehensive methodological review has been conducted and endorses the need for a methodological review of full economic evaluations of alcohol treatment.

3.2.1 Selection criteria

Selection criteria, both inclusion and exclusion criteria, are derived from the prime aim which is to review and extract the methodology that has been adopted in economic evaluations of alcohol treatment. These criteria are defined in terms of type of study, type of participants, types of interventions, and types of costs and consequences.

Decisions about the inclusion or exclusion of studies are made according to inclusion and exclusion criteria. This reduces the risk of study selection based on researchers' preferences, practices or products (Higgins and Green, 2006; Khan et al., 2001). Only studies that meet all of the inclusion criteria and none of the exclusion criteria are included in the review. Inclusion and exclusion criteria are summarized in Table 11. The text below the table provides an explanation for the defined criteria.

Table 11- Study exclusion and inclusion criteria

Criteria	Inclusion Criteria	Exclusion criteria
Type of study	Full economic evaluations (CEA, CUA, CBA)*. Studies that report both costs and consequences of alternatives (cost consequence analysis, cost minimization analysis).	Partial economic evaluations (cost-offset analysis, cost-outcome description, cost description, efficacy/ effectiveness evaluations and outcome descriptions). Methodological studies. Review studies.
Participants	Individual patients to which alcohol treatment is directed, which include: harmful, hazardous or dependent.	General population with no confirmation of problem drinking.
Intervention	Treatment of alcohol abuse, problem drinking or alcohol dependence (pharmacological or/ and psychosocial), including relapse prevention programmes and screening followed by brief interventions.	Alcohol interventions at a population level: 1) alcohol policy and legislative interventions; 2) enforcement measures of legislation; 3) prevention of alcohol misuse; and 4) screening and detection studies. Technologies that attenuate or treat health problems caused or aggravated by alcohol consumption. Mixed drug/ tobacco and alcohol interventions.
Costs and consequences	Clear description of identification, measurement and valuation methods.	Studies with no description of the methods for identification, measurement and valuation; studies representing extensions of previous ones.

*CEA, Cost Effectiveness Analysis; CUA, Cost Utility Analysis; CBA, Cost Benefit Analysis.

Types of studies- Only full economic evaluations are included. Included studies are classified as CEA, CUA and CBA, as described in Chapter 1. Thus, for any study to be included health and economic consequences, as well as costs, have to be described for each alternative and so partial economic evaluations are not included. Partial economic evaluations include studies such as: cost-offset analysis; cost-outcome description; cost description; efficacy or effectiveness evaluations; and outcome descriptions. Cost-offset studies in the alcohol literature are concerned with the valuation of the resources used to deliver an alcohol intervention. These studies focus on whether treatment costs are offset by savings in future alcohol-related medical care and set a higher hurdle for alcohol treatments when compared to other health care treatments, since a number of important avoided alcohol consequences are excluded (Ludbrook, 2004). Also excluded are systematic reviews and methodological studies, since they are not full economic evaluations studies.

Types of participants- Studies are included if they focus on harmful, hazardous and/ or dependent drinkers that are the target of a specific alcohol treatment. Studies are excluded if the population of

interest is not classified as having alcohol problems and is not the target of a specific alcohol treatment.

Types of interventions- Included interventions are alcohol interventions, more specifically alcohol treatments delivered at the individual-level consisting of psychosocial and/ or pharmacological approaches. Interventions that consist of screening followed by counselling are also included. Although some authors classify such studies as prevention it is assumed that the objective of counselling is to improve an individual's condition and when counselling is delivered to problem drinkers, these studies are classified here as treatment studies.

Excluded studies are those that do not focus on alcohol treatment, and evaluate interventions delivered at a population level, such as: 1) alcohol policy and legislative interventions (alcohol taxes, drink driving controls, licensing provisions and alcohol advertising policy); 2) enforcement measures of legislation; 3) prevention of alcohol misuse (school-based interventions and mass media campaigns); and 4) screening and detection studies (screening instruments for the detection of problem drinking, alcohol abuse and dependence and the laboratory tests that confirm results or monitor abstinence). In addition, studies that evaluate technologies that attenuate or treat health problems caused or aggravated by alcohol consumption are excluded as they do not focus on alcohol treatment *per se*. Studies where it is not possible to disaggregate alcohol interventions from other addiction interventions are not included. Therefore, mixed alcohol and drug or tobacco interventions are excluded due to the difficulty of disentangling identification, measurement and valuation procedures for the different treatments or population types.

Types of costs and consequences- Economic evaluations that allow an assessment of the identification, measurement and valuation of outcomes and cost domains are included. Studies that are a methodological extension of another one are excluded and only the published study with a more complete description of the methodology applied is selected.

3.2.2 Search strategy for identification of studies

Searches are undertaken of the following sources:

1) Electronic databases- NHS Economic Evaluation Database (EED) and MEDLINE (1996 to present). NHS EED identifies potential economic evaluations by searching the following databases: MEDLINE (from 1995 to present), EMBASE (from 2002 to present), PsychINFO (from 2006 to present) and CINAHL (from 1995 to present). The search run in MEDLINE is restricted to records added in the previous (2008) and current year (2009) of the search run in the NHS EED, in case there are relevant records not yet reviewed and added to the NHS EED.

2) Handsearching of key journals: Journal of Studies on Alcohol, Alcoholism: Clinical and Experimental Research and the British Journal of General Practice.

3) Reference lists and citation tracking: bibliographic search for reference lists of retrieved studies and citation tracking of key papers using Science Citation Index and Google Scholar.

The search terms are presented in Appendix 2- Search terms for the methodological review. Searches of electronic databases use free-text terms and keywords (and where appropriate MESH headings) for economic evaluations. As suggested by Counsell (1998) the search terms for searching electronic databases break down the research question into participants, type of intervention, type of costs/ consequences and study design. This breakdown is followed for the MEDLINE search. The search on the NHSEED database only uses population terms. This is because the study design terms are embedded in the NHSEED database, so these do not have to be specified. Also, narrowing the search down by using intervention terms does not retrieve all important full economic evaluations of alcohol treatment.

Each search terms are combined by using Boolean operators. The assessed references are managed by using Endnote X1, a bibliographic software package. The selection criteria are first applied to all citations generated from the electronic searching to decide whether full copies of potentially relevant references should be obtained. Once these copies are obtained the inclusion/ exclusion criteria are thoroughly applied to all collated literature and decisions of inclusion are made.

3.3 Methods for the methodology extraction

First, studies are classified into two groups: primary and modelling studies. In addition, studies are classified as CEA, CBA and/ or CUA. The different study design has an impact on how the costs and consequences are identified and subsequently measured and valued. The first group includes

studies based mainly on primary data collection. These studies usually measure costs and effects over a maximum period of 12 months. Primary studies can be economic evaluations conducted alongside a RCT (e.g., UKATT Research Team, 2005a; Fleming et al., 2002; Shakeshaft et al., 2002) or simply use effectiveness data from a previous trial (e.g., Barrett et al., 2006). Modelling studies usually use various sources of data and mathematical techniques. They allow long-term health and economic assessments in the absence of empirical data based on the extrapolation of known data (e.g., Palmer et al., 2000). Drummond et al. (2005c; p 277) explained that economic evaluation for decision making usually needs to draw on evidence from a range of sources and that decision analytical models provide a means of bringing evidence together.

Second, the methodology used in each selected study is extracted for society-level consequences, individual-level consequences and treatment costs according to identification, measurement and valuation methods. Identification consists of listing likely variables of the intervention. The decision of excluding or including these variables is related with the perspective of the study, as explored in Chapter 2. Measurement refers to measuring the identified variables and the changes as result of treatment. The valuation process consists of putting a value on the identified variables.

According to the definitions presented in Chapter 2, *society-level consequences* are the consequences that arise from individuals' drinking behaviour that affect society, including alcohol-related victims and drinkers' families, while *individual-level consequences* are the consequences felt by the drinkers themselves. Therefore, for the purpose of this review, societal treatment outcomes are the consequences that fall on society as a whole and not on the individual or target population (e.g. change in health services use, and utility and productivity losses to victims). Accordingly, individual treatment outcomes are the consequences that come as a result of the intervention falling on the target population for which the intervention is designed and to whom it is delivered. Finally, input costs are the costs directly related to the intervention that the study is assessing. The alcohol-consequences taxonomy presented in the previous chapter is used as a framework to stratify the identified domains and categories for the two levels of consequences identified in the selected studies.

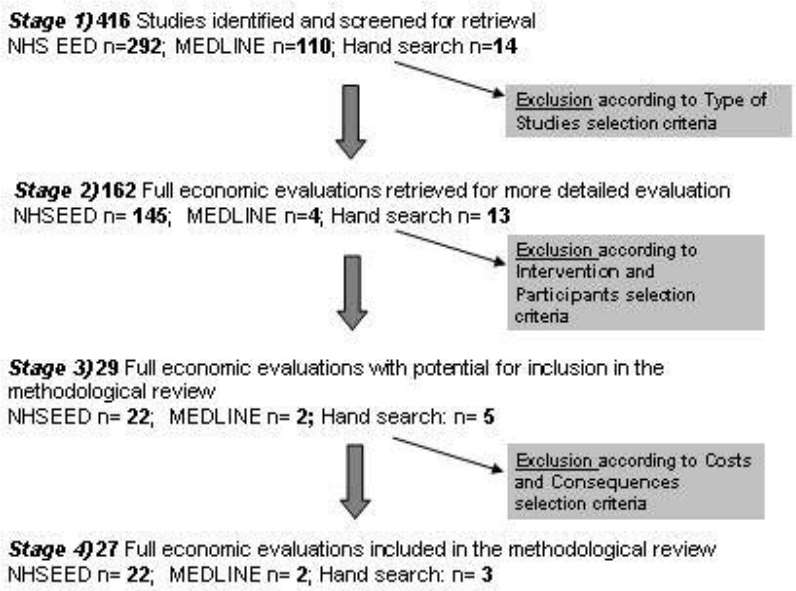
Results

The following two sections present the results of the systematic search and of the methodology extraction, respectively.

3.4 Results of the systematic search

The study selection process is presented in Figure 1 below, where the number of studies retrieved is indicated.

Figure 1- Flow chart of retrieved studies



The following four stages detail the individual steps of the selection process:

Stage 1- The search identifies 416 potential full economic evaluations, where 292 are from NHS EED, 110 from MEDLINE and 14 are identified through hand search. These studies are screened for retrieval. At this stage, studies are excluded according to the type of studies as defined in the selection criteria. Most of the studies excluded are cost-offset and cost-outcomes analysis. Duplicates of NHSEED and Medline searches are identified. A total of 162 studies are retrieved for further evaluation.

Stage 2- At this stage, 162 full economic evaluations are analysed (NHSEED n= 145, MEDLINE n= 4, Hand search n= 13). Studies are excluded according to intervention and participants selection criteria. The studies excluded are economic evaluations of various substance abuse treatments and/

or analyse prevention programmes delivered to the general population. This results in 29 studies that make it through to stage 3.

Stage 3- At this stage there are 29 economic evaluations of alcohol treatment (NHS EED n= 22, MEDLINE n= 2, Hand search n= 5). According to the types of cost and consequences selection criteria, two studies identified through hand search are excluded (O'Farrell et al., 1996a; Rychlik et al., 2001) as the methodology presented is similar to another study published by the same authors (O'Farrell et al., 1996b; Rychlik et al., 2003)

Stage 4- A total of 27 economic evaluations are included in the methodological review, from which methods for identification, measurement and valuation of outcomes and costs are retrieved.

3.5 Results of the methodology extraction

3.5.1 Classification of the studies

This section classifies the studies reviewed into modelling vs. primary and as CEA, CBA and CUA. It also provides a general view of these studies. After a short presentation of the 27 studies, the taxonomy of alcohol consequences presented in Chapter 2 is followed and the identification, measurement and valuation of society-level and individual-level consequences are presented.

Table 12 divides the selected studies (27 economic evaluations) into modelling and primary studies. In addition, the classification of the studies as CEA, CBA and CUA, is provided.

Table 12- Classification of 27 peer-reviewed economic evaluations of alcohol treatment

		Studies references	N
Primary	CEA	Alwyn et al. (2004); Babor et al. (2006); Barrett et al. (2006); Bischof et al. (2008); Fals-Stewart et al. (2005); Fleming et al. (2002)*; Humphreys and Moos (1996); Kunz et al. (2004); Lock et al. (2006); Long et al. (1998); Nalpas et al. (2003); O'Farrell et al. (1996b); Parrott et al. (2006)*; Pettinati et al. (1999); Rychlik et al. (2003); Shakeshaft et al. (2002); Sobell et al. (2002); Zarkin et al. (2008).	18
	CUA	Parrott et al. (2006)*; UKATT Research Team (2005a).	2
	CBA	Fleming et al. (2002)*.	1
Modelling	CEA	Doran et al. (2004); Gentilello et al. (2005); Lindholm (1998); Palmer et al. (2000); Schadlich and Brecht (1998); Wutzke et al. (2001).	6
	CUA	Corry et al. (2004); Mortimer and Segal (2005).	2
	CBA	------	0

CEA, Cost Effectiveness Analysis; CBA, Cost Benefit Analysis; CUA, Cost Utility Analysis. *The Fleming et al. (2002) and Parrott et al. (2006) studies fall in two classifications and therefore, the total number of studies does not add to the original 27 economic evaluations.

The majority of published economic evaluations of alcohol treatment do not use modelling techniques (19 studies) and perform a cost effectiveness analysis (18 studies). Within the eight

modelling studies identified, most of these are cost effectiveness analysis (6 studies). Two primary studies perform a cost utility analysis, where one of the studies (Parrott et al., 2006) performs both a cost utility and a cost effectiveness analysis. Only one full economic evaluation, without modelling techniques, is classified as a cost benefit analysis. This study (Fleming et al., 2002) also performs a cost effectiveness analysis. Two modelling studies are cost utility analysis and there is no modelling study that can be classified as cost benefit analysis. A summary table of the objectives, population and setting, type of treatment, perspective, study design and primary outcome measure is presented in Appendix 3- Characteristics of the studies reviewed.

Cost effectiveness analyses of brief alcohol interventions (Barrett et al., 2006; Doran et al., 2004; Fleming et al., 2002; Gentilello et al., 2005; Lindholm, 1998; Shakeshaft et al., 2002; Wutzke et al., 2001; Babor et al., 2006; Kunz et al., 2004; Lock et al., 2006; Zarkin et al., 2008) use different endpoints, various settings and different types of health professionals delivering the interventions. Two other CEA look at couples-based therapy (Fals-Stewart et al., 2005; O'Farrell et al., 1996b). Two modelling studies perform a CEA of acamprosate treatment. Schadlich and Brecht (1998) model the proportion of abstinent alcoholics, while Palmer et al. (2000) model life expectancy for abstinent and non-abstinent patients. Rychlik et al. (2003) also perform a CEA of relapse prevention with acamprosate but without using modelling techniques. The three studies that evaluate relapse prevention with acamprosate focus on an alcohol-dependent population recently detoxified. Four other CEA evaluate the cost effectiveness of different detoxification programmes for alcohol dependent patients (Long et al., 1998; Nalpas et al., 2003; Parrott et al., 2006; Alwyn et al., 2004). Sobell et al. (2002) perform a cost effectiveness analysis of advice strategies delivered using a public health approach to problematic drinkers, while Pettinati et al. (1999) assess the cost effectiveness of inpatient versus outpatient therapy based on the 12-step programme of Alcoholic Anonymous (AA), and Humphreys and Moos (1996) assess the cost effectiveness of using AA versus professional outpatient treatment.

Four recent economic evaluations are **cost utility analyses** valuing quality of life improvements. Two of the studies are economic evaluations of alcohol treatment where no modelling is involved (Parrott et al., 2006; UKATT Research Team, 2005a), where the Parrott et al. (2006) is classified as both CUA and CEA. These last two studies focus on patients seeking treatment and have QALYs as the clinical endpoint of the evaluation. In another CUA the authors model the QALYs gained (Mortimer and Segal, 2005) from interventions for prevention and treatment of problem drinking and alcohol dependence. The fourth CUA retrieved is the Corry et al. (2004) study where the authors conduct a cost effectiveness analysis of treatments for alcohol dependency and harmful use, modelling the number of years lived with disability.

Only one study values health consequences in monetary terms and is classified as a **cost benefit analysis** (Fleming et al., 2002). This study, when using a societal perspective, performs a CBA where no value is given to the individual outcomes of the drinker and only the health consequences to the victims are considered.

The following subsections are broken down as follows: firstly, all society-level consequences variables are presented under their respective domain. Secondly, individual-level consequences variables are presented, together with a quality appraisal for the selection of the outcome(s) in each study. This is followed by a section with a description of the methods used for costing the specific alcohol treatments analysed in the economic evaluations. A general picture of the variables identified in the different studies is presented. For more information regarding each study see Appendix 4- Methods for identification, measurement and valuation of individual consequences, societal consequences and treatment under evaluation costs, where a non-aggregated description of identification, measurement and valuation methods is provided.

3.5.2 Society-level consequences

Using the taxonomy of alcohol consequences presented in Chapter 2, society-level consequences are stratified into seven domains, namely: 1) criminal activity, 2) road traffic accidents, 3) workplace and productivity losses, 4) health-related quality of life, 5) general health care, 6) other specific alcohol treatment and, 7) social services and non-statutory care. Different variables are identified in the studies reviewed and these, along with a reference to the studies that include each variable, are presented for each domain. The variables identified, generally, depend on the setting of the analysis, the health/ judicial system on vigour, the perspective of the study and also the type of treatment under evaluation. Measurement and valuation processes depend on available data, whether the data is national or local for example, the setting and also the country where the study takes place.

3.5.2.1 Criminal activity

Alcohol-related crime consequences are included in five studies (Barrett et al., 2006; Fleming et al., 2002; O'Farrell et al., 1996b; Parrott et al., 2006; UKATT Research Team, 2005a). Table 13 below presents the variables of alcohol-related crime identified in the selected studies. Two categories are identified under the criminal activity domain: consequences of crime to victims and actions taken in response to crime.

Table 13- Criminal activity variables

Offences	Study reference
Consequences of crime to victims	
Property loss or damage	Fleming et al., 2002
Actions taken in response to crime	
Courts	Parrott et al., 2006; UKATT Research Team, 2005a; Barrett et al., 2006
Defence costs	Barrett et al., 2006; Fleming et al., 2002
Prison and probation services	Parrott et al., 2006; O'Farrell et al., 1996b; Barrett et al., 2006

Measurement in all studies is based on the number of events reported in criminal justice records during follow-up. The Fleming et al. (2002) study valuation process is based on a research report for the US Department of Justice (Miller et al., 1996) which identified, measured and valued victims costs and consequences. Miller et al. (1996) focused on quantifying the costs incurred directly by or on behalf of the crime victim. This report costed the following variables: property damage, medical care, mental health care, initial police response and fire services, victim services, victim's productivity losses, and victim's loss of quality of life. For this domain, police response and property damage are the variables of interest. The costs of operating the criminal justice system in Fleming et al. (2002) are not reported separately from other criminal justice-related costs such as medical care, and mental health services costs. Therefore, for this study, it is not possible to disentangle the costs falling on criminal justice from other crime-related costs.

The other four studies value criminal activity using UK government reports (Harries, 1999; HM Treasury, 2000; Home Office, 1998; Field, 1997) or US state-specific judicial data, such as that from the Massachusetts Department of Corrections used in O'Farrell et al (1996b). None of the studies identify actions taken in anticipation of crime, which would include measures that reduce the probability or risk of potential victims becoming one.

3.5.2.2 Road traffic accidents

Road traffic accidents costs are included in one reviewed study (Fleming et al., 2002) and derived from the US-based research report already described (Miller et al., 1996). In order to avoid double counting, the variables measured and valued under this domain should be drink driving offences and property damage due to road accidents. However, the estimates related to road traffic accidents in Fleming et al. (2002) are calculated for health care costs, productivity losses and quality of life losses and these are allocated to their corresponding domain in the taxonomy.

3.5.2.3 Workplace and productivity losses

Productivity losses related to the impact of alcohol misuse are included in four studies (Barrett et al., 2006; Fleming et al., 2002; Nalpas et al., 2003; Lock et al., 2006) and estimated for losses due to morbidity, more specifically due to absenteeism. The estimates of the Fleming et al. (2002) study are derived from Miller et al. (1996), and include victims' of crime and motor vehicle accidents reduced productivity due to absenteeism, calculated through the Human Capital Approach (HCA). The UK-based study (Barrett et al., 2006) also uses the HCA and production losses are valued based on the individual gross daily salary in order to reflect society's loss of work output due to drinkers' abstinence. Nalpas et al. (2003) value the work time loss due to alcohol problems according to the socioprofessional category and the corresponding salary of governmental employees. Lock et al. (2006), despite identifying absences from work, do not provide information regarding methods and valuation. Only productivity losses due to morbidity, and more specifically absenteeism, are included in the studies. Reduced efficiency, reduced employment and workplace accidents, are not taken into account in any study. Similarly, workplace and productivity losses due to mortality such as premature death and workplace fatalities are not included in the economic evaluations of alcohol treatment reviewed.

3.5.2.4 Health-related quality of life

Health-related quality of life losses to the victims of crime and drink-driving accidents are only taken into account in one study (Fleming et al., 2002). These estimates are taken from the Miller et al. (1996) report where HRQoL valuation was based on jury awards to victims. HRQoL losses to friends and family and due to fear of crime are not included in any of the reviewed studies.

3.5.2.5 General health care and other specific alcohol treatment

Alcohol consumption generates ill health which increases the use of general health care and alcohol treatment other than the intervention under analysis. In addition, victims of criminal activity or road accidents also cause an increase in the use of general health care services. All the studies that include society-level consequences identify at least one variable from these two domains. Table 14 and Table 15 below depict general health care and other specific alcohol treatment variables identified in the economic evaluations reviewed, respectively.

Table 14- General health care variables

Health services used	Study reference
Accident and emergency hospital	Parrott et al., 2006; UKATT Research Team, 2005a; Fleming et al., 2002; Barrett et al., 2006; Gentilello et al., 2005; Lock et al.,2006
Hospital out-patient	Parrott et al., 2006; UKATT Research Team, 2005a; Barrett et al., 2006; Lock et al.,2006
Hospital inpatient	Parrott et al., 2006; UKATT Research Team, 2005a; Fleming et al., 2002; Barrett et al., 2006; Rychlick et al., 2003; Gentilello et al., 2005; Lock et al.,2006
Hospital day patient visit	UKATT Research Team 2005a; Barrett et al., 2006
Practice nurse consultations	UKATT Research Team, 2005a; Barrett et al., 2006; Lock et al.,2006
General Practice (GP) surgery	Parrott et al., 2006; UKATT Research Team, 2005a; Barrett et al., 2006; Lock et al.,2006
Home visits by GP	Parrott et al., 2006; UKATT Research Team, 2005a
Home visit by practice nurse	UKATT Research Team, 2005a; Barrett et al., 2006
Occupational therapist	Barrett et al., 2006
Individual psychotherapy visit	Barrett et al., 2006
Out-patient psychological visit	Barrett et al., 2006
In-patient psychological days	Barrett et al., 2006
Ambulance services	Barrett et al., 2006
Other (no dependency) prescribed drugs	UKATT Research Team 2005a
Health care costs- not specified	Lindholm et al., 1998
Alcohol-related interventions and complications	Palmer at al., 2000; Schadlich and Brecht, 1998

Table 15- Other specific alcohol treatment variables

Alcohol-specific treatment services	Study reference
Therapeutic community alcohol treatment	UKATT Research Team, 2005a; O'Farrell et al., 1996b; Barrett et al., 2006; Bischof et al., 2008; Humphreys and Moos, 1996
Hospital detoxification or detoxification in primary care	O'Farrell et al., 1996b; Barrett et al., 2006; UKATT Research Team, 2005a; Bischof et al., 2008; Humphreys and Moos, 1996
Residential treatment	UKATT Research Team 2005a; Barrett et al., 2006; Humphreys and Moos, 1996
Hospital inpatient treatment	O'Farrell et al., 1996b; Humphreys and Moos, 1996
Specific counselling or advice	Barrett et al., 2006; Bischof et al., 2008; Humphreys and Moos, 1996

The increased use of general health care from individual's alcohol consumption and/or victims is identified in ten of the selected full economic evaluations (Barrett et al., 2006; Fleming et al., 2002; Gentilello et al., 2005; Lindholm, 1998; Lock et al., 2006; Parrott et al., 2006; Rychlik et al., 2003;

UKATT Research Team, 2005a; Palmer et al., 2000; Schadlich and Brecht, 1998). Other specific alcohol treatment utilization variables are identified in five studies (Barrett et al., 2006; Bischof et al., 2008; Humphreys and Moos, 1996; O'Farrell et al., 1996b; UKATT Research Team, 2005a).

Costs are estimated by multiplying resource quantities by a monetary valuation of the resources identified. Resource quantities for general health care and other specific alcohol treatment domains are measured with different levels of precision. In general, primary studies use the more detailed "micro-costing" methods while modelling studies usually use "gross-costing" methods. When a study is performed using micro-costing, information on resource use on a very detailed level is required. This bottom up collection of data tends to be costly and runs the risk of being context specific. For gross-costing, the intervention is broken down into larger intermediate products for which resource use is determined. This top down costing allocates a total budget to specific services which may lack sensitivity (Raftery, 2000).

In modelling studies (Gentilello et al., 2005; Lindholm, 1998; Palmer et al., 2000; Schadlich and Brecht, 1998), resource use information is modelled using secondary analysis of epidemiological information and/or assumptions. Costs are calculated by allocating expenditures to the major diagnostic categories. Monetary valuations are taken from national average estimates such as the federal statistical office in Germany (Palmer et al., 2000), the Marketscan® database in the US (Gentilello et al., 2005) and, the Swedish council on technology assessment in health care in Sweden (Lindholm, 1998).

For most of the primary economic evaluations, quantities of health services used are recorded from patient questionnaires at different follow-up times or patient diaries, this being the most informative and reliable method. If only secondary data is available, then medical records are used or, where data is inexistent, assumptions are made. Monetary valuations are taken from national sources of unit costs such as the UK PSSRU (Netten and Curtis, 2002) or alcohol treatment literature (Slattery et al., 2003) used in the UKATT Research Team (2005a) study.

3.5.2.6 Social services and non-statutory care

Social services and non-statutory care are included in three of the 27 studies (Barrett et al., 2006; Parrott et al., 2006; UKATT Research Team, 2005a). The services identified are presented in Table 16. Quantities of social services and non-statutory care used are, generally, recorded from patient questionnaires or retrieved from services records. Average unit costs are then applied to the volume of resource use in order to get a monetary valuation for the identified variables.

Table 16- Social services and non-statutory care variables

Services used	Study reference
Advisor regarding sate benefits or housing issues	Parrott et al., 2006; Barrett et al., 2006
Social worker	Parrott et al., 2006; Barrett et al., 2006
Citizens advice	Parrott et al., 2006
Advisor on legal or debt issues	Parrott et al., 2006; Barrett et al., 2006
Homeless persons agency	Barrett et al., 2006
Social services in general	UKATT Research Team, 2005a
Fire Service (call out)	Barrett et al., 2006

3.5.2.7 Summary of society-level consequences

From the 27 reviewed studies, 12 studies exclude society-level consequences from their analysis (Alwyn et al., 2004; Babor et al., 2006; Corry et al., 2004; Doran et al., 2004; Kunz et al., 2004; Long et al., 1998; Mortimer and Segal, 2005; Shakeshaft et al., 2002; Sobell et al., 2002; Wutzke et al., 2001; Zarkin et al., 2008; Fals-Stewart et al., 2005). Most of these studies rightly claim an agency or health system perspective. The studies by Mortimer and Segal (2005) and Fals-Stewart et al. (2005) state a societal perspective, although this is not the perspective actually undertaken in the analysis. The society-level consequences identified in O'Farrell et al. (1996b) are not taken into account in the ratio of costs to effects. The study presents results according to two perspectives. For the Veteran Affairs Medical Centre (VAMC) perspective, the study conducts a CEA where the ratio of treatment costs (without any economic consequences) to effects is presented. For the health system and criminal justice system perspectives, albeit the study claims that a CBA is conducted, in fact a cost analysis is presented where the benefits are restricted to reductions in health care and legal costs. Nevertheless, the society-level consequences identified in the cost analysis are included here.

A summary of the society-level consequences domains included in the studies is presented in Table 17.

Table 17- Summary of society-level consequences included in the reviewed studies

Domain		N	Study reference
1- Criminal activity	Anticipation of crime	-	
	Consequence of crime	1	(Fleming et al., 2002)
	Response to crime	5	(Barrett et al., 2006; Fleming et al., 2002; O'Farrell et al., 1996b; Parrott et al., 2006; UKATT Research Team, 2005a)
2- Road traffic accidents	Drink driving offences	-	
	Property damage	-	
3- Workplace and productivity Losses	Due to morbidity:		
	Absenteeism	4	(Barrett et al., 2006; Fleming et al., 2002; Nalpas et al., 2003; Lock et al., 2006)
	Reduced efficiency	-	
	Reduced employment	-	
	Workplace accidents	-	
	Due to mortality:		
	Premature death	-	
	Workplace fatalities	-	
	Due to criminal careers	-	
4- Health-Related Quality of Life	HRQoL of family and friends	-	
	HRQoL of victims	1	(Fleming et al., 2002)
	HRQoL population	-	
5- General health care utilization	Accident and emergency services, hospital out-patient, inpatient and day patient visits, etc.	10	(Barrett et al., 2006; Fleming et al., 2002; Gentilello et al., 2005; Lindholm, 1998; Lock et al., 2006; Parrott et al., 2006; Rychlik et al., 2003; UKATT Research Team, 2005a; Palmer et al., 2000; Schadlich and Brecht, 1998)
6- Other specific alcohol treatment utilization	Detoxification, inpatient, outpatient and residential treatment, self-help groups, etc.	5	(Barrett et al., 2006; Bischof et al., 2008; Humphreys and Moos, 1996; O'Farrell et al., 1996b; UKATT Research Team, 2005a)
7- Social services and non-statutory care	Advisor regarding state benefits and housing issues, etc.	3	(Barrett et al., 2006; Parrott et al., 2006; UKATT Research Team, 2005a)

Note: not all reviewed studies include society-level consequences; N, number of studies.

3.5.3 Individual-level consequences

According to the taxonomy of alcohol-related consequences developed in Chapter 2, individual outcomes are divided into the following two domains: 1) health consequences (clinical consequences and health-related quality of life), and 2) patients' expenditure.

The following subsections depict all variables identified along with the instruments used to measure them. The health consequence variables presented are the endpoint of the economic analysis and are pooled from all studies into the correspondent domain, so that the range of individual outcomes included in previous economic evaluations can be explored.

First, the variables included in all studies are presented alongside the instruments used for their measurement. Variables are also classified as discrete numeric or continuous according to how they are measured in each study because statistical techniques differ according to the type of variable. Discrete numeric variables can only take a finite number of values while continuous variables can take any value within the limits of the variable (Anderson et al., 2005). Second, all the outcomes of the economic evaluations reviewed are gathered in a summary table. The degree of quality in terms of how the studies define the endpoint of the economic evaluation is discussed for each study individually.

3.5.3.1 Health consequences: Clinical consequences

Within the category of clinical consequences, variables can be related to alcohol consumption (Table 18), and alcohol-related problems and life expectancy (Table 19).

Table 18- Clinical consequences: alcohol consumption

Variables identified in the studies	N	Type of variable (continuous or discrete)	Example of measurement instruments used
Drinks/ drinking day	8	Continuous- mean number of drinks in a drinking day	Self-reported consumption: - Questionnaire Form 90 AQ - Time Line Follow Back (TLFB) interview - Retrospective Drinking (RD) diary - Quantity-Frequency (QF) question - Steady Pattern Grid
Total grams consumed in X time	3	Continuous- mean grams consumed Discrete numeric- proportion drinking either side of a specified threshold	
Drinks/ X time	7	Continuous- mean number of drinks consumed Discrete numeric- proportion at-risk, where at risk is defined according to number of drinks	
Drinking days/ X time	1	Continuous- mean drinking days Discrete numeric- proportion drinking above certain number of days	
Binge drinking episodes/ heavy drinking	8	Continuous - mean number of binge episodes reported in the time period of interest Discrete numeric- proportion of those who reported any binge episode or more than X binge episodes in the time period of interest	
Percentage Days Abstinent (PDA)	4	Continuous- mean percentage of days abstinent in the time period of interest	
Alcohol status: abstinence vs. relapse	4	Continuous- mean time without relapse Discrete numeric- proportion of abstinent days or relapse days; or proportion of abstinent or relapsing patients in a given period	
Biochemical markers	1	Continuous- mean biochemical values Discrete numerical- proportion having values out of the normal reference range	- Blood analysis

N, number of studies.

Table 18 shows that a wide range of alcohol consumption variables are included in the studies reviewed. Alcohol consumption consequences are directly affected by treatment and explicitly reflect the level of consumption. The most used variables in the studies are binge drinking episodes and drinks per drinking day, both used in eight studies. Abstinence-related measures are also widely used. A challenge faced when reviewing the individual outcomes included in the studies is related to the terminology used. The variables presented in Table 18 meet definitions that vary widely between studies and international literature in general. The World Health Organization standardized nomenclature (WHO, 1992) is presented in the previous chapter. Some of the reviewed studies, however, adopt other definitions. For example, Shakeshaft et al. (2002) define binge alcohol consumption as the consumption of more than six (males) or four (females) standard drinks on any one occasion. The authors report the limits of standard units of alcohol according to an Australian report (National Health and Medical Research Council, 1992).

Alcohol consumption is measured in the studies with different questionnaires such as the Form 90 AQ (Miller WR, 1996) and the Steady Pattern Grid (Sobell and Sobell, 1979). Studies also report

the use of the Time Line Follow Back (TLFB) interview, Quantity-Frequency (QF) questions or a Retrospective Drinking (RD) diary, to measure alcohol consumption.

Table 19- Clinical consequences: alcohol-related problems and life expectancy

Variables identified in the studies	N	Type of variable (continuous or discrete)	Example of measurement instruments used
General alcohol-related problems	9	Continuous- mean number of problems reported; mean score on questionnaires	Self-completed questionnaires: - Alcohol Problems Questionnaire (APQ) - Alcohol Use Disorders Identification Test (AUDIT) - Diagnostic and Statistical Manual of Mental Disorder (DSM), 4th Edition - Health and Daily Living Form - Drinking Problems Index - Drinker Inventory of Consequences
Alcohol dependence	5	Continuous- mean score on questionnaires Discrete numeric- proportion of patients scoring above X score	Self-completed questionnaires: - Severity of Alcohol Dependence Questionnaire (SADQ) - Diagnostic and Statistical Manual of Mental Disorder (DSM), 4th Edition, alcohol dependence element - Leeds Dependence Questionnaire (LDQ) - Alcohol Use Disorders Identification Test (AUDIT) - Alcohol dependence scale (ADS)
Relationship satisfaction/ Marital functioning	1	Continuous- mean score on questionnaires, % of days separated	Self-completed questionnaire: - Marital Adjustment Test (MAT)
Social satisfaction and/ or self esteem	1	Continuous- mean score on questionnaires	Self-completed questionnaire: - Social Satisfaction Scale - Self Esteem Questionnaire
Life expectancy	4	Continuous- mean Life Years Gained (LYG) Discrete numeric- proportion of deaths	Modelling studies: - Complications of alcoholism modelled with probabilities for clinical events - Life-table method measurement with specific mortality retrieved from epidemiological literature Primary studies: - Administrative documents such as patient follow-up procedures, family member contact, and death registries

N, number of studies.

Table 19 gathers the other set of clinical consequences variables: alcohol-related problems and life expectancy. Alcohol-related problems are the outcome of the economic evaluation in many studies and are divided in Table 19 into general alcohol-related problems, alcohol dependence, relationship satisfaction and social satisfaction. Nine studies evaluate the effects of treatment by measuring the

impact of treatment on general alcohol problems using self-completed questionnaires. Studies identify alcohol-related problems using different questionnaires such as: SADQ (Stockwell et al., 1983), LDQ (Raistrick et al., 1994), AUDIT (Babor et al., 2001), ADS (Skinner and Allen, 1982), APQ (Drummond, 1990), DSM (American Psychiatric Association, 1994), Health and Daily Living Form (Moos et al., 1990), amongst others. Alcohol dependence is also another commonly used measure. Life Years Gained (LYG) is the outcome of the analysis in four studies. In modelling studies it is calculated with the application of epidemiological techniques, whilst in primary studies this is informed by patient follow-up procedures, family member contact, and death registries.

3.5.3.2 Health consequences: HRQoL

The taxonomy of alcohol-related consequences divides the category of HRQoL into three groups of variables, according to the valuation of the effects of alcohol treatment on drinkers' HRQoL. When the utility approach is used for HRQoL valuation, QALYs and Years Lived with Disability (YLD) are presented. Another study uses the health profile approach for valuing HRQoL. The monetary approach is not used in any of the reviewed studies. The variables identified in the category of HRQoL are presented in Table 20 below.

Table 20- Clinical consequences: HRQoL

Variables identified in the studies	N	Type of variable (continuous or discrete)	Example of measurement instruments used
QALYs	3	Continuous- mean QALYS	- EQ-5D, HRQoL gain directly attributed to behaviour changes
YLD	1	Continuous- mean YLD averted	- Conversion of effect sizes to disability weights
Health profile	1	Continuous- mean score	- SF 12

EQ-5D, EuroQol 5 dimensions; HRQoL, Health-Related Quality of Life; YLD, Years Lived with Disability; SF 12, Short Form 12.

The EQ5D (Brooks, 1996; Williams, 1990), a generic preference-based measure, is used in two full economic evaluations (Parrott et al., 2006; UKATT Research Team, 2005a) and QALYs are estimated using specific UK preferences. The other study that uses QALYs as an outcome measure is the Mortimer and Segal (2005) modelling study. However, QALYs are computed with disability weights taken from Southard et al. (1997), rather than observed data. Similarly, the YLD computed in Corry et al. (2004) uses weight changes taken from a published study (Sanderson et al., 2004). The Short Form 12 (SF-12) (Ware et al., 1996), which is a health profile measure that in principle can be applied across different patient populations and in different disease areas is used in one study (Lock et al., 2006). As already mentioned, general health profiles are not preference-based measures so they cannot be used to calculate QALYs.

3.5.3.3 Patients' Expenditure

Patient's expenditure is identified in Lock et al. (2006), where the authors identify the travel and time costs and out-of-pocket expenses for other health services. This is the only economic evaluation mentioning the impact of alcohol treatment on the domain of patient's expenses. However, the study does not provide any information regarding measurement and valuation methods of these variables.

3.5.3.4 Summary of Individual-level consequences

Table 21 depicts the individual outcomes identified in each one of the studies from which the methodology used is extracted.

Table 21- Summary of individual-level consequences variables included in the reviewed studies

Domains	Domain variables	Study reference
Alcohol consumption*	Drinks/ drinking day (DDD)	Parrott et al., 2006; Humphreys and Moos, 1996†; Alwyn et al., 2004; † Lock et al., 2006††; Pettinati et al., 1999; Sobell et al., 2002†; Long et al., 1998††; Shakeshaft et al., 2002
	Total quantity (grams)/ X time	Doran et al., 2004; Alwyn et al., 2004†; Bischof et al., 2008††
	Drinks/ X time	Barrett et al., 2006; Fleming et al., 2002†; Parrott et al., 2006; Shakeshaft et al., 2002; Sobell et al., 2002†; Babor et al., 2006; Kunz et al., 2004
	Drinking days/ X time	Sobell et al., 2002†
	Binge drinking episodes/ heavy drinking	Fals-Stewart et al., 2005; Fleming et al., 2002†; Shakeshaft et al., 2002; Sobell et al., 2002†; Humphreys and Moos, 1996†; Kunz et al., 2004; Zarkin et al., 2008; Bischof et al., 2008††
	Percentage of Days Abstinent (PDA)	Long et al., 1998††; O'Farrell et al., 1996b; Parrott et al., 2006; Zarkin et al., 2008
	Alcohol status: abstinence vs. relapse	Nalpas et al., 2003; Rychlik et al., 2003; Schadlich and Brecht, 1998; Alwyn et al., 2004†
	Biochemical markers	Long et al., 1998††
Alcohol-related problems*	General alcohol-related problems	Gentilello et al., 2005†; Long et al., 1998††; Shakeshaft et al., 2002; Humphreys and Moos, 1996†; Alwyn et al., 2004; Lock et al., 2006††; Kunz et al., 2004; Zarkin et al., 2008; Sobell et al., 2002†
	Alcohol dependence	Long et al., 1998††; Humphreys and Moos, 1996†; Alwyn et al., 2004; Lock et al., 2006††; Kunz et al., 2004
	Relationship satisfaction/ Marital functioning	O'Farrell et al., 1996b
	Social satisfaction and/or self esteem	Alwyn et al., 2004†
Life expectancy*	Life years gained (LYG)	Lindholm, 1998; Palmer et al., 2000; Wutzke et al., 2001; Fleming et al., 2002†
HRQoL*	Utility approach (QALYs)	Mortimer and Segal, 2005; Parrott et al., 2006; UKATT Research Team, 2005a
	Utility approach (YLD)	Corry et al., 2004
	Monetary approach	NA

Table 21- Summary of individual-level consequences variables included in the reviewed studies

Domains	Domain variables	Study reference
	Health profile approach	Lock et al., 2006††
Patients' expenditure	Out of pocket health care cost	Lock et al., 2006††
	Travel and time costs due to other health care use	Lock et al., 2006††
	Higher health insurance premium	NA
	Criminal justice related costs	NA

Note: Shakeshaft et al. (2002) includes all variables identified here in an effectiveness index; HRQoL, Health-Related Quality of Life; QALYs, Quality Adjusted Life Years; YLD, Years Lived with Disability; NA, Not Applicable *categories and variables within the health consequences domain; †Cost consequence analysis with no single endpoint specified, ††Cost minimization analysis with no single endpoint defined.

The individual-level consequences included in each one of the 27 studies reviewed are clearly shown in Table 21. Some judgements can be made about the quality of studies in how they include the effects of treatment in the economic analysis, i.e. in how studies define the endpoint of the economic evaluation. This is defined here in three points with the first one having the highest quality. First, high quality economic evaluations are those that have a well defined endpoint for the analysis and also present results in terms of a ratio of the incremental costs to the incremental health effects between interventions, known as the Incremental Cost Effectiveness Ratio (ICER). Second, studies that have a clear endpoint but only present average ratios of costs to effects or do not present any ratio are of middle quality. Third, studies that do not have a clear endpoint and present a range of effects of treatment upon the individual are the lowest quality ones. Unfortunately, many of the economic evaluations of alcohol treatment conducted so far fall in the latter category. This quality issue raises a concern with publication bias. When a study does not clearly define an endpoint at the beginning of the analysis and reports a range of individual measures, there is a possibility that only positive outcomes are presented. Also, many outcomes invite the audience of the study to choose the outcomes of their interest, which might lead to different results from the same study. Even though studies that select a single endpoint for the economic evaluation are higher quality studies, the fact that different endpoints are selected also poses problems related with standardization and comparability. An appraisal of each individual study in terms of the three quality points defined is now presented. The main objective of the economic evaluation is also presented.

1) Endpoint clearly defined and incremental cost effectiveness ratios presented

The endpoint of the economic evaluation is clearly presented in seven studies. These studies also present the results in terms of an ICER and are the highest quality economic evaluations of alcohol treatment.

Incremental cost effectiveness ratios are presented in the following seven studies: UKATT Research Team (2005a); Barrett et al. (2006); Mortimer and Segal (2005); Wutzke et al. (2001); Lindholm (1998); Zarkin et al. (2008); Corry et al. (2004).

The UKATT Research Team (2005a) study presents the results in terms of an ICER and uses QALYs as the outcome measure for the comparison of two psychosocial therapies. Barrett et al. (2006) describe a CEA of referral to an alcohol health worker compared to usual care, presenting the ratio of the incremental cost to the reduction in alcohol units consumed per week. Mortimer and Segal (2005) compare the performance of competing and complementary interventions for prevention or treatment of problem drinking and alcohol dependence and report incremental costs per QALYs. Wutzke et al. (2001) present the incremental cost per LYG for brief intervention training and support strategies. Lindholm (1998) determines the cost effectiveness of providing alcohol advice in primary health care to reduce alcohol intake and uses LYG as the endpoint of the economic evaluation. Zarkin et al. (2008) evaluate the cost effectiveness of nine treatment groups and present ICERs for 3 endpoints: percentage of abstinent days, number of patients avoiding heavy drinking, and number of patients that achieve a good clinical outcome (abstinent or moderate drinking without problems). Corry et al. (2004) conduct a CUA of "current" and "optimal" treatments for alcohol dependency and harmful drinking where the costs and benefits are combined in the form of incremental cost per YLD averted.

2) Endpoint clearly defined and average cost effectiveness ratios presented or no ratio presented

Nine of the studies reviewed select an outcome measure for the economic analysis but present the results in the form of average ratios. Three other studies with a well defined endpoint do not present results in the form of a ratio because they represent situations where treatment is more effective and less costly or where there is no difference in effects. For the latter case the study is a Cost Minimization Analysis (CMA) where just the costs of the alternatives are compared.

Average cost effectiveness ratios are presented in the following nine studies: Nalpas et al. (2003); O'Farrell et al. (1996b), Rychlik et al. (2003); Kunz et al. (2004); Pettinati et al. (1999); Doran et al. (2004); Parrott et al. (2006); Fals-Stewart et al. (2005); and Shakeshaft et al. (2002).

Nalpas et al. (2003) analyse and compare the financial cost and effectiveness of alcohol treatment programs in four hospital-based centres, presenting the ratio of the cost to the time without relapse for each treatment centre. O'Farrell et al. (1996b) assess the cost benefit and cost effectiveness of Behavioural Marital Therapy (BMT) as an addition to outpatient alcoholism treatment with or without additional couples' group therapy. Cost effectiveness results are computed using cost of improvement for percentage of days' abstinence, as well as both husbands' and wives' Marital Adjustment Test (MAT) scores, for each treatment condition. Rychlik et al. (2003) determine whether the economic benefit attributable to acamprosate is maintained in the context of standard care using a prospective cohort study design and use abstinent rates as the outcome of the analysis. Kunz et al. (2004) in their CEA of a brief intervention delivered in an emergency department, present three average ratios for three different endpoints: alcohol-related problems and two measures of alcohol consumption (number of drinks per week and percentage of patients heavy drinking). Pettinati et al. (1999) assess the cost effectiveness of inpatient versus outpatient treatment. An average cost effectiveness ratio is calculated dividing treatment cost by the probability of returning to significant drinking where significant drinking is defined as: three or more alcoholic drinks and/or admission to inpatient or detoxification due to alcohol behaviour. Doran et al. (2004) present average cost effectiveness ratios of the cost per alcohol consumption reduction after at-risk drinkers' detection and intervention by a GP.

Parrott et al. (2006) and Fals-Stewart et al. (2005) clearly select the endpoint of the economic evaluation but present other outcomes measures that are not summarized with costs. This reflects the lack of agreement in a single outcome measure of alcohol treatment. Parrott et al. (2006) describe a range of outcome measures in their economic analysis of two alcohol detoxification programmes in the UK. Four outcomes are presented in the form of a ratio together with costs (units consumed, PDA, DDD and QALYs), while another four are not aggregated with costs (SADQ, PCS, MCS, GHQ). Because ratios of costs with effectiveness and utility measures are presented, the study is classified as a CEA and also as a CUA. Fals-Stewart et al. (2005) present both the percentage days of heavy drinking and the results for relationship satisfaction (Dyadic Adjustment Scale score), but the latter effectiveness estimate is not aggregated with cost estimates. Shakeshaft et al. (2002) derive an effectiveness index based on a range of effectiveness measures: weekly and binge consumption, drinking intensity, number of alcohol-related problems and AUDIT score. The authors use this index to compute an average cost effectiveness ratio and note that their CEA is gross and conservative and that the study is more of an effectiveness one.

No cost effectiveness ratio is presented in the following three studies: Palmer at al (2000); Schadlich and Brecht (1998); Babor et al. (2006).

Three studies clearly identify an outcome measure but do not present a ratio between costs and effects. The Palmer et al. (2000) study determines the cost effectiveness of alcohol detoxification with adjuvant acamprosate therapy. The main outcome of the analysis is LYG with adjuvant acamprosate over standard therapy. The comparison of the acamprosate group with standard therapy reveals lower lifetime costs and higher LYG for the cohort treated with acamprosate. Because adjuvant acamprosate therapy leads to cost savings and improved life expectancy an incremental cost effectiveness analysis is not required. Schadlich and Brecht (1998) also determine the cost effectiveness of alcohol detoxification with adjuvant acamprosate and show that acamprosate is cost saving as it reduces long-term costs and increases the number of abstinent patients. Both Palmer et al. (2000) and Schadlich and Brecht (1998) represent situations of dominance, where the treatment evaluated (acamprosate) is more effective and less costly (more cost saving). When dominance occurs a ratio does not need to be computed.

Babor et al. (2006) define a primary alcohol consumption measure (drinks per week). They find no statistically significant difference between the two interventions compared (brief intervention delivered by doctor vs. by nurse) and do not compute a single cost effectiveness ratio. This study also presents secondary outcomes such as the frequency of heavy drinking and SF-12 quality of life measures but these are not compared to the costs of the interventions and, therefore, are not an endpoint of the economic analysis. The Babor et al. (2006) study can be classified as a CMA as no difference between effects is found and the costs of the two interventions are compared.

3) No endpoint defined: several outcome measures presented

Eight studies do not specify an outcome for the economic evaluation and present several individual-level consequences in their analysis. When costs and effects are presented desegregated studies can be classified as Cost Consequence Analysis (CCA). If costs and effects are desegregated because no difference between effects is found the study is a CMA. The CMAs described here are the ones where several endpoints are presented in the analysis. The studies that fall in this third group are by far the poorest quality economic evaluations of alcohol treatment and exemplify the lack of standardization on outcome measures used in the alcohol field. All the individual-level consequences presented in each study are depicted in Table 21.

Cost consequence analysis are conducted in the following five studies: Fleming et al. (2002); Sobell et al. (2002); Humphreys and Moos (1996); Alwyn et al. (2004); Gentilello et al. (2005)

Fleming et al. (2002) describe the 48-month efficacy and the costs and benefits of Project TrEAT (Trial for Early Alcohol Treatment), a randomized controlled trial of brief physician advice for the treatment of problem drinking. When using the health care perspective, the authors present a range

of individual effectiveness measures without combining them with costs. Sobell et al. (2002) perform a CCA of two very brief interventions with various effectiveness measures presented. Humphreys and Moos (1996) conduct a CCA of AA versus professional outpatient alcoholism treatment. Alwyn et al. (2004) assess the cost effectiveness of home detoxification with brief psychological intervention compared to detoxification only. Gentilello et al. (2005) assess the provision of brief alcohol interventions to trauma patients treated in hospitals and emergency departments. The authors do not derive a summary measure of benefit in the economic analysis.

Cost minimization analyses with no endpoint defined are conducted in the following three studies: Lock et al. (2006); Long et al. (1998); Bischof et al. (2008).

Lock et al. (2006) include many effectiveness measures when comparing screening with brief intervention by nurses versus standard advice. The authors measure alcohol consumption, alcohol-related problems and also present SF-12 scores of HRQoL. The study finds no difference between all the outcome measures described and the authors conduct a CMA. Long et al. (1998) compare the effectiveness and cost effectiveness of an original 5-week inpatient versus a revised two week inpatient (detoxification) and day-patient regime. The authors find equal efficacy between the two regimes and perform a CMA focusing on the lowest cost regime. Bischof et al. (2008) conduct a CMA of stepped care approach for at-risk drinkers.

3.5.4 Costing the alcohol treatments analysed in the economic evaluation

This section aims at providing a general overview of the methodology for costing the alcohol treatments analysed in the 27 selected economic evaluations. In this section, the level of detail when reporting costs, the methods used to determine the volume of resource use (gross-costing or micro-costing), and the valuation of these costs, are briefly analysed. This also informs the development of an economic evaluation framework in the following chapter as one of the components in an economic evaluation is costing the treatments compared. Detailed information regarding the methods used in the identification, measurement and valuation of input costs, for each individual study, is presented in Appendix 4.

Alcohol intervention costs do not differ from other health care interventions, in terms of methodology and challenges. The level of reporting identification, measurement and valuation of treatment costs on the reviewed studies is generally well detailed. However, some studies only present aggregated costs, without detailing unit costs and resource use separately (e.g. Fleming et al. (2002)). Despite this, in general the costing methodology is well described.

The reviewed studies use both gross and micro-costing techniques for costing alcohol treatments. Most of the studies predominantly use the micro-costing approach for input costs while few others

appear to only use gross-costing methods. One study (Nalpas et al., 2003) measures fixed costs in a gross way and variable costs in a more detailed way. In the study conducted by Shakeshaft et al. (2002), the authors only measure variable costs that vary between the interventions without measuring costs that are identical between the interventions (electricity and rent costs are stated as not differing between interventions). The latter approach might not be the best one as in theory all costs related to the intervention and accordingly to the perspective undertaken should be measured and valued. This allows assessing whether transferability of results between settings is applicable and also enables a clear presentation of costs and results.

In general, when a more detailed approach is followed, the health care costs related with the specific alcohol intervention identified in the studies include the following items: pharmaceuticals and other medical supplies, office supplies, laboratory procedures, health care personnel, facility/ building and institutional costs as heating, electricity, maintenance and administration. In almost all the economic evaluations reviewed the volume of resources is collected prospectively thus providing reliable estimates. For example, the cost of the intervention is measured by the average time devoted to the intervention, or number of sessions per participant recorded in attendance logs and the square foot of space of the building/ facility.

Unit costs are obtained in different ways and different levels of precision. For example, the UKATT Research Team (2005a) value the time of therapists spent on treatment delivery from individual salaries, employers' costs and overheads (Netten and Curtis, 2002), which is the most precise valuation method. Nalpas et al. (2003) use values derived from French national security system for each medical visit, which is a less precise micro-costing method. Within modelling studies, Wutzke et al. (2001) use previously published trials for valuing training and support, and Lindholm et al. (1998) use local charges to value nurse and doctor visits. With respect to the use of charges, charges do not always reflect the actual unit cost of the procedure being merely the vehicle for transferring money from payers to providers (Finkler, 1982). Charges can be more appropriate in a situation of private health care. However, in a public health care system they might not reflect resource use and a more bottom up approach is a better choice.

Depending on the perspective of the analysis, patient's expenditures related to the alcohol treatment analysed are or are not included. These are the costs that patients incur directly related to the treatment and can be seen as another component of the intervention cost. Patients' costs due to treatment uptake, such as the time spent in and getting to and from treatment and the travel costs, are estimated in three studies (Fals-Stewart et al., 2005; Fleming et al., 2002; Rychlik et al., 2003). These studies use the HCA to value the time of patients as "time out of work" due to treatment uptake but with assumptions to overcome the gaps in the HCA given that not all patients are

employed. For example, Fleming at al. (2002) assumes that the opportunity costs for subjects out of the workforce (students, homemakers, or unemployed) are equal to the average hourly wage rate. The Rychlik et al. (2003) study attributes gender-specific average income for unemployed patients under the age of 65, whereas no cost is attributed to those over 65.

3.5.5 Limitations of the methodological review

The review of the methods used for the identification, measurement, and valuation of societal and individual-level consequences in previous full economic evaluations has one limitation that is worth mentioning. The main database used in the search, NHS EED, identifies potential economic evaluation studies published after 1995. Therefore, full economic evaluations published before 1995 are not detected in the review. However, this ensures that the most up-to-date economic evaluations of alcohol treatment are identified. The intention is that the review reflects the best quality methods for undertaking economic evaluations in the field. It can be expected that more recent studies provide an improved description and quality of the methods used for the evaluation.

3.6 Discussion

Within the reviewed studies, one study particularly highlights the discussion presented in the previous chapter regarding the level of consequences that should be included in economic evaluations of alcohol treatment and how both the perspective of the analysis and the theory of consumer behaviour affect this decision. This is the Fleming et al. (2002) study where, when a societal perspective is adopted, individual consequences are disregarded. When a health system perspective is adopted the authors include individual health consequences. Apparently, the authors adopt the position that, from a societal point of view, the individual drinker does not matter and that the intervention's objective is to improve overall social welfare, which is consistent with the theory underlying cost benefit analysis. As discussed in Chapter 2, the authors assume a rational consumer (Becker and Murphy, 1988), with perfect knowledge of the consequences of drinking behaviour. The study looks at the harms of excessive alcohol consumption and their reduction through treatment as a public health concern, neglecting individual benefits achieved with the treatment of alcohol problems. In contrast, this is not the approach followed in all the other studies. The other full economic evaluations reviewed, even when adopting a societal perspective, value individual clinical consequences as the main effect of alcohol treatment.

Other reviews of substance abuse treatments, including alcohol treatment, have been conducted for adolescent programs (Homer et al., 2008), continuing care interventions (Popovici et al., 2008), alcohol services (French, 2000), and the economic benefits of addiction interventions (McCollister

and French, 2003). All these reviews provide an important insight into the methodological challenges of economic evaluations in this field. A distinguished feature of the review conducted in this thesis is the focus on full economic evaluations of alcohol treatments and on the methods used for the identification, measurement and valuation of their consequences. Previous reviews included partial economic evaluations and/ or were not focusing solely on alcohol treatment.

This review shows that a societal perspective is not taken into full account and almost half of the studies totally exclude society-level consequences from their analysis. The general health care utilization domain is the most used within society-level consequences. This later finding has also been reported in the review conducted by McCollister and French (2003). Although there may be a sound reason to exclude an item from further analysis, it is important to indicate its existence in the identification phase. Ease of measurement should not be the initial criteria for identification and this is not observed in the majority of the studies reviewed.

The economic data in the studies are limited whether by a short-term prospective study or by retrospective collection methods. Clinical estimates are derived from studies with short follow-up periods (12 months or less), which might not capture the full extent of alcohol treatment impact. Only eight economic evaluations use modelling techniques. Two of the modelling studies evaluate acamprosate treatment for the prevention of relapse and the others focus on brief interventions. An insight into the two studies that evaluate the cost effectiveness of acamprosate (Palmer et al., 2000; Schadlich and Brecht, 1998) reveals that they focus on a dependent population, previously detoxified and with abstinence as an outcome. Abstinence rates at the end of the trial informing the studies are assumed to persist after treatment follow-up and only society-level consequences related to health care utilization are included in these studies. These two studies focus on a limited number of alcohol-related diseases and crudely assume that abstinence reduces the probability of these diseases which translates into reduced health care costs and also life years gained in the Palmer et al. (2000) study. The efficacy assessment on Palmer et al. (2000) and Schadlich and Brecht (1998) is based on abstinence rates and, for this reason, improvement in morbidity and mortality due to lower levels of alcohol consumption is not modelled. No modelling study attempts to model the natural flow of patients with alcohol problems after treatment uptake.

There is a lack of agreement with respect to the best measure of effectiveness and time frame over which measurement takes place. Many studies use abstinence as the only endpoint of the economic evaluation. Some studies use test scores as an outcome measure for measuring various alcohol-related problems. The use of scales or test scores as an outcome measure poses comparison difficulties as the scores obtained are not inter-convertible. The studies reviewed identify, measure, and value “alcohol consumption” differently, even when assessing similar treatments and do not

give an explanation for the variables used. Different measures of alcohol consumption are identified, such as: drinks per drinking day, drinks per week, drinking days per week, drinking intensity, binge drinking episodes, etc. Sometimes studies even report a range of these variables. This discrepancy in alcohol consumption measures and, more specifically, in the endpoint of the economic evaluation, makes comparisons between treatments in terms of effectiveness rather difficult. Previous reviews have also noted the lack of consistency and standardization in the methods used in studies of substance abuse interventions (Popovici et al., 2008; French, 2000).

Most of the reviewed studies are cost effectiveness analyses (24 out of 27). Full evaluations included in previous reviews were also mainly cost effectiveness analyses (French, 2000; Homer et al., 2008; Popovici et al., 2008). Measures of HRQoL capturing life years and morbidity are not extensively used in the alcohol field. Only two primary studies are CUA and use the standard valid questionnaire EQ-5D. Two modelling studies are cost utility analysis and use YLD and QALYs as an outcome measure (Corry et al., 2004; Mortimer and Segal, 2005). However, HRQoL valuation in these two studies is not based on patients' preferences and is taken from secondary data.

3.6.1 Recommendations for future full economic evaluations of alcohol treatment

The recommendations provided here are those related to the findings of this particular review. More general recommendations in economic evaluations have been described in previous reviews (French, 2000; Homer et al., 2008; McCollister and French, 2003; Popovici et al., 2008) and other general economic evaluation literature (Drummond and McGuire, 2001; Drummond et al., 2005c; Gold et al., 1996b).

1. The perspective adopted by an economic evaluation determines which costs and consequences are considered and should be clearly stated. With a limited perspective, the study may be both more tractable for the evaluator and of direct relevance to the decision maker (Godfrey, 2006). However, due to the range of problems that alcohol consumption causes an intervention may yield large overall social benefits if the wider costs and consequences are taken into account. Homer et al. (2008) and French (2000) have also recognized the importance of a broad societal perspective and McCollister and French (2003) pointed out the importance of including criminal activity in economic evaluations as it represents the greatest economic benefit of addiction interventions. Society-level consequences should be identified early-on in studies using the taxonomy of consequences developed in the previous chapter and a societal perspective should be adopted.

2. Alcohol treatment has long-term health and social benefits that should be included in an economic evaluation. Long-term outcomes can be assessed when a long-term follow-up study

is conducted, usually combined with modelling techniques. Previous reviews have also mentioned the need for long-term data and modelling techniques (Homer et al., 2008; Popovici et al., 2008; French, 2000). Moving away from short-term outcomes will make it possible to know the trend of economic benefits in the long-term and assess whether the immediate effects of treatment lead to other long-term outcomes.

3. Both short and long-term consequences may be difficult to measure in a prospective study with patients. For example, while those continuing to drink hazardously may frequently drink and drive, the probability of an accident on each individual occasion is low. In addition, only modelling can capture the potential gain in life years achieved with a treatment for alcohol problems. Therefore, unless studies have very large sample sizes and long follow-up periods such effects may be difficult to detect. Therefore, this thesis argues that a modelling approach is paramount to the economic evaluation of alcohol treatment. In addition, the uncertainty in the economic evaluation inputs should be incorporated in the modelling results through the use of sensitivity analysis. Long term modelling techniques that establish a link between drinking patterns, health consequences and alcohol treatments effectiveness and cost effectiveness should be developed. The framework presented in the following chapter provides a dynamic model that allows for relapse and natural recovery.

4. All full economic evaluations should include a measure of the impact of treatment on the individuals under treatment. Many earlier economic evaluations of drug and alcohol treatments were confined to population level consequences. However, the omission of individual-level consequences could distort the assessment of the relative worth of different interventions, just as the exclusion of population level or long term consequences could (Godfrey and Parrott, 2000).

5. This thesis argues that a wider population with alcohol problems is eligible for treatment and confining treatment effectiveness to abstinence neglects other potential individual and social benefits. A treatment that has the potential to reduce drinking should represent a value to society and economic evaluations should be able to reflect this.

6. Several variables are usually used to measure alcohol consumption. Even though alcohol consumption variables can be compared by making the appropriate conversions with respect to standard units, time period and/or measurement unit, this thesis recommends the standard use of grams of alcohol per day if a study reports alcohol consumption measures.

7. The extensive use of natural effectiveness estimates for the economic evaluation of alcohol treatment has some fundamental problems. CEA is based on a single program outcome but

alcohol treatment results in a variety of outcomes which poses numerous problems related to comparability and standardization (Sindelar et al., 2004). Therefore, cost benefit analysis and cost utility analysis, because they address the issue of outcome valuation, might be preferable as they allow an assessment of broader choices than a simple CEA.

8. Health care providers and policy makers use full economic evaluations to make decisions on the allocation of scarce resources between competing programmes. For such a decision to be made treatment outcomes should be comparable and a single outcome measure should be used. Preference-based measures such as QALYs are advocated as a comprehensive health measure that permits comparison between different health technologies (Drummond and Pang, 2001; Drummond et al., 2005b; Gold et al., 1996a; NICE, 2004). Therefore, outcome scales/tests should be replaced by a standardized health measure that facilitates comparison between interventions and patient groups and captures quality and quantity of life, such as QALYs.

9. The methodological review includes two CUA that use the EQ5D to calculate the QALYs gained with the intervention (Parrott et al., 2006; UKATT Research Team, 2005a). These two studies show that the HRQoL of individuals with alcohol use disorders is poorer than that of a reference population and that QALYs are gained with treatment. However, this QALY gain is not statistically significant. In contrast, improvements in alcohol consumption variables are significant in those two studies. Some possible explanations for these results can be advanced and these are: 1) the EQ-5D used in both those studies, although presenting all the advantages of a generic preference-based measure, does not include facets of quality of life related to alcohol consumption, 2) both studies have a short follow-up (6 to 12 months) that might not capture changes in HRQoL of an alcohol drinking population and, it might be that, although there is a large scope for improvement in alcohol consumption measures, the improvement in QALYs can only be observed with a lag in time, 3) the nature and severity of problem drinking causes a delay in improvement in HRQoL. In addition, Fayers and Hand (1997) have mentioned that the variability in health-related quality of life is often greater than the variability in clinical endpoints and the sample size of studies may be insufficient to detect significant differences in such economic endpoints. Investigation into the relationship between QALYs and indicators of drinking behaviour, the extent to which improvement in alcohol consumption can be linked with QALYs gained and the time period for this to be detected, warrants closer scrutiny. More research should also be done in order to determine whether the small increase in QALYs in the short term persists for longer periods and whether generic HRQoL instruments are appropriate for a population with alcohol problems. A longitudinal study, where an alcohol drinking population is followed for a long period and where consumption levels and HRQoL

are measured, would help in answering some of these questions. In fact, many countries are now using cost per QALYs estimates for reimbursement and adoption decisions. If alcohol treatment programs are to compete with other healthcare interventions for limited resources, the relationship between alcohol treatment outcomes and QALYs is of great importance so that there is a single, comparable outcome measure.

10. A previous review strongly recommended the use of CBA (Popovici et al., 2008). While the use of utility measures is currently limited, so is the use of monetary measures of individual health benefits or more global measures of the total value of treatment interventions through community level global willingness to pay measures. Most existing so-called CBA studies have not included any measure of individual health effects and have been excluded from this review. Alcohol treatments are in general funded through health care mechanisms and CUA techniques are increasingly being used to assess other health care interventions so this thesis currently recommends the use of a CUA design.

Many issues are raised above and can be summarized as follows:

1. Society-level consequences should be identified early-on in studies, using the taxonomy of alcohol-related consequences and a societal perspective should be adopted
2. Long-term health and social benefits should be incorporated in a full economic evaluation of alcohol treatments
3. Modelling techniques should be developed in order to reflect drinking behaviour over time and to know the trend of economic benefits over the long-term.
4. All full economic evaluations should include individual-level health consequences of alcohol treatments.
5. A broader population with alcohol problems not confined to an alcohol dependent population should be considered and it should be recognized that abstinence-based measures neglect other potential individual and social benefits.
6. A standard measure of alcohol consumption, such as gram/day, should be used.
7. Analysts should move away from the use of multiple natural effectiveness measures, if a decision on the best allocation of resources is to be made.
8. Standardized health measures that facilitate comparison between interventions and patient groups and capture quality and quantity of life, such as QALYs, should be used.
9. Studies should try and link alcohol consumption measures to QALYs so that there is a single, comparable outcome measure.

10. Cost utility analyses should be conducted.

The main task in the following chapter is to consider as many recommendations generated by this review as possible in a decision analytical model for alcohol treatments and also to develop a tool that promotes consistency and uniformity in economic evaluations of alcohol treatment. This thesis does not aim at generating all the data for the incorporation of a societal perspective in the economic evaluation of alcohol treatments (point 1). In addition, an empirical study of the relationship between QALYs and drinking outcomes is beyond the scope of this thesis (point 9). These are issues for future research, the results of which would have direct relevance for the extension of the model described and tested in the next chapters of the thesis.

3.7 Conclusion

This review extends previous reviews by: 1) depicting all alcohol-related consequences included in previous studies; 2) focusing on full economic evaluations of alcohol treatment; 3) providing a clear description of the systematic search; 4) not constraining the review to geographical areas, types of treatment or treatment populations; and 5) providing several methodological recommendations for future full economic evaluations of alcohol treatment. The literature is still rather scarce in this area and it is hoped that the recommendations provided in this chapter will stimulate further work to draw harmony between studies. This chapter calls for an improvement in the quality of studies and for the need to construct an approach that can provide useful guidance for decision making. Only rigorous full economic evaluations can inform decisions on the allocation of resources to cost effective alcohol treatments.

Chapter 4. Economic model of drinking behaviour

Reviewing published economic models for the assessment of alcohol treatments, in the previous chapter, suggests that the literature is dominated by studies mainly based on premature mortality outcomes from those abstinent from drinking after an intervention. Existing modelling studies, when adopting a lifetime horizon, usually assume that the outcomes of the trials remain the same for patients' lifetime and do not attempt to model the natural flow of patients with alcohol problems. Mortimer and Segal (2005) present QALYs but these are based on disability weights determined by experts rather than empirical data from the relevant population (Stouthard et al., 2000).

There is evidence both on the individual effectiveness of different alcohol interventions (prevention, treatment and enforcement) based on short term drinking and health outcomes (Raistrick et al., 2006) and on the epidemiological risks associated with different patterns of drinking over time (Rehm et al., 2003b). However, the variety of alcohol abuse treatment approaches and the complexity and multiplicity of treatment outcomes might have created a lag in the advance of economic analysis of alcohol treatment. Alcohol consequences may be difficult to measure in a prospective study due to insufficient follow-up time. Therefore, determining the cost effectiveness and predicting population outcomes of different alcohol treatments requires modelling of the long term consequences of changing drinking patterns.

Previous economic evaluation models of alcohol treatment are here extended by: 1) exploring patterns of drinking rather than whether people are abstinent or not; 2) providing a dynamic model that allows for relapse and natural recovery; 3) including mortality, morbidity, health-related quality of life and long term costs savings; 4) considering a wider population with alcohol problems, not confined to an alcohol dependent population.

This chapter develops a decision analytic model to assist decision makers with regard to the cost effectiveness of alcohol treatment. Decision analysis is an established framework to inform decision making under conditions of uncertainty (Hunink et al., 2001; Weisntein and Fineberg, 1980) and such a framework is lacking in the alcohol field. Costs, effects and cost effectiveness are not known with certainty and this uncertainty is embedded in the model.

Economic analyses are increasingly used to inform health policy decisions and health-care systems in many countries are making these decisions using cost effective analysis to determine which interventions should be reimbursed from collective funding (Taylor et al., 2004), where both costs and effects are taken into account. For example, in England and Wales NICE makes national policy decisions on whether appraised health technologies should be made available through the public health care system. The framework used to achieve "some of the key tasks in reimbursement

decisions" is a decision analytical modelling approach (Claxton et al., 2002). This provides an explicit method to integrate the decision to adopt a technology and to demand additional information by doing further research (Claxton, 1999). The basic concepts of decision modelling in cost effectiveness analysis have been extensively covered in the literature (Drummond et al., 2005c; Hunink et al., 2001; Briggs et al., 2006).

4.1 Objectives

The remit of this chapter is to use long term modelling techniques to establish a link between drinking patterns, health consequences and alcohol treatment effectiveness and cost effectiveness. It describes a method to build a decision analytic model that simulates the drinking patterns of a cohort over lifetime. The model is designed to estimate the overall change in health-related quality and quantity of life resulting from changes in drinking behaviour. It has the potential to provide essential information regarding the cost effectiveness of alcohol treatments and which treatments represent better value for money, as well as to promote consistency and uniformity on economic evaluations of alcohol treatment.

The following section deals with modelling techniques in economic evaluation. This is followed by several sections describing the methodological development of the model of drinking behaviour where decisions regarding specific model structure, type of model inputs and generation of results are taken. This chapter deals with the development of the theoretical model providing a framework for the remaining chapters of this thesis and it can be seen as a foundation on which the following chapters rest. The next chapter generates country-specific model inputs and the last two chapters illustrate the functionality of the model with two case-studies.

4.2 Modelling in economic evaluations

4.2.1 Why use modelling techniques?

Before explaining the model structure a justification of why a modelling approach is being used should be provided. Modelling techniques are used here for two reasons.

First, the previous chapters show that alcohol has a range of both short and long term consequences and that these may be difficult to measure in a prospective study. This suggests that even in prospective studies there is a need for a modelling component for estimating the overall change in health-related quality and quantity of life which results from changes in drinking behaviour. In order to make an informed decision of whether to adopt a given alcohol treatment, an assessment of the costs and health outcomes must be made over the longer period.

Second and more general, decisions to adopt, reimburse or issue guidance on the use of health technologies are increasingly being informed by an explicit cost effectiveness analysis of the alternative interventions (Hjelmgren et al., 2001). This requires an analytical framework which can represent decision problems explicitly, combine evidence from a range of sources and facilitate the extrapolation of costs and effects over time and between patient groups and clinical settings (Claxton et al., 2002) and decision analytical modelling provides such a framework. The circumstances where a mathematical model should be employed have been described by Buxton et al. (1997) as the following: 1) the "temporal extrapolation" of cost and effectiveness parameters beyond the data observed in a clinical trial; 2) the linking of intermediate clinical endpoints to final health outcomes; 3) the "contextual extrapolation" of the results obtained in one clinical setting to other settings; 4) the analysis of head-to-head comparisons of alternative competing interventions where such direct comparisons have not been made in clinical trials and; 5) the attempt to inform resource allocation policy decisions in the absence of "hard data". By using a modelling approach trial, observational and epidemiological data can be brought together

4.2.2 Structure of decision analytic cost effectiveness models

Decision analytic models in cost effectiveness analysis identify optimum treatment decisions in the context of uncertainty about future states of the world (Sculpher et al., 2000). Different types of economic evaluation models can be used to combine information from a variety of sources and to assess the policy implications for decision making.

Determining the structure is a key initial stage in the development of a model. The extent to which the availability of data should determine the structure of a model is an area of disagreement in the literature (Philips et al., 2006). Sonnenberg et al. (1994) argued that the model structure should not be influenced by the quality, level and availability of data and should reflect the disease process. Accordingly, Sculpher et al. (2000) and Philips et al. (2006) recommended model structure to be as simple as possible, consistent with the stated decision problem and theory of disease and not defined by data availability or health service inputs alone. Nevertheless, the model should be tractable to make it comprehensive to users and some constraints end up being reflected in its structure. Model structure is usually determined by considering the relationship between the inputs (natural history of disease, clinical pathways, evidence of the intervention's effectiveness, utilities associated with health states, costs, etc), and the output measures required by the decision maker (Brennan et al., 2006). Therefore, Brennan et al. (2006) suggested that practical considerations such as availability of data, the background and skill of the researcher and the type of software available also have a considerable weight on the choice of model structure.

Model structures can be divided in aggregate or "cohort" models and individual-level models, also called Patient-Level Simulation (PLS) models (Brennan et al., 2006). Aggregate models examine the proportions of the population undergoing different events with associated costs and utilities and require large population numbers, homogeneous sub-groups and linear interactions. Individual-level or PLS models sample individuals with specific attributes and follow their progress over time and, despite being more flexible, require replications with different random numbers to estimate expected values (Brennan et al., 2006). PLS accounts for variability in all included parameters which cannot be reduced through measurement or further study, but can be characterized with empirical distributions. Variability is related to differences amongst individuals (age, gender, comorbidities, body weight, etc.) that will always exist and is also known as "first-order uncertainty" or stochastic uncertainty, which is the uncertainty arising from randomness in the data studied. This is different from uncertainty, i.e. the lack of knowledge regarding the true value of a quantity for a given patient, which can be characterized with a distribution and reduced with further investigation (Brennan et al., 2006; Culyer, 2005). Both cohort and PLS models can also take into account the potential interaction between individuals. Barton et al. (2004) stated that interaction between individuals needs to be taken into account in two main circumstances: "when modelling infectious diseases, where the risk of an individual catching the disease depends on how many other people already have it; and when constraints on resources mean that the choice of treatment for one patient affects what can be given to another" (Barton et al., 2004, pp. 115). If interaction is important and PLS modelling is undertaken the model follows a Discrete Event Simulation (DES) structure, whereas if PLS modelling is not undertaken and interaction remains important, the model can be a cohort system dynamics one or a Markov chain model. When interaction is not important there are three possible structures: decision tree, Markov model and individual sampling model depending on whether pathways can be represented by probability trees, whether a Markov model does not require an excessive number of states, and whether many health states would be required to build a Markov model and so PLS needs to be undertaken, respectively.

The analyst should choose the type of model with reference to the time dependence of the disease events, selecting the simplest format possible that adequately reflects the disease (Sonnenberg et al., 1994). In Markov models discrete health states are clearly defined and the disease process has a clear time dimension. Markov models are state transition models that better represent chronic conditions given the time dimension of such diseases process. Their main benefit is the easy representation of recurrent events. Markov models for cohorts can be deterministic (with expected values) or stochastic (using Monte Carlo simulation for model transitions). Decision trees are simpler models where the health states are defined by chance nodes and time is not modelled explicitly. In decision trees, all possible patient pathways are shown explicitly, with associated

probabilities and outcome measures and they are appropriate if the time frame is short and if patients' mortality between strategies does not differ. Decision trees for cohorts can be deterministic (with expected values) or stochastic (using Monte Carlo simulation for the mean value of each decision option).

When interaction between individuals needs to be taken into account discrete event simulations can be chosen. However, these models require specialist software or programming skills to construct, and running times are much longer than for other types of models. Patient level models without interaction (individual sampling model) track individuals taking into account their heterogeneous characteristics but individuals progress through the model independently of each other and of environmental constraints. These models generate a large number of simulated patient histories and evaluate results with a sampling algorithm. The output from a (pseudo) random number generator is used to determine which sequence of health states is followed over time by the individual patient under consideration. This can be done by using Monte Carlo simulation. Individual sampling models with no interaction may be untimed, as in PLS decision tree models or timed, as in PLS Markov models. One of the advantages of PLS lies in modelling multiple co-morbiditities which depend on multiple attributes/ covariates. Furthermore, this approach can be modified to simulate the "time to next event" rather than using equal time periods, by matching a single random number against a probability distribution. Therefore, the time spent in a state need not be an exact multiple of a fixed-length cycle. So, these models can incorporate time and patient history dependency in transitions, as the model can "record" the event history for each individual as he or she progresses through the model (Barton et al., 2004; Brennan et al., 2006).

Usually, health care modelling requires extensive sensitivity analysis to handle the inevitable uncertainties if the results are to be used for decision making. According to NICE (2008) the effect of uncertainty should be represented by Probabilistic Sensitivity Analysis (PSA). In principle, decisions on the type of model and the approach to sensitivity analysis are independent of one another, although in practice there may be limitations imposed by the available computing power and time (Barton et al., 2004). A limitation of PLS arises when uncertainty in model parameters is to be taken into account. In cohort models, parameters can be defined as random variables, and Monte Carlo simulation propagates this parameter uncertainty through the model, providing estimates of uncertainty around expected cost effectiveness. This is distinct from the use of Monte Carlo simulation in PLS where the model parameters are fixed and a random number is used to determine the path of each individual patient, reflecting 1st order uncertainty (Stinnett and Paltiel, 1997). This uncertainty is related to the fact that the results for individual patients entering the model will vary, even when the model parameters are defined with certainty. To reflect parameter

uncertainty in PLS requires a two-level simulation, where variability between patients is allowed (1st order uncertainty) and uncertainty in model parameters is also allowed (2nd order uncertainty). Cohort models do not require the simulation of individual patients and hence require fewer simulations than PLS and less time to evaluate as expected values for a cohort of patients are estimated during each simulation. This facilitates the correct estimation of expected costs and effects for nonlinear models, the estimation of decision uncertainty arising from parameter uncertainty, and the implementation of value of information techniques (Claxton, 1999). Furthermore, the issue of variability addressed by PLS can also be addressed within a cohort framework by employing a two-level simulation (Griffin et al., 2006).

4.2.3 Selection of the type of economic model for the economic evaluation of alcohol treatments

The first step in the development of a decision analytical model for alcohol treatments is the selection of the type of model. The choice about model structure and complexity is always a trade-off between descriptive realism and tractability in terms of computational burden and data requirements (Claxton et al., 2005). The chosen structure is one that provides unbiased estimates of expected costs and effects and also allows exploring the effects of uncertainty in the model inputs.

The selection process of the appropriate modelling structure, according to a range of conditions, has been described in previous studies (Barton et al., 2004; Brennan et al., 2006; Sculpher et al., 2000), and presented in the above section. Given that the individuals with alcohol problems can be regarded as independent, interaction between individuals is not considered. This leaves us with the choice between a cohort model or a PLS with no interaction. While aggregate cohort models adopt assumptions that may produce inadequate solutions, individual-level models may be more time consuming to develop and to run.

The most common type of cohort models that do not involve interaction are decision trees and Markov models (Barton et al., 2004). Despite the simplicity of decision trees structure these would not be applicable to what this thesis is concerned with. In fact, the model of alcohol consequences shall have a long time frame and patients' mortality vary with the strategies analysed throughout time. Therefore, a decision tree would become unmanageable. The adopted model structure is a cohort Markov model. The decision of a cohort Markov model over a PLS approach becomes clear after reviewing the literature that compared the two types of models.

Karnon (2003) compared cohort Markov model and PLS techniques for the economic evaluation of alternative adjuvant therapies for early breast cancer. The author found close results for both techniques which suggested that the use of one model's results over the other would lead to the

same resource allocation decision. It was concluded that the benefits of PLS, in terms of increased flexibility, were outweighed by the far greater time required to develop and evaluate the PLS model. Therefore, the author argued that given the substantially increased analytic inputs required by the PLS model, a cohort Markov process would have been the optimal technique for the reported evaluation. Similarly, Griffin et al (2007) argued that the parameterization and computational burden of PLS compared with cohort models suggests that analysts should carefully access whether these additional costs can be justified in terms of their impact on the ultimate decision. As explained in the section above, the potential conflict between PSA and PLS is pertinent in any health care system where PSA is considered the appropriate way by which the combined uncertainty in decision model parameters can be reflected. This is the case in the context of the UK NHS, where NICE has specified a reference case, within its guidance on the methods of technology appraisal, where PSA is explicitly recommended (NICE, 2008). This guidance has an impact on what is required for evaluation of health technologies internationally (Claxton et al., 2005).

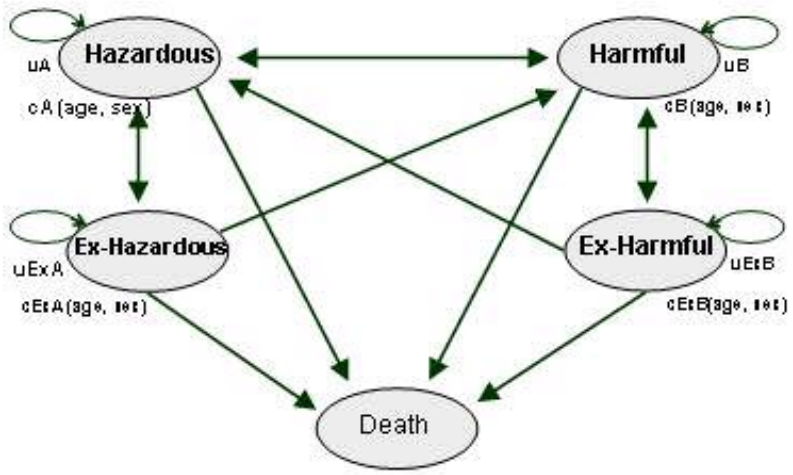
4.3 Modelling lifetime QALYs and health care costs from different drinking patterns over time: a Markov model

In this section, a probabilistic lifetime Markov model using the cohort simulation approach and examining the proportion of the population undergoing different events with associated costs and outcomes is built (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998). The main outcome measures are QALYs and health care costs. This section presents the general Markov structure. This is followed by a description of the type of country-specific data required by the model and the generation of the long-term model outcomes. An explanation of how the model deals with discounting, uncertainty and heterogeneity is then provided. The final five sections put the developed model into the context of decision making, present the potential use of the model to inform the need for conducting further research, discuss the application of the model for different settings, present the limitations of the adopted structure and conclude, respectively.

4.3.1 Markov model structure

A Markov model is adopted (Sonnenberg and Beck, 1993) due to its ability to model recurrent events and mortality, which is an ongoing risk over time. The Markov model of alcohol consumption is built in Microsoft Excel® and is presented in Figure 2 below.

Figure 2- State transition diagram



States utilities variables: *uA*, utility of Hazardous; *uExA*, utility of Ex-Hazardous; *uB*, utility of Harmful; *uExB*, utility of Ex-Harmful

States costs variables: c*A*, cost of Hazardous; c*ExA*, cost of Ex-Hazardous; c*B*, cost of Harmful; c*ExB*, cost of Ex-Harmful

States represented by the ovals and transitions between the states represented by the arrows

The Markov states in Figure 2 are represented by the ovals and possible transitions between these sates are shown by the arrows. Arrows leading from a state to itself indicate that the patient may remain in that state in consecutive cycles. Only certain transitions are allowed. For example, a transition from harmful to ex-hazardous is not allowed. Transition probabilities are assigned for the flow of patients between these drinking states over a discrete time period known as the "Markov cycle".

A hypothetical cohort of patients is modelled through the cycles according to transition probabilities for each drinking category. The whole cohort starts the model in cycle zero or baseline, in the hazardous or harmful drinking states, according to the proportion of patients in each one of these states in the setting of the analysis. Running the analysis over a large number of cycles builds up a profile of how many patients are in each state of the model over time. Then, by attaching estimates of resource use and health consequences to the states in the model, the long term costs and outcomes are estimated and their contribution to the overall prognosis depends on the length of time (number of cycles) spent in each state.

In order for the Markov process to terminate, it must have at least one state that the patient cannot leave. This is represented by the "death" state in the model, called an absorbing state because, after a sufficient number of cycles have passed, the entire cohort will have been absorbed by that state. The transition to the death state is dictated by two transition probabilities, a transition probability equal to the all-cause mortality excluding alcohol-related conditions (baseline mortality) and an alcohol-specific mortality transition probability. Both transitions are time-dependent and modelled as a function of the patient's age. This is explained in a section below.

The Markov health states are defined in the form of mutually exclusive states of drinking behaviour in the form of alcohol consumption. This structure is consistent with alcohol drinking behaviour as a recurrent behaviour with susceptibility for relapse. The drinking process cannot be modelled as a standard chronic disease because patients can move to more serious drinking groups and can also move from more serious drinking levels to less serious ones. The review conducted in the previous chapter shows that the majority of economic evaluations of alcohol treatment use individual measures of consumption as an outcome of alcohol treatment. However, there is a general lack of consensus regarding which measure of alcohol consumption should be used and how many measures are used in a single analysis. As discussed in the previous chapter, it is clear that there should be a standard measure of alcohol consumption in economic evaluations of alcohol treatment. The present model suggests the use of grams of alcohol per day (g/day) for the definition of the Markov drinking states. This allows classifying patients according to the amount drank per day and also allows following individuals through their lifetime by classifying them into a drinking category. Such a measure makes clinical data comparable as different standard units can be taken into account when calculating g/day.

4.3.2 Time horizon

A lifetime horizon is adopted. In a decision making context, economic evaluation studies should adopt a time horizon that is sufficiently long to reflect all the key differences between options in terms of costs and effects and hence cost effectiveness (Briggs et al., 2006). The economic model adopts a lifetime horizon as alcohol treatments have a potential to improve alcohol-related mortality and long-term morbidity by changing drinking behaviour. Evaluation of alcohol treatments on a short-term would seriously underestimate expected health outcomes and overestimate costs and uncertainty, since the benefits of alcohol treatment can be expected to accumulate over a much longer period of time.

4.3.3 Cycle length

A one-year cycle length is adopted. The choice of cycle length should be driven by what is known about the underlying disease process and be the minimum interval over which pathology and/ or symptoms in patients is expected to alter (Sculpher et al., 2000). Technically, the cycle length should not be determined by the availability of data with which to populate the model as rates over any interval can be translated to model probabilities for a given cycle length (Miller and Homan, 1994). Sonnenberg and Beck (1993) suggested that for a model that spans the entire life history of a patient and relatively rare events the cycle length can be one year.

The current model uses one-year cycles for the following reasons: 1) reduction of the complexity of the model as a monthly cycle length, for example, would result in a 12-fold increase in evaluation time over a yearly cycle length, and 2) it has been shown that the natural course of alcohol dependence states does not usually fluctuate on a monthly basis (Dawson et al., 2007).

4.3.4 Markov states as drinking categories

States should be chosen to represent the underlying biological process of the disease in question (Sculpher et al., 2000). The Markov states are defined by drinking categories which allows following the drinking history of individuals. Only four drinking categories are defined in order to keep the number of states as small as possible so the model is kept simple in analytical terms. The main objective of this structure is to follow patients, according to their alcohol consumption defined in grams per day, through their lifetime. The effect of alcohol treatment can then be captured as a change in drinking behaviour. Patients in each state have different morbidity rates and associated costs, different utilities and different mortality rates.

The four drinking categories are: hazardous, harmful, ex-hazardous and, ex-harmful. Patients start the model in two categories according to the proportion in each category at baseline. The drinking categories by gender, defined in grams of alcohol consumed per day, in **cycle 0** (or baseline) are the following two:

1) Hazardous drinking (A): ≤55 g/day (women); ≤80 g/day (men)

2) Harmful drinking (B): >55 g/day (women); >80 g/day (men)

In **cycle 1 and following cycles (n+1)**, patients can be in one of the following five categories:

1) Hazardous drinking (A): 20-55 g/day (women); 28-80 g/day (men)

2) Harmful drinking (B): >55 g/day (women); > 80 g/day (men)

3) Ex-hazardous drinking (ExA): <20 g/day (women); <28 g/day (men) and hazardous (or ex-hazardous) drinking in previous cycle

4) Ex-harmful drinking (ExB): <20 g/day (women); <28 g/day (men) and harmful (or ex-harmful) drinking in previous cycle

5) Death (D): patient is dead

As women often experience higher risks of disease and injury for less volume of consumption, the respective drinking categories for women have lower means (Rehm et al., 2007a). The definition of the harmful drinking category is based on the definition of "drinking category III" presented by the WHO (Rehm et al., 2004). The limits used to define the ex-categories are based on the definition of "sensible drinking" presented in the National Alcohol Strategy for England (Department of Health, 2007) which defines sensible drinking for women as drinking between 2 and 3 units a day, and for men as drinking between 3 and 4 units a day. Units are converted to g/day taking into account that one unit corresponds to approximately 8g of alcohol in the UK. Therefore, in terms of alcohol consumption, the ex-categories are defined as drinking below 20 g/day for woman (2.5 units a day) and drinking below 28 g/day for men (3.5 units a day). Hazardous drinking in cycle 0 is solely defined by an upper bound which, at first instance, might seem like a mistake. This is not the case, and such an interval is assumed so that patients drinking at what is defined as "sensible drinking" at baseline can also undertake alcohol treatment. It might be the case that those patients drinking at lower levels at baseline were actually drinking at higher levels before and are still at risk for alcohol-related diseases and, therefore, are eligible for treatment given their past history and susceptibility for relapse. There is no explicit category for starting in a sensible drinking level as this model focuses on evaluation of alcohol treatments. Had the intention been to build a model for population level interventions such as prevention, legislation and enforcement, then such a category would have a meaning as the benefits of preventing individuals from entering harmful or hazardous states would have to be accounted for. The ex-categories are defined similarly in terms of g/day, i.e. both ex-hazardous and ex-harmful states include patients drinking less than 20 g/day (women) or less than 28 g/day (men). They are distinguished by the state where the patient was in the previous cycle (hazardous or harmful or any of the two ex-states), for patient history can influence the risk of death and morbidity. This breakdown is further explained below.

A generic transition matrix presenting the transitions between Markov states and associated probabilities is presented in Table 22 below.

Table 22- Generic transition matrix for the Markov model of alcohol behaviour

		Cycle n +1				
		Hazardous (A)	Harmful (B)	Ex-Hazardous (ExA)	Ex-Harmful (ExB)	Death (D)
Cycle n	Hazardous (A)	tpA2A	tpA2B	tpA2ExA	0	tpA2D[1]
	Harmful (B)	tpB2A	tpB2B	0	tpB2ExB	tpB2D[1]
	Ex-Hazardous (ExA)	tpExA2A	tpExA2B	tpExA2ExB	0	tpExA2D[1]
	Ex-Harmful (ExB)	tpExB2A	tpExB2B	0	tpExB2ExB	tpExB2D[1]
	Death (D)	0	0	0	0	1

[1] Time-dependent transition probability.

Note: tp, transition probability; tpA2A, transition probability from hazardous to hazardous; tpB2A, transition probability from harmful to hazardous; tpExA2A, transition probability from ex-hazardous to hazardous; tpExB2A, transition probability from ex-harmful to hazardous. Example: a hazardous patient can remain in hazardous, transit to harmful, transit to ex-hazardous or transit to death.

The transition matrix in Table 22 specifies the generic transitions between drinking categories for any given cycle of the model. The cohort-based transition matrix uses a transition probability per unit time for individuals in the cohort to change to another state, with associated costs and outcomes. The rows of the transition matrix must add to one (a conservation of probability mass). The transition matrix presented above shows that transitions between some model states are not allowed. Probabilities representing disallowed transitions are zero. The transition probabilities are constant with respect to time, with the exception of the transitions to the death state that are age-dependent. When modelling, the probability of remaining in one state will depend on the probability of leaving that same state, where the age-dependent transitions to the death state are taken into account, making the overall probability of remaining in a particular state time-dependent. The proportion of patients in each drinking category is calculated sequentially for each cycle over the simulated time period according to a specific transition probability (tp).

In the first cycle a Hazardous patient can remain in Hazardous, transit to harmful, transit to ex-hazardous or transit to death. Accordingly, in the first cycle a harmful patient can remain in harmful, transit to hazardous, transit to ex-harmful or transit to death. The following cycles have the following transition possibilities:

Hazardous (A): remain in A (tpA2A) or transit to: B (tpA2B), ExA (tpA2ExA), D (tpA2D).

Harmful (B): remain in B (tpB2B) or transit to: A (tpB2A), ExB (tpB2ExB), D (tpB2D)

Ex-hazardous (ExA): remain in ExA (tpExA2ExA) or transit to: A (tpExA2A), B (tpExA2B) or D (tpExA2D)

Ex-harmful (ExB): remain in ExB (tpExB2ExB) or transit to: A (tpExB2A), B (tpExB2B) or D (tpExB2D)

Death (D): remains dead (absorbent state)

Why use Ex-categories?

A limitation of any Markov model is that the probability of moving out of a state is not dependent on the states the patient may have experienced before entering that state (Briggs and Sculpher, 1998). This is the "memoryless" feature of Markov models also referred to as the "Markov assumption" (Sonnenberg and Beck, 1993). The Markov assumption does not allow the transition probability to depend on the time a patient has spent in a given state nor the full patient's previous history before entering that state. Thus, Markov models assume that patients in a given state can be treated as homogeneous groups.

One of the methods to model a process where future events depend on past events in a Markov model is by adding additional states to the model. Using "ex-categories" in the Markov model can be seen as a way to overcome the Markovian assumption. The "ex-categories" are distinguished by the state where the patient was in the previous cycle. This breakdown is related to the fact that, even if patients reduce their alcohol consumption to a sensible level, the risk of mortality and morbidity will depend on the level at which they were drinking before. Therefore, alcohol-related transition probabilities to the death state and morbidity risks depend not only on current drinking level, age (time dependency as a function of the time in the model) and gender but also on the state where the patient was in the previous cycle. In this way previous history is included in patients' prognosis. However, the ex-categories only take into account the previous cycle and not the time patients have spent in a given cycle. The use of time-dependent transition probabilities is another way to overcome the Markovian assumption. Time dependency in the model is incorporated as a function of the time elapsed from the start of the model. When transition probabilities vary over time the Markov model can be called as a "time-dependent Markov process" (Sonnenberg and Beck, 1993). The way the transition probabilities vary with time in this model is by assuming them to be an increasing function of time (i.e. the cycle of the model), they do not, however, depend on the time patients have actually spent in each state, which is another form of time dependency that might need to be incorporated in a Markov model.

One way to circumvent the Markov assumption is by adopting a semi-Markov structure (Hawkins et al., 2005). A semi-Markov structure may be implemented in two ways. One way consists of the addition of further tunnel states to the model. These are states that an individual can only occupy for one cycle and represent both the disease state the individual is in and the number of previous

cycles spent in this state. A limitation of this approach is that the transition matrix becomes larger as the number of states and total number of cycles increase. The other way consists of using a 3-dimensional matrix of transition probabilities, with dimensions for current state, future state, and time in current state. This is logically equivalent to using a series of "tunnel" states. An alternative approach to handling time-dependency is to abandon cohort modelling and to use PLS (Hawkins et al., 2005). A semi-Markov structure and especially PLS make the model computationally complex, while it also depends on considerable data availability. In order to incorporate time dependency as a function of time in a state, long-term data from open-label trials or epidemiological data need to exist that allow this time dependency to be estimated.

4.4 Country-specific model inputs

The model requires a set of country-specific inputs such as transition probabilities between drinking states, morbidity and mortality rates, alcohol-related disease costs and utility weights for the Markov states.

4.4.1 Transition probabilities for the first cycle(s)

According to the transition matrix presented in Table 22, yearly transition probabilities for each state are used to generate the Markov trace, i.e. the number of patients in each state over lifetime. The clinical study of the alcohol treatment which cost effectiveness is analysed should provide patient-level data informing drinking behaviour at different time periods. The transition probabilities for the first cycle(s) are calculated by counting the number of patients that transit between the states for the clinical study follow-up times.

The probabilities taken from the clinical effectiveness studies are only used for the number of cycles of the model that the data informs. Most effectiveness studies in the alcohol treatment field have not surpassed a one year follow-up (Miller WR and Wilbourne PL, 2002). Therefore, data from these studies should only be used for the first cycle of the model. The number of patients in each Markov state for the first cycle(s) is calculated as presented in Table 23.

Table 23- Markov trace for the first Markov cycle

Hazardous (A):
APat*(1-tp1A2B-tp1A2ExA-mrA2D-mrbas)+BPat*(tp1B2A)+ExAPat*(tp1ExA2A)+ ExBPat*(tp1ExB2A)
Harmful (B):
APat*(tp1A2B)+BPat*(1-tp1B2A-tp1B2ExB-mrB2D-mrbas)+ExAPat*(tp1ExA2B)+ ExBPat*(tp1ExB2B)
Ex-Hazardous (ExA):
APat*(tp1A2ExA)+ ExAPat*(1-tp1ExA2A-tp1ExA2B-mrExA2D-mrbas)
Ex-Harmful (ExB):
BPat*(tp1B2ExB)+ ExBPat*(1-tp1ExB2A-tp1ExB2B-mrExB2D-mrbas)
Death (D):
APat*mrA2D+BPat*mrB2D+ExAPat*mrExA2D+ExBPat*mrExB2D+DeadPat+mrbas*(APat + BPat + ExAPat + ExBPat)

APat, number of hazardous patients in the previous cycle; tp1, transition probability for first cycle; tpA2A, transition probability from hazardous to hazardous; mr, mortality rate (alcohol specific); mrbas, mortality rate for all causes (baseline); see explanation text below.

Since the probabilities of moving between states in each cycle must sum to one (patients must be in one and only in one state at any given time) the probability of staying in a given state is one minus the probability of leaving that state. This allows the inclusion of the age-dependent probabilities to the death state in the probability of remaining in a given state. The probabilities of patients moving from other states to a specific state have to be added to the probability of patients remaining in that state. The transition probabilities are multiplied by the number of patients that were in each state in the previous cycle, represented by the name of the state with the suffix "Pat" in the table above.

Age, gender and state specific mortality rates are incorporated in the probability of patients remaining in the same state. These mortality rates have two components: 1) alcohol-specific mortality rate (mr) from one drinking category state to the death state and, 2) non-alcohol-related mortality rates (mrbas) from any state to the death state.

The number of patients in the death state is calculated by the number of patients in each state in the previous cycle, multiplied by the time-dependent alcohol-specific mortality rates. The dead patients

in the previous cycle are also brought forward, i.e. are also summed to the patients dying in the cycle to which the calculation respects. The time-dependent baseline mortality rate is multiplied by the sum of patients alive in each state in the previous cycle. This rate is the same for all states because it is non-alcohol specific (baseline). The calculation of mortality rates is explained in Chapter 5.

The transition probabilities in this section are applied to the cycles of the Markov model for which effectiveness data is available. This allows calculating the number of patients alive in the first cycle(s) and knowing how many patients are in each state at the end of the cycle, for each one of the treatments under comparison. The generation of a transition matrix with the first cycle transition probabilities is exemplified in Chapters 6 and 7 where two case-studies are presented.

In order to build the Markov trace, the same process as the one presented in Table 23 needs to be repeated for all the cycles of the model. In projecting to the lifetime of patients, assumptions need to be made concerning the duration of the effect of the alcohol treatment assessed, in terms of sustaining health-related benefits. The model assumes that a cohort of patients transit between drinking categories according to the natural history after treatment uptake, i.e. that the effectiveness of the treatments evaluated is taken forward by means of other transition probabilities that are not the same as the ones calculated with the clinical data. This is explained below.

4.4.2 Transition probabilities for the following cycles

It would be a strong assumption to use the transition probabilities taken from the effectiveness data for the lifetime of patients, i.e. for the cycles of the model following treatment. When treatment effects are taken from a clinical trial, which does not measure outcomes beyond a limited number of years, it is recommended that shorter and longer time horizons are modelled separately when the analysis must go beyond the time frame of the primary data (Gold et al., 1996b).

The review conducted in the previous chapter shows that most previous long-term modelling studies assume that the outcomes of the trials remain the same for patients' lifetime. They do not attempt to actually model drinking behaviour and only focus on few alcohol-related diseases. However, patients should transit between drinking categories according to their natural history after treatment uptake, where natural remission and relapse are taken into account.

The transition probabilities for the following cycles of the model are specific to the country where the study takes place so that lifetime drinking behaviour of a specific population, after treatment uptake, can be reflected. These transitions should be informed by a long-term follow-up study, ideally after treatment uptake. The generation of a transition matrix with transition probabilities for the following cycles is provided in the next chapter (Chapter 5).

4.4.3 Epidemiological data: morbidity and mortality

By attaching estimates of resource use and health consequences to each individual state in the model over a large number of cycles, the long term costs and health consequences can be estimated. However, in order to do so, the Markov model requires a separate analysis of the lifetime risk of mortality and morbidity that is incorporated into the main Markov model to reflect the risk incurred by each drinking state and the changing risk of transition into or out of drinking states.

Alcohol-treatment trials conducted so far do not have a sufficient follow-up that could capture mortality and long-term morbidity. Similarly, no trials with a sample big enough to capture all possible alcohol-related injuries are identified. Epidemiological data at a population level is used in order to incorporate life expectancy and morbidity costs into the model, which is achieved by specifying the level of risk attached to the levels of drinking as represented by the Markov states.

The model requires detailed country-specific epidemiological data. The extent to which a consequence can be attributed to the use of alcohol varies according to setting, both for epidemiological reasons and due to variations in the institutional arrangements for dealing with adverse consequences. For this reason, the degree of alcohol involvement in mortality and morbidity estimates has to be retrieved for the setting in which the cost effectiveness of alcohol treatments is analysed.

The degree of alcohol involvement can be described by Alcohol Attribution Factors (AAFs). There are some conditions that are by definition related to alcohol abuse and so the AAF is 100%. For example, all cases of alcoholic psychosis, alcoholic dependence syndrome and alcohol dependence are wholly attributed to the use of alcohol. For conditions where alcohol consumption is a contributory cause, there are two methods for assigning an aetiological fraction (WHO, 2000): 1) a direct method and 2) an indirect method. The direct method directly attributes alcohol use on the basis of case series studies in which alcohol's involvement is systematically investigated. This method can result in over-estimates of alcohol's contribution to some degree as there is an implicit assumption that significant amounts of alcohol are associated with direct causation. The direct method has been used for estimating AAFs for conditions associated with acute alcohol intoxication (most forms of injury), as is the case of the AAFs calculated in English et al. (1995). The indirect method uses estimates of Relative Risk (RR) of particular disorders for different levels of alcohol use combined with prevalence data on the number of persons consuming at different levels. The RR is the ratio of the chance of experiencing an alcohol-related problem if exposed to alcohol divided by the chance of experiencing it if one is not exposed to alcohol (Rothman et al., 2008). Estimates of RR for a number of conditions are published in two widely known meta-analyses

(Corrao et al., 1999; Corrao et al., 2004), amongst others. The indirect method is the preferred one for conditions partly caused by the effects of long-term consumption, mostly diseases.

Mortality and morbidity calculation for the model of drinking behaviour

The model uses country-specific mortality and morbidity rates that vary with age, gender, level of consumption, alcohol-related condition and drinking pattern. Lifetime injury and chronic disease mortality and morbidity are modelled through a number of different steps, assumptions and data sources, based on methods recently developed in Rehm et al. (2008) and Taylor et al. (2008). Briefly, after determination of diseases and injury groups causally related to alcohol consumption (Rehm et al., 2004), consumption-specific risks are developed for each age, sex, and disease/injury category. These take into account numbers of drinks and number of drinking occasions (for injury risk calculation) or average daily volume of alcohol consumed (for chronic disease risk calculation) by drinkers characterized by each drinking state, over the course of one year. A one-year alcohol-attributable risk for each disease/injury group by sex, age, and drinker type is calculated. This risk reflects actual consumption patterns of the drinking states being modelled in a population of interest, in terms of mortality/morbidity experience, alcohol consumption, and risk per occasion. An example of the calculation of mortality and morbidity rates for the model of drinking behaviour is presented in the next chapter.

4.4.4 Disease-related costs and Markov states utilities

The model also requires country-specific estimates of the costs of diseases affected by alcohol consumption. Average unit costs can be collected for each alcohol-related disease for which morbidity rates are calculated. The other set of country-specific estimates are the health utilities associated with each Markov state. This information should, ideally, reflect the preferences of the general population for the setting of the analysis. Both disease-related costs and states' utilities, together with the epidemiological data and transition probabilities, are used to calculate the model outcomes as explained below.

4.5 Model outcomes

The outcomes of the Markov model are the lifetime costs, QALYs and life years and these are specific to the treatments under evaluation and to the country of the analysis. QALYs are the standard outcome measure used to evaluate whether a health technology represents value for money in Scotland and England, and the main effect measure of the model. When comparing the cost effectiveness of two alcohol treatments in the Markov model, the data informing treatment effectiveness generate different transition probabilities and so a different number of patients in each

drinking category, which will translate into different treatment costs, utilities and life years, over the long term. When two treatments are compared the *incremental cost*, *incremental utilities* and *incremental life years* are the outcomes of interest. Drinking categories with a higher level of consumption will accrue higher associated costs, lower utility and an increased probability of dying from alcohol-attributable conditions. The estimation of the model outcomes uses the epidemiological data detailed in a section above.

4.5.1 Life expectancy

Life expectancy for the treatments evaluated is given by the number of model cycles (average amount of time) spent in each state, other than the death state, by the patients. The average life expectancy is given in terms of the model cycle length. Given that the cycle length is 1 year, the average life expectancy is already given in years. After running the model over a large number of cycles the patients alive in each cycle are summed and divided by the initial size of the cohort in order to get the average life expectancy. This process is conducted for all treatments under evaluation and, when comparing two treatments, incremental life years are calculated by subtracting the average life years for one treatment from the average life years for the other treatment. Alcohol-specific and general mortality rates are used to calculate the life expectancy of a population with alcohol problems. A lifetable for the model states (alcohol-specific) and baseline (general mortality taking out alcohol-attributable reasons) and by gender and age group is linked to each state, with rates taking into account both chronic and injury causes. An example of how to generate a lifetable is presented in the following chapter.

4.5.2 Quality Adjusted Life Years

The incorporation of QALYs into the model follows the same process as the one explained for life expectancy. The QALY scores for patients in each cycle and health state are summed over all cycles and divided by the initial cohort size thus providing the average QALYs associated with each treatment. When comparing two treatments the incremental QALY is calculated by subtracting the QALYs gained with one treatment from the QALYs gained with the other treatment. A gain in QALYs from one treatment over another can be attributed to differences in utility between the drinking categories and differences in life expectancy.

The construction of QALYs involves weighting the length of time spent in each state of health by a value representing quality of life experienced in that state. Weights representing quality of life on a standard 0 to 1 scale are attached to the Markov states. These weights are called utilities. An

example of the calculation of the utilities attached to each Markov state is presented in the following chapter.

4.5.3 Costs

The economic model has two major categories of costs, the costs of the treatments under evaluation and the disease-related costs associated with each Markov state. The treatment costs are specific to the alcohol treatments evaluated in the model. The disease costs are specific to the country and setting where the analysis takes place, preferably average unit costs. The Markov states' costs are calculated by combining the morbidity rates with the health care costs for the diseases affecting alcohol-related morbidity. Alcohol-related disease morbidity rates by gender, drinking state and for each age group are used for the calculation of the health states costs. The costs of spending one cycle in each state of the model are attached to that state. The lifetime states cost is obtained by summing the costs across all cycles of the model for each state and dividing by the initial cohort size thus providing an average health care cost of the alcohol-related diseases. The specific alcohol treatment costs are added to the alcohol-related diseases costs. When comparing two treatments with different lifetime costs, the difference between the average costs obtained for each treatment under analysis provides the incremental cost of the most expensive treatment. The calculation of the disease-related costs for each Markov state is illustrated in the following chapter.

4.6 Discounting

It is standard practice in economic evaluations to adjust costs and outcomes for differential timing by applying a rate of discount which allows comparison of costs and outcomes in terms of a Net Present Value (NPV). This is based on the fact that costs and benefits occurring immediately are valued more highly than those occurring in the future.

The discounting formula is given by:

$$V_0 = \frac{V_t}{(1+r)^t}$$

Where V_0 is the current value (NPV), V_t is the value at time t and r is the rate of discount. The discount rate is applied to the number of patients alive, costs and QALYs in each cycle. Each cycle is linked to the discounting formula presented above, allowing discounting costs and outcomes at the point in time that they occur in the model. The model is constructed in such a way that discount rates for costs and outcomes are separate, allowing the use of differential discounting rates. For

example, NICE (2008) recommends a discount rate of 3.5% for both costs and outcomes in the base-case analysis of a economic evaluation, and different discount rates in the sensitivity analysis.

4.7 Dealing with uncertainty

Uncertainty is incorporated in the model parameters. This uncertainty relates to model parameters that have a definitive value, but which cannot be known with certainty. Sensitivity analysis is a method of testing the robustness of the analysis where the deterministic variables for which there is uncertainty are varied over a range and the effects in the results are analysed. Briggs et al. (2006) presented many reasons for the importance of considering uncertainty in cost effectiveness modelling for decision making. Very briefly, the reasons the authors presented for considering uncertainty include: 1) the nonlinearity in model inputs parameters, 2) the possibility of incorrect decisions which impose a cost in terms of the benefits forgone and, 3) the possible value associated with delaying an irreversible decision.

Two types of sensitivity analyses are incorporated in the Markov model of drinking behaviour to estimate the impact that parameters uncertainty has on the cost effectiveness results, and these are 1) probabilistic sensitivity analysis and 2) univariate sensitivity analysis. PSA quantifies the uncertainty in mean outputs as in the measures of costs, effects and cost effectiveness, due to input parameters uncertainty. Guidance on the use of decision models emphasizes the use of PSA (Gold et al., 1996b). PSA is conducted in the model for the input parameters of the model that the results are uncertain about and a Cost Effectiveness Acceptability Curve (CEAC) is produced for each treatment. The CEAC shows the probability that a given treatment is cost effective for different values of the willingness to pay thresholds for that treatment. The model also incorporates univariate sensitivity analysis for a set of input parameters. One way sensitivity analysis varies each parameter individually in order to isolate the consequences of each parameter in the results of the study.

The following two subsections explain the incorporation of sensitivity analyses in the long-term Markov model of alcohol consequences.

4.7.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis is conducted in the model by assigning distributions to all input parameters of the model that the results are uncertain about, under the assumption of a homogeneous sample of patients informing parameter estimation. The input parameters that the model is most uncertain about are the transition probabilities between drinking states and the utilities attached to each Markov state. The distributions chosen to represent each set of parameters

depend on the volume and quality of the information available in which little or poor information is represented by assigning a diffuse distribution. After assigning a distribution, the resulting output of the model represents a single trial. Monte Carlo simulation randomly selects values of the parameters from the assigned distributions and propagates these distributions through the model (Doubilet et al., 1985). This process is repeated for a large number of trials and a distribution of the output from the model is estimated. The Markov model of drinking behaviour is set to run 1000 simulations. This means that, when considering uncertainty through PSA, it is the expectation over the distribution of the output parameters that represents the point estimate for the decision model (Claxton et al., 2002). An example of the application of the appropriate distributions for the model inputs is given in Chapters 5 and 6.

4.7.2 Univariate sensitivity analysis

One-way sensitivity analysis is conducted for the initial distribution of patients, where the effect of different proportions of a cohort starting in hazardous (A) and harmful (B) states (cycle 0) is analysed. This one-way sensitivity analysis assesses whether a range of different drinking behaviours at the starting cycle has an impact on the cost effectiveness of the treatments under evaluation. In addition, the impact of applying alternative discount rates can be analysed. This is exemplified in the case-studies presented in Chapters 6 and 7.

4.8 Heterogeneity

A standard Markov model assumes that all patients in a given state are homogenous. Therefore, the model structure allows subgroup analyses on patients' age and sex to be conducted, so that heterogeneity can be taken into account. Heterogeneity relates to differences that can, in part, be explained, therefore it is not a source of uncertainty (Briggs et al., 2006). Modelling heterogeneity assesses the extent to which patient characteristics affect the outcomes. Patient characteristics can affect the potential outcomes of the model, such that treatment choices may be different for patients with different characteristics. Age and sex affect both alcohol-specific and other-cause mortality rates. Alcohol-related morbidity rates are also both gender and age-specific. The model is built in such a way that changing the gender and age of the cohort is relatively straightforward. Subgroup analyses can be run for different age (20, 40 and 60 years old) and gender cohorts (male or female). The deterministic and probabilistic cost effectiveness results are assessed for these cohorts and multiple CEACs produced, where the probability of an alcohol treatment being cost effective is plotted against the willingness to pay threshold, for each subgroup. Subgroup analyses are exemplified in Chapters 6 and 7 where two model applications are presented.

4.9 Decision making

The results of the model are used for decision making. Within a decision making framework, under conditions of certainty, the more effective and less costly alcohol treatment is the one that should be adopted. In this case the treatment is said to dominate the alternative and the decision of which treatment to adopt is straightforward. However, this situation is not common for new treatments and multiple options. It is common that an intervention is both more effective and more costly or less effective and less costly than the comparator. In this case a decision has to be made as to whether the additional benefits of the more expensive alcohol treatment are worth the additional cost, for the country of interest in the analysis. Similarly, a decision needs to be made as to whether a less costly alcohol treatment justifies the reduced benefits. A measure used in order to determine whether an intervention represents good value for money is the expected incremental cost per QALY (ICER, Incremental Cost Effectiveness Ratio) between technologies against a threshold willingness to pay (λ) or equivalently, the expected monetary Net Benefit (NB= λ*QALY-Cost) (Briggs et al., 2006). The ICER compares the additional costs that one strategy incurs over another with the additional benefits and represents the additional cost required to achieve one additional unit of outcome (QALY). Hence, where one therapy does not dominate (i.e. is not both more effective and less costly) an incremental cost effectiveness ratio (ICER) can be calculated using the following formula:

$$ICER = \frac{C_B - C_A}{E_B - E_A} = \frac{\Delta C}{\Delta E}$$

where C represents the mean lifetime costs for treatment groups A and B and E represents the lifetime effects (life years or QALYs) for each treatment group.

As a reference point, NICE uses a threshold cost per QALY of around £20,000-£30,000 to determine whether an intervention represents good value for money in the NHS (NICE, 2008). The preferred option is determined by comparing the ICER with this notional threshold value which decision makers are assumed to be willing to pay for an additional unit of effect. Consequently, if the ICER for the evaluated treatment is below £20,000 then this treatment should be considered potentially cost effective. ICERs within the range itself (i.e. £20,000-£30,000) are considered borderline and an ICER above £30,000 is not typically considered cost effective.

4.10 Value of information: the decision to acquire more evidence

Given the paucity of published evidence for the cost effectiveness of alcohol treatment, the potential value of future research for the alcohol treatments considered is assessed. The model results, in

terms of expected cost effectiveness, are based on the existing evidence available. However, often the information on a number of model parameters such as the effectiveness of a particular alcohol treatment or the transition probabilities between states after treatment uptake is scarce. Therefore, another component of the model of alcohol behaviour is the examination of the value of information. This helps in making the decision whether a specific treatment under evaluation should be adopted on the basis of existing evidence or whether further evidence is required to support this decision in the future taking into account the objective and constraints on health care provision (Briggs et al., 2006).

In case decision uncertainty or the consequences of making the wrong decision are large, the decision-maker may require further evidence on which to base the adoption decision (Claxton et al., 2004). The decision to adopt a specific alcohol treatment based on expected values is uncertain, and there is a chance that the wrong decision will be made. If the wrong decision is made, there will be opportunity costs in terms of health benefits and resources forgone. The expected cost of uncertainty is determined jointly by the probability that a decision based on existing information will be wrong and the consequences of an incorrect decision. Information reduces the expected costs of uncertainty surrounding the decision (Claxton et al., 2002).

The expected costs of uncertainty associated with a decision based on current information can be interpreted as the Expected Value of Perfect Information (EVPI), as perfect information can eliminate the possibility of making the wrong decision. The EVPI places an upper limit to the value of additional research that could be undertaken to reduce the uncertainty associated with a decision regarding the adoption of a particular alcohol treatment in a health care system. If the EVPI for the population of current and future patients exceed the expected costs of further research, then it is potentially cost effective to acquire more information.

EVPI incorporation in the model

The implications of uncertainty associated with the cost effectiveness of the alcohol treatments analysed are explored in the model by incorporating analysis of the expected value of information, as described by Claxton (1999). The use of Monte Carlo simulation allows the expected costs of uncertainty associated with the initial adoption decision to be expressed as the proportion of iterations in which the uncertainty within the model results in an adoption decision other than that arising from maximising expected cost effectiveness (i.e. expected net benefits). The benefits forgone are the difference in costs and outcomes (net benefit) between the optimal strategy for a given iteration and those of the strategy identified as optimal in the adoption decision (i.e. based on the expected cost effectiveness estimates) (Sculpher and Claxton, 2005). The expectation of benefits forgone over the 1000 iterations in the model represents the EVPI for an individual patient.

More formally, this implies that for a decision involving j treatments where NB is dependent upon a set of unknown parameters θ, the EVPI is the difference between the value of the decision made with perfect information averaged over all possible realisations of uncertainty and the expected value of the decision made on the basis of existing information:

$$EVPI = E_{\theta} [max_j (NB(j, \theta))] - max_j [E_{\theta} (NB(j, \theta))].$$

The overall value of information for a population of patients who could benefit from alcohol treatment is determined by applying the EVPI per individual to the number of patients who would be eligible for alcohol treatment over the anticipated lifetime of the modelled alcohol treatment:

$$EVPI * \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

Where I_t is the eligible population in period t, T is the total number of periods for which information from research would be useful, and r is the discount rate.

An application of the methods described for EVPI is illustrated in Chapter 7.

4.11 Application of the model to different countries

The developed framework helps in assessing the cost effectiveness of alcohol treatments. However, it should be noted that the results from the model might not be transferrable between settings. The cost effectiveness of alcohol treatments will depend on a range of setting-specific conditions and this is reflected in model inputs that vary according to the population and/or setting modelled. The model requires a range of country-specific data that needs to be collected in order to inform the following model parameters:

1) Alcohol treatments effectiveness data
2) Transition probabilities for the transitions not informed by the effectiveness study or studies of the treatments being compared
3) Morbidity and mortality rates, for injury and chronic diseases, by age, gender and drinking category
4) Cost data for alcohol-related diseases and for the specific treatments evaluated
5) Utility weights for the Markov states

4.12 Discussion

The model developed in this chapter provides an innovative framework to assess the cost effectiveness of alcohol treatments. However, it is based on a number of assumptions which should be mentioned here. The main assumption in a simple Markov model is that it is essentially without memory. That is, it does not enable one to follow patients' history. The Markov assumption does not allow the transition probabilities to depend on neither the time a patient has spent in a given state (time in state dependency), nor the full patient's previous history before entering that state, meaning that the future is conditionally independent of the past, given the present. Time-dependency in the transition probabilities are accounted for only by increasing age but they do not depend on the time patients have actually spent in each state. The use of "ex-categories" can be seen as a way to overcome the lack of memory of a standard Markov model, but not to a full extent as they only consider the state where the patient was in the previous cycle and not patient's full history or pathway. Establishing transition probabilities that depend on the time the individuals spent in each state would require a PLS. However, the computational burden of PLS models compared with cohort models makes PLS less attractive.

The choices of cut-offs for the definition of "hazardous" and "harmful" categories are arbitrary even if defined in previous literature. The cut-offs obviously influence the proportion of subjects in a given state and this has an impact on the results. Defining different cut-offs requires a totally new model, not just in terms of drinking category definitions but also in terms of all epidemiological data that is calculated for specific drinking levels. However, a way to mimic the impact of changing cut-offs is to allocate higher or lower proportions of patients to each category, by doing a one-way sensitivity analysis. This one-way sensitivity analysis is embedded in the model by simply changing the proportion of the cohort starting in each drinking category.

The model is built for a health care system perspective. Economic evaluations in other fields also adopt the narrow perspective of the health care system which is also in line with current NICE guidelines. The public health impact of alcohol, however, is not only experienced by individual drinkers but also by the rest of society and treatment may also affect consequences that reduce costs to the rest of society. With a narrow perspective there is an incentive to "cost-shift" from one sector of society to another. A health care perspective could lead to the adoption of a intervention that increases overall costs to society and reduces utility, because within the health care sector, the costs are lowered and the utility is increased, which would lead to societal inefficiencies (Torgerson and Torgerson, 2008). Adopting a broader perspective where the consequences identified in Chapter 2 of the thesis are included, should be part of further extensions of the economic model developed

here. It would also be interesting to analyse the impact of a societal perspective on the ranking of alcohol treatments.

The decision analytical model is a tool that can be used to assess the value for money of a range of alcohol treatments. However, the innovative structure of the model, where alcohol drinking behaviour is of primordial interest, may present some difficulties with respect to the incorporation of treatment effects from previous studies. The ideal alcohol treatment effectiveness data are clinical trials where drinking behaviour at baseline and follow-up are recorded, so the transition matrices for the treatments under analysis can be determined. However, many published studies only present odd ratios (with effects derived from meta-analyses) and relative risks. Therefore, if the model is used for assessing the cost effectiveness of alcohol treatments for which effectiveness data is already published, the means by which effect measures are incorporated in the model to inform the transition probabilities needs to be analysed.

This thesis is concerned with alcohol treatments which involve individuals voluntarily changing behaviour. While much of the content of this thesis refers to alcohol treatment, it is possible to adapt the model for other alcohol interventions. Population-level interventions, for example, prevention, legislation and enforcement, should have a range of individual and social impacts. An adaptation of the model to incorporate different alcohol interventions warrants further research. An important contribution models the population-level impact of a range of interventions (Chisholm et al., 2004) and can serve as an umbrella for such types of model extensions.

4.13 Conclusion

Despite some of the limitations, which naturally arise when a modelling approach is adopted, the model is a contribution for the link between drinking patterns, health consequences and alcohol treatments effectiveness and cost effectiveness. This chapter provides a framework by which policymakers can evaluate alcohol treatments taking into account longer term health outcomes and costs. It enables the estimation of benefits from alcohol treatment related to a change in alcohol consumption which is not necessarily confined to abstinence. This represents a major development in the techniques traditionally used in the field of alcohol treatment, in which short-term costs and outcomes are assessed, omitting potential longer term cost savings and improvements in health-related quality of life.

Chapter 5. Economic model: country-specific model inputs, an example for the UK

This chapter presents the calculation of UK-specific model inputs which can be used to populate the Markov model for any alcohol treatment assessment in the UK. Model inputs such as treatment costs and the effects of treatment in drinking behaviour are specific to the treatments under evaluation and are presented in the next two chapters where the model is applied.

First, transitions between states after treatment uptake, epidemiological data (mortality rates and morbidity rates), lifetables and alcohol-related diseases costs and utilities for the health states are calculated. Second, the distributions used in the probability sensitivity analysis, for the transition probabilities and utilities, are described. The last sections discuss the limitations of the methods applied and conclude.

5.1 Following cycles transition probabilities for a UK population

The transition probabilities of the effects of treatment should not be used for the remaining cycles of the model, i.e. for lifetime. Ideally, the population treated with the specific alcohol treatments is followed for a long period of time after treatment delivery. However, most alcohol treatment trials conducted so far have a follow-up of one to two years.

As an application to the UK population, a UK long-term drinking behaviour follow-up study, conducted by Taylor et al. (1985), is used as the best information for the following cycles transitions available until present date. This study reported patterns of drinking over 10 years, using 68 patients who were admitted into a controlled study of treatment versus advice with 1 and 2 years follow-up.

Taylor et al. (1985) reported the proportion of patients who remain in a certain drinking status for the following year. The authors defined three drinking categories: abstinence, social drinking and troubled drinking. These categories are matched to the model categories: ex-categories (ex-hazardous and ex-harmful), hazardous drinking, and harmful drinking, respectively. There is no possible distinction between the ex-categories as the study did not report the effect of present consumption on following year consumption. The proportions reported in Taylor et al. (1985) are used in the model to describe the probability of remaining in the same state. The probability of transiting to any of the two other allowed states is assumed to be one minus the probability of remaining in the same state, divided by two. This is rather crude and assumes that the probability of transiting to the two other states is the same. The Taylor et al. (1985) study reported a yearly

stability of 81% for the abstinence category, 86% for the social drinking category and 83% for the troubled drinking category. Based on these estimates, a transition matrix for the following cycles is derived in Table 24 below.

Table 24- Transition matrix for the following cycles, for a UK population

		Cycle n +1				
		Hazardous	Harmful	Ex-Hazardous	Ex-Harmful	Death (D)
Cycle n	Hazardous (A)	0.86[2]	0.07	0.07	0	tpA2D[1]
	Harmful (B)	0.085	0.83[2]	0	0.085	tpB2D[1]
	Ex-Hazardous (ExA)	0.095	0.095	0.81[2]	0	tpExA2D[1]
	Ex-Harmful (ExB)	0.095	0.095	0	0.81[2]	tpExB2D[1]

[1]Time-dependent transition probability; [2]Yearly stability reported in Taylor et al. (1985);tp, transition probability; tpA2D, transition probability from hazardous to death; tpB2D, transition probability from harmful to death; tpExA2D, transition probability from ex-hazardous to death; tpExB2D, transition probability from ex-harmful to death.

5.2 Mortality and morbidity calculation for a UK population

The model requires data on the mortality and morbidity of the population modelled. This informs the estimation of model outcomes, such as life expectancy and lifetime costs. The general steps for the calculation of mortality risk from alcohol-attributable injury and chronic disease are discussed below, followed by a brief discussion of where the morbidity calculations differ.

Step 1: Identifying causal conditions

Step 1 is common to both injury and chronic disease mortality and morbidity risk. This step is a general step whilst the following ones produce estimates specific to the country where the analysis is done. The injury and chronic disease categories causally related to alcohol are identified using the approach of the WHO Comparative Risk Assessment (CRA) Study (Ezzati et al., 2002; WHO, 2002c; Ezzati et al., 2004; Rehm et al., 2003d; Rehm et al., 2004a). The injury and chronic disease categories used for the calculation of mortality and morbidity risks for the model are presented in Table 25 below.

Table 25- Injury and chronic disease categories causally related to alcohol and alcohol-attributable fraction/ relative risk sources

Disease category	WHO GBD code	ICD-10 code(s)	Source
		Unintentional injuries	
Road traffic accidents	W150	V01-V04, V06, V09-V80, V87, V89, V99	(WHO, 2002)
Poisoning	W151	X40-X49	(WHO, 2002)
Falls	W152	W00-W19	(WHO, 2002)
Fire	W153	X00-X09	(WHO, 2002)
Drowning	W154	W65-W74	(WHO, 2002)
Other unintentional injuries	W155	Rest of V-series not codified above and W20-W64,W75-W99, X10-X39, X50-X59,Y40-Y86,Y88,and Y89	(WHO, 2002)
		Intentional injuries	
Self-inflicted injuries	W157	X60-X84, and Y870	(WHO, 2002)
Homicides	W158	X85-Y09, and Y871	(WHO, 2002)
Other intentional injuries	W160	Y35	(WHO, 2002)
		Chronic Diseases	
Lip, oral and pharyngeal cancer	W061	C00-C14	(Corrao et al., 1999)
Esophageal cancer	W062	C15	(Corrao et al., 1999)
Liver cancer	W065	C22	(Corrao et al., 1999)
Breast cancer	W069	C50	(Corrao et al., 1999)
Alcohol use disorders	W086	F10	Own calculations based on the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (http://niaaa.census.gov/)
Hypertensive diseases	W106	I10-I13	(Corrao et al., 1999)
Ischemic heart disease	W107	I20-I25	(Corrao et al., 2004)
Ischemic stroke*	W108	I60-I69	(Corrao et al., 1999)
Haemmorhagic stroke*	W108	I60-I69	(Corrao et al., 1999)
Cirrhosis of liver	W117	K70-K74	(Corrao et al., 1999)

WHO GBD, World Health Organization Global Burden of Disease; ICD-10, International Classification of Diseases Tenth Revision (WHO, 1992);*Cerebrovascular disease; conversion between GBD and ICD-10 codes from: http://www.dcp2.org/pubs/GBD/3/Table/3.A2.

Mortality

5.2.1 Injury mortality risks

This chapter uses a recently developed approach for the calculation of injury mortality risks presented in Taylor et al. (2008). The method used for the quantification of injury mortality risk takes into account different levels of consumption per occasion and different frequencies of drinking such amounts for the UK population.

Estimation of alcohol-attributable injury mortality in the UK requires combining the absolute yearly risk of injury mortality with gender and consumption-specific relative risks, while taking into account the number of drinking occasions at a particular level per year, and then calculating the risk per occasion and the yearly alcohol-attributable risk. This requires step 1 already presented above and the following three steps.

Step 2: Dividing the risk into baseline and alcohol-attributable risk.

The estimation of the one-year absolute risk of alcohol-attributable injury death first requires the knowledge of the risk of injury mortality that is *not* alcohol-attributable, i.e. the baseline risk. The baseline risk is calculated for each injury category identified in Step 1, differentiated by gender, and the following age groups: 15-29, 30-44, 45-59, 60-69, 70-79 and +80. For this calculation, the total number of deaths by gender and age, for a UK population and for each injury obtained from the WHO Global Burden of Disease (GBD) project for the year 2005 (unpublished data, kindly given by Juergen Rehm, consists of the latest available data from WHO), with the underlying cause coded according to the GBD, is used. By dividing the number of deaths from each injury category for each age group and sex by the total population at risk, for the respective age groups and sex in the UK, for the year 2005 (unpublished data, kindly given by Juergen Rehm, consists of the latest available data from WHO), the total risk of injury death for one year per 1000 population in each age and sex group is calculated (i.e. the population-level absolute risk of mortality by injury type). The baseline risk (not including the risk due to alcohol) is obtained by multiplying the total risk by the age, gender and injury-specific AAF and subtracting the resulting number (alcohol-attributable risk) from the total risk. The baseline risk is the risk of injury mortality that would have been present in the UK in the year 2005 without any involvement of alcohol. The AAF for each injury category is derived from the WHO CRA Study for Europe A Region, which includes the UK (Rehm et al., 2004; WHO, 2002), and is defined as that fraction of injury that would disappear if alcohol were completely absent. The calculation of one year injury mortality uses the baseline risk in the following steps. It should be noted that Taylor et al. (2008) calculated lifetime alcohol attributable

risks. However, the calculations referred to here are for one year as the Markov model itself propagates the risk for a lifetime period.

Step 3: Risk function for injury: determination of relative risk for different alcohol quantities

Step 3 requires estimating the impact of different patterns of alcohol consumption on the baseline risk. It has been shown that alcohol-related injuries are the result of both the volume of alcohol consumed and the drinking pattern, i.e. the frequency and setting of drinking (Rehm et al., 2003a; Rehm et al., 2004; Rehm et al., 2007a). The RRs corresponding to consumption of standard drinks are taken from a case-crossover 10-country Emergency Room (ER) study (N = 4,320, 91% response rate) (Borges et al., 2006), in which patients presenting with an injury were asked about their alcohol consumption prior to the injury. The ER study used volume-specific RRs corresponding to a specific number of international standard drinks where one standard drink corresponded to 12.5g or 16ml of pure alcohol. This data is modelled on the basis of a quadratic equation and the RRs are converted to UK standard drinks for consumption up to 6.5 international drinks (10.27 UK drinks). Beyond 6.5 standard drinks, the ER study RR is used. A quadratic function shows the non-linear effect of alcohol on risk of injury death, indicating that risk increases at a rate that is more than proportional to the number of drinks consumed. The table below presents the risk data in 16ml standard drinks and the corresponding relative risks after conversion to UK standard drinks (Table 26).

Table 26- Conversion of alcohol intake and RR from Borges et al. (2006)

No. of International drinks [a]	**RR** [b]	**Quadratic Regression** [c]	**No. of UK drinks** [d]	**UK RR** [e]
0	1.0	$\ln RR = -0.0656D^2 + 0.758D$ *RR*- Relative Risk *D*- number of international drinks	0	1.0
1	3.3		1	1.6
2.5	3.9		3	3.3
4.5	6.5		5	5.6
>6	10.1		**7**	7.9
			9	8.9
			11	10.1

[a]Number of international drinks, taken from the Borges et al. (2006) study, where an average drink contains 12.5 g of alcohol; [b]RR, Relative Risk, taken from the Borges at al. (2006) study; [c]Regression of the number of international drinks on the RR as reported in the Borges et al. (2006) study; [d]One UK standard drink contains 7.9 g of alcohol; [e]Relative Risk for UK standard drinks calculated using the equation obtained through the regression.

Next, the RR associated with each Markov state drinking category is developed using the equation that modelled the ER data. For this calculation, the four drinking categories are modelled for men and women separately: harmful drinkers, hazardous drinkers, ex-harmful drinkers, and ex-hazardous drinkers, as shown in Table 27 below. The middle column for each gender in the table

shows the number of drinks per occasion by drinking category used to estimate the RR associated with each drinking pattern.

Table 27- Consumption levels for UK drinking patterns, by drinking category and gender

	Men			**Women**		
	Grams/ day	Drinks/occ.	Occ. /week	Grams /day	Drinks/occ.	Occ./week
Hazardous	54	9.45	5	38	6.65	5
Harmful	110	13.75	7	80	10	7
Ex-Hazardous	18	3.15	5	13	2.275	5
Ex-Harmful	37	6.475	5	27	4.725	5

Occ., occasion.

In Table 27 the definition of grams/day is the arithmetic mean of the levels of consumption that characterize each Markov state, as presented in Chapter 4. For ex-drinkers, the definition of the grams/day used for the calculation of the number of drinks per occasion is more complex. This is because the ex-categories have a lower bound of zero grams per day and so both abstinent and sensible drinkers are captured within these categories. For most injuries when no alcohol is consumed the risk becomes zero. In trying to determine a quantification which fulfils all of these assumptions, a risk which corresponds to about 1/3 of the previous level of drinking, is modelled. The number of occasions per week is estimated based on the definition of the drinking category, where a harmful drinker is assumed to drink every day and the hazardous and ex-drinker is assumed to drink five times a week. Such numbers of occasions per week are based on the CRA of the GBD attributable to alcohol study (Murray and Lopez, 1997), for the WHO region Europe A (Rehm et al., 2003c; Rehm et al., 2006c). The number of drinks per occasion is calculated based on the grams per day and occasions per week. Thus, to give an example: a hazardous drinker drinks 5 times a week 54 g/day which corresponds to 6.75 UK standard drinks per day (54/8). The 6.75 drinks per day correspond to 9.45 drinks per occasion ((6.75*7)/5). The RRs obtained for each drinking category by gender are presented in Table 28 below.

Table 28- Injury relative risks for UK drinking patterns, by drinking category and gender

	Males		**Females**	
	No. of Drinks	Relative risk	No. of Drinks	Relative risk
Hazardous	9.45	8.1	6.65	7.5
Harmful	13.75	10.1	10	8.8
Ex-Hazardous	3.15	3.4	2.275	2.6
Ex-Harmful	6.475	7.3	4.725	5.3

The next step involves combining the alcohol RR obtained for each drinking category by gender with the baseline risk in order to obtain an estimate of alcohol-attributable risks for different consumption patterns.

Step 4: Combination of baseline risk and alcohol-based RR

For this last step, the baseline risk from Step 2 is combined with the consumption-based relative risks of Step 3 to estimate the absolute alcohol-attributable risk of injury death for each drinking category in a way to reflect real-time and cumulative risk based on drinking habits, i.e. the probability of dying given the baseline risk and being a (ex-) hazardous (ex-) harmful drinker. The yearly injury mortality risk is calculated using a probability scenario that incorporates Steps 2 and 3 in the following way, using the same approach applied to Canadian and Australian data by Taylor et al. (2008) and Rehm et al. (2008), respectively:

$$\Pr(\text{death} \mid N) = 1 - (1 - (\Pr(\text{death})_d / i_d))^N$$

Where:

N = the number of drinking occasions per year. See Table 27 for a breakdown of the number of occasions in each drinking category for men and women. Seven occasions in a week corresponds to 365 drinking occasions a year and 5 occasions a week correspond to 260 drinking occasions a year, for harmful and the other drinking categories, respectively.

d = the number of drinks consumed per occasion. See Table 27 for a breakdown of the number drinks consumed per occasion for each drinking category for men and women.

Pr (death | N) = the risk of injury death (per 1000) given N one-year drinking occasions

$\boldsymbol{Pr(death)_d}$ = the risk of injury death for one drinking occasion per year, depending on the number of drinks per occasion. This is the baseline risk (from Step 2) multiplied by the consumption-specific RRs (from Step 3).

$\boldsymbol{i_d}$ = the "risk period". This is the time period in which the person is at risk of an alcohol-attributable injury death. When a person drinks one drink, for example, he or she is not at risk for an entire day (24 hours). Rather, risk should be based on the average time it takes for the liver to metabolize a certain number of drinks and this is modelled based on work from the National Institute for Alcohol Abuse and Alcoholism (NIAAA, 1997). The relative risk associated with each drinking event changes as the amount consumed increases for each drinking occasion. Rapid consumption of multiple drinks results in a higher BAC during the period following ingestion, because the liver has a relatively fixed rate of metabolism (Wilkinson et al., 1977). Generally, for 1, 3, 5, and 7 drinks per occasion, the per-occasion risk equates to periods of 30 minutes, two hours, three hours and 4.8

hours. Thus, for example, for three drinks per occasion a risk period of two hours during the 24-hour period of that day is assumed. So, i_d becomes 365*(24/2), as it is based on the probability of one year (Rehm et al., 2008).

Probabilities of injury death are added up across injuries to get final estimates by consumption group, age group and gender, as presented in Table 29 below.

Table 29- Risk of injury death for each Markov drinking category, by gender and age group, per 1000 UK population

	Hazardous		Harmful		Ex-Hazardous		Ex-Harmful	
Age	Males	Females	Males	Females	Males	Females	Males	Females
15-29	0.38	0.07	0.89	0.17	0.04	0.01	0.21	0.03
30-44	0.44	0.07	1.01	0.19	0.05	0.01	0.24	0.04
45-59	0.37	0.09	0.85	0.24	0.04	0.01	0.20	0.04
60-69	0.38	0.10	0.89	0.27	0.04	0.01	0.20	0.05
70-79	0.68	0.26	1.49	0.64	0.08	0.03	0.37	0.12
> 80	1.51	0.93	2.53	1.60	0.25	0.14	0.96	0.54

5.2.2 Chronic disease mortality risks

Estimation of alcohol-attributable chronic disease mortality in the UK requires similar steps to the injury mortality risks.

Step 2: Dividing the risk into baseline and alcohol-attributable risk.

The estimation of the one-year absolute risk of alcohol-attributable chronic disease death first requires the knowledge of the risk of disease mortality that is *not* alcohol-attributable. The baseline risk is calculated for each chronic disease category identified in Step 1, differentiated by gender, and the following age groups: 15-29, 30-44, 45-59, 60-69, 70-79 and +80. For this calculation, the total number of deaths by gender and age, for a UK population and for each chronic disease obtained from the WHO GBD project for the year 2005 (unpublished data, kindly given by Juergen Rehm, consists of the latest available data from WHO), with the underlying cause coded according to the GBD, is used. By dividing the number of deaths from each disease category for each age group and sex by the total population at risk for the respective age groups and sex in the UK for the year 2005 (unpublished data, kindly given by Juergen Rehm, consists of the latest available data from WHO), the total risk of chronic disease death for one year per 1000 population in each age and sex group is calculated (i.e. the population-level absolute risk of mortality by chronic disease type). The baseline risk (not including the risk due to alcohol) is obtained by multiplying the total risk by the age, gender and disease-specific AAF and subtracting the resulting number (alcohol-attributable risk) from the total risk. The baseline risk is the risk of specific chronic diseases mortality that would have been present in the UK in the year 2005 without any involvement of alcohol. The AAF

for each chronic disease category is derived from the WHO CRA Study for Europe A Region (Rehm et al., 2004; WHO, 2002). The approach used for the calculation of one year chronic disease mortality uses the baseline risk in the following steps.

Step 3: Determination of relative risk for different alcohol quantities

Relative risks are calculated for different average daily consumption levels and adjusted for age. As for injuries, the definition of grams per day used to calculate the relative risks is based on the arithmetic mean of the levels of consumption that define the four Markov states. The definition of the ex-categories grams per day for chronic diseases risk is also complex as chronic diseases develop many years after the onset of alcohol drinking. Clearly, risk is reduced if people reduce drinking, but it is also substantially higher when compared to lifetime abstainers (Shaper, 1990; Wannamethee and Shaper, 1997), and it depends on the amount consumed before such reduction. For most chronic diseases, risk goes down slowly, but the exact amount is hard to quantify (for an example of head and neck cancer see Rehm et al., 2007b), and there are differences between disease categories (e.g. liver cirrhosis vs. cancer). Therefore, since prior drinking may be involved in the aetiology of chronic disease, or vice versa (e.g. "sick quitter" effect) (Shaper, 1990), for ex-drinkers, an underlying level of consumption of one third of the previous level of drinking is assumed (see Table 27), resulting in a risk estimation for ex-drinkers based on their previous consumption level ("harmful" or "hazardous"), as used previously for injury risk. Most diseases relative risks are modelled using data from Corrao et al. (1999), except for ischemic heart disease, which is based on another publication by Corrao et al. (2004). Male harmful drinkers, who are assumed to be consuming an average of 110 g/day, are at risk for ischemic heart disease because their level of consumption is outside of a protective effect, as reflected in the J-shaped relationship between alcohol consumption and risk for ischemic heart disease (Corrao et al., 2004).

Age specificity of relative risks

Consumption-specific chronic disease relative risks are not age-specific. Relative risks tend to converge to one with age and not taking this into account leads to an overestimation of deaths caused and prevented by alcohol in older age groups (Rehm et al., 2006b). For this reason, the model incorporates decreasing functions of RR with age.

The RR for alcohol-attributable chronic disease mortality, for the age groups above 45 years-old, is modelled using the following equations, based on the work of Klatsky and Udaltsova (2007):

Age group 45-59 $RR_{45-59} = RR_{30-44} \times RR_{30-44}^{-0.09551}$

Age group 60-69 $RR_{60-69} = RR_{45-59} \times RR_{45-59}^{-0.57049}$

Age group 70-79 $RR_{70-79} = RR_{60-69} \times RR_{60-69}^{-0.57984}$

Age group 80+ $RR_{80+} = RR_{70-79} \times RR_{70-79}^{-0.6347}$

The special case of Alcohol Use Disorders

Alcohol Use Disorder (AUD) is 100% attributable to alcohol, i.e. it would not exist if alcohol was not present. Therefore, the issue here is not determining the portion of risk that is alcohol attributable, but rather to estimate the risk of developing AUD at a given level of drinking (Rehm et al., 2008). For this, survey data (confidential data provided by Juergen Rehm) from the US-based National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data is used (sample size = 43, 093 persons 18 years and older, response rate = 81%) (Grant et al., 2003). The risk of AUD for males and females observed with the NESARC data, for different levels of alcohol consumption, is modelled using a quadratic regression (Rehm et al., 2008). This same regression is used for calculating the risk of AUD for the four drinking categories

Step 4: Combination of baseline risk and consumption-based RR

For this last step, the baseline risk from Step 2 is combined with the consumption-based relative risks of Step 3 for each age, sex, and disease category to estimate the absolute alcohol-attributable risk of chronic disease death for each drinking category. Finally, the risks are added up across disease categories in order to get final estimates by drinking category, age group and gender, as presented in Table 30 below.

Table 30- Risk of chronic disease death for each Markov drinking category, by gender and age group, per 1000 UK population

	Hazardous		**Harmful**		**Ex-Hazardous**		**Ex-Harmful**	
Age	Males	Females	Males	Females	Males	Females	Males	Females
15-29	0.06	0.04	0.12	0.08	0.03	0.03	0.04	0.04
30-44	0.48	0.35	0.93	0.59	0.34	0.27	0.39	0.31
45-59	2.58	1.65	4.19	2.52	2.11	1.36	2.30	1.51
60-69	7.95	4.86	9.57	5.64	7.40	4.57	7.62	4.72
70-79	23.24	17.02	25.16	18.13	22.51	16.63	22.79	16.82
> 80	61.44	66.87	63.42	68.63	60.61	66.28	60.90	66.56

Morbidity

The calculation of alcohol-attributable risk for injury and chronic disease morbidity involves an identical series of steps as the ones presented above for mortality. Only the differences between the two methods are presented in this section. It can be anticipated that key differences relate to the use of morbidity total risks instead of mortality risks. Another difference is the use of AAFs for injury morbidity instead of mortality, as detailed below.

5.2.3 Injury morbidity risks

The calculation of yearly alcohol-attributable injuries morbidity risk requires the use of total morbidity risk by age group, gender and injury category. The calculation of this risk uses hospital morbidity data from the Hospital Episode Statistics (HES) 2006-07 (for inpatient data, primary diagnosis coded with three characters) for England (The NHS Information Centre, 2007b). In the NHS episode statistics, the injury categories indentified in Table 25 are coded according to the ICD-10. However, the HES are not available for the same age and gender groups previously defined. The age groups presented in the HES are 0-14, 15-59, 60-74 and +75 years old. When gender separation is presented in the HES, the number of cases is aggregated for all ages. Given that the total morbidity risk is required for the age groups15-29, 30-44, 45-59, 60-69, 70-79 and +80 and by gender, the following steps are taken:

1) Computation of all hospitalizations for each alcohol-related injury for two age groups: 15-59 and +60.
2) Determination of age and gender distributions for each injury group based on UK injury number of deaths data (the same data previously used for mortality).
3) Assumption of the same gender and age distributions for morbidity data and computation of raw numbers of injury hospitalizations for males and females separately in the following age groups: 15-29, 30-44, 45-59, 60-69, 70-79, and 80+.
4) Computation of rates of total injury morbidity for each age/ gender category by dividing the raw number of hospitalizations by the total at-risk population. At risk population is the 2006 population estimates for England by gender and age (Office for National Statistics, 2006).

The other difference, with respect to mortality rates, is that the AAFs for injuries are adjusted from the AAFs reported for injury mortality, obtained from the CRA (Rehm et al., 2004; WHO, 2002). In general, more severe outcomes are more related to alcohol than less severe outcomes (Rehm et

al., 2003b). Consequently, the AAFs for mortality should be higher than the AAFs for morbidity. The AAFs for morbidity from injuries are derived by multiplying the mortality AAFs by two thirds for motor vehicle accidents and by four ninths for all other types of injury (Cherpitel, 1993, 1996; Rehm et al., 2004; Cherpitel, 1994). Table 31 below presents the risks of injury morbidity, by gender and age group for each drinking category of the model.

Table 31- Risk of injury morbidity for each Markov drinking category by gender and age group

	Hazardous		**Harmful**		**Ex-Hazardous**		**Ex-Harmful**	
Age	Males	Females	Males	Females	Males	Females	Males	Females
15-29	0.0053	0.0024	0.0060	0.0041	0.0019	0.0003	0.0045	0.0013
30-44	0.0057	0.0029	0.0062	0.0047	0.0023	0.0005	0.0049	0.0017
45-59	0.0048	0.0033	0.0057	0.0046	0.0021	0.0007	0.0042	0.0023
60-69	0.0038	0.0025	0.0050	0.0035	0.0015	0.0005	0.0031	0.0017
70-79	0.0041	0.0030	0.0053	0.0040	0.0022	0.0013	0.0033	0.0025
> 80	0.0043	0.0031	0.0052	0.0043	0.0025	0.0021	0.0036	0.0026

5.2.4 Chronic disease morbidity risks

As for injury morbidity risks, a total risk must be computed for chronic diseases morbidity. The calculation of this risk follows exactly the same procedure as presented above for injuries, i.e.:

1) Computation of all chronic disease hospitalizations for two age groups: 15-59 and +60 from the HES 2006-07 (The NHS Information Centre, 2007b).
2) Determination of age and gender distributions for each disease category based on UK chronic disease number of deaths data (the same data previously used for mortality).
3) Assumption of the same gender and age distributions for morbidity data and computation of raw numbers of chronic disease hospitalizations for males and females separately in the following age groups: 15-29, 30-44, 45-59, 60-69, 70-79, and 80+.
4) Computation of rates of total chronic disease morbidity for each age/ gender category by dividing the raw number of hospitalizations by the total at-risk population. At risk population is the 2006 population estimates for England by gender and age (Office for National Statistics, 2006).

The sources for RR and AAF are the same as for mortality and there is no further difference regarding the methods for chronic disease alcohol-attributable morbidity risk, when compared with the methods for mortality. The table below presents the risks of chronic disease morbidity, by gender and age group for each drinking category of the model.

Table 32- Risk of chronic disease morbidity for each Markov drinking category, by gender and age group

	Hazardous		Harmful		Ex-Hazardous		Ex-Harmful	
Age	Males	Females	Males	Females	Males	Females	Males	Females
15-29	0.0010	0.0005	0.0025	0.0009	0.0004	0.0003	0.0007	0.0004
30-44	0.0088	0.0066	0.0188	0.0108	0.0048	0.0050	0.0066	0.0058
45-59	0.0357	0.0275	0.0616	0.0407	0.0265	0.0224	0.0306	0.0250
60-69	0.0259	0.0166	0.0344	0.0198	0.0226	0.0153	0.0241	0.0160
70-79	0.0685	0.0523	0.0759	0.0557	0.0657	0.0512	0.0668	0.0517
> 80	0.1464	0.1618	0.1515	0.1654	0.1445	0.1610	0.1451	0.1613

5.3 Life expectancy: generation of a UK lifetable for the economic model

In the model the transition probabilities from each state to the death state consist of two components. The first component is the probability of dying from non-alcohol-related causes, i.e. the baseline mortality, which is the same for all states and different for women and men. This probability changes over time because, as the patient gets older, the probability of dying from unrelated causes will increase continuously. The baseline mortality rate is simply the total mortality risk discounting the risk for alcohol-related injuries and diseases. The second component is the probability of dying from alcohol-related causes, taking both alcohol-related injuries and chronic diseases into account. This one is state specific and also varies with time and gender, as presented in the above section for a UK population.

Therefore, each drinking category has its own gender and age-dependent mortality transition probabilities. The way this is implemented in the model is by using a country-specific table of gender and age-specific mortality rates (lifetable) for each drinking state. The following table (Table 33) presents the age-dependent transition probabilities to death for a UK population. With a yearly cycle length, the patient's age at the end of cycle n is: $\text{Age}_{\text{cycle n}}$=Start age + n and this is introduced in an excel VLOOKUP function. For each Markov state, a VLOOKUP function looks up the index age in a lifetable in order to retrieve the transition probability from each state to the death state. For each cycle, mortality from other causes (baseline mortality in Table 33) is added to the alcohol-specific mortality rates to produce a total compound mortality for each drinking category.

Table 33- Lifetable: age-dependent transition probabilities to death by gender, for each drinking state and baseline, per 1000 UK population

		Hazardous		Harmful		Ex-Hazardous		Ex-Harmful		Baseline mortality	
Age	**A'**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
15-29	15	0.44	0.11	1.01	0.25	0.08	0.04	0.25	0.07	0.27	0.16
30-44	30	0.92	0.42	1.94	0.79	0.39	0.28	0.63	0.35	0.55	0.39
45-59	45	2.95	1.74	5.04	2.76	2.15	1.37	2.50	1.55	2.47	1.78
60-69	60	8.33	4.96	10.46	5.92	7.44	4.58	7.82	4.77	9.21	5.99
70-79	70	23.92	17.28	26.65	18.76	22.59	16.66	23.16	16.94	25.72	15.66
> 80	80	62.95	67.81	65.95	70.24	60.86	66.42	61.86	67.10	68.70	48.40

M, males; F, females; A', Age Index.

The text that follows provides a more detailed analysis of the UK mortality rates by gender and age groups. This is important for the interpretation of subgroup analyses that study the impact of population characteristics on the effectiveness and cost effectiveness of alcohol treatments. Table 34 below shows the mortality rates by gender (averaged by age group) for chronic diseases and injuries together and for injuries and chronic diseases separately. The proportion of male mortality rates compared to female rates is presented. It can be seen that overall mortality rates for males are only slightly higher than female rates for all drinking categories. The proportion of males dying from injury-related causes is more than double that of females for all drinking groups. The proportion of males and females dying from alcohol-related chronic disease is similar between the drinking groups.

Table 34- Proportion of males/females alcohol specific mortality rates by gender and drinking category

	Injuries and Chronic	Injuries	Chronic
Drinking group	M/ F	M/ F	M/F
Hazardous	1.08	2.46	1.05
Harmful	1.13	2.46	1.08
Ex-Hazardous	1.05	2.54	1.04
Ex-Harmful	1.06	2.65	1.05

M, males; F, females.

Mortality rates for males of all age groups less than 80 years old through the four drinking categories are on average higher than female rates, with the biggest difference for the lower age groups, where the rates for males are two to four times higher than those for females (Table 35). The high proportion of male vs. female mortality rates for the lower age groups is explained by the higher alcohol-attributable injury mortality risks for males in lower age groups. The proportions of the rates decrease with an increase in age, where the gender difference in mortality starts to be less pronounced. The proportion of males dying from injuries, when compared to females, is higher

than the proportion for chronic diseases. After 80 years old more females than males die from chronic diseases, which can be explained by females' higher life expectancy

Table 35- Proportion of males/ females alcohol specific mortality rates by gender and age group

	Injuries and Chronic	**Injuries**	**Chronic**
Age group	M/ F	M/ F	M/F
15-29	3.80	5.53	1.32
30-44	2.11	5.60	1.40
45-59	1.70	3.80	1.59
60-69	1.68	3.46	1.64
70-79	1.38	2.51	1.37
> 80	0.93	1.63	0.92

M, males; F, females

Table 36 shows that alcohol specific rates are higher for more serious drinking levels, with the ex-hazardous category presenting the lower mortality rates, for both males and females. Table 37 shows that alcohol specific mortality rates, for males and females, increase with age.

Table 36- Alcohol specific mortality rates by gender and drinking category, per 1000 UK population

Drinking group	**Males**	**Females**
Hazardous	16.58	15.39
Harmful	18.51	16.45
Ex-Hazardous	15.59	14.89
Ex-Harmful	16.04	15.13

Table 37- Alcohol specific mortality rates by gender and age group, per 1000 UK population

Age group	**Males**	**Females**
15-29	0.45	0.12
30-44	0.97	0.46
45-59	3.16	1.85
60-69	8.51	5.06
70-79	24.08	17.41
> 80	62.90	67.89

5.4 Calculation of disease costs for the Markov states

This section is concerned with the calculation of the alcohol-related diseases costs for a UK population. These costs are specific to each drinking category and represent the hospital alcohol-related diseases costs of the health states. The alcohol-related morbidity rates for the alcohol-related diseases identified in Table 25, by gender, drinking state and for each age group, are used for the calculation of state costs. The calculation of the morbidity rates is presented in section 5.2.4 above. WHO ICD-10, GBD and HRG codes for the diseases used for costing the Markov states are presented in Table 38 below.

Table 38- Diseases used to cost the Markov states

GBD code and description	ICD-10 code	HRG code
W061 Oral cavity, pharynx	C00-C14	C17,C27,C37
W062 Oesophageal cancers	C15	F08
W065 Liver cancer	C22	P07
W069 Breast cancer	C50	J10
W086 Alcohol use disorders	F10	Not coded in HRG*
W106 Hypertensive disease	I10-I13	E25,L53
W 107 Ischaemic heart disease	I20-I25	E23,E12
W 108 Ischaemic stroke	I60-I69	P09,A19,A23
W 108 Haemorrhagic stroke	I60-I69	P09,A19,A23
W117 Cirrhosis of the liver	K70-K74	P12,G06

GBD, Global Burden of disease (Murray and Lopez, 1997); ICD-10, International Classification of Diseases 10th revision (WHO, 1992); HRG, Health Care Resource Group;*Alcohol use disorders (W086) is not costed in elective inpatient HRG data.

Average unit costs for each one of the diseases identified as being alcohol-related are retrieved as follows. First, the GBD codes are converted to ICD-10 codes using an online conversion table available in the Disease Control Priorities Project website (The World Bank Group, 2006). Second, the ICD-10 codes of the diseases as provided in the Hospital Episode Statistics (The NHS Information Centre, 2007b) are converted to Heath Care Resource Group (The NHS Information Centre, 2007a) (see Table 38 above). The conversion from ICD-10 codes to HRG uses a casemix converter available online in the NHS website (The NHS Information Centre, 2007c). Finally, national average unit costs are retrieved from the National Schedule of Reference Costs available online, using elective inpatient HRG data (Department of Health, 2006; Appendix NSRC1 Aa) and up-rated to 2006/07 prices, using the Hospital and Community Health Services (HCHS) pay and prices index from the PSSRU Unit Costs of Health and Social Care 2007 (Curtis, 2007). Alcohol use disorders (W086) is not costed in elective inpatient HRG data. Therefore, the average cost is calculated based on the unit cost reported by the PSSRU (Curtis, 2007) and on the mean length of

stay reported in the Hospital Episode Statistics (The NHS Information Centre, 2007b). The mean cost used is £1,469.70 (£213 per inpatient day taken from PSSRU 2006/07, combined with a mean length of stay of 6.9 days, as reported in the HES 2006/07). The average unit costs for each disease are presented in Table 39.

Table 39- Unit average costs for the alcohol-related diseases

GBD	GBD description	Average unit cost
W061	Oral cavity, pharynx	£1,989.68
W062	Oesophageal cancers	£1,275.63
W065	Liver cancer	£2,138.80
W069	Breast cancer	£1,091.27
W086	Alcohol use disorders	£1,469.70
W106	Hypertensive disease	£1,329.48
W107	Ischaemic heart disease	£1,515.50
W108	Ischaemic and Haemorrhagic stroke	£2,345.72
W117	Cirrhosis of the liver	£1,961.69

GBD- Global Burden of disease (Murray and Lopez, 1997); 2006/07 prices.

The average unit costs of each disease are then weighted by the disease-specific morbidity risk, by gender, age and drinking group. The weighted costs for all alcohol-related diseases, by age and gender, are linked to each drinking state. Given that the morbidity risks are disease, age, gender and consumption specific, it would be exhaustive to present all the calculations. An example of the computation of disease-related costs is presented in Table 40 for males of the 30-44 year old group. The table presents the morbidity rates for each disease, the weighted costs (average unit costs presented in Table 39 multiplied by the morbidity rate) and the overall state cost (last line of the table), for a males with 30 to 44 years old.

Table 40- States costs computation for males with 30 to 44 years old, UK population

	Hazardous		Harmful		Ex-Hazardous		Ex-Harmful	
GBD	mr*	Cost £	mr*	Cost £	mr*	Cost £	mr*	Cost £
W061	0.18	0.36	0.34	0.67	0.09	0.18	0.13	0.26
W062	0.11	0.14	0.25	0.31	0.06	0.08	0.09	0.11
W065	0.03	0.06	0.04	0.08	0.02	0.05	0.03	0.06
W069	0.02	0.03	0.04	0.04	0.02	0.02	0.02	0.02
W086	4.50	6.62	11.52	16.93	1.26	1.85	2.85	4.19
W106	0.50	0.66	1.10	1.46	0.30	0.39	0.39	0.52
W107	2.33	3.53	2.78	4.21	2.33	3.53	2.33	3.53
W108	0.79	1.85	2.14	5.01	0.52	1.21	0.55	1.28
W117	0.32	0.62	0.61	1.20	0.18	0.35	0.25	0.48
SUM	**8.78**	**13.87**	**18.80**	**29.91**	**4.77**	**7.66**	**6.62**	**10.45**

GBD, Global Burden of disease (Murray and Lopez, 1997); mr, morbidity rate; 2006/07 prices; * per 1000.

A table with each drinking category cost by age and sex per year is then constructed with the sum of the weighted costs of the alcohol-related diseases. The expected state costs are presented in Table 41 below. The economic model is linked to the table of state costs in a similar way as it is linked to the lifetable explained above. For each Markov state, a VLOOKUP function looks up the index age in the state cost table in order to retrieve the average cost of that state and cycle. Costs are accumulated according to the number of patients in a given category in each cycle and an estimate of the average disease-related costs over lifetime is obtained.

Table 41- Yearly state cost by age and sex for each drinking category, UK population

		Hazardous		Harmful		Ex-Hazardous		Ex-Harmful	
Age	**Age index**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
15-29	15	1.65	0.74	3.99	1.47	0.72	0.54	1.13	0.64
30-44	30	13.87	8.76	29.91	15.02	7.66	6.54	10.45	10.45
45-59	45	56.65	36.89	99.16	56.63	41.96	30.03	48.26	33.48
60-69	60	41.82	25.00	55.55	30.26	36.46	23.13	38.73	24.06
70-79	70	113.87	85.93	126.75	92.22	109.00	84.22	110.73	84.96
> 80	80	253.03	288.24	262.64	295.73	249.45	286.90	250.42	287.29

*2006/07 prices, pound sterling (£, GBP).

Comparing health care costs by gender and age subgroup reveals that costs are higher for males of all age groups below 80 years old. For an older cohort (more than 80 years old), females' costs are higher which can be explained by females higher life expectancy. For both men and women, state costs increase with age (Table 42). Therefore, if alcohol treatments have the potential to reduce alcohol-related costs, more health care savings can be achieved for older age cohorts and a bigger

difference in health care savings by gender should be observed for younger age groups. The biggest gender difference is observed for the younger age cohort (15-29 years old) and this can be explained by the higher morbidity rates for younger males.

Table 42- Health care costs by gender and age group, averaged for all drinking groups

Age group	Males (M)	Females (F)	Proportion M/ F
15-29	£1.87	£0.85	2.21
30-44	£15.47	£10.19	1.52
45-59	£61.51	£39.26	1.57
60-69	£43.14	£25.61	1.68
70-79	£115.09	£86.83	1.33
> 80	£253.89	£289.54	0.88

When comparing the same drinking category and with no age differentiation, health care costs are slightly higher for men than for women (Table 43). The drinking state with higher associated health care costs is the harmful state, followed by the hazardous, ex-harmful and ex-hazardous states. Therefore, it is shown that a higher level of alcohol consumption is associated with increased hospital alcohol-related diseases costs.

Table 43- Health care costs by gender and drinking group, averaged for all age groups

Drinking group	Males (M)	Females (F)	Proportion M/ F
Hazardous	£80.15	£74.26	1.08
Harmful	£96.33	£81.89	1.18
Ex-Hazardous	£74.21	£71.89	1.03
Ex-harmful	£76.62	£73.48	1.04

5.5 Calculation of utility weights for the Markov states

The estimation of utilities associated with each Markov state for the UK uses the UKATT trial data (UKATT Research Team, 2005a). This is the only economic evaluation of alcohol treatments conducted alongside a clinical trial that used a standardised preference-based measure of health status, the EQ-5D questionnaire (Williams, 1990), in a population with alcohol problems. Patients in the study classified their own health state using the multiattribute instrument EuroQol and UK population norms were used to value patients' health states (Kind et al., 1999). This trial used the EQ5D at baseline, 3 months and 12 months to measure each patient's utility. Similarly, drinking variables were reported at baseline, 3 months and 12 months. The calculation of utility weights for the Markov states involves three steps.

1) Calculation of variables in terms of grams per day

The UKATT trial did not present individual-level outcomes in terms of grams per day but drinking categories are defined in these terms. The estimation of grams per day per patient for each follow-up period involves the following steps (using SPSS 15). The variable "drinks per drinking day" is multiplied by the variable "number of drinking days" for each patient to derive the total number of drinks per patient. As alcohol consumption was assessed using Form 90 (Miller WR, 1996), the total number of drinks was consumed over a period of 90 days. The number of drinks per patient is divided by 90 in order to get the number of drinks per patient per day. Given that in the UK a standard drink has 8 g of Ethanol the number of drinks per patient per day is multiplied by 8 to get the total grams of alcohol consumed per patient per day.

In order to get utility weights for the model states, all UKATT sample (n=742) is used and patients are divided into drinking categories according to g/day at 6 months. The 6-month drinking in grams/day for the UKATT is obtained by using linear interpolation between 3 and 12-month follow-up data. First, 3 and 12-month g/day are obtained for each patient. Then an "incremental variable" computed as the difference between 3 and 12-month g/day divided per 3 gives an estimate of the 3-month decrement in g/day between 3 months and 12 months. Finally, the computed increment is deducted from the 3-month g/day for each patient. This method of calculating 6-month g/day for each patient in the trial assumes a linear negative relation between consumption at 3 and 12 months.

Patients are allocated according to their level of drinking at 6 months and utilities are retrieved for 12 months due to the possibility that participants' utility at time *t* can just be captured at time *t+1*. The trial data provides 414 patients with EQ-5D values at 12 months that can be allocated to a drinking category according to the level of drinking, in g/day, at 6 months.

2) Drinking categories definition for calculation of utilities

No gender differentiation is possible with the data due to the low number of female patients with utility values at 12 months. Therefore, the grams per day that define each Markov state are collapsed in order to estimate the drinking level for each category with no gender differentiation.

The drinking categories for estimating utilities with no gender differentiation at *baseline* are the following two:

1) Hazardous drinking (M): $\leq$ 67.5 g/day (67.5 g/day is the mean of 55 g/day and 80 g/day)

2) Harmful drinking (H): >67.5 g/day

At *6 months* patients can be in one of the following drinking categories:

1) Hazardous drinking (M): 24-67.5 g/day (24 g/day is the mean of 20 g/day and 28 g/day)

2) Harmful drinking (H): >67.5 g/day

3) Ex- Hazardous drinking (ExM): <24 g/day and hazardous drinking in previous cycle

4) Ex-Harmful drinking (ExH): <24 g/day and harmful drinking in previous cycle

3) Utility estimates for the Markov states

After dividing the patients according to the above drinking categories, the utility estimates at 12-month follow-up are retrieved for each Markov state. These estimates are presented in Table 44, along with the standard error and number of patients informing the values.

Table 44- Utilities for the Markov States per cycle

States' utilities	Hazardous	Harmful	Ex-Hazardous	Ex-Harmful
Utility/ weight	0.6597	0.6349	0.7001	0.6459
Standard error	0.02582	0.0245	0.07591	0.0436
n	160	180	15	59

The utilities estimates reflect a decrease in HRQoL for higher consumption levels. The harmful state has the lowest utility, followed by the ex-harmful, hazardous and ex-hazardous, respectively. The ex-states have a higher utility than the states where they derive from which is related with a sensible level of drinking. The high standard errors observed in the ex-categories are related to the small number of patients in those states. However, this uncertainty can be taken into account in the probabilistic sensitivity analysis that is incorporated in the Markov model, as explained below.

5.6 Probabilistic sensitivity analysis: application of specific distributions

This chapter focus on the model inputs that are country-specific and independent of the treatments under evaluation. Chapter 4 explains how probabilistic sensitivity analysis deals with uncertainty in the model inputs (see section 4.7 in the previous chapter). The model inputs that the results are most uncertain about are the transition probabilities and the utilities associated with each Markov state. Therefore, it is appropriate to explain the probabilistic distributions used for the transition probabilities of the following cycles and the utility weights, given that the two inputs are calculated in this chapter. The distributions applied depend on the type of data that generates model inputs. Even though the inputs considered are UK-specific, it can be expected that an adaptation of the model for other countries will need the same type of data and therefore, the same distributions should apply.

5.6.1.1 Distribution for the following cycles transition probabilities

The following cycle probabilities are based on the study conducted by Taylor et al. (1985). This study reported the proportion of patients remaining in a given category (p) and used a sample of 68 patients (n) (Taylor et al., 1985). The probabilities of transiting to any one of the two other allowed states are derived from the reported probability of remaining in a given state. Therefore, two categories can be considered. One category is remaining in the state and the other category is leaving that state, where the probability of the latter is half of one minus the probability of remaining in the state. When two categories are considered, where one category is remaining in a state and the other category is leaving that state, the transitions probabilities between the two categories are estimated from a binomial proportion.

In Bayesian inference, a prior distribution is a probability distribution representing a belief about an unknown quantity and a posterior distribution is a conditional distribution of the uncertain quantity given the data. The beta distribution is a conjugate of binomial data, which means that specifying a beta prior distribution on binomial data results in a beta posterior distribution (Briggs et al., 2006). The beta distribution allows the probability rules to be maintained, i.e. probabilities keep taking values between the range of zero and one, and probabilities of mutually exclusive events keep summing to one. Therefore, the chosen distribution for representing uncertainty in the following cycles transition probabilities is a beta distribution.

Fitting the beta distribution in the Markov model of drinking behaviour for the following cycle transition probabilities

The beta distribution is constrained on the interval 0-1 and is characterized by two shape parameters, α and β. The beta distribution is fitted in the model by the method of moments (Briggs et al., 2006). The moments of the beta distribution, for θ ~ beta (α, β), are given by:

$$E[\theta] = \frac{\alpha}{\alpha + \beta}$$

$$\text{var}[\theta] = \frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

The sample moment proportion (p) and the sample size (n) are used to calculate the standard error (se) and the sample moments are equated to the distribution moments as follows:

$$p = \frac{\alpha}{\alpha + \beta}$$

$$s^2 = \frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

$$se = \sqrt{p(1-p)/n},$$

where s^2 is the error variance, n= 68 and p= yearly stability reported in Taylor et al. (1985) as in Table 24.

Rearranging the above equations allows the calculation of the unknown parameters α and β as a function of the known sample proportion and standard error (se) of the proportion. The model is developed in Microsoft® Excel and in this software a beta distribution is fitted as: BETAINV(RAND(),α, β), where RAND() is the command for drawing a random value from the beta distribution in Excel. The reason why BETAINV is specified in Excel is because it is the inverse of the cumulative distribution function that gives the expected value when an integrated probability is specified (Briggs et al., 2006).

5.6.1.2 Distributions for utilities

Utility parameters are constrained between infinity at the lower end (representing the worse possible health state) and 1 at the upper end (representing perfect health). Given that the utilities used in the model are far from zero (see Table 44 above), a beta distribution is used in order to reflect uncertainty in these parameters.

Fitting the beta distribution in the Markov model of drinking behaviour for utility weights

The same approach as explained above for fitting the beta distribution is used for utilities. The sample moments $\bar{\mu}$ (sample mean) and s^2 (error variance) are taken from the utility data presented in Table 44 for the corresponding drinking states and are equated to the distribution moments as follows:

$$\bar{\mu} = \frac{\alpha}{\alpha + \beta}$$

$$s^2 = \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$$

Rearranging the above equations allows the calculation of the unknown parameters α and β as a function of the known sample mean utility and standard error. As described above for the transition probabilities, the BETAINV function is used to generate random draws from the distributions specified for each utility parameter.

5.7 Discussion

Epidemiological approach

Some limitations of the epidemiological approach should be pointed out. The definition of the ex-categories grams per day for injury and chronic diseases risk calculation is complex. For most injuries when no alcohol is consumed the risk becomes zero while chronic diseases develop many years after the onset of alcohol drinking. The definition of ex-categories, for risk calculation, is based on the assumption that the consumption for these categories corresponds to about 1/3 of the previous level of drinking. The ex-categories have a lower bound of zero grams per day and so, both abstinent and sensible drinkers are captured within these categories. If the midpoint between 0g and the upper bound of these categories had been used, no distinction between the risk for ex-harmful and ex-hazardous drinkers would have been possible.

Injury consumption-specific mortality risks are calculated with a regression equation based on an emergency rooms study, Borges et al. (2006), which focused on non-fatal injury. Although the focus of the study was on non-fatal injuries, the reasons for the use of this study not presenting a major limitation, when the reported RRs are used for alcohol-related injury mortality, are twofold. On the one hand, the relevant literature indicates that injuries tend to be more severe when alcohol is involved, and thus the RR and AAF are larger for mortality when compared to morbidity (Rehm et al., 2003a; Rehm et al., 2004; Cherpitel, 1993; Rootman et al., 2007; Cherpitel, 1996; Li et al., 1997; Fuller, 1995; Humphrey et al., 2003). Therefore, it can be assumed that the RR for the number of drinks would underestimate the AAF, since Borges et al. (2006) is based on morbidity data, not mortality as for WHO (2002). On the other hand, ER studies may lead to an overestimate of the effects. Clearly, the attendees of ERs are not representative of the general population. They may be characterized as higher risk-taking, and thus the RR for alcohol in this population may be higher than in the general population. The two aforementioned effects have opposite directions and it could be assumed that they cancel each other out. However, Rehm et al. (2008) pointed out that the impact of these potential biases on the estimates for risk injury is not clear and more research is needed.

Most research to determine AAFs for injury did not explicitly separate morbidity and mortality (English et al., 1995; Single et al., 1996; Stinson et al., 1993). Nevertheless, the meta-analysis conducted by Ridolfo and Stevenson (2001), in Australia, separated the AAFs for motor vehicle accidents for males. It was based on this work and that of Cherpitel (1994, 1996), that Rhem et al.

(2004) derived the ratio of AAF for morbidity as two thirds for motor vehicle accidents and as four ninths for all other injuries. However, these weights are only a best estimate.

Total morbidity risk for each chronic disease and injury is based on hospital data (NHS episode statistics), which presents some limitations such as: 1) hospital admissions can be selective in terms of personal characteristics, severity of the disease, associated conditions and admission policies; 2) hospital records are not designed for research and they may be incomplete, illegible or missing and variable in quality; and 3) population at risk is generally not defined (Gordis, 2009). Also, as the data from the HES is not disaggregated for the age and gender groups required in the model, it is assumed that the same age and gender distribution as that of mortality rates can be used. In addition, the HES are reported for England and not the whole of the UK. For this reason, for a matter of consistency, the population at risk for morbidity is the population for England for the same year as the HES data (2006). Nevertheless, it can be expected that the morbidity rates calculated for England are very close to the ones for the whole UK population.

Limitations of the model for UK-specific input parameters

There are some limitations concerning the specific UK data used to populate the theoretical model. In particular, drinking behaviour after treatment uptake is taken from a longitudinal study with a small sample size. The transition matrix for the following cycles' transition probabilities is derived from Taylor et al (1985). These estimates are based on strong assumptions, namely: 1) drinking groups as defined in the Taylor et al. (1985) study can be matched to the model categories; 2) transitions remain constant over time; 3) transition to the two other states, not informed by the Taylor et al. (1985) study are the same; 4) transitions reported in the study are observed right after the cycles for which clinical effectiveness data is available; 5) transitions do not differ by gender; 6) once treatment stops transition rates are assumed to be the same between the compared arms of the model. One of the biggest assumptions related to using long-term follow-up data that does not follow the specific treatments evaluated is that the model assumes that exposure to other alcohol interventions (enforcement and prevention) is the same for the alternative groups in the long run. Therefore, the outcomes after treatment are the same for a group of patients in the same drinking category and with the same age and sex. Further information regarding the rate of relapse after treatment and transitions between drinking categories over the lifetime of individuals is highly required for a UK alcohol treated population. Moreover, in order to take into account the effect of different exposures on drinking behaviour a long-term follow-up study for the specific intervention groups is needed. In addition, possible interactions between exposures would need to be taken into account. Nevertheless, the use of transition probabilities taken from a peer reviewed study

overcomes the assumption that treatment effects remain after the end of a trial, over patients' lifetime, which would be an even stronger assumption as there is no evidence for such.

Markov states' utilities are calculated with data from the UKATT trial. However, using utilities taken from the UKATT trial for the computation of the utilities for each drinking state in the model might present some limitations. For example, the trial was UK-based and utility valuations were that of a UK population which might hamper utilities transferability to other settings. Nevertheless, it is common practice that economic evaluations conducted worldwide use UK preferences for QALY calculations and, more importantly, the data obtained in this chapter intends to be UK-specific. Health-related quality of life should be dependent on age and sex and this is shown in the published HRQoL norms for the UK (Kind et al., 1999). For this reason, state utilities should be age and gender-dependent. This is not the case for the valuation of the model states as the sample size informing the utilities would not allow gender and age differentiation. Also, these utilities were generated from the EQ-5D questionnaire which may not include facets of HRQoL related to alcohol consumption. Nevertheless, for comparison between health technologies, NICE recommends the use of utilities taken from the general population and not disease-specific valuations. Therefore, the Markov state utilities are in line with the published UK guidelines (NICE, 2008).

The economic model only considers two major categories of costs: the costs of the specific treatments analysed (not covered in this chapter) and the chronic disease hospital costs. Regarding the latter, disease related costs are the hospital costs related with a sustained intake over 80 years, i.e. the long-term disease hospital costs. Injury costs are not included in the costs of the four health states. Even with the narrow health services perspective taken, injury morbidity costs should be included in future developments. However, in order to do so methods for costing alcohol-related injuries also need to be developed. More broadly, the social consequences of alcohol consumption are not considered, which is in accordance with the health system perspective adopted. Social outcomes including family problems, criminal activity, or productivity losses need to be considered if a societal perspective is advocated. Given the wider social and economic benefits of alcohol treatments the economic analysis should aim at being more complete. Further extensions of the model should consider these wider social costs associated with each drinking category. Data regarding alcohol-related UK criminal activity and productivity losses needs to be collected. This represents a challenge, especially in the field of criminal activity given the different definitions and measurement techniques associated with the different types of crime.

5.8 Conclusion

This chapter presents the calculation of country-specific inputs that feed into the economic model of drinking behaviour developed in the previous chapter. This data is UK- specific and can be used for the economic evaluation of alcohol treatments in the UK. Despite the acknowledged limitations, the methods presented allow the incorporation of patterns of drinking and levels of drinking on morbidity and mortality risks. This helps in achieving more accurate estimates of the cost effectiveness of alcohol because health and economic consequences can be estimated based on lifetime drinking behaviour and associated risks.

Chapter 6. Model application to the UKATT trial

This chapter consists of an application of the Markov model of drinking behaviour to a UK setting. It brings together the results of Chapter 4, where the model is developed, and of Chapter 5, where UK-specific model inputs are generated, for the cost effectiveness analysis of two psychosocial therapies delivered in the UKATT trial (UKATT Research Team, 2001, 2005b, a). The published cost effectiveness analysis did not find any significant differences in terms of costs and effects between the two treatments and this might be related to the short time horizon of the analysis.

This case-study aims at applying the Markov model of drinking behaviour to the UKATT trial data in order to assess the incremental costs, survival and QALYs of Motivational Enhancement Therapy (MET) vs. Social Behaviour and Network Therapy (SBNT) in the long term. This is achieved by augmenting the trial patient-level data with evidence from other sources, thereby extending the trial-based economic evaluation with synthesis and modelling. The model application also deals with heterogeneity and so it helps in assessing whether any of the therapies represents better value for money for a specific subgroup of patients, based on age and gender characteristics.

This is not an attempt to validate the model as clinical trials can provide inputs for decision analytical models but cannot provide a valid test of their predictions (Sculpher et al., 2000). Sculpher et al. (2000, pp 463) argue that clinical trials and decision analytical models are not directly comparable because "their objectives are fundamentally different: a model combines information already available in an explicit and formal framework, a clinical trial generates new information about one or more parameters of interest". Therefore, the purpose of applying the model to the UKATT trial is to inform decision making based on long-term costs and outcomes. See Appendix 5- Markov model features, for a summary table of the model characteristics.

6.1 The UKATT trial and why modelling UKATT data?

The UKATT trial was designed to compare the effectiveness and cost effectiveness of SBNT, a new treatment for alcohol problems, with that of the proved MET (UKATT Research Team, 2001, 2005b, a). The trial aimed at testing the following two main null hypotheses: 1) less intensive motivationally based treatment- MET, is as effective as more intensive socially based treatment- SBNT; 2) more intensive socially based treatment- SBNT, is as cost effective as less intensive motivationally based treatment- MET, particularly in improving patients' quality of life (UKATT Research Team, 2001).

The UKATT trial was a pragmatic multicentre randomized controlled trial with open follow-up at three months after entry and blind follow-up at 12 months. The design and methods are fully

detailed in the UKATT trial protocol (UKATT Research Team, 2001). The trial was conducted in five treatment centres, comprising seven UK treatment sites, including NHS, social services and joint NHS/ non-statutory facilities.

In the UKATT trial, MET combined the principles of 'motivational interviewing' (Miller WR and Rollnick S, 2002) with objective feedback to the client of the results of assessments carried out prior to the first session of MET (Miller WR et al., 1992). A large and growing body of research has confirmed the effectiveness of motivational interviewing principles (Lundahl and Burke, 2009; Burke et al., 2003). Motivational interviewing has become extremely popular in the alcohol field in Britain and is now widely used throughout the country, either as a form of treatment in its own right for clients with relatively less severe problems, or as a component of treatment for those with more severe difficulties (UKATT Research Team, 2001). In the UKATT trial MET was viewed as a usual form of treatment that any other treatment must surpass in effectiveness or cost effectiveness to be considered for routine application in service provision. MET in the UKATT trial compromised three 50 minute sessions over eight to 12 weeks.

SBNT was a treatment modality developed for UKATT, it had a strong theoretical and empirical basis using a range of cognitive and behavioural strategies to build social networks supportive of change involving the client and other network members (family and friends) (Copello et al., 2002). It has been shown that within intensive treatments better outcomes are obtained for interventions with a strong social component (Holder et al., 1991; Miller WR and Wilbourne PL, 2002; Project MATCH Research Group, 1997) and for family and friends involvement (Orford, 1994). In the UKATT trial, SBNT was carried out over eight 50 minute sessions for eight to 12 weeks.

The UKATT cost effectiveness results concluded that there was no strong evidence about the effectiveness and cost effectiveness of the two treatments compared. The study showed that, in the short term, SBNT was more cost-saving and less effective than MET but these differences were not statistically significant. The trial supported evidence that treatment for alcohol problems leads to net savings (Holder et al., 2000; Parthasarathy et al., 2001; UKATT Research Team, 2001).

Why modelling UKATT data?

The UKATT trial was a multicentre pragmatic trial and such design confers both the internal validity (freedom from bias) associated with RCTs and the external validity (generalisability to practical clinical settings) typically associated with models. A pragmatic trial mimics reality (Torgerson and Torgerson, 2001) and is directly applicable to decision making in clinical practice (UKATT Research Team, 2001). Pragmatic clinical trials represent a major improvement in the availability of data for economic evaluation (Buxton et al., 1997). A pragmatic assessment provides

the actual costs and benefits, including patient's utilities, that will apply to future patients (Fayers and Hand, 1997).

Nevertheless, the UKATT trial had a one-year follow-up after treatment initiation which might be too short to capture any differences between the two therapies. The trial could not distinguish the two treatments compared in terms of both effectiveness and cost effectiveness. By using a modelling approach in this chapter, intermediate outcomes, such as alcohol consumption, can be linked with UK epidemiological data in such a way that lifetime costs and QALYs can be estimated. The long-term analysis might help to determine which treatment has a higher probability of being cost effective and whether the same decision is reached for different patient subgroups.

6.2 Modelling the UKATT trial results

6.2.1 Objective

The objective of this case-study is to conduct a long-term cost effectiveness and cost utility analysis using patient-level data collected in the UKATT trial and the cohort model of drinking behaviour populated with UK-specific data, as developed in the previous two chapters, to inform decision making in the UK NHS. The results of the model aim to extend the results of the published cost effectiveness analysis of the analysed trial (UKATT Research Team, 2005a). The probability that one therapy is more cost effective than the other is assessed over the long term. Another important objective of this case study is to explore possible variations in the cost effectiveness results based on the age and gender of the cohort analysed to inform whether these characteristics change the decision of which therapy is more cost effective.

6.2.2 Comparators

Just as in the UKATT trial, MET is compared to SBNT. The UKATT trial recruited 742 patients, 617 (83.2%) were interviewed at 12 months and 608 of these patients yielded data for economic analysis (98.5% of 617). From the patients with complete economic data, 347 patients received MET and 261 received SBNT. The UKATT study used the 608 patients with complete data for the economic analysis (UKATT Research Team, 2005a). Costs and effects were analysed for patients according to the group to which they were originally randomized, also know as "intention to treat strategy". An Intention to Treat (ITT) analysis means that all patients are analysed in the group to which they were initially randomized, even if they "cross over" to the other intervention arm, discontinue the intervention, are lost to follow-up or did not start the allocated intervention (Estellat et al., 2009; Hollis and Campbell, 1999). However, a full ITT would only be possible if all patients

had been followed up for 12 months and had provided all the data required for the analysis , which was not the case in the UKATT trial as there were 134 (742-608) patients that did not meet those requirements.

Similarly to the UKATT study, the model uses all patients that were followed up with economic data (n=608) and also for whom there is data on drinking behaviour at baseline and 12 months, which gives a total of 495 patients (81.4% of 608). Missing data is dealt with by using complete case analysis, in which patients with a missing response for grams per day at baseline or 12 months follow-up are excluded from the analysis. For this reason, it is important to analyse whether there is any attrition bias, where randomization would be lost if the characteristics of people lost to follow-up or with missing data differ between the randomized groups (Dumville et al., 2006). Comparing the sample used for the model (n=495) to the 608 patients used in the UKATT cost effectiveness published study, 64 are lost from the MET group (18.4 % of 347) and 49 are lost from the SBNT group (18.7 % of 261). If there are different numbers of participants leaving the trial arms, the likelihood that participants in one group are not balanced with similar participants in the other trial arm is increased. However, the rates of lost to follow-up are similar between the two arms, which is a first prognostic that there is no attrition bias.

The baseline characteristics of the patients used in the model (n=495), of the group used in the published cost effectiveness analysis (n=608) and of those not included in the case-study (n=113) are presented in Table 45. A comparison of the baseline characteristics for the 113 patients not used in the case-study (due to missing data), between each arm, reveals that there is no statistically significant difference between baseline characteristics (Table 45). This shows that there is some confidence that the analysed sample reflects the groups compared in the published cost effectiveness analysis. Furthermore, the baseline characteristics of those patients used in the model are well balanced as there are no significant differences between the SBNT and MET arms (Table 45). In addition, a comparison between the two arms of the trial for the 247 (742-495) patients lost to follow-up or with missing data also showed no statistically significant difference in terms of baseline variables. Therefore, the internal validity of the UKATT design is maintained for the sample used in the economic model.

Table 45- Baseline characteristics in the UKATT trial: patients with economic data, patients with missing data not used in the model and patients used in the model

Baseline variables	All patients (n=608)		Patients with missing data (n=113)		Patients used in model (n=495)	
	MET (n=347)	SBNT (n=261)	MET (n=64)	SBNT (n=49)	MET (n=283)	SBNT (n=212)
Mean (SD) age (years)	42 (10)	42 (10)	43 (10)	41 (9)	42 (10)	42 (10)
Mean (SD) PDA (days)	29 (26)	27 (26)	36 (28)	27 (27)	28 (25)	27 (26)
Mean (SD) g/day	139 (92)	142 (98)	137 (90)	155 (121)	140 (93)	139 (92)
Males	74 (256)	74 (194)	77 (49)	69 (34)	73 (207)	75 (160)
Females	26 (91)	26 (67)	23 (15)	31 (15)	27 (76)	25 (52)
Employed	34 (119)	31 (80)	43 (27)*	22 (11)*	33 (92)	33 (69)
Detoxification**	26 (90)	32 (83)	19 (12)	31 (15)	28 (78)	32 (68)

*Difference not significant at 99% confidence level (p-value=0.024), all other values are not statistically different at 95% and, hence, at 99% confidence levels (p-values higher than 0.05); **Detoxification done between screening and recruitment; PDA, Percentage Days Abstinent; SD, Standard Deviation; n, number of patients. Note: values are percentages (numbers) unless stated otherwise.

6.2.3 Base case

The base-case cohort is a UK male cohort with an average starting age of 40 years old. The cohort of patients is modelled for an 80 year time horizon by which time all patients will have been predicted to die (WHO, 2008). The distribution of the patients in the two initial Markov states, modelled in the base-case, is 25% hazardous and 75% harmful. This is based on the UKATT trial where 26% of the male cohort is drinking hazardously at baseline and 74% is drinking harmfully (the respective percentages for females are 21% and 79%). Therefore, the base-case considers a severe population with the majority of patients drinking harmfully at baseline.

6.2.4 Discounting and price year

The long term simulation evaluates costs from the perspective of the NHS, expressed in pound sterling (GBP, £) at a 2007 price base. Both costs and outcomes are discounted using a 3.5% annual discount rate, in line with current NICE guidelines (NICE, 2008).

6.3 Model Inputs

The model inputs that are UK-specific and independent of the treatments under analysis are the transition between states after treatment uptake, mortality rates, morbidity rates, state utilities and disease costs, as presented in Chapter 5. Only the model inputs that are specific to the treatments

under evaluation, which are the effects of treatment in drinking behaviour and the treatment costs, are presented here.

6.3.1 Transition probabilities for the first cycle

The first cycle transition probabilities, for the cohort delivered MET and SBNT, are derived from the UKATT trial (UKATT Research Team, 2005b) and represent the effectiveness of the treatments compared. These transition probabilities are calculated by counting the individuals that moved between the drinking categories from baseline to follow-up. The drinking categories are defined in terms of grams per day. However, the trial did not present individual-level outcomes in terms of grams per day. The calculation of grams of alcohol consumed per day is explained in Chapter 5 (see section 5.5). The number of patients in each drinking category, by gender, at baseline and 12 months is calculated for each treatment.

The number of patients, by gender, in each state for each treatment is presented in the following four tables. The corresponding transition matrices are presented in the bottom part of each one of these tables. In order to obtain point estimates of the transition probabilities for the model, each transition probability in the matrix corresponds to the observed cell count divided by the row total. A value of 1 (vague prior) is added to each observed count from the data. This overcomes the possibility of observing zero counts and is explained further in the probabilistic sensitivity analysis section presented below.

Table 46- Counts of transition between model states and transition matrix for SBNT (males)

SBNT- Counts of transitions between the five states for the 12 months period for males*							
MALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	12	13	17	NA	0	42
	Harmful	29	52	NA	43	0	124
	N	41	65	17	43	0	166
Transition matrix							
MALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.285714	0.309524	0.404762	0	TD	1
	Harmful	0.233871	0.419355	0	0.346774	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

Table 47- Counts of transition between model states and transition matrix for SBNT (females)

SBNT- Counts of transitions between the five states for the 12 months period for females*							
FEMALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	4	5	7	NA	0	16
	Harmful	6	17	NA	19	0	42
	N	10	22	7	19	0	58
Transition matrix							
FEMALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.25	0.3125	0.4375	NA	TD	1
	Harmful	0.142857	0.404762	NA	0.452381	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

Table 48- Counts of transition between model states and transition matrix for MET (males)

MET- Counts of transitions between the five states for the 12 months period for males*							
MALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	13	20	25	NA	0	58
	Harmful	38	52	NA	65	0	155
	N	51	72	25	65	0	213
Transition matrix							
MALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.224138	0.344828	0.431034	NA	TD	1
	Harmful	0.245161	0.335484	NA	0.419355	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

Table 49- Counts of transition between model states and transition matrix for MET (females)

MET- Counts of transitions between the five states for the 12 months period for females*							
FEMALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	3	6	5	NA	0	14
	Harmful	11	39	NA	18	0	68
	N	14	45	5	18	0	82
Transition matrix							
FEMALES		12 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.214286	0.428571	0.357143	NA	TD	1
	Harmful	0.161765	0.573529	NA	0.264706	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

6.3.2 UKATT costs

The UKATT cost effectiveness study used a mean net public sector savings for MET and SBNT of £593 (SD 4,114) and £798 (SD 3,817), respectively (net reduction in public sector resource costs minus costs of trial treatments) (UKATT Research Team, 2005a). The costs of SBNT and MET are taken from the UKATT study and are up-rated from the original data (2000/01 prices) to 2006/7 prices, using the HCHS pay and prices index from the PSSRU Unit Costs of Health and Social Care 2007 (Curtis, 2007). The UKATT costs are only applied to the first cycle of the model, given that follow-up after trial entry did not surpass 12 months. The model uses a mean net public sector savings for MET of £760 and for SBNT of £1,023 (2006/07 prices). Full details of the treatments and public sector resource use measurement and unit costs used for valuation are presented in the UKATT cost effectiveness paper (UKATT Research Team, 2005a). The UKATT study is included in methodological review conducted in Chapter 3. A summary of the methods used in the trial for the identification, measurement and valuation of treatment costs and economic consequences is presented in Appendix 4- Methods for identification, measurement and valuation of individual consequences, societal consequences and treatment under evaluation costs.

6.4 Sensitivity analysis and heterogeneity

6.4.1 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis is conducted in the model by assigning distributions to the input parameters of the model that the results are uncertain about. As explained in the previous chapter, uncertainty in the following cycle's transition probabilities and on the utility weights attached to each drinking state is represented by a beta distribution. The distribution explained in this section is the one used for the first cycle transition probabilities, which is an input parameter specific to the intervention under evaluation (i.e. the first cycle transition probability values are informed by the UKATT trial in this case-study).

The data used to estimate the first cycle transition probabilities are multinomial as the total sample is split not between 2 categories, as in the binomial case, but between 5 categories (the four drinking states and the death state). Multinomial data favours an unconditional probability structure to the model with multiple branches from each chance node representing the probability of moving to other states of the model. For this case, the Dirichlet distribution, a continuous multivariate probability distribution, is used (Briggs et al., 2003).

The Dirichlet is the multivariate generalization of the beta distribution (explained in the previous chapter), with parameters equal to the number of categories in the multinomial distribution. In

Bayesian inference, the Dirichlet distribution is conjugate to the multinomial distribution, which means that specifying a Dirichlet prior distribution (i.e. a probability distribution representing a belief about an unknown quantity) on multinomial data results in a Dirichlet posterior distribution (i.e. a conditional distribution of the uncertain quantity given the data) (Briggs et al., 2003). The posterior distribution parameters are simply the prior distribution parameters plus the respective observed cell counts.

While assigning the Dirichlet distribution to these transition probabilities a problem can be raised because there might be cases of zero counts in one of the transition cells and then a zero transition would be assigned to such a cell. When using counts to estimate a transition matrix for the Markov Model, it is important that 1) no potential transitions are excluded simply because they were not observed in the study that informs the data, and 2) uncertainty in the possible values of the estimated transitions is adequately reflected (Briggs et al., 2003). A Bayesian approach overcomes the possibility of observing zero counts as the intuition that a probability is nonzero can be formally expressed through the prior distribution (Briggs et al., 2003). The approach used in the model is that of employing a "vague" or minimally informative prior distribution. The prior distribution specified is an uniform distribution expressing the believe that each outcome is equally likely which is given by a Dirichlet (1,1,1,1), where the transitions for not allowed states are kept as zero (for example, the transition from harmful to ex-hazardous is null). This effectively assigns a 0.25 probability to all transitions, but with a high level of uncertainty (Briggs et al., 2003). The posterior distribution for each transition matrix is obtained by summing 1 (vague prior) to each observed count from the data. Thereby, the expected values of the transition probabilities for any row are the posterior Dirichlet means divided by their row totals (this is illustrated in section 6.3.1 above where the transition probabilities for the first cycle of the model are presented).

After generating uncertainty in the transition probabilities, this uncertainty needs to be propagated through the decision model. A detailed description of fitting the Dirichlet distribution in the economic model is given in Appendix 6- Transition probabilities from multinomial data: fitting a Dirichlet distribution. Monte Carlo simulation is then conducted to select values of the parameters at random from the selected distribution, where RAND() is the command for drawing a random value from a distribution in Excel. The simulation is introduced in the Markov model as part of a program know as "macro" in Excel using the record function, the looping command and relative cell referencing as explained in Briggs et al. (2006). The model is run for 1000 simulations.

6.4.2 Univariate sensitivity analysis

Sensitivity analyses are undertaken to assess the robustness of the base-case results to variations in alternative assumptions related to key parameters in the model. One-way sensitivity analysis is conducted for the initial distribution of patients, where the effect of the same proportion of patients starting in hazardous (A) and harmful (B) states is analysed (50% A-50% B). The effect of a less severe drinking population at baseline is also analysed (75% A-25% B). According to NICE guidelines for sensitivity analysis on the discount rate, the impact of an alternative discount rate of 6% for costs and 1.5% for outcomes is investigated (NICE, 2008).

6.4.3 Heterogeneity

The analysis is run for cohorts of males and females of 20, 40 and 60 years old in order to deal with heterogeneity. This subgroup analysis is also conducted for the three different distributions in the first cycle. Multiple CEACs are produced, where the probability of MET being cost effective is plotted against the willingness to pay threshold for each age and gender group.

Table 50 below depicts the base-case used in the model and the variations in the base-case for which results are presented in the results section below. Four alternative scenarios are considered and for each element the position in the base-case analysis is outlined alongside the alternative assumption applied.

Table 50- Key elements of the base-case analysis and alternative scenarios, case-study 1

Scenario	Element	Position in base-case analysis	Alternative scenario
1	Discount rate	3.5% applied to both costs and outcomes (NICE, 2008)	6% costs, 1.5% outcomes (NICE, 2008)
2	Cohort distribution	25% hazardous, 75% harmful (UKATT Research Team, 2005a)	50% hazardous, 50% harmful 75% hazardous, 25% harmful
3	Population	All males, average age=40 years (UKATT Research Team, 2005a)	Separate analysis for males and females Alternative starting ages assumed: 20, 40 and 60 years
4	Cohort distribution+ population (scenarios 2+3)	All males, average age=40; 25% hazardous, 75% harmful	Males or females, 20, 40 or 60 years old AND 50% harzadous, 50% harmful or 75% hazardous, 25% harmful

6.5 Case-study results

Firstly, the cost effectiveness results are presented for the deterministic and probabilistic base-case analyses. Secondly, the results of one-way sensitivity and subgroup analyses are considered.

Thirdly, a conclusion regarding decision making and policy implications for the results of the study is given. The last section discusses the limitations of the study and topics for future research.

6.5.1 Deterministic cost effectiveness results

For the base case analysis (male cohort of 40 years old with 75% of the patients drinking harmfully at baseline), on average MET is more costly (less cost saving) and more effective than SBNT. Therefore, the additional costs and benefits that MET incurs over SBNT can be compared in the form of a ratio (i.e. the ICER) in order to estimate the additional cost required to achieve one additional unit of outcome. The deterministic ICER is £37,439/ QALY, which falls above the upper bound of the £20,000 to £30,000 per additional QALY benchmark used in England and Wales (NICE, 2008), suggesting MET is not a cost effective treatment compared to SBNT in this patient population. A breakdown of the costs and QALYs associated with MET and SBNT is presented in Table 51.

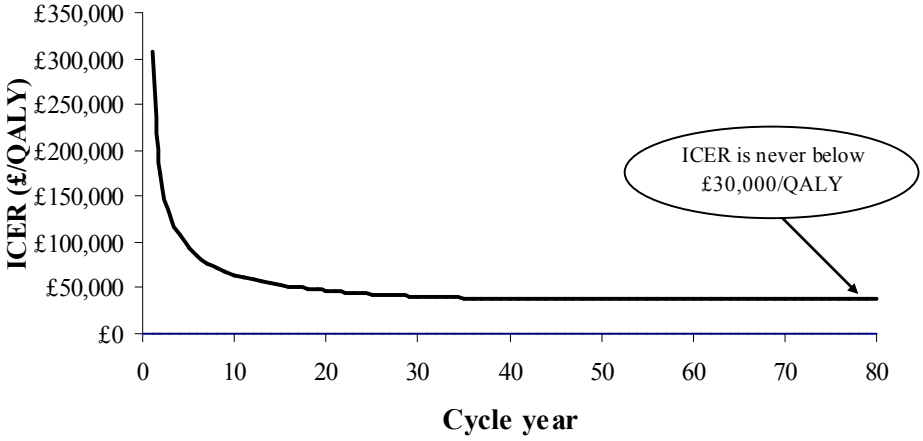
Table 51- Base-case analysis, deterministic results for the cost effectiveness of MET compared to SBNT

Males, 40 years old	MET	SBNT	MET vs. SBNT
Deterministic results			
Costs (£, 2006/07 prices)	£499	£241	£259
QALYs	12.989	12.982	0.007
Life Years	19.853	19.847	0.006
ICER (Δcost/ ΔQALY)			**£37,439**
ICER (Δcost/ ΔLYG)			£43,459

ICER, Incremental Cost Effectiveness Ratio; QALY, Quality Adjusted Life Years; LYG, Life Years Gained; MET, Motivational Enhancement Therapy; SBNT, Social Behaviour Network Therapy; 3.5% discount rate for costs and outcomes. Estimates rounded for presentation.

In an attempt to illustrate the importance of a long-term model in the cost effectiveness analysis of alcohol treatments the ICER for each model cycle is obtained. The reduction in the ICER as the short-term analysis progresses to a long-term one is depicted in Figure 3. The innovative figure represents the ICER, computed as the cumulative difference in costs and QALYs for each cycle year. It is shown that the ICER is never below £30,000/ QALY for the base-case, reassuring the idea that MET is not cost effective in the base-case, even when the long term benefits and costs are taken into account.

Figure 3- Incremental cost effectiveness ratio of MET vs. SBNT per cycle year



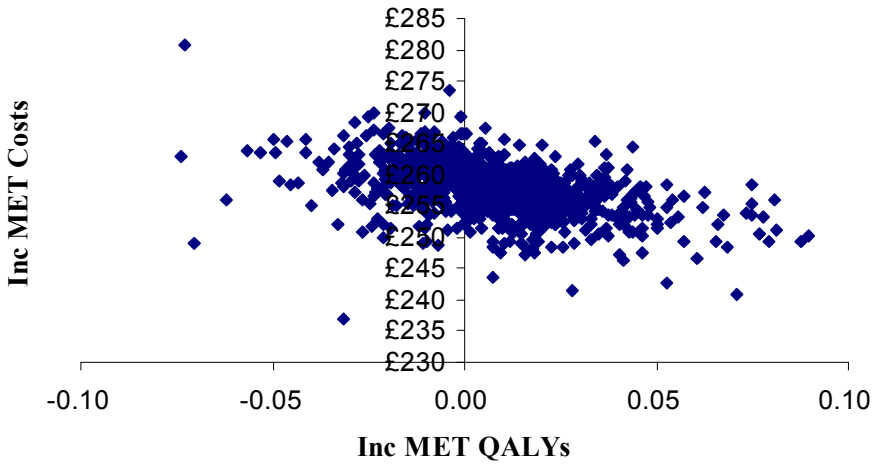
6.5.2 Probabilistic cost effectiveness results

The outputs of the probabilistic sensitivity analysis, using Monte Carlo simulation, provide the distribution over the incremental cost, incremental effect and the joint cost-effect distribution. The mean cost effectiveness ratio of MET vs. SBNT estimated from 1000 random draws is £34,080 per QALY.

Briggs et al. (2006; pp 78) state that the "difference between the expectation over the output of a probabilistic model and that model evaluated at the mean values of the input parameters is likely to be modest" and this is the case for the probabilistic results, which are very close to the deterministic ones. Therefore, when accounting for the effect of uncertainty of model inputs in the outputs, the ICER keeps falling within £30,000 to £40,000 per additional QALY, for the base-case.

The simulation results of the overall uncertainty in the model are presented in a cost effectiveness plane (Briggs and Tambour, 2001) and in a cost effectiveness acceptability curve (Briggs et al., 2006). Figure 4 below shows the results of 1000 Monte Carlo simulations in a cost effectiveness plane. The cost effectiveness plane shows the difference (MET minus SBNT) in effectiveness per patient against the difference in cost per patient. The plane shows that the simulations fall on the northeast area, where MET is more costly and effective than SBNT, and on the northwest area, where MET is more costly and less effective than SBNT.

Figure 4- Incremental cost effectiveness plane of MET vs. SBNT

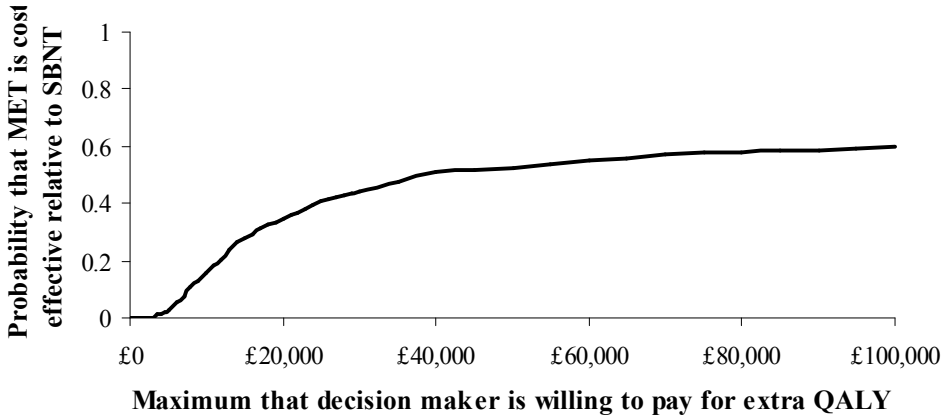


The overall high level of uncertainty associated with economic models means that some of the simulation results cross the vertical axis and/ or the horizontal axis. For this case-study, many simulations cross the vertical axis and given the high density on both northern quadrants the relative effectiveness of MET appears to be very uncertain. The standard ICER figure does not differentiate situations where ratios have the same sign but not the same interpretation. If there were situations where MET is less effective and more costly and situations where it is more effective and less costly both would produce negative ICERs where the interpretation from the point of view of the intervention under evaluation is not possible. The former situation would lead to the rejection of MET while the latter would lead to the opposite. The same happens with positive ICERs, where positive ratios can have the opposite interpretation. This is overcome by presenting a CEAC as a result of the simulation to represent uncertainty instead of using the frequentist confidence intervals (Briggs et al., 2006).

The CEAC derived from the model is presented in Figure 5 where the resulting probability that one therapy is better than the other is plotted against the maximum that decision makers might pay for an additional QALY. The CEAC shows that the probability that MET is cost effective cuts the horizontal axis for threshold values below £3,000 per QALY, where SBNT is more cost effective than MET (when thresholds are small, SBNT seems preferable to MET). Therefore, when the decision maker is only interested in the cheaper option, SBNT has a probability of 100 percent to be cost-saving. As the threshold increases and therefore, health gains are more highly valued, the probability that MET is cost effective increases, being 0.5 at the value of the ICER where both treatments have the same probability of being cost effective. If decision makers were willing to pay more than around £34,080 per QALY gained, then MET would be adopted for it has a higher

probability of being cost effective after the value of the ICER. However, the probability that MET is the most cost effective therapy is only 0.3 and 0.4 for threshold values of £20,000 and £30,000, respectively.

Figure 5- Cost effectiveness acceptability curve for MET vs. SBNT



6.5.3 Univariate sensitivity analysis

Modelling a cohort equally distributed between the hazardous and harmful categories makes MET treatment less cost effective, with an ICER of £82,113/ QALY which is well above the upper bound £30,000/ QALY. This can be explained by the fact that with a lower proportion of male patients in the harmful drinking state there is a higher potential to benefit from SBNT and, therefore, the incremental QALYs of MET vs. SBNT are less pronounced. Accordingly, when modelling a 40 years-old male population with only 25% of harmful drinkers at baseline MET is even less cost effective (Table 52). For these two situations, the level of uncertainty is close to the base-case and the probability that MET is more cost effective is around 0.3 and 0.4 for thresholds WTP between £20,000 and £30,000 per QALY, respectively.

The base-case results are robust when the model is tested via sensitivity analysis on the discount rate, where the alternative discount rates slightly improve the cost effectiveness (ICER= £30,446/ QALY) (Table 52). For a discount rate of 6% on costs and 1.5% on health outcomes, the probability that MET is the most cost effective therapy is slightly higher than for the base-case: 0.4 and 0.5 for threshold values of £20,000 and £30,000, respectively.

Table 52- Probabilistic results for one-way sensitivity analysis (MET vs. SBNT)

MET vs. SBNT	Incremental costs	Incremental QALYs	ICER
Initial cohort distribution			
75% hazardous; 25% harmful	£263	0.0002	£1,452,277
50% hazardous; 50% harmful	£261	0.0032	£82,114
25% hazardous; 75% harmful*	£258	0.0076	£34,080
Discount rate			
3.5% cost and outcomes*	£258	0.0076	£34,080
6% costs; 1.5% outcomes	£259	0.0085	£30,446

*Base-case conditions; ICER, Incremental Cost Effectiveness Ratio; QALY, Quality Adjusted Life Years; Costs in GBP (£); price year 2006/07; MET, Motivational Enhancement Therapy; SBNT, Social Behaviour Network Therapy. Estimates rounded for presentation.

6.5.4 Modelling heterogeneity

The analysis of the effect of heterogeneity in the results shows that SBNT dominates MET for the three simulated age cohorts of females and for all the simulated initial distributions in hazardous and harmful drinking (see Table 53). Therefore, for a female cohort SBNT is always more cost saving and more effective than MET. An ICER is not computed for dominant cases as the decision on which treatment is more cost effective is straightforward. There is a clear improvement in female drinking behaviour with SBNT when compared to MET, as can also be seen in the transitions probabilities presented in Table 47 and Table 49. In fact, a considerable percentage of females delivered MET therapies got worse (43% drinking hazardously at baseline were drinking harmfully at follow up) or did not get better (57% drinking harmfully at baseline kept drinking harmfully at follow-up).

Table 53- Probabilistic results for the subgroup analysis with variations in the cohort distribution at baseline (MET vs. SBNT)

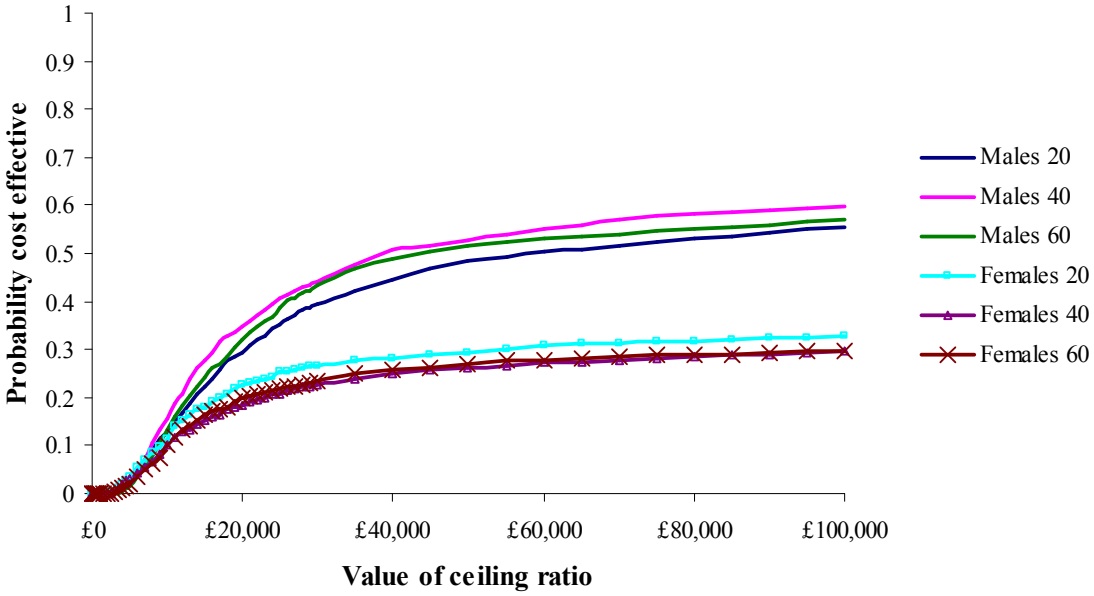
	Incremental Cost	Incremental QALY	ICER
Probabilistic results for subgroup analysis (75% Harmful-25% Hazardous)			
Males, 20 years old	£262	0.0058	£45,093
Males, 40 years old*	£258	0.0076	£34,080
Males, 60 years old	£256	0.0062	£41,055
Females, 20 years old	£263	-0.0131	NA
Females, 40 years old	£267	-0.0157	NA
Females, 60 years old	£261	-0.0156	NA
Probabilistic results for subgroup analysis (50% Harmful-50% Hazardous)			
Males, 20 years old	£262	0.0026	£101,243
Males, 40 years old	£261	0.0032	£82,114
Males, 60 years old	£257	0.0031	£82,413
Females, 20 years old	£263	-0.0190	NA
Females, 40 years old	£267	-0.0246	NA
Females, 60 years old	£261	-0.0212	NA
Probabilistic results for subgroup analysis (25% Harmful-75% Hazardous)			
Males, 20 years old	£263	-0.0008	NA
Males, 40 years old	£263	0.0002	£1,452,277
Males, 60 years old	£258	-0.0001	NA
Females, 20 years old	£263	-0.0241	NA
Females, 40 years old	£267	-0.0276	NA
Females, 60 years old	£261	-0.0253	NA

*Base-case conditions; ICER, Incremental Cost Effectiveness Ratio; QALY, Quality Adjusted Life Years; NA, Not Applicable; Costs in GBP (£); price year 2006/07; discount rate, r= 3.5%; MET, Motivational Enhancement Therapy; SBNT, Social Behaviour Network Therapy. Estimates rounded for presentation.

The subgroup analysis shows that, for males, the lowest ICER is observed for 40-years-old for all initial cohort distributions. For the base-case distribution (75% harmful, 25% hazardous) and for an equal distribution (50% harmful, 50% hazardous) the ICER of a 20-year old cohort is higher than of a 60-year old cohort. The age variation in the ICER can be explained by two factors: 1) impact on the numerator of the ICER and therefore on the incremental costs and, 2) impact on the denominator of the ICER and therefore on the incremental effects. Mortality rates, morbidity rates and drinking behaviour affect the two aforementioned factors. The smallest ICER of a 40-year old male cohort can be explained by the higher potential for gaining QALYs without other competing factors such as the high chronic disease mortality rates of an older cohort or the high injury rates, coupled with more years for discounting health benefits, of a younger cohort.

Each subgroup of patients is represented by a different CEAC in Figure 6 below and for an initial distribution of 75% harmful and 25% hazardous. This allows the assessment of the extent to which the results vary across different subgroups and whether different treatment decisions should be made for different categories of patients, according to the decision maker's threshold for treatment adoption.

Figure 6- Multiple CEAC for different age and sex cohorts for MET vs. SBNT



The CEACs for each group of patients encourage the decision maker to make different treatment decisions across the different categories of patients, based on the expected cost effectiveness for the set of patient characteristics and associated uncertainty. It is clearly shown that MET is dominated by SBNT for females and the decision maker can be very confident about these results as the CEACs show that SBNT is the most cost effective option in about 70% of the situations at conventional WTP thresholds. For males, MET can be more effective than SBNT but at very high costs and this is associated with a high level of uncertainty. Also, the probability that MET is more cost effective than SBNT for males is never above 60%, no matter how much the decision maker would be willing to pay.

6.5.5 Summary of the cost effectiveness results

Table 54 details the results of each of the alternative scenarios considered for the cost effectiveness analysis of MET vs. SBNT. The table reports the ICER and the probability that MET is cost effective at thresholds of £20,000 and £30,000 per additional QALY. The base-case ICER of

£34,080/ QALY provides the benchmark for assessing whether the cost effectiveness results appear robust to particular assumptions made in the base-case analysis.

The base-case scenario suggests that MET is slightly more effective and costs much more than SBNT. The results show that the ICER of MET vs. SBNT, £34,080/ QALY, is over the range of conventional thresholds used to identify whether a particular treatment is considered to be cost effective in the NHS, and this is associated with high levels of uncertainty.

When simulating a 40-year-old male population with a higher percentage of hazardous drinkers than in the base-case the ICER increases considerably. Applying an alternative discount rate of 6% for costs and 1.5% for health outcomes (compared to 3.5% for both in the base-case analysis) improves the cost effectiveness by a minor amount.

Heterogeneity in patient characteristics (age and gender) is explored using a series of separate scenarios. These scenarios are explored by varying the mortality and morbidity rates according to the particular age and sex characteristics considered. The results are presented for different assumptions regarding the initial distribution of patients in harmful and hazardous drinking states. The cost effectiveness estimates in these scenarios are affected by the number of patients who can potentially stand to gain from HRQoL improvements associated with MET and SBNT over time. The results demonstrate that SBNT dominates MET for females. SBNT is the most cost effective strategy for females and this is associated with very low levels of uncertainty. The cost effectiveness results for a male cohort suggest that MET is associated with very high costs which might not justify the situations where MET is more effective than SBNT and this is associated with a high levels of uncertainty.

Table 54- Summary of cost effectiveness results (MET vs. SBNT)

	ICER	Probability cost effective for max WTP	
		£20,000	£30,000
Initial cohort distribution			
75% hazardous; 25% harmful	£1,452,277	0.305	0.370
50% hazardous; 50% harmful	£82,114	0.314	0.383
25% hazardous; 75% harmful*	£34,080	0.348	0.443
Discount rate			
3.5% cost and outcomes*	£34,080	0.348	0.443
6% costs; 1.5% outcomes	£30,446	0.405	0.504
Subgroup analysis (75% Harmful-25% Hazardous)			
Males, 20 years old	£45,093	0.294	0.394
Males, 40 years old*	£34,080	0.348	0.443
Males, 60 years old	£41,055	0.319	0.434
Females, 20 years old	NA	0.225	0.267
Females, 40 years old	NA	0.185	0.226
Females, 60 years old	NA	0.199	0.236
Subgroup analysis (50% Harmful-50% Hazardous)			
Males, 20 years old	£101,243	0.305	0.382
Males, 40 years old	£82,114	0.314	0.383
Males, 60 years old	£82,413	0.264	0.345
Females, 20 years old	NA	0.210	0.246
Females, 40 years old	NA	0.182	0.217
Females, 60 years old	NA	0.188	0.226
Subgroup analysis (25% Harmful-75% Hazardous)			
Males, 20 years old	NA	0.264	0.326
Males, 40 years old	£1,452,277	0.305	0.370
Males, 60 years old	NA	0.288	0.336
Females, 20 years old	NA	0.231	0.262
Females, 40 years old	NA	0.227	0.257
Females, 60 years old	NA	0.222	0.254

*Base-case conditions; ICER, Incremental Cost Effectiveness Ratio; WTP, Willingness to Pay; Costs in GBP (£); price year 2006/07; NA, Not Applicable. Estimates rounded for presentation.

6.6 Decision making

The case-study shows that, even when comparing low intensive treatments with very similar effectiveness and costs, the model provides information highly valuable for decision making. The long-term analysis shows that there is considerable uncertainty about the most cost effective treatment for a male cohort and that different decisions should be adopted according to the gender of the patients and the decision maker threshold for treatment adoption.

The ICER for a male cohort of 40 years old is around £34,000/QALY, which is over the upper limit of the current benchmark of £20,000 to £30,000 adopted in England and Wales. Looking at the base-case point estimate of the probabilistic results suggests that MET may be a more effective approach for the treatment of alcohol problems, but at a very high cost which might not represent good value for money according to the benchmark. Furthermore, the cost effectiveness of MET is associated with a very high level of uncertainty and even if the decision maker is willing to pay much more than £34,000 for additional QALY, the probability of MET being more cost effective is never higher than 60%. At a threshold of £30,000 per QALY, the probability that MET is more cost effective than SBNT is only 0.4 and hence there is a 60% chance that adopting MET is the wrong decision.

Current evidence suggests that the decision on whether MET is more cost effective than SBNT for a male cohort is very uncertain and further research should be done before supporting any decision. Decision makers might be more confident on adopting SBNT for a less severe male cohort, given that the QALYs gained are more or less the same as MET and SBNT is more cost saving. The most interesting outcome of this analysis is that SBNT clearly represents better value for money than MET when delivered to females.

6.7 Policy implications

When allocating health care resources from a limited budget, as in the NHS, the decision maker aims to maximize health outcomes given available resources. Therefore, the policy maker needs to decide whether she or he is willing to invest additional health care resources funding MET and pay an average of £34,000 in order to acquire an additional unit of health outcome in a 40-year old male population drinking mainly harmfully. This is based on current evidence and modelling techniques, however the estimates are associated with high uncertainty and more research needs to be done in order to support this decision.

When a higher percentage of males are drinking less heavily at baseline it appears that SBNT delivers more QALYs. Perhaps a less severe male population is more receptive to socially based

interventions than a more severe one. Surely, this difference amongst males needs further assessment.

SBNT dominates MET for all female age-groups. The reasons for such difference should be further analysed. It might be that the more intense social component of SBNT is the reason for the more effective and cost effective results for females. The findings suggest that there may not be a "single" optimal treatment for all patients with alcohol problems and it is important to take into account patient's gender when reporting the results in economic evaluations of alcohol treatments.

6.8 Discussion

The case-study presents the long-term cost effectiveness results of a brief intervention versus a new more socially based approach for the treatment of alcohol problems. The long-term analysis applies the economic model developed in previous chapters to the results of a UK multicentre trial-based cost effectiveness analysis, the UKATT trial. Patient-level data from the UKATT trial is used and combined with epidemiological risks for a UK population and with the NHS costs of alcohol-related diseases.

The limitations of the study regarding the UK-specific model inputs and general model features are detailed in the two previous chapters. Regarding this specific case-study, it should be recognized that the treatments compared are very similar in terms of costs and effects making the application less favourable to the potentialities of the model.

In this case-study MET is compared to SBNT and this is in line with the published cost effectiveness analysis on which the case-study is based (UKATT Research Team, 2005a). The costs used are the net costs which take into account the treatment costs (SBNT is significantly more expensive than MET) and the public sector resource savings (SBNT is not significantly more cost saving than MET). The UKATT effectiveness study (UKATT Research Team, 2005b) showed that SBNT was less effective than MET, but this difference was not significant. Therefore, if cost-savings were not being used MET would probably have dominated SBNT (MET would be cheaper and equally effective when compared to SBNT) and no deterministic point estimate of the ICER would be computed. However, SBNT appears to be more effective for a female cohort, but the UKATT trial did not report results for males and females separately. In this last case, MET would not dominate SBNT and an incremental analysis would make sense even without using cost-savings (SBNT would be more effective and more costly). The choice of using cost-savings is based on the UKATT Research Team (2005a) published paper. If only the costs of treatment were used in the model, it can be expected that, in most simulations, MET would dominate SBNT for a male cohort and SBNT would be both more costly and more effective for a female cohort.

A full application of the intention to treat approach is only possible when complete outcome data are available for all randomized patients. However, there is no follow-up data for some participants and missing data is dealt with by using complete case-analysis, as in the published cost effectiveness study of the UKATT trial. Different approaches can be used to deal with missing data and there appears to be no consensus on the best approach to use. However, this is out of the scope of this thesis as the main objective here is to apply the novel economic model to patient level data taken from the UKATT trial. In addition, a review has shown that most studies deal with missing data through complete case-analyses albeit classifying their analysis as intention to treat (Hollis and Campbell, 1999). Furthermore, the baseline comparisons for the patients not included in the case-study do not show any significant differences between the two arms, suggesting that attrition bias is not a problem.

The application of the model to the UKATT data enables determination of costs and effects, by gender and age, over the long term and makes important contributions to the published study in terms of subgroup analyses and certainty of the results. However, the long term simulation model used in the case-study analysis employs a NHS perspective. A wider societal impact of alcohol is not modelled. The application of a wider societal perspective might have an important impact on the results and should be part of future extension of the model and the case-study in particular.

Patient preferences were not assessed in the UKATT trial. In a randomized controlled trial, patients may have a preference for one of the therapies or be indifferent to both treatments. If patients with preferences consent to be randomised then some patients will get their preferred treatment and others will not (Preference Collaborative Review Group, 2008). Patients who do not receive their preferred treatment may experience "resentful demoralisation" (Torgerson et al., 1996). They may be less motivated and not report accurately during follow-up or even drop out of the trial (King et al., 2005). It is possible that patients had a preference for one of the treatments and it might be that, had the trial been a randomized patient preferences trial, where preferences are assessed before randomization, the effectiveness and cost effectiveness of the therapies would have been different for different preferences (Manca et al., 2006; Preference Collaborative Review Group, 2008). Had the information on patient preferences been available from the UKATT trial, the long-term impact of preferences on the relative effectiveness and cost effectiveness for different subgroups could be assessed with the economic model, which would be an interesting exercise.

The UKATT trial was a RCT with blinded assessment at 12-months follow up and due to its good internal validity produces trustworthy results to be inputted into the model (Estellat et al., 2009; Hollis and Campbell, 1999). The external validity of the results is related to their generalisability to practical clinical situations (UKATT Research Team, 2001). Pragmatic trials are the best design for

an economic evaluation as this design more closely resembles routine clinical practice which is what needs to be costed and evaluated (Torgerson and Torgerson, 2008). The pragmatic approach of UKATT together with modelling of the UKATT results should ensure external validity. However, the application of these particular results will depend on the setting and patients to which treatments are delivered. Specific considerations should be made before applying the results generated in this case-study to other patients. The trial used in the case-study was conducted in the UK in seven treatment sites, including NHS, social services and joint NHS/ non-statutory facilities. Patients were selected in a way to avoid excluding those who would normally be offered treatment at UK alcohol specialist treatment centres. The UKATT patients were drinking high levels of alcohol and presented more alcohol-related problems and dependence levels than average problematic drinkers (Drummond, 1990; UKATT Research Team, 2005b). These characteristics of the UKATT population are modelled through lifetime and for this lifetime propagation, the epidemiological risks of a UK-based population are used. The characteristics of the population modelled should, therefore, be adapted for another setting. The model provides the potential to conduct subgroup analysis. However, the results of the interventions are still the ones observed in the specific population modelled, even when a specific age and gender is specified. The model compares SBNT, a new more socially based psychosocial approach, with MET. In the UKATT study MET was considered to reflect standard practice in the UK which might or might not be the situation in another country. The clinical effects for both treatments are taken from the UKATT trial where therapists were highly trained and experienced, and this might not be possible to reproduce in different settings. The perspective on costs is that of the NHS and thus represents therapists working in the UK public sector, which needs to be adapted if the analysis is conducted in another country. In conclusion, if SBNT and MET are to be compared in another setting and/or for a different population, model inputs such as transition probabilities, epidemiological risks and costs data might need to be adapted accordingly.

This chapter shows that modelling a cost effectiveness analysis of alcohol treatments conducted alongside a clinical trial offers the potential to explore the results over the long term while incorporating evidence on drinking behaviour and associated health risks and costs. The model application provides a means to increase the relevance for the decision context based on subgroup analyses and to quantify decision uncertainty.

Chapter 7. Model application for a new treatment compared to standard care in the UK

The aim of this chapter is to model the cost effectiveness of a new pharmacological treatment for alcohol problems in a UK setting. The second application of the model uses patient-level data from two randomized controlled trials conducted in different countries and with different populations.

The new alcohol treatment "Treatment A" (the names of the treatment and trial are confidential information) is compared to "usual" care in a UK setting. The evidence for the new treatment is taken from a US-based trial, whereas current practice is informed by a UK-based trial.

This case-study provides an example of how the model can be used to aid decision making when there is limited evidence for new treatments. There is just one clinical trial for the new alcohol treatment assessed and this was an efficacy trial with a short time horizon conducted in a different setting. Cost effectiveness varies by country and context and the second model application suggests a useful example of how to deal with this while using the limited information available for a new treatment.

There are numerous challenges that do not have to be dealt with in the first case study. Several analyses are carried out before conducting the economic evaluation. The trials compared were conducted in different countries, with different populations and different follow-up periods. Therefore, the comparators for the economic evaluation have to be defined as to find the best match in terms of patient characteristics. In addition, the effects of the treatments should be compared at similar follow-up points.

The perspective of the analysis is that from the health system, in this case the NHS, which is in line with NICE recommendations for the UK (NICE, 2008). The cost effectiveness of Treatment A in the NHS is determined by a number of potential factors. These factors relate to the clinical evidence base that is available and the generalisability of this evidence to the NHS. For the new treatment to be cost effective it is important to demonstrate that the additional costs result in potential long-term gains in HRQoL, in the UK. This represents the common situation where a cost effectiveness analysis helps decision making regarding a new more costly and potentially more effective treatment. The results of the model can inform the decision about adoption, rejection or requirement of more information for the new alcohol treatment.

Before going into the case-study cost effectiveness modelling, a description of the two treatments compared is presented followed by the procedure for matching the populations.

7.1 The compared trials

Treatment A trial

The new treatment trial was conducted in the US and consisted of a 6-month, double-blind, randomized, placebo controlled, efficacy, multicentre trial of Treatment A. Exclusion criteria and randomization procedures were well detailed. The trial randomized 627 treatment-seeking alcohol-dependent adults actively drinking to one of three treatment groups: a group receiving Treatment A (208 patients); a group receiving a different dose of Treatment A (210 patients) and a group receiving placebo (209 patients), each group also received a psychosocial intervention. The trial showed significant results in the reduction of alcohol consumption for Treatment A and that these results were greater amongst men. Whilst more information about the US trial cannot be detailed here, it can be assumed that the new treatment is an effective treatment but also highly costly.

Treatment A is designed to help problematic drinkers reduce their consumption of alcohol and can be delivered in non specialist medical settings. For this case-study, the treatment population for Treatment A is potentially the significant number of problematic drinkers in the UK seeking community-based treatments, only excluding those very dependent drinkers who may require more intensive psychological and medical care. Given the current limited identification of alcohol problems and the limited supply of alcohol treatments in the UK, it is difficult to determine the proportion of these drinkers who may, once identified, be motivated to seek treatment.

In accordance with NICE guidelines (NICE, 2008), the appropriate comparator in economic evaluation should be the treatment that will most likely be replaced, and should reflect current UK practice rather than "best" practice. For this reason it is not appropriate to use the US clinical trial comparator (placebo) as the comparator for the economic evaluation.

UK usual care trial

Set in the context of alcohol treatment, usual care is assumed to be the current standard of care for the management of problematic drinkers who seek community-based treatment in the UK. There are currently only limited studies of the range of problematic drinkers seeking community-based treatment in the UK setting. The UK Alcohol Treatment Trial (UKATT Research Team, 2005a, b) was a pragmatic trial of alcohol dependent individuals drawn from a wide range of alcohol treatment agencies, with open follow-up at 3 months after entry and blind follow-up at 12 months. The participants were drawn from all those attending the alcohol agencies with exclusions kept to a minimum. This trial provides the cost and effectiveness data for a low-intensity manual based psychosocial therapy based on SBNT and MET. The UKATT trial design, interventions and results are described with more detail in the previous chapter. The UKATT clinical study showed evidence

of a statistically non-significant difference in effectiveness between MET and SBNT (UKATT Research Team, 2005b). In addition, despite the protocol defining a higher number of sessions for the SBNT group than the MET group, patients randomized to both treatment groups ended up taking a similar number of sessions. For those two reasons, the data from both groups is pooled and forms the comparator to the US therapy. The UKATT trial is taken as providing the current standard of care in the UK and is used as the comparator to Treatment A for modelling purposes.

7.1.1 Why modelling the two trials?

The two trials from which effectiveness and treatment cost data come from had a short follow-up period. One trial had 6 months follow-up (Treatment A trial) and the other had 12 months follow-up (UKATT). The model estimates the effects of changes in drinking behaviour over the long term costs, morbidity and mortality. It allows the projection of effects and also costs beyond the short follow-up periods, as explained throughout the model development chapter (Chapter 4). This is achieved by augmenting the trials' patient-level data with evidence from other sources, namely UK epidemiological data and NHS costs. The model allows comparing the two treatments over lifetime, even though their effectiveness has not been studied in a head to head randomized controlled trial. Furthermore, it deals with heterogeneity and so it helps in assessing whether any of the therapies represent better value for money for a specific subgroup of patients, based on age and gender.

7.2 Can the two trials be compared?

There is no evidence from a direct comparison between Treatment A and current UK practice which makes it difficult for the decision maker to choose the alternative that is most cost effective for UK patients and/ or to make a decision on whether treatment A should be implemented in the UK.

The comparison drawn for this study departs from an indirect comparison in which two interventions are compared through their relative effect versus a common comparator (Song et al., 2003). The UK and US trials do not have a common comparator. Nevertheless, the validity of indirect comparisons depends on the internal validity and similarity of the included trials and it might be reasonable to assume that these two factors are also of importance for the two trials compared here. The internal validity of the trials is important because any biases in the two trials will affect the validity of the comparison of costs and effects. The similarity of the trials is also important so the effects of the interventions compared can be consistent across patients from the two trials.

The UKATT trial, as previously mentioned, was a multicentre pragmatic trial and such design confers both the internal validity (freedom from bias) associated with RCTs and the external

validity (generalisability to practical clinical settings) typically associated with models. The design of the US trial also confers internal validity but this was an efficacy trial conducted under highly controlled conditions and, hence, with lower external validity.

Regarding the similarity of the two trials, both the UK and the US trial were multicentre trials. However, the UK patients were much more severe than the US patients and the results from the US trial might not be directly applicable to a UK population. In fact, the UKATT patients had a slightly above-average level of alcohol-related problems for a British treatment sample (Drummond, 1990; UKATT Research Team, 2005b) which may also not accurately reflect the general UK population seeking for alcohol treatment. There might be a range of different prognostic characteristics between study participants among the trials and these different patient characteristics may interact with the effect of treatments. It is important to assess how comparable the populations are and whether Treatment A can be delivered to a UK population, i.e. if the UKATT population or a subgroup of it has some similarities with the US population so the effects of Treatment A can be extrapolated to UK patients. This is dealt with in the next section, where the UK and US population trials are matched according to baseline characteristics.

7.3 Comparators: matching patients characteristics

In a randomized design treatment groups are randomly selected from a population. With randomization treatment status does not depend on potential health outcomes, and it may be assumed that, on average, those individuals exposed to an intervention are not different from those not exposed to it either regarding observable characteristics or unobservable ones. Thereby, any statistically significant difference in health outcomes between both groups can be attributed solely to the intervention's impact (Moreno-Serra, 2007). When using non-experimental data, the bias caused by omitted variables is extremely important for the reliability of the estimates of an intervention's impact.

Although the data used in the model comes from two randomized controlled trials, the power of randomization is lost when comparing treatments from each trial. The population used in the model has not been randomized between the two treatments compared, Treatment A and UKATT treatment. The comparison in this case-study suffers from the same biases as observational data, in which patients are drawn from separate populations, with the likelihood that differences in prognosis unrelated to treatment will bias the comparison of effectiveness (Dehejia and Wahba, 1999). Using the whole sample of US and UK patients can be a source of selection bias if the two groups are not comparable at baseline and it might not be appropriate to directly compare the two trials. Using matching methods is one alternative for explicitly addressing and eliminating selection

bias, while assuming that selection on unobservables that are correlated with heath outcomes is not a problem in the relevant data.

Estellat et al. (2009) stated that for a comparison to be valid and to avoid bias, the groups must be similar at baseline, undergo the same care apart from the treatment under study and be assessed in the same way at the end of the study. The first condition is dealt with in the section below. The last two conditions are assumed to be valid for this case-study.

7.3.1 Baseline comparison

When comparing the US Treatment A trial with the UKATT trial it is important to minimise any potential bias, and in particular to ensure that Treatment A results are not biased in favour of the US trial as a consequence of differences in patient characteristics at baseline.

The UKATT trial data used for the case study encompasses all observations that were followed up with economic data (608 patients), with information on grams of alcohol per day at baseline, 3 and 12 months follow-up and on baseline covariates (a total of 437 patients out of the 608 patients with economic data). The US trial data for the case-study comprises the data from patients in the active arm of the trial- Treatment A arm (208 patients), and with information on grams of alcohol per day at baseline and 6 months and on baseline covariates (a total of 201 patients). Therefore, missing data is dealt with by using complete case analysis in which patients with a missing response are excluded from the analysis.

An analysis of the baseline characteristics for the two groups compared (437 UK patients and 201 US patients) is shown in the following table.

Table 55- Sociodemographic, mental and physical scores and alcohol use characteristics of the US and UK groups at baseline

Variable	UK (n = 437)	US (n = 201)	*P*
Age (SD)	41.7 (9.6)	45.2 (10.0)	0.000**
Number of males (%)	326 (74.6)	134 (66.7)	0.038***
Number employed (%)	146 (33.4)	175 (87.1)	0.000***
Mental Score* (SD)	31.9 (12.8)	38.7 (12.5)	0.000**
Physical Score* (SD)	46.9 (10.1)	53.6 (8.0)	0.000**
Percentage of days abstinent (SD)	27.6 (25.5)	24.0 (23.4)	0.094**
Alcohol (g/day) (SD)	138.2 (89.0)	84.5 (44.1)	0.000**

*From SF-36 questionnaire; **P-value from two-sample t-test with equal variance; ***P-value for chi-squared test of homogeneity; SD, Standard Deviation. Note: values are means, unless stated otherwise.

The results of the tests for the difference in the mean values of the baseline characteristics show that there are statistically significant differences (at a 95% confidence level) between the two

populations in terms of baseline characteristics, for all the variables studied but the percentage of days abstinent at baseline (Table 55). The UKATT sample has a slightly higher proportion of males than the US group (p-value= 0.038). In terms of age, the US group is older than the UK group (mean age 45.2 vs. 41.7, p-value = 0.000). The UK group shows considerable lower employment levels than the US group (33.4% vs. 87.1%, p-value = 0.000). A higher proportion of baseline abstinent days is observed for the UK group but this is not statistically significant different from the US group (p-value = 0.094). The UK group drinks considerably more alcohol at baseline than the US group (138 g/day vs. 85g/day; p-value = 0.000). A comparison using health status scores based on the SF-36 questionnaire (Ware and Sherbourne, 1992), emphasizes the difference between the two samples. The UKATT sample is in both poorer physical and mental health than the Treatment A sample (p-value = 0.000).

The sample drawn from that proportion of the UK problem drinking population receiving psychosocial therapies is more severe than the Treatment A population. The comparison of data from the UKATT sample to those from the US trial would seem therefore to be inappropriate, as it would risk biasing the comparison in favour of Treatment A, and reinforcing the perception that alcohol treatments achieve better results in the US than in the UK or Europe. Hence, it seems inappropriate to compare the 437 patients of the UK trial to the 201 patients from the US trial as the groups are not comparable at baseline. The two trial groups need to be matched in terms of those characteristics so selection bias can be eliminated and the differences in drinking behaviour can be solely attributed to differences in treatments (assuming any unobservable factors to be balanced between the two groups). Comparing the two full samples is likely to mask considerable confounders that affect treatment effects. Consequently, the next step in this case-study is to find the best match for comparison from which the transition probabilities and treatment costs can be derived.

One method widely used in observational studies consists of the use of propensity scores for matching baseline characteristics. This thesis explores the use of the propensity score for obtaining populations that are comparable at baseline and so a direct comparison between treatment A and UKATT therapies can be more meaningful. The application of propensity score for this case study falls somehow outside of its general use. Propensity scores have been widely used for obtaining average treatment effects of a treated population in observational studies (Moreno-Serra, 2007). Recently, they have also been used as an approach to estimating the cost effectiveness of medical therapies from observational data (Mitra and Indurkhya, 2005). However, the application of the propensity score here is not for obtaining an average effect as the lifetime effect from each treatment is calculated by means of the Markov model. The aim of propensity score matching for

this specific case is to select the patients from each trial that are comparable in terms of baseline characteristics, i.e. to select the patients that should be used for the economic analysis. Patients with similar distribution of baseline characteristics will have a similar propensity to be delivered the new treatment and will therefore be more comparable.

7.3.2 General principles of propensity score matching

The propensity score is the conditional probability of assignment to a particular treatment given a vector of observed covariates. Matching sampling has been described by Rosenbaum and Rubin (1983) as a method for selecting units from a large reservoir of potential controls to produce a control group of modest size that is similar to a treated group with respect to the distribution of observed covariates.

Rosenbaum and Rubin (1983) proposed propensity score matching as a method to reduce bias in the estimation of treatment effects with observational datasets. In observational studies subjects' assignment to the treatment and control groups is not random and the estimation of the effect of treatment may be biased by the existence of confounding factors (variables related to both exposure and outcome). Propensity score matching is a way to "correct" the estimation of treatment effects controlling for the existence of these confounding factors based on the idea that the bias is reduced when the comparison of outcomes is performed using subjects who are as similar as possible.

It has been shown that adjustment for the scalar propensity score is sufficient to remove bias due to all observed covariates (Rosenbaum and Rubin, 1983). Matching on the propensity score balances the observed covariates but, unlike randomization, it does not balance unobserved confounding factors. This means that matching will not remove selection bias if individuals that uptake Treatment A or the standard therapy differ in terms of unobserved characteristics which are themselves correlated with their potential outcomes. For example, cultural differences such as different lifestyles might have an impact on the type of patients randomized. Unfortunately, there is no way to empirically validate this assumption from the data. Therefore, as much information as possible about potential confounders should be captured.

The methods of propensity score matching assume that "treatment assignment is strongly ignorable", meaning that any other factors jointly affecting treatment effects and exposure to treatment, whether unobservable or unknown, are controlled for in the analyses. A second assumption is that observations with the same propensity score must have the same distribution of observable (and unobservable) characteristics independently of treatment status (balancing hypothesis) (Rosenbaum and Rubin, 1983). Based on the two assumptions, for a given propensity score, exposure to

treatment is random and therefore the matched groups should be on average observationally identical (Becker and Ichino, 2002)

The matching method is a non-parametric approach that tries to re-establish conditions of an experiment when only non-experimental data is available. The propensity score calculation is done parametrically and matching on the propensity score results in a semi-parametric method. The general idea is to construct a matched comparison group based on individual observable characteristics and compare individuals who are similar in terms of these observable factors.

The propensity score matching method evaluates pre-treatment characteristics of each treatment group computing a single propensity score which, for this case-study, is the conditional probability of being assigned to Treatment A, given pre-intervention characteristics. The idea is to mimic the properties of the US group in the properly designed experimental context from a statistically strong match between the US and UK groups based on their observable characteristics (Becker and Ichino, 2002; D'Agostino, 1998).

There are different types of propensity score matching techniques and the most widely used are Nearest-Neighbour Matching (one to one or k-nearest neighbours), Radius Matching, Kernel Matching, and Stratification Matching (Becker and Ichino, 2002). The practical advantages of each matching estimator are still inconclusive (Imbens, 2004). The full details of the theory underpinning these methods are accessible in the existing statistical literature (Becker and Ichino, 2002; D'Agostino, 1998; Imbens, 2004; Rosenbaum and Rubin, 1985; Rosenbaum and Rubin, 1983). The theory is not covered in depth in this thesis, but a brief summary of the method used is provided.

When choosing covariates for propensity score matching four points should be taken into consideration (Moreno-Serra, 2007). Matching variables should include pre-treatment variables (baseline measurements), time invariant characteristics (such as gender) and variables deterministic with regards to time (such as age). Also, covariates that are only weakly correlated with the treatment variable and health outcome may decrease the precision (increase expected mean squared error). In addition, covariates affected by the health programme (such as intermediate outcomes) should not be included. Finally, factors which affect only treatment status or the potential health outcome do not need to be controlled for.

The simplest form of applying propensity score matching is by using Nearest-Neighbour Matching (NNM) without replacement, where each comparison observation (UK patient) can serve as a match for at most one treated person (US patient). The minimum distance between the propensity scores defines the comparators matched to the treated patients. However, the simplest form of NNM can lead to considerable bias if it results in many bad matches, due to treated individuals being matched

to comparison counterparts with very different propensity scores (despite being the "closest" neighbours). Some flexibility can be introduced by allowing the matching procedure to be performed with replacement. Matching with replacement allows extreme observations within the comparison group to be used more than once. If re-use occurs, matching with replacement will use better matches for each treated individuals thus reducing bias. However, the variance of the estimates will probably be higher than in the no-replacement case due to the smaller number of different comparison observations used to construct the counterfactual (Moreno-Serra, 2007).

The quality of matching may be improved by imposing the common support restriction. However, with this approach there is a possibility that high quality matches are lost at the boundaries of the common support and the sample may be considerably reduced (Lechner, 2000). Nevertheless, matching without common support can introduce severe bias by relying on the matching of treated individuals to substantially different comparison individuals (Moreno-Serra, 2007).

7.3.3 Propensity score matching for the US and UK trials

The matching method used for this case-study is the NNM method which basically takes each treated unit (US patient) and searches for the control (UK patient) with the closest propensity score to use as a match. The method is applied here with replacement meaning that after a UK patient is used as a match it is put back into the sample and can be used more than once if it is the closest match for many different US patients. The weight accruing to each individual of the UK group, when constructing the comparator for the US treatment, depends on the distance between the propensity scores of the UK and US patients and it reflects the number of times an individual is used as a match (frequency weight). The matched sample consists of all the original US patients, along with all the UK patients used as matches and this is the sample used for the economic evaluation. All analyses are conducted in STATA v 10.1 (Stata Corp, 2009).

Before matching the correct specification for the propensity score needs to be defined. This is done using the command *pscore* in STATA, which tests for the balancing property. The correct specification is also tested using the *psmatch2* command followed by the *pstest* command to inspect the extent of covariate balancing (Leuven and Sianesi, 2003). Overall, taking out the variable "percentage of abstinent days at baseline" (which is the only variable not statistically different between the two groups at baseline) does not produce better results in terms of the balancing property in the *pscore* and *pstest* results. The covariates used for estimating the propensity score are the following seven baseline variables: age, sex, employment, Mental Component Score (MCS) from the SF-36 questionnaire, Physical Component Score (PCS) from the SF-36 questionnaire, Percentage of Days Abstinent (PDA), and grams of alcohol consumed per day (g/day). All

covariates are highly correlated with treatment and the amount of alcohol consumed at follow-up (p-values of pairwise correlations less than .05 at a 95% confidence level). A linear regression between treatment and all the selected covariates shows that there is no collinearity between baseline variables (the variance inflation factor calculated with command "estatvif" in STATA is 1; when estatvif is smaller than 10 there is no collinearity).

A logit specification is used for estimating the individual probability of being exposed to the US treatment conditional on the seven baseline covariates defined above, using the *psmatch2* STATA command. The results of the one-to-one Nearest-Neighbour propensity score matching method in STATA, with replacement, are presented in Appendix 7- Matching the UK and US group

The region of common support should be analyzed to see if there is enough overlap between the two groups to make reasonable comparisons. Figure 7 below graphs the propensity score histogram by treatment status. It can be seen that there are more UK patients with low propensity scores and more US patients with high propensity scores. If there is a common support problem it might happen that for some treated units the nearest neighbour has a very different propensity score. However, a second analysis plotting a histogram of the UK patients with a propensity score greater than 0.1 shows, more clearly, that the UK group spans the full range of propensity scores (Figure 8). When there are relatively few UK cases that are similar to high propensity score US cases, as matching is done with replacement, the few control cases with high propensity score must be used over and over again as matches to the US cases.

Figure 7- Propensity score histogram by treatment status

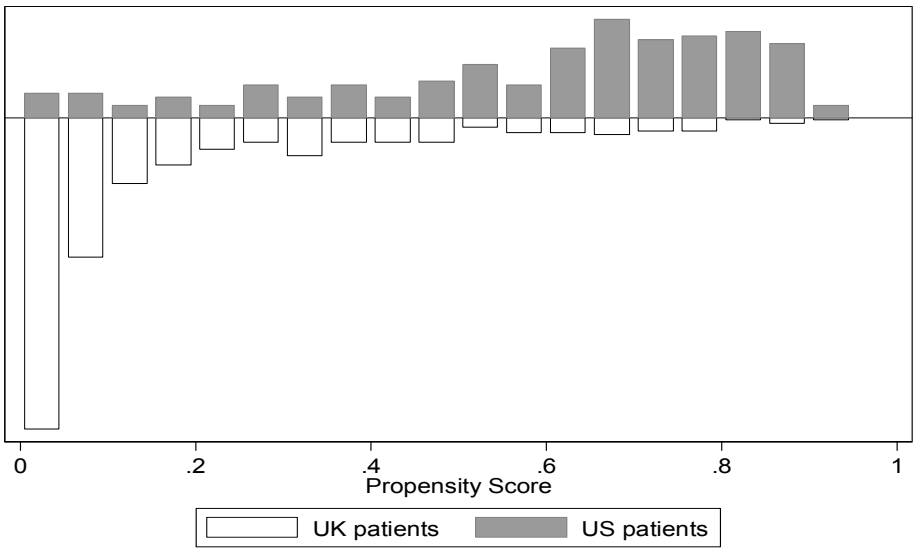
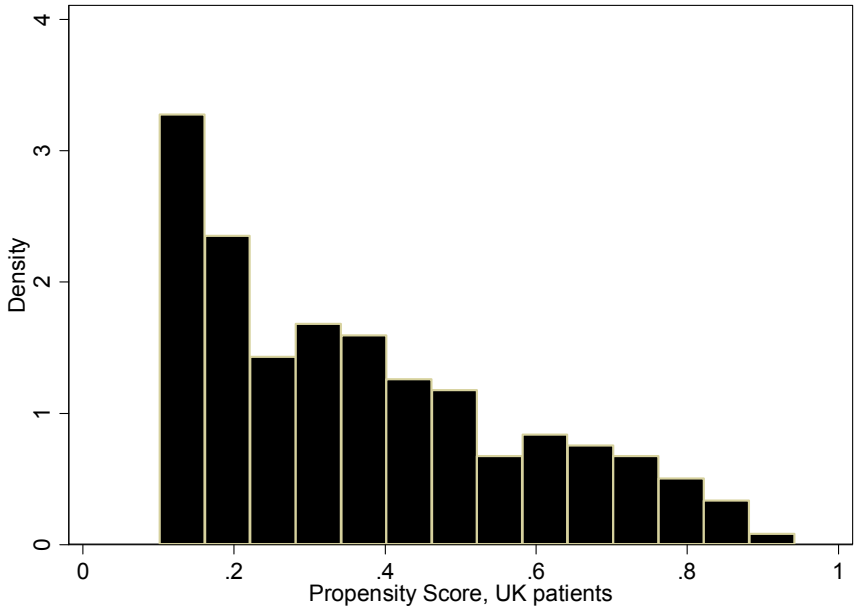


Figure 8- Propensity score >0.1 histogram, UK patients



Overall, 95 UK patients are used to match the 201 US patients and some of these 95 patients are used several times (see Appendix 7- Matching the UK and US group, to check the weights assigned in the matching process). The characteristics of the 201 UK patients matched to the 201 US patients are analysed in Table 56 below. The quality of the matching is tested using the STATA 10 *pstest* command. The output of the *pstest* command shows two rows for each variable, unmatched and matched. In each row, it shows the mean of the variable for the US group and the mean for the UK group. The *pstest* calculates several measures of the balancing of the variables before and after matching. In particular, for each variable it calculates (a) t-tests for equality of means in the UK and US groups, both before and after matching, (b) the standardised bias before and after matching, together with the achieved percentage reduction in absolute bias. The standardised bias is the difference of the sample means in the US and UK (full or matched) sub-samples as a percentage of the square root of the average of the sample variances in the US and UK groups (Rosenbaum and Rubin, 1985). The percentage reduction in bias is how much of this bias is eliminated by matching. Table 56 shows that, after NNM on the propensity score, there is no statistically significant difference between the two groups in all covariates analysed and there is a considerable reduction in absolute bias. The matched samples are similar regarding their baseline characteristics and, therefore are used for the economic evaluation.

Table 56- Baseline variables balance before and after matching (results from the *pstest* command in STATA 10)

Variable	Sample	Mean		% bias	% reduct |bias|	t-test	
		US	UK			t	p>|t|
Age	U	45.244	41.694	36.2		4.28	0.000
	M	45.244	44.579	6.8	81.3	0.75	0.456
Proportion of males	U	0.667	0.746	-17.5		-2.08	0.038
	M	0.667	0.751	-18.6	-6.6	-1.87	0.062
Proportion employed	U	0.871	.334	130.9		14.50	0.000
	M	0.871	.871	0.0	100.0	0.00	1.000
Mental Score	U	38.694	31.938	53.4		6.24	0.000
	M	38.694	38.28	3.3	93.9	0.33	0.742
Physical Score	U	53.603	46.883	73.9		8.33	0.000
	M	53.603	52.837	8.4	88.6	0.99	0.325
Percentage of abstinent days	U	24.017	27.574	-14.5		-1.68	0.094
	M	24.017	24.914	-3.7	74.8	-0.34	0.738
Alcohol (g/day)	U	84.469	138.18	-76.5		-8.11	0.000
	M	84.469	75.986	12.1	84.2	1.72	0.087

U, Unmatched; M, Matched; *Negative values for the percentage reduction in bias mean that bias increases as a result of matching. However, taking out the sex variable gives a worse balance in all other covariates.

7.4 Modelling the UK and US trials

7.4.1 Objectives

The objective of this case-study is to conduct a long-term cost effectiveness and cost utility analysis of a new pharmacological treatment for a UK population with alcohol problems when compared to what can be considered as standard therapy in the UK, using patient-level data collected in two trials and the model of drinking behaviour, to inform decision making in the UK NHS.

7.4.2 Comparators

The new Treatment A is compared to standard UK therapies. The comparators for the economic analysis are based on the results of the matching procedures presented in the previous section, where 201 UK patients are matched to 201 US patients.

7.4.3 Base case

The base-case cohort for the present model is a male cohort with an average starting age of 40 years old. The cohort of individuals with alcohol problems is modelled through 80 cycles, as it is expected that on the 80th cycle all patients are in the death state (WHO, 2008). The distribution of patients in the two initial Markov states (hazardous and harmful) is the one observed in both trials

distribution. Approximately 50% of the population modelled is drinking hazardously and another 50% is drinking harmfully. Therefore, the base-case considers a cohort equally distributed between the two initial drinking states.

7.4.4 Discounting and price year

In accordance with NICE (2008) guidance a discount rate of 3.5% is applied to both costs and outcomes. The price year of the economic analysis is 2006/07. The currency used in the economic evaluation is pound sterling (GBP, £).

7.5 Model Inputs

The model inputs that are UK-specific and independent of the treatments under analysis are presented in Chapter 5. The model inputs presented here are the effects of treatment in drinking behaviour (the first cycle transition probabilities) and treatment costs.

7.5.1 Transition probabilities for the first cycle

Transition probabilities for the first cycle of each treatment are derived from the 201 patients of the US trial (confidential data) and the matched 201 patients of the UKATT trial (UKATT Research Team, 2005b, a). Transition probabilities for each trial are calculated through counting the individuals that moved between the drinking categories from baseline to follow-up.

The UK and US trials have different follow-up periods, the former was a 12-month trial while the latter was a 6-month trial. The studies ought to be comparable in terms of the time of assessment as this can have an impact on the corresponding drinking level. Therefore, baseline and 6 month drinking categories are defined for both trials, according to the grams of alcohol consumed per day. However, none of the trials presented individual-level outcomes in terms of grams per day. For the UK trial, the calculation of grams of alcohol consumed per day is presented in Chapter 5 (see section 5.5). The US trial provided similar data to the UK data but for 30 days instead of 90 days. The same general procedure as the one used for the UKATT study is applied, for both baseline and 6 month follow-up, but the grams of alcohol consumed per patient is obtained by multiplying the number of drinks per day by a factor of 13.6, as in the US one drink has 13.6g of absolute EtOH. The calculation of grams per day at 6 months for the UKATT trial uses linear interpolation between 3 and 12 months grams per day, in the same way as explained in section 5.5.

The number of patients in each drinking category, by gender, at baseline and 6 months, is presented in the following four tables for each trial. The corresponding transition matrices are presented on the bottom part of each table.

Table 57- Counts of transition between model states and transition matrix for the US trial (males)

US trial- Counts of transitions between the five states for the 6 months period for males*							
MALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	20	1	43	NA	0	64
	Harmful	26	14	NA	36	0	76
	N	46	15	43	36	0	140
Transition matrix							
MALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.3125	0.0156	0.6719	NA	TD	1
	Harmful	0.3421	0.1842	NA	0.4737	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

Table 58- Counts of transition between model states and transition matrix for the US trial (females)

US trial- Counts of transitions between the five states for the 6 months period for females*							
FEMALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	14	2	19	NA	0	35
	Harmful	16	11	NA	11	0	38
	N	30	13	19	11	0	73
Transition matrix							
FEMALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.4000	0.0571	0.5429	NA	TD	1
	Harmful	0.4211	0.2894	NA	0.2895	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

Table 59- Counts of transition between model states and transition matrix for the UK trial (males)

UK trial- Counts of transitions between the five states for the 6 months period for males*							
MALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	27	31	20	NA	0	78
	Harmful	36	21	NA	22	0	79
	N	63	52	20	22	0	157
Transition matrix							
MALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.3462	0.3974	0.2564	NA	TD	1
	Harmful	0.4557	0.2658	NA	0.2785	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

Table 60- Counts of transition between model states and transition matrix for the UK trial (females)

UK trial- Counts of transitions between the five states for the 6 months period for females*							
FEMALES		6 months					
		Hazardous	Harmful	Ex-Haz	Ex-Harm	Death	N
Baseline	Hazardous	4	20	6	NA	0	30
	Harmful	7	10	NA	9	0	26
	N	11	30	6	9	0	56
Transition matrix							
FEMALES		6 months					
		Mod	HE	Ex-Haz	Ex-Harm	Death	
Baseline	Hazardous	0.1333	0.6667	0.2	NA	TD	1
	Harmful	0.2692	0.3846	NA	0.3462	TD	1

Ex-Haz, Ex-Hazardous; Ex-Harm, Ex-Harmful; NA, Not Applicable; TD, Time Dependent; N, total number; *A value of 1 was added to each cell count assuming an uniform Dirichlet prior distribution.

7.5.2 Cost of the treatments

The costs of each treatment are calculated with the trials' data and are based on the actual treatment received by the individuals matched according to the propensity score for each trial. These costs are only applicable to the first cycle of the model, given that treatment is only given in the first cycle.

The economic model compares a time-limited psychosocial treatment with a new pharmacological treatment. The new pharmacological treatment, Treatment A, is delivered monthly, as in the US randomized controlled trial. The standard care treatment is based on the therapies delivered in the UKATT pragmatic trial. The costs of screening and identifying problematic drinkers or referring such drinkers to those delivering the treatments are assumed to be the same between the groups and therefore these costs are excluded from the analysis.

Treatment A

The costs of Treatment A are made up of the active drug and an accompanying psychosocial treatment. The psychosocial treatment sessions are assumed to last for 20 minutes per patient. The average number of psychosocial sessions taken per patient was 10.1 (SD. 2.68, n=201).

The cost per minute derived from the UKATT trial is used to estimate an approximate cost of psychosocial sessions per patient. The mean UKATT session length was 50.8 minutes, with a cost of £1.62/ min (£82.12/ 50.8min). The cost per psychosocial session (20min) is then £32.4 (£1.62*20min). The mean cost of psychosocial therapy per patient used is £326.74 (SD 86.86, n=201).

The cost of the pharmacological treatment of the 201 patients who received the active drug takes into account the mean number of doses received by this sample which was 4.80 (SD 1.80, n=201). The cost per dose used in the base-case is £350. The total cost of the pharmacological component

of treatment per patient is estimated at £1,679 (4.80*£350). In addition, one GP contact per treatment per patient is included. The estimate of this cost is £30 (Curtis, 2007), for a 2006/07 price year. It is assumed that Treatment A was administered on the first visit by the GP and on the subsequent visits by the nurse as part of the psychosocial sessions. Therefore no additional costs for administration of the pharmacological component are included. The total cost of the new pharmacological treatment putting all these components together is presented in Table 61 below.

Table 61- Treatment A costs

Resource	Unit	Cost (£) unit	Units consumed	Total cost (£)
Pharmacological component	1 dose	£350	1/ month total of 4.80	£1,679
Psychosocial treatment	20 minute contact	£32.4	Mean 10.1 sessions per patient (202 minutes per patient)	£327
GP contacts	Contact	£30	1 contact for referral	£30
Total Treatment Costs				**£2,035**

UKATT treatment

UKATT therapies are costed as delivered in the trial. These therapies were time limited over a 12 week period. One treatment type had a maximum of 3 sessions – 50 minutes in length and the other treatment type had a maximum of 8 sessions – 50 minutes in length. Such time limited treatments are not necessarily the norm in the UK and therefore the costs of these therapies may be lower than average treatment costs. Also no attempt was made to cost adjunct pharmacological treatments which some patients were offered, e.g. acamprosate or disulfiram. This and other UK alcohol treatment trials indicate that patients will take up a range of other alcohol treatment services. The take-up of such other alcohol services was measured at the 12 months follow-up period for the previous 6 months and at the 3 months follow-up in the UKATT trial. Such costs may be seen as an overestimation of treatment costs within the treatment period but UKATT treatment costs alone may be seen as an underestimate of the true costs. It is important to note that UKATT clients showed a "saving" of total alcohol treatment costs after their UKATT therapy.

The costs used for the economic evaluation are up-rated from the original data (2000/01 prices), using the HCHS pay and prices index from the PSSRU Unit Costs of Health and Social Care 2007 (Curtis, 2007) to 2006/7 prices. The total treatment cost of UKATT therapies, for the sample matched to the US trials, is £336.60 (SD 122.19) and the alcohol service cost at 3 months is £43.15 (SD 311.03). The matched UKATT sample took up an average of 178 min of psychosocial therapies per patient. The costs used in the model are the total treatment costs plus the other alcohol services, which adds to £379.5.

It can be seen that even with other alcohol services included, the cost of UKATT therapies are only equivalent to the psychosocial and GP input for the treatment arm of the US trial. The new treatment is almost 6 times more expensive than standard therapy. It may be that the new drug delivered in the UK is accompanied by a lower psychosocial component. This may reflect different overall patient and health service practice between the US and UK. However, the major component is the cost of the new pharmacological treatment.

7.6 Sensitivity analysis and heterogeneity

7.6.1 Probabilistic Sensitivity Analysis

Two different distributions are chosen in order to conduct the probabilistic sensitivity analysis. Transition probabilities for the first cycle are estimated from multinomial data and, therefore, assigned the Dirichlet distribution. Transition probabilities for the following cycles and utilities are both derived from binomial data and, therefore, assigned a beta distribution (see section 6.4.1 in the previous chapter).

7.6.2 Univariate sensitivity analysis

Sensitivity analyses are undertaken to assess the robustness of the base-case model results to variations in alternative assumptions related to key parameters in the model. One way sensitivity analysis is conducted for the initial distribution of patients, where the effect of a different proportion of patients starting in hazardous (A) and harmful (B) states is analysed (25% A-75% B and 75% A - 25% B). The impact of an alternative discount rate of 6% for costs and 1.5% for outcomes is analysed. One-way sensitivity analysis is also conducted for the market price of the pharmacological component of Treatment A.

7.6.3 Heterogeneity

The analysis is run for cohorts of males and females of 20, 40 and 60 years old in order to deal with heterogeneity. Multiple CEACs are produced, where the probability of Treatment A being cost effective is plotted against the willingness to pay threshold, for each subgroup.

Table 62 below depicts the base-case used in the model and the variations in the base-case for which results are presented in section 7.7 below. Four alternative scenarios are considered and for each element, the position in the base-case analysis is outlined, alongside the alternative assumption applied.

Table 62- Key elements of the base-case analysis and alternative scenarios, case-study 2

Scenario	Element	Position in base-case analysis	Alternative scenario
1	Population	Male cohort with starting age of 40 years old	Separate analysis for males and females Alternative starting ages assumed: 20, 40 and 60 years
2	Discount rate	3.5% applied to both costs and outcomes (NICE, 2008)	6% costs, 1.5% outcomes (NICE, 2008)
3	Cohort distribution	50% hazardous, 50% harmful	75% hazardous, 25% harmful 25% hazardous, 75% harmful
4	Treatment A drug price	£350	£300, £350, £400, £450, £500

7.7 Case-study results

The model results are first presented according to a particular set of assumptions employed as part of the base-case analysis. The impact of employing alternative assumptions to those presented in the base-case analysis is then explored. This is followed by a section taking into account the value of information analysis. The last sections present the implications and limitations of the study.

7.7.1 Deterministic cost effectiveness results

The summary deterministic results of the model are the incremental costs and incremental effectiveness of Treatment A compared with standard UK therapy. For the base case analysis (male cohort of 40 years old, drug price of £350, discount rate of 3.5% for costs and outcomes, and initial distribution of 50% in hazardous and 50% in harmful drinking states), Treatment A is more costly and more effective than the standard treatment approach. The ICER is £22,772/ QALY, which is within the £20,000 to £30,000 per additional QALY benchmark used in England and Wales (NICE, 2008) suggesting that Treatment A may be a cost effective treatment compared to standard UK therapy in the population studied. A breakdown of the costs and QALYs for the base case is presented in Table 63 below.

Table 63- Base-case analysis, deterministic results for the cost effectiveness of Treatment A compared to UKATT therapies

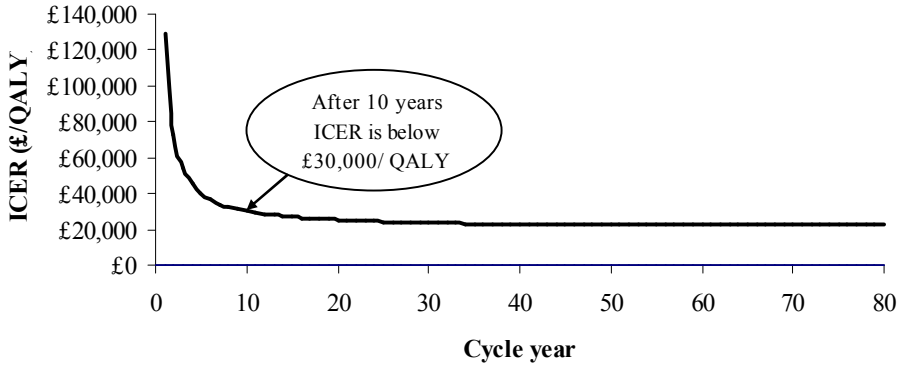
Males, 40 years old Deterministic results	Treatment A	UKATT treatment	Difference (Treatment A vs. UKATT)
Costs (£, 2006/07 prices)	£3,283	£1,654	£1,629
QALYs	13.09	13.02	0.072
Life Years	19.89	19.86	0.030
ICER (Δcost/ ΔQALY)			**£22,773/ QALY**
ICER (Δcost/ ΔLYG)			£54,292/ LYG

QALY, Quality Adjusted Life Year; LYG, Life Years Gained; costs and effect discount rate=3.5%; drug price £350; initial distribution of 50% in hazardous and 50% in harmful drinking states. Estimates rounded for presentation.

Clearly, the new treatment is more expensive than standard UK therapy, being two times more expensive if a long term analysis is conducted and almost 6 times more expensive on the short term. However, Treatment A is more effective in terms of life years gained and especially in terms of QALYs gained as presented in Table 63.

The importance of a long-term model in the analysis of the cost effectiveness of the new alcohol treatment is reflected in the ICER obtained for each model cycle. The reduction in the ICER as the short-term analysis progresses to a long-term one is depicted in Figure 9. The chart represents the ICER, computed as the cumulative difference in costs and QALYs, for each cycle year. It is shown that after the tenth cycle the new treatment for alcohol problems is cost effective, achieving an ICER below £30,000/ QALY.

Figure 9- Incremental cost effectiveness ratio of Treatment A vs. UKATT therapies



7.7.2 Probabilistic cost effectiveness results

The results of the PSA for the base case analysis are presented in Table 64. Even when accounting for the effect of uncertainty in model inputs on the outputs, Treatment A is cost effective. The mean cost effectiveness ratio of Treatment A vs. standard UK therapy estimated from 1000 random draws is £21,722 per QALY.

Table 64- Base-case analysis, probabilistic results for the cost effectiveness of Treatment A compared to UKATT therapies

Males, 40 years old Probabilistic results	**Treatment A**	**UKATT treatment**	**Difference (Treatment A vs. UKATT)**
Costs (£, 2006/07 prices)	£3,280	£1,651	£1,628
QALYs	13.10	13.03	0.075
Life Years	19.89	19.86	0.031
ICER (Δcost/ ΔQALY)			**£21,722/ QALY**
ICER (Δcost/ ΔLYG)			£52,514/ LYG

QALY, Quality Adjusted Life Year; LYG, Life Years Gained; costs and effect discount rate=3.5%; drug price £350; initial distribution of 50% in hazardous and 50% in harmful drinking states. Estimates rounded for presentation.

The simulation results of the overall uncertainty in the model are presented in a cost effectiveness plane and cost effectiveness acceptability curve (Briggs et al., 2006; Briggs and Tambour, 2001). Figure 10 below shows the results of 1000 Monte Carlo simulations in a cost effectiveness plane. The cost effectiveness plane shows the difference (Treatment A minus UKATT) in effectiveness per patient against the difference in cost per patient.

Figure 10- Incremental cost effectiveness plane of Treatment A vs. UKATT therapies

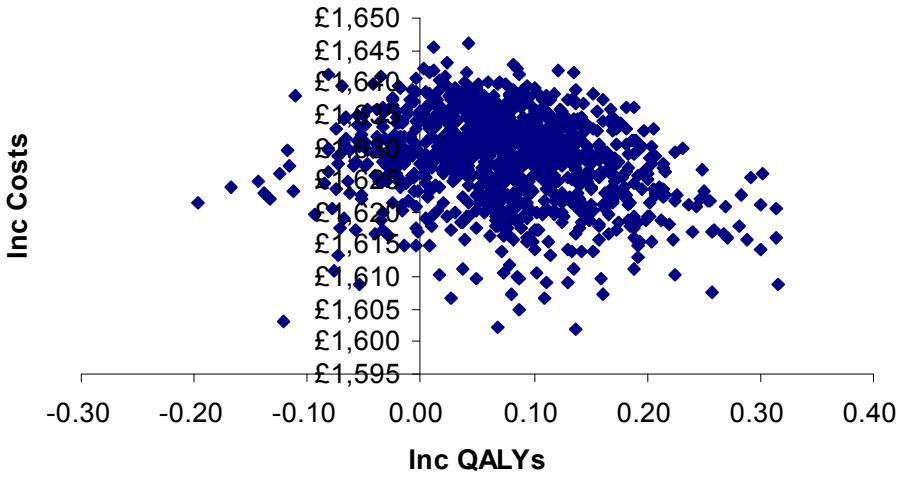
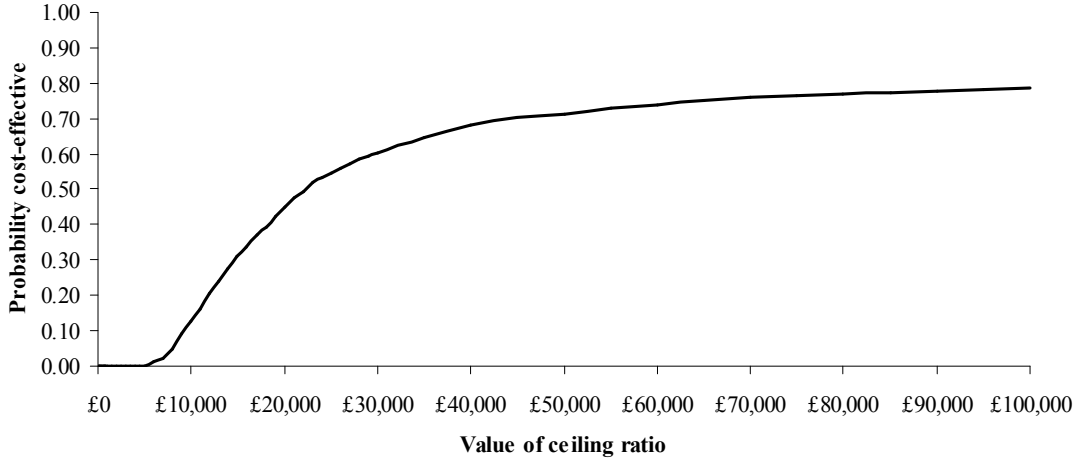


Figure 10 shows that the new drug is more costly than the UKATT treatment for all simulations as all simulation fall above the horizontal line of the cost effectiveness plane. Some of the simulation results cross the vertical axis (the new treatment is less effective than UKATT based therapies). However, for the biggest part of the simulations, Treatment A is more effective than UKATT therapies, as more dots fall on the right quadrant of the plane.

The standard ICER figure does not differentiate situations where ratios have the same sign but not the same interpretation. This problem can be solved by drawing a line in the cost effectiveness plane that goes through the origin and represents the maximum that decision makers are willing to invest to achieve a unit of effectiveness. In this case, if the computed ICER lies below the threshold ratio the intervention should be adopted. Usually, a decision analytical framework uses CEAC to represent uncertainty. The CEAC presented below, in Figure 11, shows the probability that Treatment A is cost effective for a range of cost effectiveness thresholds, i.e. it shows how many of the 1000 simulations fall below and to the right of a line representing the threshold cost per QALY. The CEAC for UKATT treatment is the perfect complement of the Treatment A curve.

Figure 11- Cost effectiveness acceptability curve for Treatment A vs. UKATT therapies



The CEAC in Figure 11 shows that the probability that Treatment A is cost effective cuts the horizontal axis (probability is zero) for threshold values below £6,000/ QALY and increases thereafter. Therefore, when the decision maker is only interested in the cheaper option, standard UK therapy has a probability of 100 percent to be cost effective. Both treatments have the same probability of being cost effective when the decision maker is willing to pay around £21,722 per QALY, which is the value of the ICER. At this threshold the decision maker is indifferent between the two options. If the decision maker is willing to pay more than £21,722/ QALY then Treatment A should be adopted for it has a higher probability of being cost effective. The probability that Treatment A is the most cost effective therapy is 0.45 and 0.60 for threshold values of £20,000 and £30,000, respectively.

7.7.3 Univariate sensitivity analysis

One way sensitivity analysis is conducted for the initial distribution of patients, where the effect of different proportion of patients starting in hazardous (A) and harmful (B) states is analysed (75% A-25% B; 25% A-75% B). This sensitivity analysis reflects the impact of delivering the treatments compared to a population drinking at levels different from the base-case. Table 65 shows that if Treatment A is delivered to a mainly hazardously drinking population (75% hazardous) it is even more cost effective mainly because of a higher scope for QALYs gained (ICER= £14,773/ QALY). In contrast, it appears that the new treatment is not so cost effective if given to a population mainly represented by harmful drinkers (ICER= £45,397/ QALY). This shows that the new treatment might represent a very cost effective option to a 40-year-old UK male population with moderate drinking problems but not drinking too heavily.

One way sensitivity analysis is also conducted for a discount rate of 6% for costs and 1.5% for health outcomes. The results are presented in Table 65, where it can be seen that the alternative discount rates improve the cost effectiveness by a minor amount. This is mainly because a lower discount rate on the outcomes values them higher which is reflected in a higher QALY gain and therefore, in a higher denominator of the cost effectiveness ratio reducing the overall ICER.

As would be expected, a reduction in the price of the pharmacological component of Treatment A reduces the ICER significantly due to a reduction in the incremental cost of Treatment A versus UKATT therapies. A reduction in the base-case price of the new treatment supports the decision of adopting it from a NHS/ payer perspective. A price higher than £500 results in an ICER above the upper accepted limit of £30,000/ QALY.

Table 65-Probabilistic results for one-way sensitivity analysis (Treatment A vs. UKATT therapies)

	Incremental costs	**Incremental QALYs**	**ICER £/ QALY**
Initial cohort distribution			
75% hazardous; 25% harmful	£1,620	0.1096	£14,773
50% hazardous; 50% harmful*	£1,628	0.0750	£21,722
25% hazardous; 75% harmful	£1,636	0.0360	£45,397
Discount rate			
3.5% cost and outcomes*	£1,628	0.0750	£21,722
6% costs; 1.5% outcomes	£1,629	0.0823	£19,782
Treatment A price			
£350*	£1,628	0.0750	£21,722
£300	£1,388	0.0774	£17,944
£400	£1,867	0.0755	£24,730
£450	£2,106	0.0746	£28,244
£500	£2,346	0.0789	£29,724

*Base-case conditions; QALYs, Quality Adjusted Life Years; ICER, Incremental Cost Effectiveness Ratio; price year 2006/07. Estimates rounded for presentation.

7.7.4 Modelling heterogeneity

The incremental probabilistic results of Treatment A when compared to UKATT therapies, for the six patient groups analysed, are presented in Table 66 below.

Table 66- Probabilistic results for the subgroup analysis (Treatment A vs. UKATT therapies)

	Incremental Cost	Incremental QALY	ICER £/ QALY
Males, 20 years old	£1,651	0.0694	£23,775
Males, 40 years old*	£1,628	0.0750	£21,722
Males, 60 years old	£1,613	0.0695	£23,189
Females, 20 years old	£1,653	0.0893	£18,499
Females, 40 years old	£1,638	0.0979	£16,724
Females, 60 years old	£1,631	0.0970	£16,805

*Base-case conditions; ICER, Incremental Cost Effectiveness Ratio; QALY, Quality Adjusted Life Year; price year 2006/07; discount rate r= 3.5%; drug price £350; initial distribution of 50% in hazardous and 50% in harmful drinking states. Estimates rounded for presentation.

The gender and age variation in the ICER can be explained by two factors. One factor is the variation in costs by subgroup, which can be explained by gender variation in the first cycle transition probabilities (treatment effect) and variations in morbidity rates by gender and age. The second factor is the variation in effects by subgroup, which can be explained by gender variation in the first cycle transition probabilities (treatment effect) and variations in mortality rates by gender and age.

The subgroup analysis presented in Table 66 shows that the lowest ICER is observed for 40-year-old females and the highest for 20-year-old males. Comparing females and males of the same age shows that the ICER is always slightly lower for the female cohort and, therefore, Treatment A is more cost effective for females than males, in the UK. This is a very interesting result also because the US trial showed that Treatment A was more cost effective for males. However, the results from the model cannot be directly compared to the trial results. The model conducts a lifetime analysis while the trial had a 6-month time horizon. Also, the model uses a range of data to generate results and models a specific cohort.

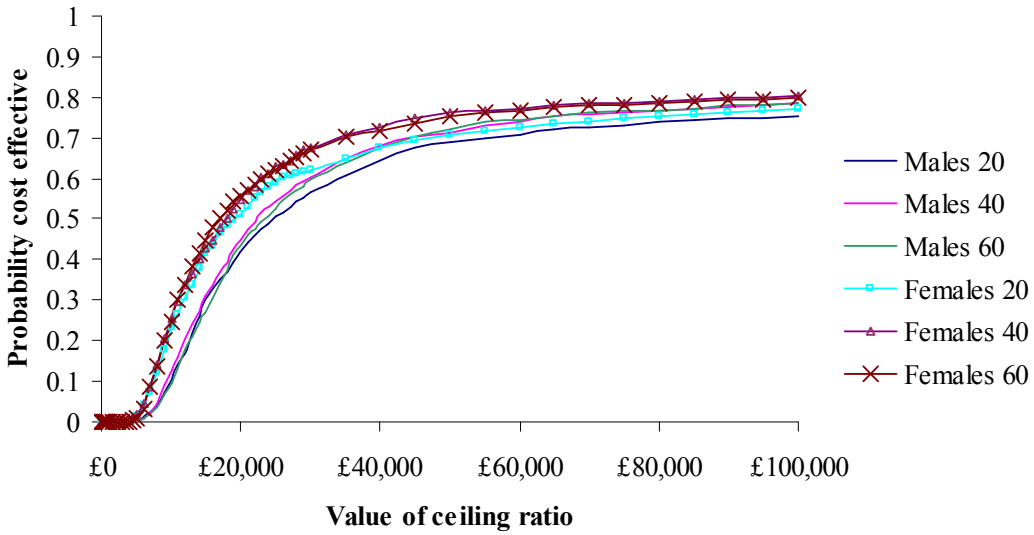
Within the same age groups, the biggest difference between males and females is in terms of QALYs gained. It appears that females gain more QALYs with the new treatment than males. The states' utilities are the same for men and women and actually by looking at the first cycle transition probabilities (Table 46-Table 49) it appears that males improved more than females for each treatment individually. Even though there is a higher absolute improvement for males, when comparing the incremental utility for males with that for females, between treatments, there is a higher gain for a female cohort. This might be related to the rather intense psychosocial therapy

that is part of Treatment A. This psychosocial treatment has a strong network component, to which women are said to be more responsive than men (Schneider et al., 1995). However, UKATT therapies also had a strong network component (as delivered in SBNT) and it might be that the better improvement for females is related to a higher response to the pharmacological drug. Nevertheless, it should be noted that the psychosocial component of Treatment A was more intense, in terms of average duration per patient, than the UKATT therapies (202 min vs. 178 min, respectively). This gender difference is also explained by the lower mortality rates for females than males and therefore, a higher scope for QALYs gained throughout lifetime. With respect to the incremental costs, Table 66 shows that these are very similar for males and females of the same age group. This is because the lower cost of female's drinking categories is balanced with their higher life expectancy and therefore, lifetime incremental costs are similar between males and females (as shown in Table 41, Chapter 5). In summary, the lower ICERs for a female cohort are explained by the QALYs gained and not so much by differences in costs.

The model results presented in Table 66 show that the ICER for males increases for a 40, 60 and 20-year old cohort, respectively. The QALY gain for men is higher for 40-year old men than 60-year old men due to the competing effect of a higher mortality rate. The ICERS for 60 and 20 years old cohorts are very similar for males. For females, similarly to males, the ICER increases for a 40, 60 and 20-year old cohort, respectively. Both female and male young cohorts (20 years old) have higher costs and lower utility gains. The higher costs might be related with the fact that there are more potential years in the model for accruing health care costs. The lower utility gains might be related to the fact that the benefits of treatment fade with time (which is enhanced with more years of discounting).

Nevertheless, for all the analysed cohorts the ICER is below or around £24,000/ QALY and the ICERs are very similar for the different age groups of the same gender. Each subgroup of patients is represented by a different CEAC in Figure 12 below. This allows the assessment of the extent to which the results vary across different subgroups and whether different treatment decisions should be made for different categories of patients, according to the decision maker's threshold for the new treatment adoption. The CEACs are very close to each other and treatment is potentially cost effective for all age and gender cohorts and more cost effective for a female cohort. The CEACs for each group of patients encourage the decision maker to make similar treatment decisions across the different categories of patients, based on the expected cost effectiveness for the set of patient characteristics and associated uncertainty. However, if the decision maker is not willing to pay more than £20,000/ QALY he or she might be more confident in adopting Treatment A for a female cohort.

Figure 12- Multiple CEAC for different age and sex cohorts for Treatment A vs. UKATT therapies



7.7.5 Summary of the cost effectiveness results

Table 67 details the results of each of the alternative scenarios considered for the cost effectiveness analysis of Treatment A. The table reports the ICER and the probability that Treatment A is cost effective at thresholds of £20,000 and £30,000 per additional QALY. The base-case ICER of £21,722/ QALY provides the benchmark for assessing whether the cost effectiveness results appear robust to particular assumptions made in the base-case analysis.

The base-case scenario suggests that the new treatment is likely to be considered cost effective. The ICER of Treatment A vs. UKATT (£21,722/ QALY) is within the range of conventional thresholds used to identify whether a particular treatment is considered to be cost effective in the NHS. For thresholds between £20,000 and £30,000 per QALY, the probability that Treatment A is more cost effective than UK standard treatment is 0.45 and 0.60.

Some deviations from the base-case assumptions improve the ICER and make the new treatment more cost effective, such as: delivering the treatment to less severe patients, to females, or decreasing the price of the pharmacological component. Theses options should be considered in case the decision maker is willing to pay less than £20,000/ QALY. If the price of the drug is set at £300 per dose, the new treatment has a 52% chance of being a more cost effective option than UKATT therapies, for a threshold value of £20,000/ QALY. If Treatment A is delivered to a population where drinkers are mainly hazardous, the chance of cost effectiveness increases to 60% and 70%, for a £20,000 to £30,000 threshold, respectively. Applying an alternative discount rate of

6% to costs and 1.5% to health outcomes (compared to 3.5% for both in the base-case analysis) improves the cost effectiveness by a minor amount. The ICER is then below the lower bound of the £20,000 threshold.

Heterogeneity in patient characteristics is explored using a series of separate scenarios. The results demonstrate that cost effectiveness is improved in female subgroups. However, differences within the subgroups are relatively minor.

Table 67- Summary of cost effectiveness results (Treatment A vs. UKATT therapies)

	Probability cost effective for max WTP		**ICER**
	£20,000	**£30,000**	
Initial cohort distribution			
75% hazardous; 25% harmful	0.596	0.694	£14,773
50% hazardous; 50% harmful*	0.449	0.604	£21,722
25% hazardous; 75% harmful	0.136	0.308	£45,397
Discount rate			
3.5% cost and outcomes*	0.449	0.604	£21,722
6% costs; 1.5% outcomes	0.507	0.638	£19,782
Injection price			
£350*	0.449	0.604	£21,722
£300	0.520	0.673	£17,944
£400	0.393	0.572	£24,730
£450	0.343	0.520	£28,244
£500	0.328	0.503	£29,724
Subgroup analysis			
Males, 20 years old	0.421	0.565	£23,775
Males, 40 years old*	0.449	0.604	£21,722
Males, 60 years old	0.434	0.596	£23,189
Females, 20 years old	0.511	0.621	£18,499
Females, 40 years old	0.547	0.676	£16,724
Females, 60 years old	0.555	0.669	£16,805

*Base case conditions; ICER, Incremental Cost Effectiveness Ratio; WTP, Willingness to Pay; price year 2006/07. Estimates rounded for presentation.

7.7.6 Value of information

Value of information is related to the value of reducing uncertainty such that a decision may include the option to acquire more information (see Chapter 4, section 4.10). This involves balancing the costs of acquiring more information with its value (Briggs et al., 2006). The effective population for alcohol treatment in England each year is taken from the report of Alcohol Needs Assessment Research Project (Drummond et al., 2005a). The report estimated that approximately 8.2 million

people in England have an alcohol use disorder and that around 1,125 million per annum are alcohol dependent drinkers eligible for treatment. The population EVPI is estimated using the latter value and assumes that the information would be valuable for a 10-year lifetime of the alcohol treatments. A 3.5% annual discount rate is applied. Individual patient and population EVPI are calculated for the base-case model. Figure 13 below illustrates the population EVPI for Treatment A when compared to UKATT therapies for the base-case analysis.

Figure 13- Population expected value of perfect information for Treatment A vs. UKATT therapies

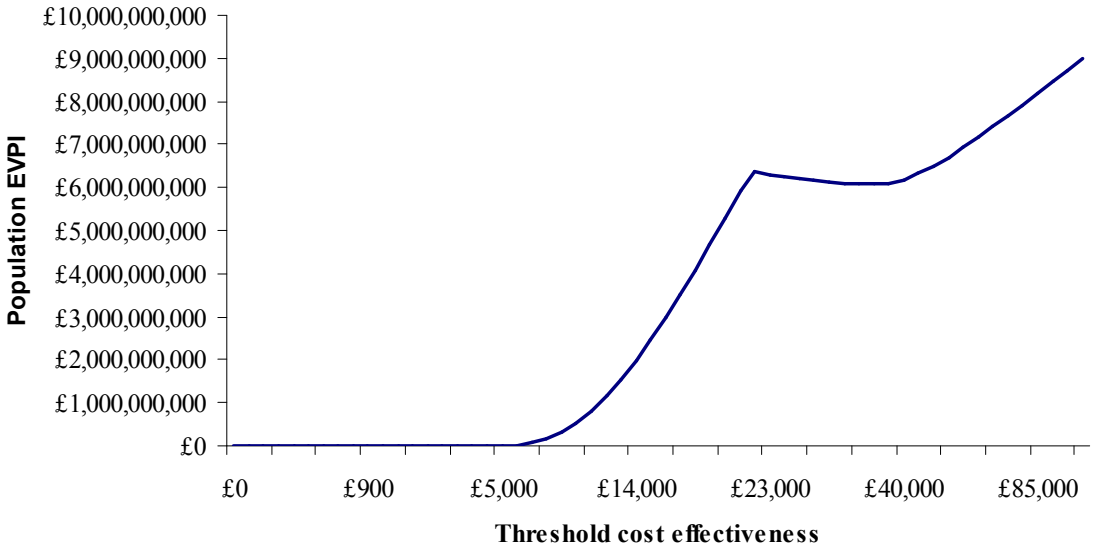


Figure 13 shows that when the decision maker is not willing to spend much on alcohol treatments (cost effectiveness thresholds below £6,000) the EVPI is low. This is because additional information is unlikely to change the decision about adopting UKATT therapies for low thresholds. In this case, there is minimal decision uncertainty that Treatment A is not optimal, and current evidence can be regarded as sufficient to support the decision to adopt UKATT therapies. Between threshold values of around £6,000 and £21,722 (the base-case ICER) the value of information on whether treatment A is better value for money, increases. This means that, as the decision maker is willing to pay more for alcohol treatments, he or she is also willing to finance the more expensive treatment (Treatment A) or research that reduces the uncertainty regarding which treatment is more cost effective. The population EVPI reaches a peak at the point where the threshold for cost effectiveness is equal to the expected ICER. This peak occurs when there is uncertainty on whether to adopt or reject Treatment A based on current evidence (i.e. at £21,722 per QALY) because the probability of each treatment being cost effective is 50%. The decision to require more information is based on the cost of further research, the threshold and the cost of uncertainty or value of information. Therefore, if further research were expected to cost, say £300m then, further research

would be requested in order to accept Treatment A for thresholds above £9,000. This is because for thresholds above £9,000 the value of information is always higher than the hypothetical value of £300m and so further research would be considered cost effective.

After the threshold value of the ICER the cost of uncertainty decreases slightly with a steep increase for thresholds higher than £30,000. When the threshold is higher than the ICER, the new intervention is expected to be cost effective and this decision is slightly less likely to be changed by further research until the threshold reaches £30,000. The small EVPI decrease is justified by a slight reduction in decision uncertainty which offsets the increased value of the consequences of an error. As the threshold increases the cost of uncertainty increases and further research becomes highly important because the increased value of the consequences of an error is not offset by a reduction in uncertainty. The decision that Treatment A is the most cost effective option, for threshold values between £22,000 and £30,000, needs more research in case the cost of further research is lower than the cost of uncertainty. The value of information is very high and it can be expected that the costs of further research would be lower than the costs of uncertainty for the conventional range of threshold willingness to pay (£20,000-£30,000). Therefore, the EVPI curve shows that further research should be conducted before accepting Treatment A in the UK.

The population EVPI can be scaled back to provide results for the individual per patient EVPI. This allows decision makers to apply the results to the potential size of their own population of interest. Table 68 provides a summary of the population and individual EVPI estimates for selected threshold values.

Table 68- Individual patient and population EVPI for selected values of the threshold for the base-case (Treatment A vs. UKATT therapies)

	Individual EVPI for maximum WTP		**Population EVPI for maximum WTP**	
	£20,000	**£30,000**	**£20,000**	**£30,000**
Base-case	£537	£614	£5 billions	£6 billions

EVPI, Expected Value of Perfect Information; WTP, Willingness to Pay; price year 2006/07.

7.8 Decision making

The new treatment for alcohol problems, Treatment A, analysed in the Markov model of drinking behaviour appears to be both more effective and more costly than UKATT-based therapies. The probabilistic results of the economic analysis show that the additional benefits of Treatment A appear to be worth the additional cost in the UK for all age and gender cohorts analysed under base-case conditions. The delivery to a population where half is drinking heavily (harmful drinkers) and another half is drinking high amounts (hazardous drinkers) is very close to the £20,000 lower bound of the threshold willingness to pay. The cost effectiveness of the new treatment is greatly improved

if it is delivered to a population that consists mainly of hazardous drinkers. In addition, a lower price of the pharmacological component of Treatment A increases its cost effectiveness. The subgroup analysis shows that Treatment A is even more cost effective for a female cohort and the ICER for this cohort is below £20,000/ QALY for all age groups.

The ICER for a male cohort of 40 years old is £21,722/ QALY, which is just slightly above the lower bond of the benchmark of £20,000 to £30,000 adopted in England and Wales. If the decision maker is willing to pay more than £21,722 per QALY, then the new treatment might be adopted for it has a higher probability of being cost effective. However, the value of additional evidence for Treatment A is very high. Perhaps a randomized controlled trial of Treatment A in the UK would reduce some of the uncertainty. Furthermore, some of the model inputs such as the states utilities and the transition probabilities for the following cycles are associated with high uncertainty and more research to produce more certain estimates would be very important.

7.9 Policy implications

The cost effectiveness of the new treatment is greatly improved if it is delivered to a population that consists mainly of hazardous drinkers. Therefore, the decision maker might prefer the adoption of this treatment in settings where a less severe population can be found, such as in the workplace if employers are willing to invest in controlled alcohol drinking, or first points of contact with patients where a screening programme is established (primary care in England).

When compared to psychosocial therapies, as delivered in the pragmatic UKATT trial, the major addition with the new treatment is the requirement for specialist staff to deliver the pharmacological drug. The setting where the treatment will be delivered needs to be defined. If the treatment is to be delivered at the workplace then special arrangements with employers need to be done. If the treatment is to be delivered at a primary care setting some specific points need to be addressed such as: 1) more training in generalist staff and medical schools, 2) more specialist staff, 3) more screening of problematic alcohol drinkers, etc.

7.10 Discussion

The case-study presents the long-term cost effectiveness results of a new alcohol treatment versus standard UK therapies. The long-term analysis applies the economic model developed in previous chapters to the results of two randomized controlled trials. Patient-level data from both trials is used and combined with epidemiological risks for a UK population and with the NHS costs of alcohol-related diseases.

The limitations of the study regarding the general model features and UK-specific model inputs are presented in Chapters 4 and 5, respectively. There are four specific limitations worth mentioning here. First, the economic model directly compares two treatments with costs and effects taken from two randomized controlled trials conducted in different countries. This might be considered a naïve comparison, in which results from individual arms between different trials are compared as if they were from a single trial. However, before assessing the costs and effects of the two trials, in the model of drinking behaviour, several analyses are carried out such as: matching patients on baseline covariates and adjusting outcomes for the same follow-up time. One of the main limitations of propensity score matching is the impossibility to control for unobserved confounding factors. Such problem is present in all observational studies and the comparison drawn here suffers from the same type of biases as those studies.

Second, there is no current definition of standard care for problem drinking in the UK. The appropriate comparator for the purpose of economic evaluation should be the treatment that will most likely be replaced, and should reflect current UK practice. The therapies delivered in the UKATT trial are used as the comparator to Treatment A. In the UKATT study these therapies were delivered in a specialist setting and to a very severe population which may not represent current UK problem drinkers (UKATT Research Team, 2005b). The ideal comparator for Treatment A in the UK would include a broader range of problematic drinkers and therapies delivered in a community setting, by a GP, nurse or psychologist. To date there is little data on the costs and effects of therapies delivered in a community setting. Cost effectiveness data on standard alcohol treatment delivered in the community setting is highly required for the UK. Such information would provide a benchmark to which treatments, such as Treatment A, would need to surpass in order to be deemed cost effective.

Third, the appropriateness of the assumption related to using long-term follow-up data that did not follow the specific treatments evaluated in the long run is explored in the conclusion of Chapter 5. Regarding this case-study one specific limitation is that any other interventions are assumed to be the same across UKATT therapies and the US treatment. For this reason, it is valid to assume that other possible interventions received in each trial are not relevant for the incremental analysis (Drummond et al., 2005c).

Finally, it must be emphasized that the perspective of the study is narrow and many economic benefits might have been left out of the analysis. The costs and benefits of alcohol treatment are realized in multiple sectors such as criminal justice, workplace, transport and so on. For this specific case-study, workplace productivity costs have been overlooked and its inclusion in the analysis would have probably provided stronger evidence for the cost effectiveness of Treatment A

for a less severe population. Also, the inclusion of family and friends costs, such as care giving activities, would have been an important contribution to the cost effectiveness analysis. A broader societal perspective should be part of future extensions of the case-study as the impacts of alcohol are beyond those confined to the health services.

The clinical trial of Treatment A showed that this treatment was more effective amongst men, when comparing Treatment A to placebo (the psychosocial component). It is possible that the study did not have enough power to detect effects amongst females because the number of females recruited was well below the number of males recruited. Even though this is consistent with prevalence patterns in Europe and North America, the women who participated in that study may not be representative of women in general. Another possibility is that the intensive psychosocial component of the placebo did not enable the detection of an added effect of Treatment A in women. The model of drinking behaviour shows that the new Treatment is more cost effective when delivered to a female population. Even though the results from the model cannot be directly compared to the trial results, an explanation for the better long-term cost effectiveness results of Treatment A amongst a female cohort needs to be explored. The results of the subgroup analysis show that when comparing the benefits of Treatment A to UKATT therapies between females and males, the relative gain in utility is higher for females. Perhaps one justification for the better results amongst females is that by modelling the effects of alcohol treatments these effects can be more extensively captured and in fact alcohol treatments can be highly cost effective for females. However, the new treatment was accompanied by an intensive psychosocial component and, when compared to the less intensive UKATT therapies, females might improve more than men because they tend to respond better to a variety of psychosocial interventions (Sanchez-Craig et al., 1989; Schneider et al., 1995). Women are more likely than men to have a history of psychological problems or to perceive alcohol-related problems such as depressed mood as psychological in nature rather than a consequence of substance use (Weisner and Schmidt, 1992). It would be interesting to disentangle the effects of the intensive psychosocial treatment and the pharmacological treatment, Treatment A, when comparing to UKATT therapies. This would enable an understanding of the real reason why females have better results than males in the long term model.

The external validity of the case-study results is related to their generalisability to practical clinical situations. As mentioned, the UKATT trial had a pragmatic design and the Treatment A trial was an efficacy trial. Nevertheless, the UKATT trial population is more severe than the UK problem drinking population. Therefore, the results might not be generalisable to the UK population eligible for Treatment A. In addition, the generalisability of the results might be hampered by the fact that

the UKATT population is matched to the US population and a US-like population is modelled. The application of these particular results will depend on the setting and patients to which treatment A will be delivered. The characteristics of the population modelled should be adapted for another setting. UKATT therapies are used as the comparator to Treatment A, which may or may not be the situation in another country. The clinical effects for both treatments are taken from two randomized trials where therapists were highly trained and experienced and this might not be possible to reproduce in different settings. The perspective on costs is that of the NHS and needs to be adapted if the analysis is conducted in another country.

Overall, this case-study provides an example of how the model of drinking behaviour can be applied to a situation where there is only efficacy data derived from a single trial for a new treatment and where this data comes from a setting that does not correspond to the setting of the analysis. It demonstrates that a cost effectiveness analysis of two alcohol therapies delivered in two clinical trials to different populations and in different jurisdictions can be conducted. The model of drinking behaviour explores cost effectiveness results over the long term, provides useful information for decision makers and deals with the imperfections of the data by incorporating decision uncertainty and value of further research.

Chapter 8. Discussion

Alcohol drinking is associated with various health and social negative problems worldwide. For such an important area of health, it is striking that only 27 full economic evaluations were identified as being published since 1995. Far more economic studies in the field have focused on issues such as the total cost of alcohol misuse. The main aim of this thesis was to explore how future economic evaluations of alcohol treatment could be rigorously conducted in order to provide better information to decision makers.

This thesis identified many issues that make economic evaluations of alcohol treatments particularly challenging: alcohol drinking imposes societal as well as individual costs, alcohol treatment effects are not fully captured in a short term period, there are many alcohol abuse treatment approaches and, there are multiple treatment outcomes with different definitions, interpretations and impact at the societal and individual-level. Therefore, the ability of economic evaluations of alcohol treatment to frame cost effective decisions is currently restrained for two reasons: first, the lack of accumulated evidence that can aid on decision making; second, the lack of rigour in individual studies due to differences in the inclusion of society-level consequences, inconsistencies in measurement and valuation of alcohol-related consequences, lack of agreement on the individual health measure of alcohol treatment, inability to capture long-term effects, and particular technicalities related to economic evaluation studies.

8.1 Summary of the main findings and limitations

Chapter 2 identified all consequences that could be included in an economic evaluation of alcohol treatments. The methods used for identification, measurement and valuation of individual and society-level consequences were given full consideration. The consequences were stratified in a taxonomy with special attention to prevent double counting. The taxonomy was designed to help appraising existing studies and also for guiding in the identification of consequences for economic evaluations of alcohol treatment.

Chapter 3 reviewed the methods for identification, measurement and valuation of costs and outcomes used in previous cost effectiveness analyses of alcohol treatments. The review showed that a societal perspective has never been taken into full account and almost half of the studies totally excluded society-level consequences from their analysis. Previous economic evaluations used short-term data to derive clinical effects and constrained their economic data either by a short-term prospective study or by retrospective collection methods. Many studies have confined treatment effectiveness to abstinence-based measures and alcohol dependent patients. Most of the

full economic evaluations conducted in the past were cost effectiveness analyses where individual-level consequences were not consistently identified, measured and valued. Few studies used a cost utility design and measures of HRQoL capturing life years and morbidity have not been extensively used in the alcohol field. All these drawbacks formed the foundation for the set of recommendations drawn in Chapter 3. Most of these recommendations were pursued throughout the remaining thesis and more specifically through the development of an economic model for the economic evaluation of alcohol treatments.

Chapter 4 presented a framework where long term modelling techniques establish a link between drinking patterns, health consequences and alcohol treatments effectiveness and cost effectiveness. A probabilistic lifetime Markov model using the cohort simulation approach, with QALYs and lifetime costs as the main outcome measures was constructed. The decision analytical model moved away from abstinence-based measures by taking into account the benefits of reduced drinking and change in drinking patterns. The Markov model included mortality, morbidity, and long term costs savings and considered a wider population with alcohol problems, not confined to an alcohol dependent population. The grams of alcohol consumed per day were used as a common natural effectiveness measure. Such consumption-based measure classified the different drinking categories that define the four health states in the Markov model. Defining the Markov states in terms of grams of alcohol consumed per day facilitated modelling alcohol drinking behaviour as a recurrent behaviour with susceptibility for relapse.

The economic model of drinking behaviour is extremely data demanding and needs country-specific data such as: mortality and morbidity rates that vary with age, gender, level of consumption, alcohol-related condition and drinking patterns; alcohol treatment effectiveness data; transition probabilities after treatment; cost data for alcohol-related problems and for the specific treatments evaluated; and utility weights for the Markov states.

UK-specific model inputs have been generated in Chapter 5 and can be used to populate the Markov model for any alcohol treatment assessed in the UK. If the economic evaluation is conducted in another country then the same level of data needs to be drawn for that country.

The Markov model of drinking behaviour requires a separate epidemiological model of lifetime injury and chronic disease mortality and morbidity which in itself is based on numerous assumptions and data requirements. Despite the acknowledged limitations, the approach presented in Chapter 5 allowed the incorporation of patterns of drinking and levels of drinking on mortality and morbidity risks. This allows for more accurate estimates of the cost effectiveness of alcohol because health and economic consequences are estimated based on lifetime drinking behaviour and associated risks.

Previous economic evaluations assumed that treatment effect remains the same over patients' lifetime, which is a strong assumption that this thesis overcame with the calculation of transition probabilities informed by a UK long-term drinking behaviour follow-up study (Taylor et al., 1985). One of the limitations associated with the use of this study is that exposure to other alcohol interventions is assumed to be the same for the compared treated groups in the long run.

UK-specific utilities for the drinking states were generated. The utilities assigned to the Markov states were calculated based on individual patient level data from the UKATT trial. The trial used the EQ-5D instrument with scores valued using a sample of the UK general public. Given that the relationship between Health-Related Quality of Life instruments, such as the EQ-5D, and effectiveness measures have not as yet been studied, attaching utilities to health states defined by consumption levels circumvents making assumptions about this relationship for which there is not yet evidence. However, the utilities estimates were associated with some limitations. It was assumed that utilities could be propagated though lifetime based on the drinking categories on which patients were classified. In addition, the number of patients used for collecting preference values for each Markov state was small and estimates had associated high standard errors. The utilities associated with the Markov states were used in the case-studies to generate a generic outcome measure of health, the QALY. This is considered the appropriate methodology for current decision makers (NICE, 2008) but is not universally accepted (Dolan, 1999). There is a concern that the QALY does not capture all outcomes of interest for a population with alcohol problems.

The economic model of drinking behaviour and the UK-specific data were used in two case-studies presented in Chapters 6 and 7. While both case-studies were cost effectiveness and cost utility analyses that compared two different alcohol treatments in a UK setting, they differed in a number of aspects. The first case-study analysed two treatments that had presented similar costs and effects in a short-term UK multicentre pragmatic randomized controlled trial (UKATT Research Team, 2005a). The long-term analyses enabled drawing more directions in terms of the level of certainty around the cost effectiveness of the two treatments, by gender and age. It also showed that the therapy with a slightly higher probability of being cost effective for a male cohort (MET) had a very low probability of being cost effective for females and was dominated by the more socially-based therapy (SBNT), for all female age groups. The discrepancy of MET and SBNT cost effectiveness according to gender was an extremely interesting result. While it was not clear that MET was the most cost effective strategy for males (high level of uncertainty), it was definitely clear that SBNT was cost effective for females (high level of certainty).

The first case-study used the model to extrapolate the results of the UKATT trial. However, the use of a single RCT as a vehicle for economic analysis and a basis for decision making has been

criticized by some authors (Sculpher et al., 2006). The arguments given for such criticism are the following: 1) failure to compare all relevant options producing a partial analysis; 2) a truncated time horizon, where QALYs gained would only allow for differences in survival duration until the end of the trial; 3) possible lack of relevance to the decision context; 4) failure to incorporate all evidence; and 5) inadequate quantification of decision uncertainty. The application of the model to the UKATT case-study solved many of the arguments against the use of a single RCT for economic evaluations. More specifically, arguments two, three, and five above were solved. It was demonstrated that there is potential for using modelling techniques in a single randomized controlled trial to guide on the decision regarding the choice of the interventions compared in a trial.

However, arguments one and four above were not solved. According to arguments one and four given by Sculpher et al. (2006), a comprehensive evidence synthesis of all psychosocial treatments would seem more appropriate for the model. Some reviews and meta-analyses have been conducted for alcohol treatments (Heather et al., 2006; Ludbrook, 2004; Raistrick et al., 2006) and more specifically for psychosocial treatments of alcohol problems (Burke et al., 2003; Kaner et al., 2007; Lundahl and Burke, 2009; McQueen et al., 2009). However, previous systematic reviews and meta-analysis have pooled data from a very heterogeneous sample of studies regarding the population of interest (e.g., with higher or lower degree of alcohol problems), the setting of the study (e.g., general practice, hospital wards, specialist clinics), the type of intervention (e.g., within psychosocial treatments there is not yet a standard definition of brief intervention), and the health systems organization (e.g., a National Health Service in the UK and private insurance in the US). This thesis did not focus on evidence synthesis of all psychosocial treatments, but it can be foreseen that due to the factors presented above this is particularly challenging in the alcohol field.

The second case-study differed from the first in that it compared two treatments with clinical effects taken from two randomized controlled trials, with short follow-up periods conducted in different countries and with populations with significantly different characteristics at baseline. The cost effectiveness comparison was made possible by first matching the patients in terms of baseline characteristics with the use of propensity score matching techniques. An adjustment for the different follow-up times was done. The model of drinking behaviour compared the matched populations and explored the results over the long term, incorporating decision uncertainty. The model results showed that the new treatment would be a cost effective alternative to standard UK therapies, represented by UKATT therapies, especially when delivered to a less severe cohort of patients and to females. The lower the price of the new treatment the more cost effective it was, achieving ICERs well below the lower bound of the decision maker threshold. In this case-study UKATT therapies were assumed to represent standard UK therapy. However, even if these

therapies are accepted to be the standard approach, it should be recognized that their effectiveness was drawn from a RCT where the population was more severe than what would be expected from UK problem drinkers.

Whilst this thesis dealt with almost all the challenges identified in full economic evaluations of alcohol treatment, there is still one point that could not meet the recommendations set up in Chapter 3. The application of a full societal perspective was not possible due to data limitations on the costs and epidemiological risks associated with the social consequences of alcohol. The model was built from a health care system perspective which does aid decisions where the decision maker does not have any benefit from changes on the levels of consequences borne by others than the person in treatment. However, as explained in this thesis, the extent of externalities, that is the un-compensated consequences to third parties, generates strong normative arguments for the adoption of a broad societal perspective in the economic evaluation of alcohol treatment. A health care perspective could lead to the adoption of a treatment with lower health care costs but higher costs and lower utility to society, which for a wider perspective would lead to an inefficient allocation of resources. With a broader perspective, where social consequences are also taken into account, alcohol treatments may be more cost effective due to the large scope for society-level improvements. It might also be the case that a societal perspective changes the ranking of treatments.

8.2 Recommendations for future research

The limitations to the analyses presented above form the basis of the recommendations for future research.

A keystone of any economic evaluation is the perspective the analyst employs. The perspective of the analysis dictates the range of costs and consequences included in an economic evaluation. Different perspectives foster different outcomes which can result in different resource allocation decisions. This thesis recommends the used of a broader perspective in economic evaluations of alcohol treatment. With a broader perspective, where all consequences, no matter on whom or where they fall are identified, the analyst can also explore the impact of taking a narrower perspective which may be required by a decision maker, for example NICE in England or other health care financing regulators. The taxonomy of alcohol consequences presented in Chapter 2 can help in the identification of the types of consequences that could be measured and valued. The development of consistent methods for the measurement and valuation of the broader consequences of alcohol treatment is a topic for further research. Once these methods are developed and data is generated a societal perspective can then be part of future extensions of the model and of the case-studies.

The follow-up of most clinical studies of alcohol treatments have not surpassed one to two years. Alcohol problems differ from many other health problems for the psychological and social dimensions that characterize them. These special characteristics make the need of long-term analysis even more important, so drinking behaviour can be captured and better understood. Also, in order to take into account the effect of different exposures on drinking behaviour, long-term follow-up studies of the treatments evaluated are required.

An area of research that needs to be investigated is the relationship between QALYs and measures of alcohol consumption. The extent to which improvement in alcohol consumption can be linked with QALYs gained and the time period for this to be detected warrants closer scrutiny. More research should also be done in order to determine whether a small increase in QALYs in the short term persists for longer periods. A longitudinal study, where an alcohol drinking population is followed for a long period and where consumption levels and HRQoL are measured, would help to answer some of these questions.

The results of the first case-study showed clear differences on the cost effectiveness of MET and SBNT by gender. Based on these results, it is recommended that future effectiveness and cost effectiveness analyses of alcohol treatments take into account patient's gender when reporting the results. The heterogeneity on cost effectiveness results by gender is a topic for further research.

For the second case-study, it would have been important to also compare the new treatment with other alcohol treatment alternatives in a community setting. This would inform not only whether the new treatment is cost effective compared with standard therapy, but also which intervention is most cost effective compared with each other. Even though creating a network of evidence comparing several alternatives was out of the scope of this thesis, the economic framework developed in Chapter 4 has the potential to incorporate such analyses.

So far, the model has been developed to use patient-level data as the source of effectiveness. Developing other methods using results already published in meta-analysis is a matter for future research. Whilst further research is required, the results produced in the case-studies can, in the future, be used with a comprehensive synthesis of evidence in this area and so other strategies could be compared to the treatments considered in the model applications.

8.3 Future applications of the model

The model has been applied to a UK setting. The potential for demonstrating the cost effectiveness of alcohol treatments that reduce alcohol consumption will probably be greatly extended if the model is applied to a setting with higher alcohol-related mortality and morbidity rates, i.e. a setting

where alcohol problems have a higher impact compared to other health conditions. Within the WHO European region, the number of deaths and DALYs attributable to alcohol are the highest in Europe C region (Rehm et al., 2009). Europe C is also believed to be the one with the most detrimental patterns of drinking (Rehm et al., 2004). This region encompasses countries such as Belarus, Estonia, Hungary, Latvia, Lithuania, Republic of Moldova, Russian Federation, and Ukraine. These countries have an extremely high prevalence of alcohol dependence and average volume of drinking (Rehm et al., 2006c). Therefore, applying the model of drinking behaviour to these populations will fully depict the effect of treatments that aim at a reduction in alcohol consumption. An application of the model of drinking behaviour to former Soviet Union countries would be of great interest if treatments that aim at reducing consumption are compared to treatments that focus on abstinence or to other health care interventions that compete for the same source of funding.

Current discussions are assessing the use of the model in an ongoing European project. The Alcohol Measures for Public Health Research Alliance (AMPHORA) project, work package 6, is concerned with the public health impact of individually directed alcohol interventions in European countries. The research in this work package is divided into 4 elements and one of them is the secondary analysis of the impact and cost effectiveness of alcohol interventions in Europe. This study aims to conduct a meta-analysis to compare treatment outcomes from brief interventions and specialist interventions between Europe and the rest of the world. This information will be used to assess the cost effectiveness of alcohol interventions in Europe, using the model developed in this thesis.

8.4 Conclusion

This thesis explored the methods used in previous studies, developed and implemented a framework that links drinking patterns, health consequences and the effectiveness and cost effectiveness of alcohol treatments over patients' lifetime. It is hoped that the research conducted throughout this thesis will stimulate further work to bridge the gap between studies and will provide guidance on the conduct of more and better economic evaluations of alcohol treatments.

This thesis contributed to the development of an innovative methodology that deals with many of the difficulties identified in previous studies. It is proved, both theoretically and empirically, that rigorous full economic evaluations can be conducted for the analysis of alcohol treatments.

Appendices

Appendix 1- Scoping strategy

For primary studies, this search is undertaken in a range of relevant databases, such as MEDLINE, EMBASE, CINAHL, PsycLINT, NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) Database.

Appendix 2- Search terms for the methodological review

Search terms used in NHS EED (search conducted on the 20th February 2009):

MeSH Alcohol-Related Disorders EXPLODE 1 2
MeSH Alcohol Drinking EXPLODE 1
MeSH Temperance EXPLODE 1
MeSH Alcohol Deterrents EXPLODE 1
"alcohol drinking"
alcoholism
dispomania
"alcohol consumption"
drink* NEAR excess*
drink* NEAR binge
drink* NEAR heavy
drink* NEAR hazard*
drink* NEAR problem*
drink* NEAR abuse
drink* NEAR misus*
drink* NEAR dependen*
drink* NEAR harm*
alcohol* NEAR excess*
alcohol* NEAR binge
alcohol* NEAR heavy
alcohol* NEAR hazard*
alcohol* NEAR problem*
alcohol* NEAR abuse
alcohol* NEAR misus*
alcohol* NEAR dependen*

alcohol* NEAR harm*

"alcohol intake"

#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27

Search term used in Ovid MEDLINE(R) <1996 to June Week 3 2009>

1 exp "Costs and Cost Analysis"/ (82400)

2 "Value of Life"/ (1918)

3 Economics/ (4946)

4 Economics, Nursing/ or Economics, Medical/ or exp Economics, Hospital/ or Economics, Pharmaceutical/ (10206)

5 or/1-4 (92049)

6 (econom$ or cost$ or pric$ or pharmacoeconomic$).ti,ab. (211115)

7 (expenditure$ not energy).ti,ab. (7686)

8 (value adj1 money).ti,ab. (5)

9 budget$.ti,ab. (7551)

10 or/6-9 (218522)

11 5 or 10 (256051)

12 letter.pt. (345003)

13 editorial.pt. (157702)

14 historical article.pt. (87278)

15 12 or 13 or 14 (582776)

16 11 not 15 (242581)

17 Animals/ (1855341)

18 Humans/ (5020366)

19 17 not (17 and 18) (1233871)

20 16 not 19 (222896)

21 (metabolic adj cost).ti,ab. (324)

22 ((energy or oxygen) adj cost).ti,ab. (1055)

23 20 not (21 or 22) (221855)

24 *Alcohol Drinking/ (12245)

25 exp Alcohol-Related Disorders/ (26846)

26 *Temperance/ (477)

27 Alcohol Deterrents/ (671)

28 exp Self-Help Groups/ (3755)

29 "alcohol drinking".mp. (20904)

30 Alcoholism.mp. (20011)

31 dipsomania.mp. (7)

32 "alcohol consumption".mp. (11894)

33 (drink$ adj excess$).tw. (59)

34 (drink$ adj binge).tw. (48)

35 (drink$ adj heavy).tw. (61)

36 (drink$ adj hazard$).tw. (31)

37 (drink$ adj problem$).tw. (319)

38 (drink$ adj abuse).tw. (10)

39 (drink$ adj misus$).tw. (1)

40 (drink$ adj dependen$).tw. (7)

41 (drink$ adj harm$).tw. (9)

42 (alcohol$ adj excess$).tw. (61)

43 (alcohol$ adj binge).tw. (45)

44 (alcohol$ adj heavy).tw. (20)

45 (alcohol$ adj hazard$).tw. (4)

46 (alcohol$ adj problem$).tw. (1451)

47 (alcohol$ adj abuse).tw. (4908)

48 (alcohol$ adj misus$).tw. (686)

49 (alcohol$ adj dependen$).tw. (4500)

50 (alcohol$ adj harm$).tw. (41)

51 "alcohol intake".tw. (4549)

52 or/24-51 (56921)

53 23 and 52 (2454)

54 Rehabilitation Centers/ (2426)

55 Health Behavior/ (16257)

56 Health Education/ (17506)

57 Preventive Health Services/ (4364)

58 Preventive Psychiatry/ (25)

59 Directive Counseling/ (403)

60 exp Behavior Therapy/ (18354)

61 exp Cognitive Therapy/ (7964)

62 exp Evidence-Based Medicine/ (33317)

63 Hospitalization/ (26490)

64 (Referral and Consultation).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (21707)

65 Health Promotion/ (24792)

66 Health Maintenance Organizations/ (7158)

67 "relapse prevention".mp. (976)

68 "harm reduction".mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1410)

69 (naltrexone or acamprosate or disulfiram or opioid-antagonist).tw. (3630)

70 campral.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (12)

71 anti?craving.tw. (52)

72 dis?lfiram.tw. (506)

73 disulfiram.tw. (506)

74 dissulfiram.tw. (1)

75 disulfuram.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2)

76 "brief intervention".tw. (616)

77 "motivational interviewing".tw. (582)

78 "motivational enhancement therapy".tw. (96)

79 "social behavio?r".tw. (2120)

80 "cognitive behavio?ral therapy".tw. (2355)

81 "aversion therapy".tw. (28)

82 "relapse prevention".tw. (976)

83 "skills training".tw. (1531)

84 treatment.mp. (1322331)

85 or/54-84 (1448580)

86 53 and 85 (1076)

87 limit 86 to yr="2008-2009" (110)

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Appendix 3- Characteristics of the studies reviewed

General characteristics of the 27 economic evaluations: Primary studies

Study ID	Objectives	Population/ Setting	Intervention	Perspective	Ec. Ev./ endpoint*
Alwyn et al., 2004	To assess the cost effectiveness of a psychosocial intervention for use as an adjunct to a home detoxification programme, in comparison to detoxification only.	Patients suitable for home detoxification: delivered in 4 centres. UK.	Home detoxification with brief psychological intervention vs. detoxification only, delivered by Community Psychiatric Nurses (CPNs).	Health care system.	CEA, CCA. Effectiveness included alcohol consumption and alcohol-related problems. No endpoint specified.
Babor et al., 2006	To evaluate the effectiveness and costs of Brief Intervention (BI) for patients screening positive for at risk drinking in Managed Care Organizations (MCOs).	Patients 18 years of age or older. 15 clinic sites within 5 MCO settings. USA.	BI delivered by licensed practioners compared to BI delivered by nurses.	Health service provider perspective.	CEA, CMA. Number of drinks per week.
Barrett et al., 2006	To assess the cost effectiveness of referral to an Alcohol Health Worker (AHW) for alcohol misusing patients attending an Accident and Emergency Department (AED).	Adults drinking hazardously attending an AED in a general hospital in London. UK.	AHWs brief intervention lasting 20 and 50 min versus usual care (an information leaflet "Think About Drink").	Societal perspective.	CEA. Unit reduction in the amount of alcohol consumed per week. ICER presented.
Bischof et al., 2008	To compare a Stepped Care (SC) approach for at-risk consumers and individuals with alcohol use disorders in primary health care settings compared to a Full Care (FC) intervention and a Control Group (CG).	Patients between 18 and 64 years old screening positive were separated into: Alcohol Dependence (AD), Alcohol ABuse (AAB), At Risk (AR) and Heavy Episodic Drinking (HED). German general practices. GERMANY.	SC: a computerized intervention plus up to three 40 min telephone-based interventions depending on the success of the previous intervention; FC: a computerized intervention plus a fixed number of four 30 min telephone-based interventions; CG: untreated.	German health system.	CEA, CMA. Effectiveness included alcohol consumption measures. No endpoint defined.
Fals-Stewart et al., 2005	To examine the clinical efficacy and cost effectiveness of the new Brief Relationship Therapy (BRT). This was a shortened version of Standard Behavioural Couple Therapy (S-BCT).	Heterosexual couples with males seeking treatment for alcohol problems. Male was alcohol dependent (DSM-IV). Female was no substance-abusing. USA.	BRT compared to S-BCT, Individual-Based Treatment (IBT) and Psychoeducational Attention Control Treatment (PACT).	Health service and patient's perspective.	CEA. Percentage Days of Heavy Drinking (PDHD). Average effectiveness/ cost ratios presented.

General characteristics of the 27 economic evaluations: Primary studies					
Study ID	**Objectives**	**Population/ Setting**	**Intervention**	**Perspective**	**Ec. Ev./ endpoint***
Fleming et al., 2002	To describe the 48-month efficacy and benefit cost analysis of Project TrEAT (Trial for Early Alcohol Treatment), a randomized controlled trial of brief physician advice for the treatment of problem drinking.	Men and women ages 18-65. Community-based primary care practices in 10 southern Wisconsin counties. USA.	Two physician visits (15 min sessions 1 month apart) and two nurse follow-up calls (5 min, 2 weeks after each physician session). Subjects in the control group received a general health booklet; as well as those in the experimental group.	Health care and patient's perspective (CEA). Societal perspective (CBA).	CEA, CCA. Effectiveness included consumption. No endpoint defined. CBA: monetary benefits of avoided suffering, pain and reduction in quality of life of victims.
Humphreys and Moos, 1996	To assess the cost effectiveness of using Alcoholics Anonymous (AA) versus professional outpatient treatment.	Patients seeking help for alcoholism, with no previous treatment history. USA.	AA, a self-help and mutual aid programme versus professional outpatient alcoholism treatment.	Health care sector.	CEA, CCA. Four indicators of alcohol problems. No endpoint specified.
Kunz et al., 2004	To examine the cost and cost effectiveness of an alcohol Screening and Brief Intervention (SBI) delivered in an inner city hospital Emergency Department (ED) to an underserved population.	Patients 18 years of age or older present in the ED to receive medical care and screened positively for alcohol problems. USA.	Brief counselling session and a health information packet delivered by Health Promotion Advocates (HPAs) vs. only the packet.	Health service provider perspective.	CEA. Three average cost/effectiveness ratios for three endpoints AUDIT score, number of drinks and percentage of patients heavy drinking.
Lock et al., 2006	To evaluate the effectiveness and cost effectiveness of nurse-led screening and brief intervention in reducing excessive alcohol consumption.	Patients 16 years of age or older, screened with the AUDIT test. 40 general practices. UK.	Screening and brief intervention (5-10 min using the "Drink-Less protocol") by nurses versus standard advice with the leaflet "Think about Drink".	NHS perspective and patients' costs.	CEA, CMA. Alcohol problems and HRQoL measures. No endpoint specified.
Long et al., 1998	To compare effectiveness and cost effectiveness of a 5-week inpatient versus a revised two week detoxification and day-patient regime. The revised programme had a cognitive behavioural orientation.	Males and females with an ICD-10 diagnosis of Alcohol Dependence Syndrome. UK.	A 5-week residential programme (current treatment) was compared with a 2 week in and day- patient programme.	NHS perspective	CEA, CMA Alcohol consumption and related problems. No endpoint specified.

General characteristics of the 27 economic evaluations: Primary studies					
Study ID	**Objectives**	**Population/ Setting**	**Intervention**	**Perspective**	**Ec. Ev./ endpoint***
Nalpas et al., 2003	To analyse and compare the financial cost and effectiveness of alcohol treatment programs in four hospital-based centres, from inpatient stay to follow-up 1 year later.	Alcohol dependent (DSM-IV) patients, 18 years of age or older, admitted for alcohol detoxification. FRANCE.	Four specialized alcohol treatment centres. Each consisted of a protocol that started with an alcohol detoxification period- inpatient or outpatient- and continued with a follow-up period.	French national health insurance service.	CEA. Time without relapse. Average cost/ effectiveness ratios presented.
O'Farrell et al., 1996b	To assess the cost benefit and cost effectiveness of Behavioural Marital Therapy (BMT) as an addition to outpatient alcoholism treatment with or without additional couples group therapy.	Newly abstinent married male alcoholics under outpatient alcoholism counselling. Spouses are non-alcoholic. USA.	BMT with individual counselling compared to individual counselling alone and compared to individual counselling with Interactional Couples Therapy (ICT).	Veterans Affairs Medical Centre perspective (VAMC) (CEA)	CEA. PDA and improved marital functioning. Average cost/effectiveness ratios presented
Parrott et al., 2006	To examine the relationship between service use and outcomes using an economic analysis of two alcohol detoxification programmes in the Smithfield Centre and the Plummer Court. Each programme was compared with no intervention (baseline compared to 6 months after intervention).	Alcohol dependents. Smithfield Centre: direct-access admissions for alcohol detoxification. Plummer Court: all admissions for alcohol detoxification. UK.	Smithfield Centre- 10-day detoxification service staffed by mental health nurses with 24 hour support from a GP and social care interventions. Plummer Court- partial hospitalisation, 3-day inpatient detoxification with counselling, followed by day programme.	Health service and public sector perspective.	CEA and CUA. CEA- PDA, mean DDD and units consumed over 60 days. CUA- QALYs gained. Average cost/effectiveness ratios presented.
Pettinati et al., 1999	To assess the cost effectiveness of inpatient versus outpatient treatment of selected subjects with alcohol dependence.	Subjects with alcohol dependence (DSM-III-R). Non-profit hospital. USA.	Inpatient vs. outpatient treatment. Both treatments were based on the 12-step programme of Alcoholics Anonymous, but inpatient received more treatment hours and attendance at support groups.	Payer perspective.	CEA. Rates of "significant drinking". Average cost/ effectiveness ratio presented.
Rychlik et al., 2003	To determine whether the economic benefit attributable to acamprosate is maintained in the context of standard care using a prospective cohort study design.	Alcohol dependent patients (DSM-IV) prescribed acute detoxification, followed by rehabilitation. GERMANY.	Cohort of patients delivered adjuvant acamprosate treatment (1,998 mg/ day), compared to cohort with no acamprosate treatment.	German health insurance and patient's perspectives.	CEA. Abstinence rate. Average cost/ effectiveness ratio presented.

General characteristics of the 27 economic evaluations: Primary studies					
Study ID	**Objectives**	**Population/ Setting**	**Intervention**	**Perspective**	**Ec. Ev./ endpoint***
Shakeshaft et al., 2002	To examine the effectiveness and cost effectiveness of a Brief Intervention (BI) and Cognitive Behaviour Therapy (CBT) for alcohol abuse in an outpatient, community-based setting.	Clients attending a free, community-based, substance abuse counselling service. AUSTRALIA.	BI (one or multiple sessions of varying length not exceeding 90 min, maximum of six weeks) versus CBT (six 45-minute weekly sessions).	Agency perspective.	CEA. Effectiveness Index (weekly and binge consumption, drinking intensity, number of alcohol-related problems and AUDIT score). Average cost/effectiveness ratios presented.
Sobell et al., 2002	To compare the effectiveness and costs of Motivational Enhancement Personalized Feedback (MEPF) and BDG Bibliotherapy Drinking Guideline (BDG).	Problem drinkers (more than 12 drinks per week or 5 or more drinks on 5 or more days in the past week). CANADA.	MEPF consisted of advice and personalized feedback by post to help reduce consumption. BDG consisted of two informative pamphlets.	Payer perspective.	CEA, CCA. Effectiveness included alcohol consumption. No endpoint specified.
UKATT Research Team, 2005a	To compare the cost effectiveness of Social Behaviour and Network Therapy (SBNT), a new treatment for alcohol problems, with Motivational Enhancement Therapy (MET).	Patients seeking treatment for alcohol problems of all ages above 16. Seven treatment sites. UK.	SBNT (up to eight 50 min sessions) versus MET (three 50 min sessions).	Health service and public sector perspective.	CUA. QALYs gained. ICER presented.
Zarkin et al., 2008	To evaluate the costs and cost effectiveness of the COMBINE (Combined Pharmacotherapies and Behavioural Intervention) study interventions after 16 weeks of treatment.	Alcohol dependent participants (DSM-IV) abstinent for 4 to 21 days. Eleven US clinical sites. USA.	Nine treatment groups: 4 received Medical Management (MM) for 16 weeks with naltrexone, acamprosate or both, and/or placebo; 4 received the same but with Combined Behavioural Intervention (CBI), and 1 received CBI only.	Treatment provider perspective.	CEA. Three ICERs for 3 endpoints: percentage of abstinent days, number of patients avoiding heavy drinking, and number of patients achieving a good clinical outcome.

*The endpoint used in the economic analysis is the one presented; ID, Identification; Ec. Ev., Economic Evaluation; CEA, Cost Effectiveness Analysis; CUA, Cost Utility analysis; CBA, Cost Benefit Analysis; CCA, Cost Consequence Analysis; CMA, Cost Minimization Analysis; ICER, Incremental Cost Effectiveness Ratio

General characteristics of the 27 economic evaluations: Modelling studies					
Study ID	**Objectives/ Model structure**	**Population/ Setting**	**Intervention**	**Perspective**	**Ec. Ev./ endpoint***
Corry et al., 2004	To compare the cost effectiveness of "current" and "optimal" treatments of alcohol dependency and harmful use, each one in comparison with "no treatment".	Hypothetical cohort of the Australian population who met the criteria for an alcohol-use disorder (ICD-10) and who identified it as their main principal complaint. AUSTRALIA.	For current care, harmful use had two or more contacts with the same health professional and treatment either with CBT or counselling, while alcohol dependency additionally required medication. Optimal care was a hypothetical treatment informed by evidence-based practice.	Australian National Health Service.	CUA. Years Lived with Disability (YLD) averted. ICER presented.
Doran et al., 2004	To evaluate the effectiveness and the costs of GPs detecting at-risk drinkers and offering an intervention to modify drinking behaviour. Decision tree.	Hypothetical cohort of patients presenting at a GP for any reason. Patients were at least 14 years of age. At-risk alcohol consumption was defined as a score of 5+ (males) and 4+ (females) to the first three items of the AUDIT questionnaire. AUSTRALIA.	The current level of detection and intervention was compared with four different scenarios: 1) increased rate of detection by 5, 10 or 100%; 2) increased rate of intervention by 5, 10 or 100%; 3) increased rate of effectiveness of the intervention by 5, 10 or 100%; 4) increases in rates of detection and intervention by 5%, rates of intervention and effectiveness by 5%, and rates of detection and effectiveness by 5%.	Australian National Health Service.	CEA. Consumption reduction. Average cost/ effectiveness ratio presented.
Gentilello et al., 2005	To estimate the cost savings resulting from routine provision of BIs to patients in general wards or EDs. Markov model.	Injured patients treated in an ED or admitted to a hospital. Patients were 18 years of age or older, and had either a blood alcohol level ≥ 100mg/dl or a positive result on a standard brief alcohol disorder screening questionnaire. USA.	Patients who screened positive and offered a brief intervention compared to injured patients not screened and not offered the intervention.	Health service perspective.	CEA, CCA No endpoint defined.
Lindholm, 1998	To determine the cost effectiveness of providing alcohol advice in primary health care to reduce alcohol intake from a "high" to a "moderate" level.	Two hypothetical cohorts of 100 men who were 40 years old. One cohort consisted of "heavy drinkers" while the other consisted of "moderate drinkers". SWEDEN.	5 GP visits during 1 year compared to "do nothing" (no advice to reduce alcohol consumption). 25 GP visits during 5 years compared to "do nothing".	Swedish health care system.	CEA. Life years gained. ICER presented.

General characteristics of the 27 economic evaluations: Modelling studies					
Study ID	**Objectives/ Model structure**	**Population/ Setting**	**Intervention**	**Perspective**	**Ec. Ev./ endpoint***
Mortimer and Segal, 2005	To compare the performance of competing and complementary interventions for prevention or treatment of problem drinking and alcohol dependence. Separate Markov models for each intervention.	Brief intervention for problem drinking: heavy drinkers ≥ 19 years old and hazardous drinkers not physically dependent 17-70 years old. Psychotherapy for mild to moderate dependence: patients seeking help for alcohol problems and drinkers 15-59 years old. Drug therapy for detoxified patients with a history of severe dependence: no significant psychological disorder and no coexisting drug use. AUSTRALIA.	Interventions were divided into three clusters of mutually exclusive programs: 1) brief interventions for problem drinking, 2) psychotherapy for mild to moderate dependence and 3) drug therapy adjuvant to counselling for detoxified patients with a history of severe physical dependence.	Payer perspective.	CUA. QALYs. gained. ICER presented.
Palmer et al., 2000	To determine the cost effectiveness of alcohol detoxification with adjuvant acamprosate therapy. Separate Markov models for each disease.	Detoxified alcoholic male cohort with average age of 41 years, 80% with fatty liver, 15% with cirrhosis, 22% with chronic pancreatitis, and 1% with cardiomyopathy at baseline. GERMANY.	Standard counselling therapy versus standard therapy plus 48 weeks of adjuvant acamprosate in detoxified alcoholic patients.	German third-party payer (health insurance).	CEA Life years gained from abstinence. No ratio: acamprosate is dominant.
Schadlich and Brecht, 1998	To determine the cost effectiveness of alcohol detoxification with adjuvant acamprosate therapy. Decision tree with Monte Carlo simulation.	Patients included in the Prevention of Relapse with Acamprosate in the Management of Alcoholism (PRAMA) study (Sass et al. 1996): alcohol-dependent patients, recruited from 12 psychiatric outpatient clinics. GERMANY.	Standard therapy versus standard therapy plus 48 weeks of adjuvant acamprosate in detoxified alcoholic patients. Standard care consisted on counselling or psychotherapy according to routine practices.	German healthcare system.	CEA. Proportion of abstinent alcoholics. No ratio: acamprosate is dominant.
Wutzke et al., 2001	To determine the cost effectiveness of a BI. Decision tree.	Hazardous and harmful drinkers from a BI trial (Gomel et al., 1994): ≥ 16 years of age. AUSTRALIA.	Four training and support strategies compared: control, no-support, minimal support and maximal support.	Health service perspective.	CEA. Life years gained. ICER presented.

*The endpoint used in the economic analysis is the one presented; ID, Identification; Ec. Ev., Economic Evaluation; CEA, Cost Effectiveness Analysis; CUA, Cost Utility analysis; CBA, Cost Benefit Analysis; CMA, Cost Minimization Analysis; CCA, Cost Consequence Analysis; ICER, Incremental Cost Effectiveness Ratio

Appendix 4- Methods for identification, measurement and valuation of individual consequences, societal consequences and treatment under evaluation costs

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Alwyn et al., 2004	1) Alcohol consumption; 2) Dependence; 3) General alcohol-related problems; 4) Social satisfaction; 5) Self esteem.	1) Number of days abstinent in the previous 90 days, drinks per drinking day (1 unit=8g ethanol), total consumption during the 90 previous days (all measured with Form 90), and time to first drink following treatment; measured at baseline, 3 months and 12 months after treatment; 2) SADQ, at baseline and 12 months; 3) APQ, baseline and 12 months; 4) Social Satisfaction Scale, baseline, 3 months and 12 months after treatment; 5) Self Esteem Questionnaire.	Comparison between intervention and control groups. 1) Differences in changes from baseline to 3 months and to 12 months. Number of participants abstinent or moderate drinking (≤ 3 units a day); 2, 3) Differences in changes in score from baseline to 12 months; 4) Differences in changes in score from baseline to 3 and 12 months; 5) Differences in changes in score.
Babor et al., 2006	Primary alcohol consumption: number of drinks per week Secondary alcohol consumption: frequency of heavy drinking (4 or more drinks); "Drinkers Index" Other secondary: Health-Related Quality of life (HRQoL)	Interviews at 3 and 12 months. Alcohol consumption: measured using the AUDIT questionnaire. The primary outcome used the first two AUDIT questions (quantity and frequency), and the secondary used the third AUDIT question. "Drinkers Index" consisted of a summary score of the first three AUDIT items. HRQoL- used the SF-12 for physical and mental functioning.	Changes between baseline and 3 and 12-month follow-up, between the two interventions and between interventions together and comparison group. SF12 was not administered at baseline. Primary: reduction in number of drinks per week. Secondary: decrease in heavy drinking, improvement in the index's score and change in SF 12 (not explicitly showed in the study).
Barrett et al., 2006	Alcohol consumption- alcohol consumed per week.	Number of units of alcohol consumed per week- self-reported using Form 90AQ and the Steady Pattern Grid, at 6 and 12 months follow-up.	Reduction in the number of units of alcohol consumed per week.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Bischof et al., 2008	Alcohol consumption for: all patients, AD, AAB/AR or HED patients, for SC and FC separately, for SC+FC together, and for CG.	Measured at baseline and 12 months follow-up QF estimation. 1) Gram alcohol per day follow-up; 2) Mean difference in gram of alcohol per day baseline to follow-up; 3) Percentage binge criteria at follow-up. Also, regression to compare effectiveness of SC +FC with CG.	AR defined according to British Medical Association; AD, AA defined according to DSM-IV; HD defined according to authors' own criteria. Differences in 1, 2 and 3 between intervention (SC+FC) and CG and between SC and FC. Percentage reduction in alcohol consumption at follow-up with intervention vs. CG.
Fals-Stewart et al., 2005	1) Alcohol-related problems: global relationship satisfaction to female partner; 2) Alcohol consumption.	Measurements at baseline, completion at discharge and every 3 months thereafter for 1 year. 1) Dyadic Adjustment Scale (DAS); 2) Days of heavy drinking- TLFB.	1) DAS score; 2) Percentage days of heavy drinking. Heavy drinking defined as drinking six or more standard drinks.
Fleming et al., 2002	1) Alcohol consumption: mean number of drinks during the past 7 days, number of binge drinking episodes in the past 30 days, any binge drinking in the past month, and excessive drinking in the past week; 2) Health status included: depression, medication use, tobacco use, and illicit drug use; 3) Mortality.	1) Follow-up at 6, 12, 24, 36, and 48 months post intervention, using TLFB methods; 2) Assessed at the follow-up interviews; 3) Obtained through patient follow-up procedures, family members contact, the Social Security Death Index, and the Wisconsin Department of Administration Records Management Section.	1) Reductions in alcohol use by comparing intervention and control groups: differences in 7-day alcohol use and 30-day binge drinking episodes during the last 30 days, changes in the proportions of heavy drinkers and binge drinkers; 2) Change from baseline- not presented; 3) Number of deaths in each group (control vs. intervention).
Humphreys and Moos, 1996	Four indicators of alcohol problems: 1) Alcohol consumption; 2) Alcohol dependence symptoms in the past six months; 3) Adverse consequences of drinking in the past six months; 4) Depression.	Follow-up at one and three years after study entry. 1) Number of days intoxicated in the past month and number of ounces of ethanol consumed on a typical drinking day on the past month (1 US unit=14g=0.5oz); 2) Modified 11-item version of the ADS; 3) Nine-item scale and also from collaterals; 4) Nine-item depression scale from the Health and Daily Living Form.	1) Difference in improvement in alcohol consumption between the two treatments at follow-up; 2, 3, 4) Difference in improvement in scores between the two treatments at follow-up.
Kunz et al., 2004	1) Alcohol-related problems; 2) Alcohol consumption: weekly drinks and heavy drinking.	Measured at baseline and 3 months. 1) AUDIT; 2) Average number of drinks per week and percentage patients heavy drinking in the past month: quantity and frequency questions pertaining to the past 3 months.	1) Drop in AUDIT score; 2) Mean differences in average reduction in weekly number of drinks and in reduction in percentage of heavy episodic drinker, at follow-up between the two groups.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Lock et al., 2006	1) Alcohol-related problems; 2) Alcohol consumption: drinks per drinking day; 3) Drinking problems in older adults; 4) HRQoL for mental and physical health.	Measured at baseline, 6 and 12 months. 1) AUDIT score; 2) TLFB; 3) Drinking Problems Index (DPI) score; 4) SF-12 questionnaire score.	Difference in mean scores between intervention and control (for baseline, 6 and 12 months) and differences in change from baseline to 6 and 12 months and from 6 to 12 months, between intervention and control.
Long et al., 1998	1) Alcohol consumption: days abstinent, intensity of drinking; 2) Alcohol-related problems: alcohol-related life problems, SADQ score; 3) Global Measure of Drinking Outcome and Relapse: alcohol-related consequences and problems-patients were categorized into abstinent, non-problem drinkers, drinking but improved and unimproved groups.	Patients were followed-up at 6 and 12 months after discharge: 1) Percentage of days abstinent, Intensity of drinking (total units consumed-1unit=8g alcohol-during the follow-up period divided by the number of actual drinking days); 2) Alcohol-related life problems (range 0-18), Self-reported SADQ score (range 0-60); 3) Categorization of patients based on: a) Drinkers profile, b) Collateral report, c) Blood test, on intake and at 12-months.	1, 2) Mean values at baseline and follow-up and differences between the groups at 1 year; 3) Differences in the percentages of categorized patients between groups. Blood test: MCV and GGT.
Nalpas et al., 2003	Alcohol status: abstinence or relapse.	Relapse: any alcohol consumption. Evaluations were scheduled at months 3, 6, 9, and 12.	Mean time without relapse.
O'Farrell et al., 1996b	1) Alcohol-related problems: marital satisfaction and marital stability; 2) Alcohol consumption: abstinence.	Measurements 12 months before and 24 months after. 1) Marital Adjustment Test (MAT) was used to assess marital satisfaction, and the number of days separated to assess marital stability; 2) TLFB method.	1) Comparisons between husbands' and wives' MAT scores and percentage of days separated; 2) Comparison between percentages of days abstinent.
Parrott et al., 2006	1) Alcohol consumption variables: percent days abstinent, mean number of drinks per drinking day, total quantity of alcohol consumed by a patient; 2) Alcohol-related problems; 3) Health-related quality of life measures: QALYs and health profiles.	Assessments at baseline and at follow-up 6 months after discharge. 1) Form 90 (covering the previous 60 days); 2) SADQ; 3) Questionnaires SF-12 (PCS and MCS), EQ5D and GHQ.	Mean changes per patient for the questionnaires' scores assessed with a set of regressions. QALYs were calculated using the area under the curve between the EQ-5D score at baseline and 6 month follow-up assuming a linear change over the time period.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Pettinati et al., 1999	Alcohol consumption: significant drinking defined as three or more alcoholic drinks in a sitting and/ or admission to inpatient or detoxification.	TLFB: number of drinking days and whether there was significant drinking on drinking days, during treatment and at 3, 6 and 12 months after treatment.	Differences between the outpatient and inpatient groups in the rate of return to significant drinking following treatment up to 12 months after treatment (survival analysis), intention to treat and treatment completers. Differences between the outpatient and inpatient groups in the rate of return to significant drinking at all 3 follow-up points while covarying subjects for the number of lifetime drinking consequences (hierarchical logistic regression analysis).
Rychlik et al., 2003	Alcohol consumption- Abstinence rates.	Abstinence was assessed by the treating physician.	Abstinent/ not abstinent/ unknown. The patient was assessed as abstinent only if both the patient and the doctor confirmed this.
Shakeshaft et al., 2002	1) Weekly alcohol consumption, National Health and Medical Research Council (1992) criteria, low risk: 28 (males) or 14 (females) standard drinks or less per week, hazardous: 29-42 (males) or 15-28 (females) standard drinks per week, harmful: more than 42 (males) or 28 (females); 2) Binge alcohol consumption: more than six (males) or four (females) standard drinks on any one occasion; 3) Alcohol-related problems; 4) Effectiveness Index.	Baseline and 6 months after intervention measurements. 1) Assessed using a 1-week RD diary; 2) Assessed using the QF index; 3) Assessed using the APQ and a composite measure, the AUDIT questionnaire; 4) Based on 5 drinking outcomes: weekly consumption, number of binge drinking episodes, drinking intensity (number of drinks consumed per week divided by number of drinking days), number of alcohol-related problems and AUDIT score	1) Change in mean weekly consumption and proportion of clients at-risk at pre versus post-test (at risk is hazardous or harmful consumption); 2) Change in mean number of binge episodes reported and proportion of those who reported any binge episode, and the proportion of those who reported 12 or more binge episodes; 3) Change in mean number of problems reported. AUDIT- Proportion of clients scoring 8 or more at post-test, relative to pre-test; 4) A self-reported increase in each drinking outcome: score of 1, no change in outcome: score of 2 and decrease: score of 3. Scores for each treatment outcome were summed.
Sobell et al., 2002	1) Alcohol consumption: drinking days per week, drinks per drinking day, drinks per week, days drinking five or more drinks; 2) Alcohol-related problems.	TLFB questionnaire covering the period of time from initial screening through to 12-month follow-up.	1) Percentage change on mean alcohol consumption measures (1 drink= 13.6g); 2) Percentage change on mean alcohol problems (the number of consequences ranged from 0 to 8).
UKATT Research Team, 2005a	Health-related measure: QALYs.	Participants completed the EQ5D questionnaire at baseline and at 3 and 12 months.	UK population norms for the valuation of health states and linear interpolation to identify the areas under the QALY curve.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Zarkin et al., 2008	Alcohol consumption: 1) Abstinence; 2) Heavy drinking; 3) Good clinical outcome (abstinent or moderate drinking without problems).	1) Percentage of days abstinent; 2) Proportion of patients who did not return to heavy drinking; 3) Proportion of patients who maintained a good clinical outcome.	Differences in: 1) Mean percentage of days abstinent; 2) Proportion of patients who did not return to heavy drinking; 3) Proportion of patients who maintained a good clinical outcome.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Modelling studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Corry et al., 2004	Years Lived with Disability (YLD) averted.	The effectiveness of optimal care was derived from two meta-analyses. For current care, the Australian survey of residents was reviewed.	YLD were calculated as the product of prevalence and disability. The conversion of changes in symptoms severity, expressed as effect sizes, into disability weights used a linear function. The YLD averted for "no treatment" were assumed to be null.
Doran et al., 2004	Alcohol consumption.	Number of at risk drinkers reducing their alcohol consumption after detection and intervention by a GP.	Several published sources were used to populate the model. It was assumed that the rate at which at-risk drinkers consult a GP was similar to that of the general population.
Gentilello et al., 2005	Intoxication or alcohol problems, with injuries requiring ED visits or hospitalization.	Number of patients with subsequent injuries and having to repeat an ED visit or having to repeat hospitalization.	Reduced probability of a patient having to repeat an ED visit or having to repeat hospitalization due to subsequent injuries. A literature review was conducted. Authors' assumptions were applied. The reduced probability was directly calculated by the model, however values were not presented. The authors only considered cost-savings from this reduction.
Lindholm, 1998	Life years gained.	Survival curves were presented to calculate the number of years of life gained in average if heavy drinkers reduce their consumption of alcohol before the age of 40.	Moderate drinkers were assumed to have the same annual age-specific mortality risk as the average figures for Swedish men. Heavy drinkers were assumed to have a doubled mortality risk during the ages 40-70. After the age of 70 years, the two cohorts were assumed to have the same risk. Discount rate 5%.
Mortimer and Segal, 2005	HRQoL: QALYs.	HRQoL gain: proportion of patients drinking either side of a specified threshold at 6 or 12- month follow-up and relapse rates in the base-case.	HRQoL gain directly attributable to behaviour change depends on the severity of alcohol problems as per disability weights from Southard et al. (1997) such that returning problem and dependent drinkers to a "safe" consumption pattern is assumed to imply annual QALY-gains of 0.110 and 0.330, respectively. Discount rate 5%.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Individual outcomes	**Modelling studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Palmer et al., 2000	Life years gained.	Complications of alcoholism modelled: relapse, alcohol-related hepatic disease, acute and chronic pancreatitis, acute and chronic gastritis, oropharyngeal carcinoma, oesophageal carcinoma, alcoholic cardiomyopathy, alcohol-related peripheral neuropathy, alcoholic psychosis, accidental death and suicide.	Probabilities for clinical events were retrieved from published literature, mostly German studies. For each of these complications different events were attributed probabilities which were different if the individual relapsed or abstained. Abstinence rates for the acamprosate-treated cohort were taken from a single long-term study, the PRAMA study (Sass et al., 1996) and projected for 5 years. Life years gained with adjuvant acamprosate over standard therapy calculated from the lifetime model. Discount rate 5%.
Schadlich and Brecht, 1998	Abstinence.	Proportion of abstinent alcoholic at 48 weeks follow-up after a 48-week intervention.	Percentage of patients remaining abstinent at the end of the medication taken from the follow-up period in the PRAMA study (Sass et al., 1996). Discount rate 5%.
Wutzke et al., 2001	Life years gained.	Life years gained was derived by combining the estimates of the impact of the programme if it were implemented nationally with available evidence on the health effects of excess alcohol consumption.	The results of the drink-less trial (Gomel et al., 1994) were used to estimate the number of people who would be screened in GP practice, the proportion of those screened who would be "at-risk" drinkers, and the proportion of "at-risk" drinkers who would be subsequently counselled. Number of lives saved: pre and post-intervention aetiological fractions of alcohol-caused mortality taken from epidemiological sources. Discount rate 3%.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Alwyn et al., 2004	Not taken into account.		
Babor et al., 2006	Not taken into account.		
Barrett et al., 2006	1) Other alcohol services; 2) Hospital services; 3) Primary care services; 4) Other social and non statutory services; 5) Criminal justice; 6) Productivity losses. Mentioned that childcare and travel costs were not included because they were likely to be negligible.	Measurements at 6 and 12 month follow up, based on Parrott (2001) questionnaire. 1) Inpatient days, attendance at outpatient and day patient, contacts with other alcohol support; 2) Attendance at AED, outpatient and day patient, call outs to emergency ambulance and inpatient days; 3) Contacts with GP, practice nurse, district nurse, community psychiatric nurse, psychiatrist, psychologist, occupational therapist, and counsellor; 4) Contacts with social worker, social worker assistant, home help, advice service, solicitor, fire service, and other community service; 5) Contacts with police and probation officer, night in Prison and days in court; 6) Number of days out of work due to alcohol misuse.	1, 2, 3, 4) Average costs: taken from Trust Financial Returns and NHS reference cost from the Department of Health; National unit costs: Netten and Curtis (2002), British Medical Association & Royal Pharmaceutical Society of Great Britain; 5) Government sources: contacts with police- costed using the Metropolitan Police Ready Reckoner; Time spent in prison- costed using the Prison Service Annual Report; 6) Human capital approach (number days taken off work*individual gross daily salary). Unit costs not presented, but quantities of resources presented. Price year 2001/02, inflated using HCHS (Netten and Curtis, 2002). Discounting NA.UK pound sterling.
Bischof et al., 2008	Utilization of formal help: professional advice, alcohol detoxification, rehabilitation treatment or visits to self-help groups.	1) Percentage of patients seeking help at follow-up for SC+FC and CG by AD and AA/ AR subgroups. 2) Percentage of patients seeking help at follow-up for SC and FC by AD and AA/ AR	1) Statistically significance of the difference between SC+FC and CG reported 2) Statistically significance of the difference between SC and FC reported Monetary valuations not reported.
Fals-Stewart et al., 2005	Not taken into account.		

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences		**Primary studies**	
Study ID	**Identification**	**Measurement**	**Valuation**
Fleming et al., 2002	1) Motor vehicle events; 2) Legal events; 3) Medical use; 4) Victims' work loss.	1,2) Motor vehicle and legal events, during the 48-month follow-up period, numbers for treatment and control groups- records from the Wisconsin Department of Justice, Crime Information Bureau (1994, 1999) and the Wisconsin Department of Transportation (1994, 1999); 3) Patients were asked to recall, since last interview. 1) Motor vehicle crash with fatalities, with non-fatal injuries or with property damage only, operating while intoxicated or other moving violations; 2) Assault/ Battery/ Child abuse, Resist/ Obstruct officer/ Disorderly conduct, Controlled substance/ Liquor violation, Criminal damage/ Property damage, Theft/ Robbery, other arrests; 3) days of hospitalization, number of emergency department visits.	Health care utilization/ benefits of avoided health services utilization: Average Medicare reimbursement rates for per day hospitalizations and per emergency department visit- used in the medical care system perspective and societal perspective. Reductions in legal events and motor vehicle accidents- derived from estimates reported in Miller et al. (1996): include direct expenses such as medical care, mental health services, property damage, victim work loss, public service costs, and other monetary losses. Costs of crime and motor vehicle crashes include victims' pain and suffering and reduction in quality of life- used in the societal perspective. Medical care expenses for legal events pertain to health care for victims of crimes. Miller et al (1996) estimated the costs of reduced quality of life caused by crimes or accidents from jury awards of pain, suffering, and morbidity resulting from physical injuries and fear. To avoid the possibility of double counting hospitalizations and emergency room visits resulting from accidents, the estimated medical costs provided by Miller et al. (1996) were excluded from the total cost of accidents. Unit costs not reported separately from quantities of resources. Price year 1993. Discounting was not conducted. US dollars.
Humphreys and Moos, 1996	Additional care: detoxification, inpatient and residential treatment.	Measured at one and three years after study entry. Detoxification- number of days; inpatient and residential treatment- number of days.	Costs for the different services were computed based on published information (Holder et al., 1991). Quantity of resources reported. Unit costs not presented. Price year 1994 dollars. Discount rate 5%. USA dollars.
Kunz et al., 2004	Not taken into account		

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Lock et al., 2006	1) NHS resources; 2) Individuals' costs: travel and time costs, absences from work, property damage or accidents.	Resources use by individual patients reported by self-completion questionnaire, at 12 months follow-up for the previous 12 months. 1) Number of visits: GP and nurse, AED, hospital inpatient, and hospital outpatient; 2) Time travelling, waiting at surgeries and hospitals, and spent in appointments, transport costs, number and length of absences from work, out-of-pocket expenses related to property damage or accidents.	Resource use and mean cost per patient described for health care costs, but not for the individual costs identified. Average patient costs reported but a breakdown of these costs was not given. Unit costs taken from Netten and Curtis (2002). Price year 2001/2002. Discounting NA. UK pound sterling.
Long et al., 1998	Not taken into account.		
Nalpas et al., 2003	Work interruptions related to alcohol problems.	Number of days lost at work due to alcohol problems.	Costs of work interruptions- calculated according to the socioprofessional category and the corresponding salary of governmental employees. Average costs presented. Price year 2000. Discounting NA. Francs, converted to Euros.
O'Farrell et al., 1996b	1) Inpatient hospitalizations (for alcohol detoxification or rehabilitation programs) and alcohol halfway houses; 2) Legal Costs: jail for alcohol-related reasons.	Measurements 24 months after as compared to 12 months before: 1) Days spent in inpatient hospitalizations and in alcohol halfway houses- TLFB drinking interview; 2) Days in jail for alcohol-related reasons (simple arrest-1 day).	1) Per diem rate for hospitalization was taken from the VA Cost Distribution Report; per diem rate for halfway house stays was based on the cost paid on a contract basis by the VA to local halfway houses for VA patients placed there; 2) Per diem rate in jail- reported by the Massachusetts Department of Corrections. Unit and average costs presented. Price year 1992. Discounting NA. US dollars.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences		**Primary studies**	
Study ID	**Identification**	**Measurement**	**Valuation**
Parrott et al., 2006	1) Statutory and non-statutory services; 2) Other health care service; 3) Criminal justice.	Quantities of resource used were recorded from patient questionnaires (baseline and 6 month follow-up, for 6 month pre-baseline and 6 months after the start of treatment). 1) Visits to: social worker, state benefit advisor, housing benefit advisor and other social advisors, and citizens advice; 2) GP surgery visits, GP home visits, Accident and Emergency (no stay), outpatient visits, and inpatient stays; 3) Arrest, Magistrates court/ appearance, County court/ plea.	1,2) National source of unit costs: Netten et al. (1999); 3) Government source of unit costs: Field (1997), HM Treasury (2000), Home Office (1998), Harries (1999) Unit costs presented. Price year 2003/4, inflated using HCHS (Hospital and Community Health Services) index (Netten and Curtis, 2002). Discounting NA. UK pound sterling.
Pettinati et al., 1999	Not taken into account		
Rychlik et al., 2003	Hospitalisations and rehabilitation.	Hospitalisations and rehabilitation were documented retrospectively, over one year, by the physician: number of patients hospitalised, number of hospitalisations and number of hospitalisations/ patient.	Total average costs presented for hospitalisation and rehabilitation, for each cohort, taken from the medical departments. No unit costs presented. Price year 1998/99. Discounting NA. Euros.
Shakeshaft et al., 2002	Not taken into account.		
Sobell et al., 2002	Not taken into account.		
UKATT Research Team, 2005a	1) Health care and alcohol treatment outside the trial; 2) Social services; 3) Criminal justice.	Questionnaire at baseline and 12 months of clients' use over the previous six months. 1) Hospital inpatient/ night, Hospital day patient/ visit, Hospital outpatient/ appointment, Hospital accident and emergency department/ visit, GP at home/ home visit, GP surgery/ consultation, Prescriptions, Community psychiatric nurse/ home visits, Detoxification in primary care/ episode, Alcohol agency- rehabilitation/ night, Alcohol agency-consultation/ appointment, 2) Social services/ contact; 3) Court attendance- Crown court/ appearance, Court attendance- Magistrates court attendance/ appearance	1,2) National source of unit costs: Netten and Curtis. (2002), alcohol treatment: literature (Slattery et al., 2003; UKATT Research Team, 2005b); 3) Government sources of unit costs: HM Treasury (2000), Home Office (1998), Harries (1999) Unit costs and quantities fully presented. Price year 2000/1. Discounting NA. UK pound sterling.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Zarkin et al., 2008	Not taken into account		

Note: This is a summary of the methods used in each individual study. For more detailed information of specific procedures and of the references used see the original source. NA, Not Applicable

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences	**Modelling studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Corry et al., 2004	Not taken into account.		
Doran et al., 2004	Not taken into account.		
Gentilello et al., 2005	Health care use: annual ED injury recidivism (hazard ratio) and annual injury recidivism requiring hospitalization (hazard ratio).	Reduction of subsequent health care use taken from another study by the same authors	Costs of ED visit and of hospitalization- MarketScan database. Unit costs and quantities of resources reported separately. Price year 1998, adjusted with CPI. Discount rate 3%, US dollars. 3 years time horizon.
Lindholm, 1998	Health care costs.	It was assumed that moderate drinkers have the same health care costs per person as the average costs for the Swedish population, while the costs for heavy drinkers were twice as high.	Annual health care costs per age group from The Swedish Council on Technology Assessment in health care. Unit costs and quantities of resources presented separately. Price year 1997. Discount rate 5%. European Currency Units.
Mortimer and Segal, 2005	Not taken into account		

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Economic consequences	**Modelling studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Palmer et al., 2000	Alcohol-related interventions and complications: Relapse, Liver disease, Gastrointestinal disease, Cardiomyopathy, Alcohol psychosis, Peripheral neuropathy.	Cost items used in the model (broken down by event +first 12 month costs following event and annual follow up after first 12 months): Alcohol dependence syndrome, Fatty liver, Cirrhosis, Ascites (non-infected), Ascites (infected), Hepatic encephalopathy, Oesophageal varices (no bleeding), Primary hepatic carcinoma, Liver transplant, Bleeding oesophageal varices (treated by beta-blockers or endoscopic sclerotherapy), Bleeding oesophageal varices (treated by distal spleno-renal shunt), Alcoholic cardiomyopathy, Heart transplantation, Acute gastritis, Chronic gastritis, Acute pancreatitis, Chronic pancreatitis, Oropharyngeal carcinoma, Oesophageal carcinoma, Peripheral neuropathy, Alcoholic psychosis.	Costs for each of the alternative intervention strategies and complications were calculated from published German sources. The mean total lifetime costs by relapse, liver disease, gastrointestinal disease, cardiomyopathy, alcohol psychosis, and peripheral neuropathy were valued for standard therapy alone or with adjuvant acamprosate. Unit costs and quantities of resources not reported separately. Price year 1996. Discount rate 5%. Lifetime model. German Deutschmarks.
Schadlich and Brecht, 1998	Avoided target events, were coded with ICD 9: alcohol dependence syndrome, chronic alcoholic liver diseases, and alcoholic psychoses. The costs for these events were: 1) Case-related hospital treatment costs: hospital and treatment costs; 2) Case-related rehabilitation treatment costs: rehabilitation units and treatment costs.	Number of target events for the acamprosate and standard-care group (1000 hypothetical patients in each group): taken from secondary analysis of epidemiological information, from official and administrative statistics and expert knowledge. 1) Average hospitalisation per ICD position given by the disease statistics of the National Association of Local Sickness Funds; 2) Average duration of rehabilitation according to ICD position.	Follow up was assumed to remain constant over time. 1) Costs per treatment day in hospital given by the Federal Statistical Office (1993 values); 2) Costs per treatment day in rehabilitation units given by the Federal Association of Pension Funds (1992 values). No unit costs presented. Price year 1995. Discount rate 5%. Lifetime model. German Deutschmarks.
Wutzke et al., 2001	Not taken into account		

Note: This is a summary of the methods used in each individual study. For more detailed information of specific procedures and of the references used see the original source. NA, Not Applicable

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Input costs	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Alwyn et al., 2004	Home, inpatient and outpatient detoxification, programmes.	In patient: number of days and follow-ups. Out-patient: number of attendances and follow-ups. Home-based: number of visits and time (minutes) spent on visits and follow-ups.	Unit local costs (Cardiff and Vale Community NHS Trust Finance Department) and unit national costs used (Netten et al., 2001). Pharmacological treatment costs not reported. Unit costs and resources reported. Price year 2001. Discounting NA. UK pound sterling.
Babor et al., 2006	1) Labour costs; 2) Space costs; 3) Media cost.	1) Average number of minutes spent by MCO staff per patient; 2) Square footage occupied by each patient; 3) Number of screening and patient education materials.	1) Weighted average wage per minute; 2) Dollar value of the space. More costs information in another study. Unit costs and quantities of resources not presented. Price year not reported. Discounting NA. US dollars.
Barrett et al., 2006	Treatment costs: AHW and overhead costs (capital, administration, managerial etc.).	Number of interventions and session time plus paperwork and onward referral.	Mid-point of the relevant AHW salary scales including all employer costs and overhead costs (Netten et al., 1998). Unit costs not presented, but resource use presented. Price year 2001/02, inflated using HCHS (Netten and Curtis, 2002). Discounting NA. UK pound sterling.
Bischof et al., 2008	Costs savings of SC vs. FC in an average medical practice.	Average duration of counselling sessions for SC and FC, for all patients and, AD, AA/AR or HED patients separately.	Time spent counselling multiplied by hourly wages. Costs saved per counselled patient with SC reported. Unit costs and average costs not reported. Price year not reported. Discounting NA. Euro.
Fals-Stewart et al., 2005	1) Treatment costs: equipment and overheads, staff (counsellor), space used for treatment and administration, urine tests; 2) Time costs for patient and female partners'; 3) Travel costs for patient and female partners'.	1) Time spent by counsellor and space used for treatment and administration - square footage cost per patient/month. Overheads- divided equally amongst patients at the facility; 2) Measured by session time in attendance logs and self reported time in transit; 3) Miles travelled.	1) Staff time valued with the pay rate (salary+ fringe benefits). Space - square footage cost obtained from a local realtor divided by number of patients; 2) Time costs-pay rate shown on patient pay stubs brought to sessions; 3) Travel costs- mileage reimbursement rate used by the university ($0.35 per mile) or self-reported cost of public transportation used. Resources and unit costs not presented. Price year not stated. Discounting NA. US dollars.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Input costs	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Fleming et al., 2002	1) Clinic costs- supplies (booklets, pencils, etc), overhead-benefit, rent, screening, assessment, interventions, follow-up calls and training sessions for physicians and staff; 2) Patient costs- travel cost and waiting times.	1) Obtained by surveying the manager at each clinic. Average hourly wage for each category of medical personnel (provided by the clinic manager)*per-patient time necessary for the screening, assessment and intervention. Medical personnel included medical records clerks, receptionists, registered nurses, and physicians; 2) Average travel to and from the clinic (travel cost) and waiting times (lost work time) (minutes) assessed through surveys.	1) Clinic costs (used in the medical care system and societal perspectives) - Overheads- assessed at 25% of staff salaries; 2) Patient costs (used in the societal perspective) were determined by occupation data from the Wisconsin Career Information System (1994). The opportunity cost for subjects who were students, homemakers, or unemployed was assumed equal to the average hourly wage rate for all occupations in Wisconsin. Unit costs not reported separately from quantities of resources. Price year 1993. Discounting was not conducted. US dollars
Humphreys and Moos, 1996	Outpatient treatment and AA.	Measured at one and three years after study entry. Outpatient treatment- number of visits; AA- number of visits.	Costs were computed based on published information (Holder et al., 1991). AA free of charge but assigned a specific cost per meeting. Quantity of resources reported but aggregated with other alcohol services. Unit costs not presented. Price year 1994. Discount rate 5%. US dollars.
Kunz et al., 2004	Interventions resources: personnel, supplies and materials, contracted services, buildings and facilities, equipment, patient incentives and "miscellaneous items".	Measurement at follow up and at 3 months. The Drug Abuse Treatment Cost analysis Program (DATCAP) (French et al., 2002) was used to collect resource utilization and cost data. Patient incentives-money given at baseline and follow-up for survey completion.	Total SBI costs, average costs of screening per patient and of brief intervention session per patient were reported. Percentage spent on personal salaries and benefits, on overheads and patient incentives and on "miscellaneous supplies" and equipment were reported. Patient monetary incentive was reported. Unit costs and quantity of resources were not given. Control group costs were assumed to be zero. Price year not reported. Discounting NA. US dollars.
Lock et al., 2006	Treatment costs: 1) Programme materials; 2) Intervention delivery.	1) Allocated to intervention patients using the equivalent annual cost method (materials were assumed to last for 10 years); 2) Nurse time (minutes) per patient.	Programme materials: 6% rate of interest applied. Unit costs and resources reported. Price year 2001/2002. Discounting NA. UK pound sterling.
Long et al., 1998	1) Treatment costs: length of time in treatment; 2) Use of aftercare.	1) Mean period of treatment- days and hours; 2) Use of aftercare- hours of follow-up sessions.	1, 2) Cost per patient= number of hours of inpatient and/ or outpatient days and follow-up sessions, multiplied by the standard rate per day for each type of care. Percentage changes were given, but not unit costs. Price year not reported. Discounting NA. UK pound sterling.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Input costs	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Nalpas et al., 2003	1) Hospitalization for alcohol withdrawal: type of medical visits, drugs, tests, administration, hospital ward and employees and no medical support services; 2) Follow-up after alcohol discharge: stays in the Post Withdrawal Unit (PWU), type of medical visits, biological and medical evaluations, drugs, use of ambulance transportation, social interventions.	1) Fixed costs: hospital ward, no medical support services (nurses, food), and administration expenses. Variable costs: number and type of medical visits, drugs and tests performed during this period; 2) Number and length of stay in PWU (days), sanitary transportation, paramedical acts, laboratory investigations, social interventions (hour), drugs, medical visits (psychiatrist/ psychologist, emergency units, gastroenterologist, general practitioner, other specialist, specialist in alcohol treatment).	1) Fixed costs evaluated by using the lower official refund price from the French national social security service for a 1-day stay, multiplied by the number of days in the unit. Variable costs taken from the French general professional act nomenclature (the price of each medical act was calculated according to its medical code and its financial value). Costs of drugs- public sale prices; 2) PWU- highest cost of a 1-day stay for such a centre*number of days stayed. Ambulance costs calculated according to the official rate. Social interventions- cost of a 1-hr intervention with a social worker. Average and total costs presented. Price year 2000. Discounting NA. Francs, converted to Euros.
O'Farrell et al., 1996b	Treatment costs.	Number of sessions/ participant=Determined from research project attendance logs and progress notes in VA medical records.	Session cost- VA cost accounting information. Unit and average costs presented. Price year: 1992. Discounting not reported. US dollars.
Parrott et al., 2006	Treatment costs: Staff, building, drugs, overheads, non-staff costs and 24 hour GP cover and daily site visits.	Treatment resource use (daily) taken from the centres. Staff included: nursing, management, catering, nursing assistants, relief workers, and administration.	Local costs from the two services: all costs valued at centre prices. Unit costs presented. Price year 2003/04, inflated using HCHS. Discounting NA. UK poundssterling.
Pettinati et al., 1999	1) Treatment costs; 2) Patient costs: transportation to outpatient sessions and wage loss due to treatment uptake.	1) Number of treatment service hours and support groups hours attended each week via interviews with the subject. 2) Transportation costs and wage loss- no details.	Weighted cost-to-charge ratio applied to the billing charges for services to adjust for geographic- or institution-specific charges. Average costs of treatments reported. Some quantities reported separately from costs. Unit costs not reported. Price year not reported. Discounting NA. US dollars.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Input costs	**Primary studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Rychlik et al., 2003	1) Treatment costs; 2) Patient costs- time off work; 3) Patient costs- travel expenses.	1) Use of treatment resources documented by the treating physicians and presented for each cohort: number of physician visits and days of treatment; 2) Evaluated using the human capital approach; 3) Kilometre travelled.	1) Costs calculated according to a standardized evaluation scale in Germany, where all medical interventions are coded; 2) Time off work- for employed patients the salary was used for the calculation of the cost per day off work. Unemployed patients under the age of 65 were attributed gender-specific average income, whereas no cost was attributed to those over 65; 3) Each patient visit was attributed a fixed rate per travel. Unit costs not presented. Price year 1998/99. Discounting NA. Euros.
Shakeshaft et al., 2002	1) Treatment costs: CBT and BI; 2) Training costs: CBT and BI; 3) Resource.	1) Time spent by counsellor; 2) CBT: two half-day training workshops, BI: half-day in house workshop; 3) Number of treatment manuals printed.	1, 2) Treatment and training costs- salary. Average costs presented. Price year not stated. Discounting NA. Australian dollars.
Sobell et al., 2002	Research assistant costs, materials and advertisement costs.	Cost per participant: one year's salary and fringe benefits for a research assistant, one year's charge for a telephone line, and number of: mailed-out feedback material.	The costs and quantities were not presented separately. Prices were taken from the authors' setting. Price year not reported. Discounting NA. US dollars.
UKATT Research Team, 2005a	Treatment costs: 1) Training and supervision; 2) Treatment delivery.	1) Time trainers and therapist spent, use of space and materials; 2) Time therapist spent, space and other resources used at individual sites.	1) Time valued from individual salaries: national source (Netten and Curtis, 2002); 2) Time valued in the same way as training costs. Space and other resources- local costs. Session length and number of sessions were provided. Average cost presented. Price year 2000/01. Discounting NA. UK pound sterling.
Zarkin et al., 2008	Each COMBINE intervention: space, labour, medication, non laboratory (medical history, physical examination, and other assessments) and laboratory costs.	Labour: number of times staff conducted each activity and time spent on each activity (MM, CBI, physical examinations and so on); Medication: number of tablets per day of treatment; Space- not reported; Laboratory- number of tests.	Acamprosate and naltrexone costs: Federal Supply Schedule, unit daily costs presented. Labour cost: median weighted hourly wage. Mean cost of each intervention separated into medication, labour costs of MM and CBI, and costs of laboratory and non-laboratory. Cost methodology detailed in another study. Price year 2007 (updated from the cost study using the CPI). Discounting NA. US dollars.

Note: This is a summary of the methods used in each individual study. For more detailed information of specific procedures and of the references used see the original source. NA, Not Applicable

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Input costs	**Modelling studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Corry et al., 2004	Health services use: alcohol detoxification, relapse prevention and health consultation with a health professional. Identified: Inpatient care, psychiatric care, psychology care, mental health team care, general practitioner care, medical specialist care and pharmaceuticals.	Quantities of resources under the current care option were derived from National Survey of Mental Health and Wellbeing. Quantities of resources used under optimal care were derived from recommendations in the literature. It was assumed that the medication was acamprosate.	Unit costs- derived from national sources: Commonwealth Department of Health and Aged Care (1999) and Medical Benefits Schedule; and a published study. "No treatment" was assumed to have no cost. Unit costs presented. Price year 1997/98, adjusted with CPI. Discounting NA. Australian dollars.
Doran et al., 2004	The only cost included in the analysis was the cost of the GP visit.	GP fees for consultation of less than 20 min and GP consultation lasting at least 20 min but less than 40 min were used.	Unit costs- derived from national sources: Commonwealth Department of Health and Aged Care (2001) and Medical benefits Schedule. Unit costs of the two types of GP consultation were presented. Price year 2000. Discounting NA. Australian dollars.
Gentilello et al., 2005	1) Screening costs: BAC (blood alcohol concentration) test, Brief alcohol-disorder screening questionnaire; 2) Cost of Brief Alcohol Intervention.	1) Number of BAC for all eligible patients and number of brief alcohol-disorder screening questionnaires; 2) Professional expenses and materials. Professional costs- work time per intervention including administrative time, taken from the HMC (Harboview Medical Center, Seattle) brief intervention programme.	1) BAC test- Medicare fee schedule in 2000, Screening questionnaire: cost of paper; 2) Hourly salary range- Bureau of Labour Statistics. Unit costs and quantities of resources presented. Price year 2000, adjusted with CPI. Discount rate 3%. US dollars.
Lindholm, 1998	Intervention costs: 1) Screening; 2) Visit to a GP; 3) Visit to a nurse; 4) GT-test.	1) One screening per person; 2, 3) Number of visits; 4) Number of tests.	1) Value assumed per person; 2, 3, 4) Costs taken from the district of Umea University hospital. Unit costs presented. Price year 1997. Discount rate 5%. European Currency Units.
Mortimer and Segal, 2005	Cost analysis available from the authors upon request. It was noted that patient costs as waiting time and transport costs were excluded.	Incremental programme costs were based on a description of resource use in intervention and control groups obtained from the study reports.	Unit costs and resource use not reported. Price year 2003. Discount rate 5%. Australian dollars.
Palmer et al., 2000	Acamprosate treatment.	Acamprosate treatment for 48 weeks.	Unit cost of acamprosate presented. Price year 1996. Discount rate 5%. German Deutschmarks.

Methods for identification, measurement and valuation of individual outcomes, economic consequences and input costs			
Input costs	**Modelling studies**		
Study ID	**Identification**	**Measurement**	**Valuation**
Schadlich and Brecht, 1998	Acamprosate treatment.	Acamprosate treatment for 48 weeks.	Unit cost of acamprosate presented. Price year 1995. Discount rate 5%. German Deutschmarks.
Wutzke et al., 2001	1) Marketing / recruitment strategy; 2) Providing training and support; 3) Costs of screening and counselling Services; 4) Costs of the intervention.	1,2) Published study; 3) Costs of screening and counselling (no more than 5 min of GP's time per patient); 4) Costs of the intervention- level C consultation by GP (lasting at least 20 min).	1, 2) Published study; 3) Medicare Fee Schedule 4) Costs of the intervention- difference between costs for consultation level C and B. Average costs for each intervention presented. Price year 1996. Discount rate 3%. Australian dollars.

Note: This is a summary of the methods used in each individual study. For more detailed information of specific procedures and of the references used see the original source. NA, Not Applicable

Appendix 5- Markov model features

Model Structure	
Type of model	Markov model
Markov states	5 Markov states: Hazardous drinking (A), Harmful drinking (B), Ex-Hazardous drinking (ExA), Ex-Harmful drinking (ExB) and Death (D)
Time horizon	Lifetime
Cycle length	One year
Model inputs	
Population	The model uses the cohort simulation approach. A base-case population should be specified (age and gender).
Treatment effect	Treatment effect is the change in drinking behaviour, reflected in the flow of patients between the Markov states. This is incorporated with the tp for the first cycle(s). This parameter is specific to the treatments under evaluation
Transition probabilities (tp) informed by clinical study	These transitions are informed by the clinical data by counting the number of patients in each drinking category at baseline and follow-up. The number of model cycles informed by the clinical data depends on the duration of the clinical study.
Transition probabilities for the following cycles	These transitions are informed by country-specific data on the drinking behaviour of patients after treatment uptake. The ideal source of data is a longitudinal study that assesses drinking behaviour after treatment uptake.
Mortality rates	This is country-specific. Mortality rates have two components: alcohol-specific mortality rates and baseline mortality rates. Alcohol-related mortality rates for both injury and chronic diseases causes, by gender, age and drinking category. Baseline mortality rates are age and gender-specific.
Morbidity rates	This is country-specific. Morbidity rates should be calculated for both injury and chronic alcohol-related events. These vary by gender, age and drinking category.
Markov state utilities	Utilities attached to each Markov state are country-specific. Ideally, the utility associated with each drinking category is estimated using general population valuations and a generic preference-based measure.
Discount rate	The model applies an annual discount rate for costs, LYG and QALYs
Model Outcomes	
Years of life	These are calculated by total number of cycles spent in each state, other than the death state. The years of life with each treatment under analysis can be compared and the incremental LYG computed.
Quality adjusted life years	These are calculated by multiplying the time in each state by the utility weights and summing over all cycles. The QALYs associated with each treatment under analysis can be compared and an incremental QALY gain is computed.
Lifetime costs	There are two categories of costs: the treatment costs and Markov state costs. The treatment costs are specific to the treatment under evaluation and the Markov state costs are country and setting-specific. The total costs for each treatment can be compared and an incremental cost computed.
Sensitivity analysis and Heterogeneity	
Probabilistic sensitivity analysis (PSA)	PSA, using Monte Carlo simulation, is incorporated in the model for the input parameters of the model that the results are uncertain about: transition probabilities and utilities.
One-way	Sensitivity analysis on different discount rates and changes in the proportion starting in hazardous or harmful states.
Heterogeneity	The model can assess the impact on the results of modelling different age and gender cohorts (subgroup analysis).

Appendix 6- Transition probabilities from multinomial data: fitting a Dirichlet distribution

Simulation of the Dirichlet distribution can be done in WinBUGS (Bayesian Inference Using Gibbs Sampling for Windows) software, Microsoft Excel, TreeAge DATA and SAS (Briggs et al., 2003). The last three software packages do not include direct representations of the Dirichlet distribution and two approaches can be used to generate a Dirichlet distribution: 1) normalized sum of independent gamma variables and 2) series of conditional beta distributions. The normalized sum of independent gamma variables approach is chosen for sampling from the Dirichlet distribution in Microsoft® Excel. The gamma distribution is constrained on the interval 0 to positive infinity. The gamma distribution is parameterized as gamma (α, β) in Excel, where α is the shape parameter and β is the rate parameter. The expectation and variance of the distribution are expressed as functions of these parameters as:

$\theta \sim \text{gamma}(\alpha, \beta)$

$E[\theta] = \alpha\beta$

$\text{var}[\theta] = \alpha\beta^2$

In order to construct the Dirichlet distribution for generating a probabilistic transition matrix in the model the following two steps are followed:

1) Assigning independent single parameter gamma distributions for each possible transition, where the single parameter (alpha) is the count number, as observed in the data, and the second parameter (beta) is set to 1. In Microsoft® Excel this is defined as: GAMMAINV(RAND(),α, 1), where RAND() is the command for drawing a random value from the gamma distribution in Excel. The reason why GAMMAINV is specified in Excel is because it is the inverse of the cumulative distribution function that gives the expected value when an integrated probability is specified (Briggs et al., 2006).

2) Assigning probabilities for each possible transition by dividing the correspondent random draw by the sum of the random draws within each category.

Appendix 7- Matching the UK and US group

STATA results using "psmatch2" command: Nearest-Neighbour propensity score Matching

```
. *One-to-one, nearest-neighbor propensity score matching, with replacement.
. psmatch2 treatm  age sex employ mcs_Bas pcs_Bas perAbsBas baseline_gramsday, o
> utcome(follow_up_gramsday) logit

Logistic regression                               Number of obs   =        638
                                                  LR chi2(7)      =     280.61
                                                  Prob > chi2     =     0.0000
Log likelihood = -257.21928                       Pseudo R2       =     0.3529

------------------------------------------------------------------------------
      treatm |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   .0425534   .0117074     3.63   0.000     .0196074    .0654994
         sex |  -.2602159   .2443577    -1.06   0.287    -.7391481    .2187164
      employ |   2.260808   .2594842     8.71   0.000     1.752228    2.769387
     mcs_Bas |    .018433    .008925     2.07   0.039     .0009403    .0359256
     pcs_Bas |   .0591141   .0133523     4.43   0.000     .0329441    .0852841
   perAbsBas |  -.0054985   .0046057    -1.19   0.233    -.0145256    .0035286
baseline_g~y |  -.0126934   .0020668    -6.14   0.000    -.0167441   -.0086426
       _cons |  -6.029533   .9850511    -6.12   0.000    -7.960198   -4.098869
------------------------------------------------------------------------------

> ----------
        Variable     Sample |    Treated     Controls   Difference          S.E.
>    T-stat
-------------------------------+----------------------------------------------
> ----------
follow_up_gram~y  Unmatched | 32.5383041   79.9196678  -47.3813636   5.13234474
>     -9.23
                        ATT | 32.5383041   73.5276359  -40.9893318   9.38653434
>     -4.37
-------------------------------+----------------------------------------------
> ----------
Note: S.E. for ATT does not take into account that the propensity score is estim
> ated.
```

psmatch2: Treatment assignment	psmatch2: Common support On suppor	Total
Untreated	437	437
Treated	201	201
Total	638	638

Balancing test: pstest

```
. pstest  age sex employ mcs_Bas pcs_Bas perAbsBas baseline_gramsday
```

Variable	Sample	Mean Treated	Mean Control	%bias	%reduct |bias|	t-test t	t-test p>|t|
age	Unmatched	45.244	41.694	36.2		4.28	0.000
	Matched	45.244	44.579	6.8	81.3	0.75	0.456
sex	Unmatched	.66667	.746	-17.5		-2.08	0.038
	Matched	.66667	.75124	-18.6	-6.6	-1.87	0.062
employ	Unmatched	.87065	.3341	130.9		14.50	0.000
	Matched	.87065	.87065	0.0	100.0	0.00	1.000
mcs_Bas	Unmatched	38.694	31.938	53.4		6.24	0.000
	Matched	38.694	38.28	3.3	93.9	0.33	0.742
pcs_Bas	Unmatched	53.603	46.883	73.9		8.33	0.000
	Matched	53.603	52.837	8.4	88.6	0.99	0.325
perAbsBas	Unmatched	24.017	27.574	-14.5		-1.68	0.094
	Matched	24.017	24.914	-3.7	74.8	-0.34	0.738
baseline_g~y	Unmatched	84.469	138.18	-76.5		-8.11	0.000
	Matched	84.469	75.986	12.1	84.2	1.72	0.087

Weights assigned in the matching process

```
. *How many controls are used and what is the weight ?
. tab _weight if treatm==0
```

psmatch2: weight of matched controls	Freq.	Percent	Cum.
1	58	61.05	61.05
2	18	18.95	80.00
3	6	6.32	86.32
4	4	4.21	90.53
5	2	2.11	92.63
6	1	1.05	93.68
7	1	1.05	94.74
8	3	3.16	97.89
12	1	1.05	98.95
14	1	1.05	100.00
Total	95	100.00	

```
. *95 controls are used, one of them is used 14 times!!! and sum(freq*weight)= 2
> 01, so each US observation is matched to one and just one UK observation- the
> matched sample will have 201 observations from each group
```

List of abbreviations

AA	Alcoholics Anonymous
AAB	Alcohol ABuse
AAF	Alcohol Attribution Factor
AD	Alcohol Dependence
ADS	Alcohol Dependence Scale
AED	Accident and Emergency Department
AHW	Alcohol Health Worker
APQ	Alcohol Problems Questionnaire
AQoL	Assessment of Quality of Life
AR	At Risk
AUD	Alcohol Use Disorders
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood Alcohol Concentration
BDG	Bibliotherapy Drinking Guideline
BI	Brief Intervention
BMT	Behavioural Marital Therapy
BRT	Brief Relationship Therapy
CBA	Cost Benefit Analysis
CBI	Combined Behavioural Intervention
CBT	Cognitive Behaviour Therapy
CCA	Cost Consequences Analysis
CCTV	Closed-Circuit Television
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CG	Control Group
CHD	Coronary Heart Disease
CMA	Cost Minimization Analysis
COMBINE	Combined Pharmacotherapies and Behavioural Intervention
CPI	Consumer Price Index
CPN	Community Psychiatric Nurse
CRA	Comparative Risk Assessment
CRD	Centre for Reviews and Dissemination

List of abbreviations

CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
DAS	Dyadic Adjustment Scale
DDD	Drinks per Drinking Day
DES	Discrete Event Simulation
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders 3rd edition revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
ED	Emergency Department
EVPI	Expected Value of Perfect Information
EQ-5D	EuroQol 5 Dimensions
ER	Emergency Room
FC	Full Care
FEE	Full Economic Evaluation
GBD	Global Burden of Disease
GGT	Gamma-Glutamyl Transferase
GHQ	General Health Questionnaire
GP	General Practioner
HCA	Human Capital Approach
HCHS	Hospital and Community Health Services
HED	Heavy Episodic Drinking
HES	Hospital Episode Statistics
HPA	Health Promotion Advocate
HRG	Health Care Resource Group
HRQoL	Health-Related Quality of Life
HUI	Health Utility Index
IBT	Individual-Based treatment
ICD-10	WHO 10th revision codes International Classification Disease
ICD-9	WHO 9th revision codes International Classification Disease
ICER	Incremental Cost Effectiveness Ratio
ICT	Interactional Couples Therapy
ITT	Intention to Treat
LDQ	Leeds Dependence Questionnaire

List of abbreviations

LYG	Life Years Gained
MAT	Marital Adjustment Test
MCO	Managed Care Organization
MCS	Mental Component Score
MCV	Mean Cell Volume
MEPF	Motivational Enhancement Personalized Feedback
MET	Motivational Enhancement Therapy
MI	Motivational Interviewing
NB	Net Benefit
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NIAAA	National Institute for Alcohol Abuse and Alcoholism
NICE	National Institute for Health and Clinical Excellence
NNM	Nearest-Neighbour Matching
NPV	Net Present Value
PACT	Psychoeducational Attention Control Treatment
PCS	Physical Component Score
PDA	Percentage of Days Abstinent
PDHD	Percentage Days of Heavy Drinking
PLS	Patient-Level Simulation
PRAMA	Prevention of Relapse with Acamprosate in the Management of Alcoholism
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
PTO	Person Trade-Off
PWU	Post Withdrawal Unit
QALY	Quality Adjusted Life Year
QF	Quantity Frequency
QWB	Questionnaire of Wellbeing
RCT	Randomized Controlled Trial
RD	Retrospective Drinking
RR	Relative Risk

List of abbreviations

SADQ	Standard Alcohol Dependence Questionnaire
SBI	Screening and Brief Intervention
SBNT	Social Behaviour and Network Therapy
S-BCT	Standard Behavioural Couple Therapy
SC	Stepped Care
SF-12	Medical Outcomes Study 12- Item Short Form Health Survey
SF-36	Medical Outcomes Study 36- Item Short Form Health Survey
SF-6D	Short Form 6 Dimensions
TLFB	Timeline Followback
tp	transition probability
TrEAT	Trial for Early Alcohol Treatment
TTO	Time Trade-Off
UK	United Kingdom
UKATT	United Kingdom Alcohol Treatment Trial
USA	United States of America
VA	Veterans Affairs
VAMC	Veterans Affairs Medical Centre
WHO	World Health Organization
WTP	Willingness to Pay
YLD	Years Lived with Disability
YLL	Years of Life Lost

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