Alcohol Measures for Public Health Research Alliance (AMPHORA)

Report on the European public health impact and cost effectiveness of early diagnosis and treatment of alcohol use disorders

Deliverable 3.3, Work Package 6

The public health impact of individually directed brief interventions and treatment for alcohol use disorders in European countries

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1. Introduction

In previous meta-analyses, data from European trials have typically been combined with data from the rest of the world, where the health systems in which treatment is delivered may be very different from Europe. Such differences could have important implications on public health policy in Europe as distinct from the rest of the world. The main aim of this work package is to examine more closely the similarities and differences in outcomes between comparable clinical trials conducted in European countries compared to the rest of the world. While these trials may not be fully representative of the typical interventions and treatments provided in different countries, a meta-analysis may provide a better understanding of the variations in treatment outcome in different countries, as well as providing a measure of efficacy of alcohol interventions specifically in Europe. In light of this, the objectives of present meta-analysis are to: firstly, identify and synthesize the relevant published evidence on the impact of brief interventions and specialist treatment for alcohol use disorders; secondly, conduct a meta-analysis of published trials of brief alcohol interventions and specialist treatment for alcohol use disorders conducted in Europe compared to the rest of the world; thirdly, take into account and compare the subject characteristics of patients recruited into clinical trials as defined above between European countries and the rest of the world. The final objective of this work package is to generate an estimate of the typical cost effectiveness of interventions and specialist treatments in Europe based on published research.

1.1 Alcohol related harms in the European region

Globally, alcohol is the third most significant factor for poor health and premature death, following tobacco and high blood pressure (Anderson & Baumberg, 2006). In terms of global health risks, alcohol is ranked as the third most important factor, after childhood underweight and unsafe sex (WHO, 2009). The European region has the greatest burden of alcohol attributable harm, with about 6.5% of deaths and 11.6% of DALYs attributable to alcohol (Rehm et al., 2009). Alcohol consumption rates in Europe are the highest in the world, with an average of eleven litres of pure alcohol consumed each year by adults aged 15 years or older (WHO, 2004).

Alcohol use disorders ranging from hazardous and harmful drinking to severe alcohol dependence, and are likely to require a range of types and intensities of treatment. There is much variability in the effects of alcohol use across countries and regions of the world in terms of the disease burden, and the prevalence of hazardous and harmful alcohol use varies across countries in the European region. The Primary Health Care European Project on Alcohol (PHEPA) assessed the availability of resources for hazardous and harmful drinking across 17 European countries and found that only 57% of Member States had policies on the management of alcohol use disorders, 50% reported specific funding for treatment, and quality of care was monitored in only two countries (PHEPA Project Team, 2009). Additionally, the large inequalities in life expectancy due to alcohol use, particularly for men, directly impede human capital and productivity as well as threaten the cohesion and

stability of the European Union. Based on cost-effectiveness analyses of health strategies designed specifically for the prevention and early identification of hazardous and harmful alcohol consumption, Chisholm *et al.* (2004) have recommended the urgent implementation of evidence-based policies, particularly in the newer Member states of the European Union.

1.2 Brief intervention studies in primary health care and accident and emergency settings

A number of reviews and meta-analyses have reported the effectiveness of brief alcohol interventions in primary health care. It has been found that brief interventions are more effective than standard care (Kaner et al., 2007) and are often equivalent to interventions of greater intensity (Bien et al., 1993; Miller et al., 1995). There is some inconsistency in the literature regarding the efficacy of brief interventions for heavy drinkers. Wilk et al., (1997) found that harmful drinkers who received brief interventions were twice as likely to moderate their drinking compared with heavy drinkers who did not receive any intervention. A subsequent meta-analysis conducted by Poikolainen (1999) of 14 clinical trials conducted in primary care reported less conclusive results about the effectiveness of brief interventions for heavy drinking, particularly in relation to males. And in terms of designing therapeutic intervention, the existing literature is sparse when accounting for the mechanisms that provide greatest change (Nock, 2007).

More recently, attention has been drawn to the emergency department (ED) as a practical setting for identifying and intervening with patients presenting with alcohol related problems and injuries (e.g. Nilsen et al., 2008; Sommers et al., 2006; Dyehouse & Sommers, 1998). Previous studies have indicated that up to 36% of injured patients presenting to EDs show positive blood alcohol concentrations (e.g. Cherpitel, 1993; Soderstrom et al., 1987) and 14% of injured ED patients met criteria for hazardous and harmful drinking (Longabaugh et al., 2001). The ED visit provides a window of opportunity to identify individuals showing hazardous and harmful levels of alcohol consumption (D'Onofrio et al., 2002). Findings have indicated that screening and brief interventions for hazardous and harmful alcohol consumption when administered in the ED and compared to a control condition may be modestly effective in reducing alcohol consumption or consequences (Bazargan-Hejazi et al., 2005; Bernstein et al., 1997; Blow et al., 2006; Longabaugh et al., 2001; Walton et al., 2008; Gentilello et al., 1999; Mello et al., 2005). On the other hand, Daeppen et al., (2007) and D'Onofrio et al., (2008) failed to show favourable treatment effects in trials conducted in the ED.

1.3 Specialist treatments for alcohol use disorders

A comprehensive review and meta-analysis was conducted examining the evidence for effectiveness of the structured psychological therapies, Cognitive Behavioural Therapy and Motivational Techniques, for the National Institute for Health and Clinical Excellence (NICE) Guideline on Diagnosis Assessment and Management of Harmful Drinking and Alcohol Dependence (NICE, 2011). It was found that Motivational techniques were no more effective in sustaining abstinence or a reduction in alcohol intake than other

psychological therapies for example CBT and Twelve Step Facilitation. The NICE guidelines reported that, on the whole, the effectiveness of CBT in the treatment of the harmful alcohol use or dependence of alcohol in comparison to other psychological therapies was minimal. Factors such as the delivery technique, the treatment setting, intensity and length, and the target outcome (abstinence versus controlled drinking) are likely to vary considerably between research studies examining the effectiveness of the same psychological therapy, particularly when considering the diversity of the healthcare systems of the countries in which the studies are conducted (see AMPHORA workpackage 6 Report on the mapping of European need and service provision for early diagnosis and treatment of alcohol use disorders for a comprehensive analysis; Wolstenholme et al., 2013). It is possible that differences in the effectiveness of treatment interventions may therefore be seen when taking into consideration the country in which the research is conducted.

In conjunction with psychological interventions, pharmacological interventions may be prescribed to promote abstinence or a reduction in alcohol consumption. Acamprosate and naltrexone are the most commonly used pharmacological treatments in harmful use or dependence on alcohol and will therefore be focused on in this report. The evidence base for another commonly used pharmacotherapy, disulfiram, is hampered by poor quality trial design, including a lack of patient blinding for ethical and safety reasons (NICE, 2011) and will therefore not be considered in this review. The two medications under consideration have distinct biological mechanisms in the process of relapse prevention. The action of acamprosate is currently not fully understood, but it is believed to act on the glutamatergic system preventing a hyper-glutamatergic state during alcohol withdrawal effecting the negative reinforcement of addictive behaviour (Mann et al., 2009). The consumption of alcohol leads to an increase in the release of endorphins (endogenous opioids) in the brain, which are reported to mediate the positive reinforcing effect of alcohol (Gianoulakis, 2009; 2004). Naltrexone is an opiate receptor antagonist, blocking the release of endorphins caused by alcohol consumption and thus potentially decreasing the rewarding effects of alcohol consumption (Rösner et al., 2010; Swift et al., 1994; Volpicelli et al., 1992). Meta-analyses that have been conducted have shown that acamprosate has a significant but small to moderate effect on maintaining abstinence in clients with alcohol dependence and naltrexone a significant (small to moderate) effect in reducing the risk of relapse to heavy drinking (Maisel et al., 2013; NICE, 2011; Rösner et al., 2010).

1.4 European cost-effectiveness studies of brief interventions and specialist treatment for alcohol use disorders

There are only a few studies dedicated to understanding the economic benefits of alcohol treatment (McCollister & French, 2003). Financial constraints and scarce health care resources point towards cost-effectiveness analyses as increasingly important as clinical effectiveness analyses. Indeed, health care utilisation varies greatly across European countries, as does the nature of services (European Commission, 2004; Wolstenholme et al., 2013). The cost effectiveness differences between European countries are not distinguished from cost-effectiveness analyses compared to the rest of the world. Such differences could have

important implications of public health policy in Europe as distinct from the rest of the world. It is likely that these differences are due to political, financial, practical and ethical considerations. However there is currently a lack of comparative data on variations in alcohol treatment across European countries. Any variation may be a function of the way in which the interventions are delivered (expertise and training of staff), the context of the treatment system and background treatments being provided (e.g. setting, intensity, elements of care), or the characteristics of the subjects recruited into different trials (e.g. severity, demographics), or a combination or interaction between these factors (Drummond et al., 2011).

2. Overall conclusions and recommendations

2.1 Conclusions from the meta-analysis of screening and brief intervention in primary care

The results indicate that in primary care settings at 6 month follow-up, the overall effects of brief intervention on hazardous and harmful drinkers, when compared to a control group, for trials conducted in both Europe and the rest of the world, were significant. Secondly, the sub-group differences of the effects of brief intervention on hazardous and harmful drinkers, when compared to a control group at 6 month follow-up, between trials conducted in Europe compared to the United States, were not significant. Thirdly, the overall effect of brief interventions on hazardous and harmful drinkers group at 12 month follow-up, when compared to a control group, for trials conducted both in Europe and the United States, were significantly in favour of brief intervention. Finally, the results of the meta-analysis indicate that the sub-group differences of the effects of brief interventions on hazardous and harmful drinkers at 12 month follow-up, when compared to a control group, between trials conducted in Europe and the United States, were not significant.

2.2 Conclusions from the meta-analysis of screening and brief intervention in the emergency department

A meaningful interpretation of the results is limited on account of the small number of studies included in the meta-analysis. Despite this, for the studies included, the results indicate that in emergency department settings, the overall effects of brief intervention on hazardous and harmful drinkers at 6 month follow-up, when compared to a control group, for trials conducted in both Europe and the United States, were significant. Secondly, the sub-group differences of the effects of brief intervention on hazardous and harmful drinkers at 6 month follow-up, when compared to a control group, between trials conducted in Europe compared to the United States, were not significant. Thirdly, in emergency department settings at 12 month follow-up, the overall effects of brief interventions on hazardous and harmful drinkers, when compared to a control group, for trials conducted both in Europe and the United States, were significantly in favour of brief intervention. Finally, the results indicate that the sub-group differences of the effects of brief interventions on hazardous and harmful drinkers at 12 month follow-up, when compared to a control group, between trials conducted in Europe and the United States, were not significant.

2.3 Conclusion from the meta-analysis for specialist treatment

A sufficient amount of evidence to enable sub-group meta-analysis for Europe and the rest of the world comparing the effectiveness of the psychological therapies MT and CBT was not available. This was due to heterogeneity in the study methodologies and their measurement and reporting of treatment outcomes. A standardised approach to the measurement and reporting of treatment effects would enable comparability of studies and better estimation of the effectiveness of psychological therapies in different countries.

There was little conclusive evidence provided by the sub-group analysis that there is a significant difference in efficacy of acamprosate and naltrexone according to the country in which it is administered (i.e. Europe versus the rest of the world) with naltrexone being more effective in the rest of the world compared to Europe, and vice versa for acamprosate. This may be partly related to the preponderance of naltrexone studies conducted in the United States compared to Europe, and vice versa for acamprosate. Further investigation into the effect of symptom severity and the impact on treatment outcome for acamprosate and naltrexone taking into consideration the country specific context in which it is administered is required.

2.4 Conclusions on the cost-effectiveness of brief interventions and specialist treatment

Presenting a meaningful comparison and summary of the health economic evidence is difficult on account of the lack of relevant studies and methodological differences across studies including the types of comparator treatments considered, the study populations, and importantly, the costs and outcomes reported. In conclusion there is evidence of the cost effectiveness of both screening and brief intervention for hazardous and harmful drinkers, and in the case of various specialist treatments for people with alcohol dependence. However meaningful comparisons between cost effectiveness research in Europe and the rest of the world was not possible in this review.

2.5 Recommendations

- There is sufficient evidence conducted specifically in Europe to support widespread implementation of screening and brief interventions in both primary care and emergency departments. However in the case of emergency departments there is also evidence of greater barriers to implementation which will need to be overcome to achieve implementation.
- There is sufficient evidence conducted specifically in Europe to support widespread implementation of relapse prevention medications including naltrexone and acamprosate as an important part of the specialist treatment response to alcohol dependence.
- There is a need for more research on the cost effectiveness of alcohol interventions in Europe to strengthen the case for implementation of both SBI and specialist alcohol treatment, including studies which compare interventions across countries.
- There is a need for greater standardisation of treatment trials with agreed methodology in terms of outcome evaluation to allow meaningful comparison between studies and across countries and support future meta-analyses.

3. Meta-analysis of brief interventions for hazardous and harmful alcohol consumption in primary care

3.1 Introduction

European trials have typically been combined with data from the US and the rest of the world, where the health care systems, as well as many other relevant factors including the nature of research participants, may be very different from Europe. The trials mentioned above have generally relied on the same or similar methodologies. However, they have reported different outcomes in relation to levels of improvement following comparable treatments. The precise reasons for these differences are unclear although any significant differences could have important implications for public health policy in Europe as a region distinct from the rest of the world. As the outcomes reported in previous meta-analyses may not be fully representative of the typical interventions provided in different European countries, a meta-analysis may provide a better understanding of variations in treatment outcome in different countries, as well as providing a measure of efficacy of alcohol interventions specifically in Europe.

3.1.2 Aims and objectives

Firstly, to conduct a systematic review of the relevant published evidence on the impact of brief interventions for hazardous and harmful alcohol consumption in primary care health settings; secondly, to conduct meta-analysis of published trials of brief alcohol interventions conducted in Europe compared to the rest of the world; and finally, to take into account and compare the subject characteristics of patients recruited into clinical trials as defined above between European countries and the rest of the world.

3.2 Methods

3.2.1 Search strategy

An initial systematic review of brief intervention in primary care was conducted by Kaner et al (2007). This was supplemented by an identical search for papers published since the original Kaner et al review specifically for this project. The original Kaner review did not however consider differences between studies conducted in Europe compared to the rest of the world. Databases searched include: MEDLINE (1966 to June 2012), Social Sciences Citation Index (1970 to June 2012), Science Citation Index (1970 to June 2012), EMBASE (1980 to June 2012), PsycINFO (1840 to June 2012), CINAHL (Cumulative Index to Nursing & Allied Health Literature - 1982 to June 2012), Cochrane Drug and Alcohol Group specialised register (June 2012), Cochrane Effective Practice & Organisation of Care Group specialised register (June 2012) and the Alcohol and Alcohol Problems Science Database (ETOH) (1972 to June 2012). No language restrictions were imposed. A Medical Subject Headings (MeSH) search strategy was used to search relevant electronic databases up to June 2012

(specific terms, main terms and text headings used are listed in Annex 1). Also hand-searched were the reference lists of key articles and reviews as well as searching the indexes of major alcohol journals. Relevant experts were also contacted to identify any unpublished trials.

3.2.2 Selection criteria

All randomised controlled trials and controlled clinical trials which included a control arm comprising of either an assessment only (screening) or treatment as usual or a minimal intervention (e.g. provision of patient information leaflets) were eligible for inclusion. Studies without a control arm were considered to be ineligible and therefore excluded. The participants were adults aged 16 years and older attending primary care for any reason other than specifically for alcohol treatment. Patients routinely presenting to primary care for a range of health problems and whose alcohol consumption is identified as being hazardous or harmful or who have experienced harm as a result of their drinking behaviour were included. Hazardous and harmful drinking is understood here as regular average consumption of 20g-40g and > 40g of alcohol per day for women and 40g-60g and > 60g per day for men respectively (Rehm et al., 2004). Screening and brief intervention refers to opportunistic screening and early intervention delivered by non-specialist personnel carried out in non specialist settings directed at hazardous and harmful drinkers who are not typically complaining about or seeking help for an alcohol problem (Raistrick et al., 2006; Nilsen, 2010). These interventions might vary in length from 5 minutes to 30/40 minutes, from a single session to more repeat sessions. Control groups vary from assessment only to 'treatment as usual' or minimal intervention such as the provision of an information leaflet.

Studies were included if i) it was a parallel group trial with two or more intervention arms, ii) participants were suitably recruited and selected according to clearly defined and detailed inclusion criteria, iii) participants were randomly allocated to clearly described interventions, iv) participants were hazardous and harmful drinkers; v) brief interventions were applied specifically in primary care settings; vi) if they used standard screening methods at baseline and follow-up such as the Alcohol Use Disorders Identification Test (Saunders et al., 1993); vii) if outcome assessments were provided at follow-up of 6 or 12 months; viii) if adequate descriptions of a priori outcomes appropriate for a meta-analysis were reported, and ix) if the studies reported exclusion and withdrawal rates. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications of one study, or had been updated in more recent publications were subsequently excluded. Excluded studies included those conducted in other health settings and brief interventions for alcohol delivered alongside other health programs. In contrast to the Kaner review, due to heterogeneity of studies conducted in different healthcare settings, we excluded trials conducted in emergency departments. These were considered in a separate systematic review (below). The references to included studies and to those that were potentially relevant but did not meet the inclusion criteria are mentioned below.

3.2.3 Types of participants

Adults aged 18 years and older attending primary care for any reason other than specifically for alcohol treatment. Patients routinely presenting to primary care for a range of health problems and whose alcohol consumption is identified as being hazardous or harmful or who have experienced harm as a result of their drinking behaviour.

3.2.4 Identification of included studies

Retrieved papers were selected for inclusion based on the criteria outlined above. The inclusion criteria were piloted on the first ten papers generated from the search strategy. One reviewer verified all studies excluded at the second stage of the review to ensure relevant studies were included. Any disparities between the two reviewers on the appropriateness of study for inclusion were settled by a third reviewer. Two reviewers independently extracted data and assessed trial quality. All retrieved references were managed within EndNote Version 5 for Windows program (Thomson Reuters, 2011).

3.2.5 Risk of Bias

Data was subsequently added to a data extraction recording form and a risk of bias form. The risk of bias form assessed selection, performance, attrition and detection bias. Two reviewers independently evaluated the quality of each study following standards recommended by the Cochrane Collaboration Systematic Review for Interventions. Study features were assessed based on whether there was i) a random sequence generation; ii) allocation concealment; iii) attrition bias; iv) blinding of assessors; v) a priori statement of outcomes and comparability at baseline and post-intervention follow-up. In terms of blinding, in trials of psychological therapies it is generally considered difficult to blind participants or mask clinicians to the treatment condition which may possibly result in performance and/or detection bias. Failing to conceal treatment allocation to participants and treatment providers may amount to an overvaluation of the treatment effect (Schulz et al., 1995; Moher et al., 1998). Nevertheless, it still may be possible in clustered randomised trials, and so the extent and type of blinding was duly noted i.e. a double blinding of both participant and clinician, a single blinding or whether blinding and masking was unclear. Also noted was whether the investigators were blinded to treatment allocation at assessment outcome.

3.2.6 Statistical methods

Based on previous work conducted by Kaner et al., (2007), outcome data for quantity of alcohol consumed in a specific time period (for days, multiplying by seven, and for months, multiplying by fifty-two divided by twelve) was converted to grams of pure ethanol per week, if required (see Annex 8.3 for Conversion

Table). Standard drinks were converted to grams using the conversion factor reported in the paper, or when unreported, using conversion factors for the specific country (Miller et al., 1991; Kaner et al., 2007). For outcomes, the standardised mean difference and standard deviation between the final value of the outcome measure for quantity of alcohol consumed for the treatment group and control group were calculated. When standard deviations were not reported (Fernandez et al., 1997; Huas et al., 2002; Ockene et al., 1999; Romelsjo et al., 1989), change scores were used or standard deviations were imputed (Kaner et al., 2007). When standard deviations were incalculable from standard errors or confidence intervals, the trial was excluded from the analysis.

For continuous outcome measures, the type of statistical method used was an inverse variance model to measure the effect of treatment using standardised mean differences. The extent of heterogeneity between trials was calculated using the I^2 statistic (Higgins & Thompson, 2002; Higgins & Green, 2011) where statistical significance of heterogeneity was checked using P-values from χ^2 tests (Deeks, Altman & Bradburn, 2008). Thresholds for the interpretation of I^2 are as follows: 0% to 40%: might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, 75% to 100%: considerable heterogeneity. A random effects model was used to account for the heterogeneity across populations and interventions between trials. Forest plots are presented with trials arranged by the country in which they were conducted – subgrouped by Europe or the rest of the world. The analysis was conducted using Review Manager (RevMan, 2011)

3.3 Results

3.3.1 Excluded studies

McIntosh et al., (1997), Seppa et al., (1992), Casset et al., (2008) did not report the corresponding standard deviation and were excluded from the meta-analysis.

3.3.2 Studies by country

For primary care, 24 studies (reported in 28 papers) were included in the review. Where necessary, one key reference was used for multiple reports of the same trial. Overall, fifteen trials took place in Europe and nine trials took place in the rest of the world, eight of these in the United States (Table1 section 3.3.3).

3.3.3 Description of characteristics of subjects

Table 1: Description of study characteristics

Study	Country	Sex	Number of Cases	Type of Sample
Europe				
Aalto et al., 2000	Finland	Female/Male	Randomised = 414	Aged 20–60 years. 71% male. Mean age = 41.6
Altisent et al., 1997	Spain	Female/Male	Randomised = 139 (75 intervention group and 64 control)	Aged 15-75 years. Mean age = 45.
Beich et al., 2007	Denmark	Female/Male	Randomised = 906 (442 intervention group and 464 control)	Aged between 18-64 years. Mean age = 37.
Cordoba et al., 1998	Spain	Male	Randomised = 229 (104 Intervention group and 125 control)	Mean age = 36.5; 95.6% employed; 70.1% married
Diez Manrique *et al.*,2002	Spain	Male	Randomised = 1022 (592 Intervention group and 430 Control group)	Aged 18-65 years. Mean age = 42.4
Fernandez et al., 1997	Spain	Male	Randomised = 152 (67 Intervention group and 85 control group)	Aged 18–64 years. Mean age = 40.3
Huas et al., 2002	France	Male	Randomised = 541	Aged 18-65 years. Mean age = 51.8

Heather et al., 1987	UK	Female/Male	Randomised = 104	Aged 18–65 years. 75% Male. Mean age = 36.4 years
Kaner et al., 2013	UK	Female/Male	Randomised = 756 (251 patient information leaflet, 251 brief advice and 254 lifestyle counselling)	Mean age = 45. 62% Male. 92% White.
Lock et al., 2006	UK	Female/Male	Randomised = 127 (67 Intervention Group and 60 Control Group)	Aged 16 years plus. 50% Female. Mean age = 44.1
Romelsjo et al., 1989	Sweden	Female/Male	Randomised = 83 (41 Intervention group and 42 control)	Aged 18-64 years. 84% Male. 86% Employed. Mean age = 46.3.
Rubio et al., 2010	Spain	Female/Male	Randomised = 752 (371 Treatment Group, 381 Control)	Aged 18-65 years.
Scott & Anderson, 1991 /Anderson & Scott, 1992	UK	Female/Male	Randomised = 226 (113 Intervention Group and 113 Control)	Aged 17-69 years. 68% male. Mean age = 44.7
Wallace *et al.*, 1988	UK	Female/Male	Randomised = 909 (450 Intervention Group and 459 Control Group)	Aged 17-69 years. 71% male. Mean age = 42.4 years

Rest of the World				
Chang et al., 1997	US	Female	Randomised = 24 (12 Intervention group and 12 standard care	Aged 18 plus. Mean age = 39.3. 45.9% Black, 54.2% White
Curry et al., 2003	US	Female/Male	Randomised = 307 (151 intervention and 156 control)	65% male, mean age 46.9 years; 16% unemployed; 91% post-high school education; 68% income = $35,000/ye; 80% Caucasian
Fleming et al., 1997	US	Female/Male	Randomised = 774 (392 Intervention group and 382 Control group)	Aged 18-65 years. 482 males and 292 females
Fleming et al., 1999	US	Female/Male	Randomised = 158 (87 Intervention group and 71 control)	Aged 65-75 years. 66% male
Fleming et al., 2004	US	Female/Male	Randomised = 151 (81 Intervention group and 70 control group)	Aged 30- 60 years. 45% male. Mean age = 48.7
Maisto et al., 2001	US	Female/Male	Randomised = 301 (100 Brief Advice Group, 100 Motivational Enhancement Group and 100 Standard Care Group)	Aged 21 years plus. 70% Men. Mean age = 45.6. 77% White, 22% Black. 60% Employed.

Ockene et al., 1999/ Reiff-Hekking et al., 2005	US	Female/Male	Randomised = 530 (274 Treatment Group and 256 Control)	Aged 21-70 years. 64.7% male. 94.6% White. Mean age = 43.9
Richmond et al., 1995	Australia	Female/Male	Randomised = 378 (96 Minimal Intervention, 93 No Intervention, 93 No Assessment and 96 Alcohol Screen)	Aged 18–70 years. Mean age = 37.7
Senft et al., 1997	US	Female/Male	Randomised = 516 (260 Intervention Group and 256 Control)	Aged 21 years plus. 71% male. 82% white. Mean age = 42.4

The total combined number of participants included at 6 months follow-up was 3671 and at 12 months was 5049 (see Figures 1 and 2 for numbers of participants in experimental and control groups per trial per region).

6 Month outcomes

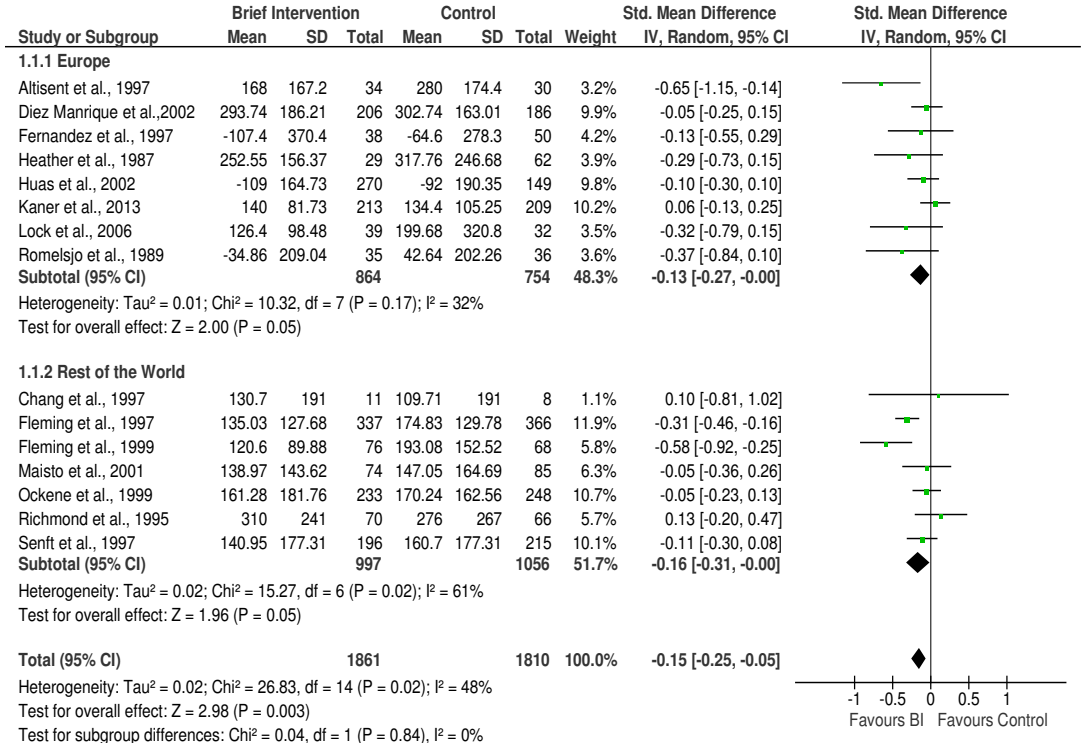
When the European data on outcomes for brief alcohol intervention in primary care at 6 month follow-up were pooled (see Figure 1), a small effect size was observed in terms of the reduction in grams of alcohol per week, which was marginally statistically significant at the 95% significance level (SMD = -0.13; Z = 2.00; *P* = 0.05). There was moderate heterogeneity between the pooled European trials (I^2 = 32%) which was not significant. The test for subgroup differences between Europe and the rest of the world at 6 month follow-up was not significant and the heterogeneity between the subgroups was not statistically substantial. Combining all the available data sets for trials conducted in the rest of the world showed a small effect size for brief intervention group at 6 month follow-up, which was marginally significant (SMD = -0.16; Z = 1.96; *P* = 0.05). Substantial heterogeneity was observed for trials conducted in the rest of the world and this was statistically significant (*P* = 0.02). Overall, the meta-analyses indicated that participants receiving brief intervention drank less alcohol per week than those who were allocated to the control condition, and this difference was statistically significant (SMD = -0.15; Z = 2.98; *P* = 0.003).

12 Month outcomes

For the European trials, the meta-analysis showed a statistically significant small effect size for brief alcohol intervention in primary care at 12 month follow-up for reduction in grams of alcohol consumed per week (SMD = -0.19; Z = 2.67; *P* = 0.008 – see Figure 2). Substantial heterogeneity was found between the European trials (I^2 = 71%) which was statistically significant (*P* = 0.001). The meta-analysis results showed a small effect for the brief alcohol interventions group at 12 months in trials conducted in the rest of the world (SMD = -0.18; Z= 1.78; *P* = 0.08). This effect size was similar to that found in European studies but was not statistically significant due to the smaller pooled sample size of rest of the world studies compared to European studies. Substantial heterogeneity (I^2 =72%) was found and this was statistically significant for trials conducted in the rest of the world (*P* = 0.003). The test for subgroup differences of effects for brief alcohol interventions between Europe and the rest of the world at 12 months was not statistically significant. Overall, substantial heterogeneity was found for all trials (I^2 =69%) which was statistically significant (*P* = 0.0001). The overall effect size for brief alcohol interventions in reducing grams of alcohol consumed per week at 12 month follow-up was small yet statistically significant (SMD = -0.18; Z = 3.36; *P* = 0.0008).

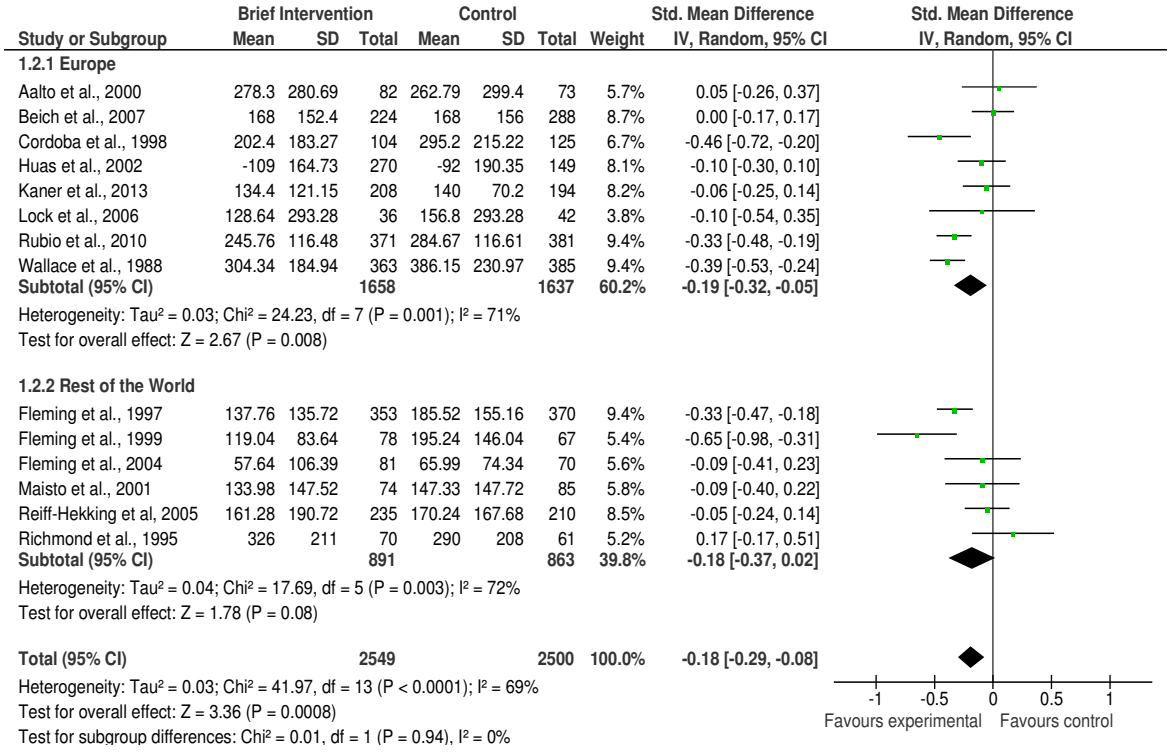
3.3.4 Standardised mean difference in alcohol consumption at 6 months

Figure 1. Forest plot taken from primary care meta-analysis. Estimated standardised mean difference (with standard deviation) of final quantity value for alcohol consumption in grams per week at 6 months follow-up between brief intervention and control groups in included trials for the Europe region and the rest of the world.



3.3.5 Forest plot of standardised mean difference in alcohol consumption at 12 months

Figure 2. Forest plot taken from primary care meta-analysis. Estimated standardised mean difference (with standard deviation) of final quantity value for alcohol consumption in grams per week at 12 months follow-up between brief intervention and control groups in included trials for the Europe region and the rest of the world.



3.4 Discussion

The results presented here show that a statistically significant difference does not exist between the outcomes of brief intervention for trials conducted primary care settings in Europe compared to the rest of the world in terms of alcohol consumption at 6 and 12 month follow-up.

In the European trials at six month follow-up, a marginally statistically significant difference indicated an effect in favour of brief intervention for hazardous and harmful drinkers when compared to the control group. There was a moderate level of heterogeneity detected in the European trials at six months, three of which were conducted in Spain, three in the UK, one in France and one in Sweden. All trials included subjects of both sexes, the majority of which were white middle-aged men. Of the trials included for the rest of the world at six month follow-up, six were conducted in the United States and one was conducted in Australia. A moderate level of heterogeneity was detected between these trials, and the effect observed for the brief

intervention versus control group was marginally significant. The majority of subjects included in the US trials at six month follow-up were white, middle-aged males. The test for subgroup differences between European and the US trials was not significant, though the overall effect for all trials combined significantly favoured brief intervention compared to the control group at six month follow-up.

In the European trials at 12 month follow-up, a significant effect in the reduction of alcohol consumption was observed for the brief intervention group when compared to the control group. A moderate level of heterogeneity was detected between the European trials, three of which were conducted in Spain, three in UK, one in Denmark and one in Finland. However, despite including subjects of both sexes, the majority of subjects included in the European trials were middle-aged white males. A moderate level of heterogeneity which was statistically significant was detected in the trials conducted in the rest of the world at 12 month follow-up. All trials were conducted in the United States apart from one, which was Australian, and the overall effect size of brief intervention compared to the control condition was not significant. Similar to the European findings at 12 month follow-up, the overwhelming majority of subjects included in the trials conducted in the US and Australia were white, middle-aged males. The test for subgroup differences between European and the US and Australian trials at 12 month follow-up were not significant. The combined analysis showed a significant difference in favour of brief intervention.

There are a number of important issues concerning the generalisability of positive results from the special research conditions of clinical trials to primary care populations (Drummond, 1997). In some studies potential flaws have been noted in the procedural design of previous controlled trials such as not all of the physicians contacted to screen and deliver the brief intervention have agreed to participate, indicating that only those who demonstrated motivation and willingness were included in the study (e.g. Fleming et al., 1997). In which case, the results will be more an evaluation of interventions delivered by motivated practitioners. In another study, participants were recruited by a postal questionnaire from a sample taken from an age-sex register (Wallace et al., 1988) which could have led to a selection bias that is not representative of a true general practice population (Heather, 1995).

Heather (1995; 2002) suggests that brief interventions delivered naturalistic settings are likely to show smaller effects than efficacy studies indicate. In all cases, it seems some of the purported benefits of brief interventions could be lost when translated from a special research condition to the natural conditions of typical clinical practice. Indeed, a common criticism of brief intervention trials is that they are efficacy studies (optimizing internal validity) rather than pragmatic trials. Therefore, as Drummond et al., (2009) point out, a more appropriate methodology for evaluating effectiveness might be to involve a pragmatic balance between internal and external to provide a better indication of 'naturalistic effectiveness'.

There are often systematic biases particularly associated with the population under study. In this case, across both the European trials and the trials conducted in other regions of the world, the majority

focused on middle-aged, male drinkers with other social groups drastically under-represented. This may limit the generalisability of the results. In terms of sex differences, overall pooled findings for males and female outcomes might result in more weight being accorded to the trial, but is unlikely to result in any major differences (Kaner et al., 2007). In addition, most of the results were generated from self-report data, which if collected appropriately with validated measures has been regarded as appropriate for research purposes, as well as being less intrusive for participants (Babor et al., 2000). Further statistical heterogeneity between trials exists possibly on account of the screening instruments used, the populations included and the types of assessments and brief interventions delivered to the experimental and control groups. Additionally, as the optimal intensity of brief alcohol intervention for clinical trials is currently unclear, this was reflected in the variability of brief intervention included trials. However, the recent meta-analysis (Kaner *et al*. 2007) found no significant additional benefits of longer brief intervention compared to shorter brief interventions, a result recently confirmed by the SIPS trial which was purpose designed to test the relative effectiveness of brief interventions of different intensity in a pragmatic trial (Kaner et al., 2013). Finally, the difficulty in blinding participants and researchers is potentially an important source of bias.

3.5 Summary

The meta-analysis of trials of screening and brief intervention in primary care indicates the following:

- Firstly, in primary care settings, the overall effects of brief intervention on hazardous and harmful drinkers, when compared to a control group at 6 and 12 month follow-up, for trials conducted in both Europe and the rest of the world, are significant. Therefore the effects of brief intervention persist beyond the initial improvements seen at 6 months.

- Secondly, the subgroup differences of the effects of brief intervention on hazardous and harmful drinkers, when compared to a control group at 6 and 12 month follow-up, between trials conducted in Europe versus the United States, are not significant. Therefore brief interventions are equally effective in Europe and the rest of the world (primarily the US).

- Thirdly, tests of heterogeneity indicate that trials conducted in Europe are less heterogeneous than those conducted in the rest of the world (primarily the US). However this different in heterogeneity is only seen at 6 and not 12 month follow up.

4. Meta-analysis of brief interventions for hazardous and harmful alcohol consumption in the emergency department

4.1 Introduction

Existing evidence for the efficacy alcohol screening and brief intervention in unselected hazardous and harmful drinkers attending ED is limited to six trials (Drummond et al., under review). Further systematic reviews of emergency department attenders have been published including studies conducted in trauma patients (Kaner et al., 2007; Havard et al., 2008; Forsythe et al., 2011) but none have previously examined differences between Europe and the rest of the world. As mentioned previously, European trials have typically been combined with data from the US and the rest of the world, where the context of treatment, as well as many other contributing factors, may be very different from Europe. Brief alcohol intervention trials conducted in the ED have generally relied on the same or similar methodologies, but have reported different outcomes in relation to levels of improvement following comparable treatments. The precise reasons for these differences are unclear although these differences could have important implications of public health policy in Europe as a region distinct from the rest of the world. As the outcomes reported in previous meta-analyses may not be fully representative of the typical interventions provided in different European countries, a meta-analysis may provide a better understanding of variations in treatment outcome in different countries, as well as providing a measure of efficacy of alcohol interventions specifically in Europe.

4.1.1 Aims and Objectives

Firstly, to identify and synthesize the relevant published evidence on the impact of brief interventions for hazardous and harmful alcohol consumption in ED settings; secondly, to conduct a meta-analysis of published trials of brief alcohol interventions conducted in Europe compared to the rest of the world; and finally, to take into account and compare the subject characteristics of patients recruited into clinical trials as defined above between European countries and the rest of the world.

4.2 Method

4.2.1 Search strategy

Databases searched include: MEDLINE (1966 to June 2012), Social Sciences Citation Index (1970 to June 2012), Science Citation Index (1970 to June 2012), EMBASE (1980 to June 2012), PsycINFO (1840 to June 2012), CINAHL (Cumulative Index to Nursing & Allied Health Literature - 1982 to June 2012), Cochrane Drug and Alcohol Group specialised register (June 2012), Cochrane Effective Practice & Organisation of Care Group specialised register (June 2012) and the Alcohol and Alcohol Problems Science Database (ETOH) (1972 to June

2012). No language restrictions were imposed. A Medical Subject Headings (MeSH) search strategy was used to search relevant electronic databases up to June 2012 (specific terms, main terms and text headings used are listed in Annex 1). Also hand-searched were the reference lists of key articles and reviews as well as searching the indexes of major alcohol journals.

4.2.2 Selection criteria

The types of studies included all randomised controlled trials and controlled clinical trials which included a control arm comprising of either an assessment only (screening) or treatment as usual or a minimal intervention (e.g. provision of patient information leaflets) were eligible for inclusion. Studies without a control arm were considered to be ineligible and therefore excluded. The participants were adults aged 16 years and older attending the emergency department for any reason other than specifically for alcohol treatment. Patients routinely presenting to emergency departments for a range of health problems and whose alcohol consumption is identified as being hazardous or excessive or who have experienced harm as a result of their drinking behaviour were included. Hazardous and harmful drinking is defined here as regular average consumption of 20g-40g and > 40g of alcohol per day for women and 40g-60g and > 60g per day for men respectively (Rehm et al., 2004). The types of interventions were individually directed brief intervention refers conceptually to opportunistic screening and early intervention delivered by non-specialist personnel carried out in non-specialist settings directed at hazardous and harmful drinkers who are not typically complaining about or seeking help for an alcohol problem (Raistrick et al., 2006; Nilsen, 2010). These interventions might vary in length from 5 minutes to 30/40 minutes, from a single session to multiple sessions. Control groups typically comprise assessment only, or 'treatment as usual' or a minimal intervention such as provision of an information leaflet.

4.2.3 Included Studies

Studies were included if i) it was a parallel group trial with two or more intervention arms, ii) participants were appropriately recruited and selected according to clearly defined and detailed inclusion criteria, iii) participants were randomly allocated to clearly described interventions, iv) participants were hazardous and harmful drinkers not selected for specific diagnosis or presentation (i.e. general emergency department attenders rather than only injured attenders; v) brief interventions were applied specifically in the emergency department; vi) used standard screening methods at baseline and follow-up such as the Alcohol Use Disorders Identification Test (Saunders et al., 1993); vii) outcome assessment was provided at follow-up of 6 or 12 months, viii) reported adequate description of a priori outcomes appropriate for a meta-analysis, ix) reported exclusion and withdrawal rates. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications of one study, or had been updated in more recent publications were subsequently excluded. Excluded studies included those conducted in other health settings and brief interventions for alcohol delivered alongside other health programs. The references to included studies and to

those that were potentially relevant but did not meet the inclusion criteria can be found below. One unpublished study was included as it otherwise met the inclusion criteria (Drummond et al., under review). This study is currently under journal review.

4.2.4 Identification of included studies

Retrieved papers were selected for inclusion based on the criteria outlined above. The inclusion criteria were piloted on the first ten papers generated from the search strategy. One reviewer verified all studies excluded at the second stage of the review to ensure relevant studies were included. Any disparities between the two reviewers on appropriateness of study for inclusion were settled by a third reviewer. The strength of this review is all available databases and a large number of journals were searched, reference lists of all relevant trials were checked, relevant experts for identification of unpublished trials were contacted, and publications were included without language restrictions. All retrieved references were managed within EndNote Version 5 for Windows program (Thomson Reuters, 2011).

4.2.5 Risk of bias

Data was subsequently added to a data extraction recording form and a risk of bias form. The risk of bias form assessed selection, performance, attrition and detection bias. Two reviewers independently evaluated the quality of each study following standards recommended by the Cochrane Collaboration Systematic Review for Interventions. Study features were assessed based on whether there was i) a random sequence generation; ii) allocation concealment; iii) attrition bias; iv) blinding of assessors; v) a priori statement of outcomes and comparability at baseline and post-intervention follow-up. In terms of blinding, in trials of psychological therapies it is generally considered difficult to blind participants or mask clinicians to the treatment condition which may possibly result in performance and/or detection bias. Failing to conceal treatment allocation to participants and treatment providers may amount to an overvaluation of the treatment effect (Schulz et al., 1995; Moher et al., 1998). Nevertheless, it still may be possible in clustered randomised trials, and so the extent and type of blinding was duly noted i.e. a double blinding of both participant and clinician, a single blinding or whether blinding and masking was unclear. Also noted was whether the investigators were blinded to treatment allocation at assessment outcome.

4.2.6 Statistical methods

Following the statistical methods outlined in Kaner et al., (2007), outcome data for quantity of alcohol consumed in a specific time period (for days, multiplying by seven and for months, multiplying by fifty-two divided by twelve) was converted to grams of pure ethanol per week, if required (see Annex 8.3 for Conversion Tables). Standard drinks were converted to grams using the conversion factor reported in the paper, or when unreported, using conversion factors for the specific country (Miller et al., 1991; Kaner et al., 2007). For

outcomes, the standardised mean difference and standard deviation between the final value of the outcome measure for quantity of alcohol consumed for the treatment group and control group were calculated. When standard deviations were not reported, change scores were used or standard deviations were imputed. When standard deviations were incalculable from standard errors or confidence intervals, the trial was excluded from the analysis.

For continuous outcome measures, the type of statistical method used was an inverse variance model to measure the effect of treatment using standardised mean differences. The extent of heterogeneity between trials was calculated using the I^2 statistic (Higgins & Thompson, 2002; Higgins & Green, 2011) where statistical significance of heterogeneity was checked using P-values from χ^2 tests (Deeks, Altman & Bradburn, 2008). Thresholds for the interpretation of I^2 are as follows: 0% to 40%: might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, 75% to 100%: considerable heterogeneity. A random effects model was used to account for the heterogeneity across populations and interventions between trials. Forest plots are presented with trials arranged by the country in which they were conducted – subgrouped by Europe or the rest of the world. The analysis was conducted using Review Manager (RevMan, 2011)

4.3 Results

4.3.1 Excluded studies

In the emergency department setting, fourteen trials reported insufficient information to analyse the outcomes by alcohol consumption in grams per week. More specifically, the follow-up end point for Barzargan-Hejazi et al., (2005) and Dent et al., (2008) was three months so this trial was excluded from the meta-analysis. Field et al., (2010) and Roudsari et al., (2009) reported their outcomes according to ethnicity rather than treatment arm (brief intervention versus control group), so both trials were excluded from the meta-analysis. Sommers et al., (2006) did not report final values for the control arm and so was excluded on this basis. Goodall et al., (2008) and Smith et al., (2003) were excluded as the trials took place in oral and maxillofacial surgical outpatient clinics rather than emergency departments. The primary outcomes reported in the trials of Longabaugh et al., (2001) and Mello et al., (2008) were alcohol-related negative consequences. The brief intervention delivered in the trials of Maio et al., (2005) and Neumann et al., (2006) were computerised and the brief intervention in the trial of Mello et al., (2005) was delivered by telephone rather than face-to-face so all three trials were excluded from the meta-analysis on these grounds. Rodriguez Martos-Dauer et al., (2006) and Soderstrom et al., (2007) reported reduction in alcohol consumption in percentage of patients by treatment in a specified time period but without the corresponding standard deviation or any useable standard outcomes and so were also excluded. The primary outcome reported in Schermer et al., (2006) was driving under the influence of alcohol and reduction in alcohol consumption was not reported so this trial was excluded from the meta-analysis.

4.3.2 Description of included studies by country

For emergency departments, 8 studies (reported in 10 papers) were included in the review. Where necessary, one key reference was used for multiple reports of the same trial. Overall, four trials took place in Europe, and four trials took place in the rest of the world, all of which were conducted in United States (Table 2 section 4.3.3)

4.3.3 Description of characteristics of subjects

Table 2: Description of characteristics of subjects for trials conducted assessing brief interventions in the Emergency Department.

Study	Country	Sex	Number of Cases	Type of Sample
Europe				
Cherpitel et al., 2010	Poland	Female/Male	Randomised = 446 (147 Intervention group, 152 assessment group and 147 screened)	Aged 18 years plus.
Crawford et al., 2004	UK	Female/Male	Randomised = 599 (287 Treatment group and 312 control)	Aged 18 years plus. 78.1% male. Mean age = 44 years.
Daeppen et al., 2007	Switzerland	Female/Male	Randomised = 987 (310 Treatment group, 342 control with assessment, 335 control with no assessment)	Aged 18 years plus. Mean age = 36.7. 78.2% Male

Drummond et al., (Under Review)	UK	Female/Male	Randomised = 1204 (403 brief advice, 395 brief lifestyle counselling and 406 minimal)	Aged 18 years plus. Mean age = 36.4. 65% male. 88% White. 39% educated to degree level or equivalent.
Rest of the World				
Blow et al., 2006	US	Female/Male	Randomised = 575 (129 Tailored advice, 120 generic no advice, 124 generic advice and 121 tailored no advice)	Aged 19-76 years. Mean age = 27.8. 71% male. 86% White. 80% College education or higher
D'Onofrio et al., 2008	US	Female/Male	Randomised = 494 (247 Treatment group and 247 control)	Aged 18 years plus.
D'Onofrio et al., 2012	US	Female/Male	Randomised = 889 (297 Treatment, 295 Treatment plus telephone follow-up, 148 standard care, 149 standard care no assessments)	Aged 18 years plus. 73% male.
Gentilello et al., 1999	US	Females/Males	Randomised = 762 (366 Intervention group and 396 control group)	Aged 18 years plus. 82% male. Mean age = 36.1.

The emergency department meta-analysis of follow-up data included an overall number of 22371 participants at 6 months, and an overall number of 3061 participants at 12 months (refer to Figures 3 and 4 for aggregate numbers of participants in experimental and control arms per trial per region).

6 Month outcomes

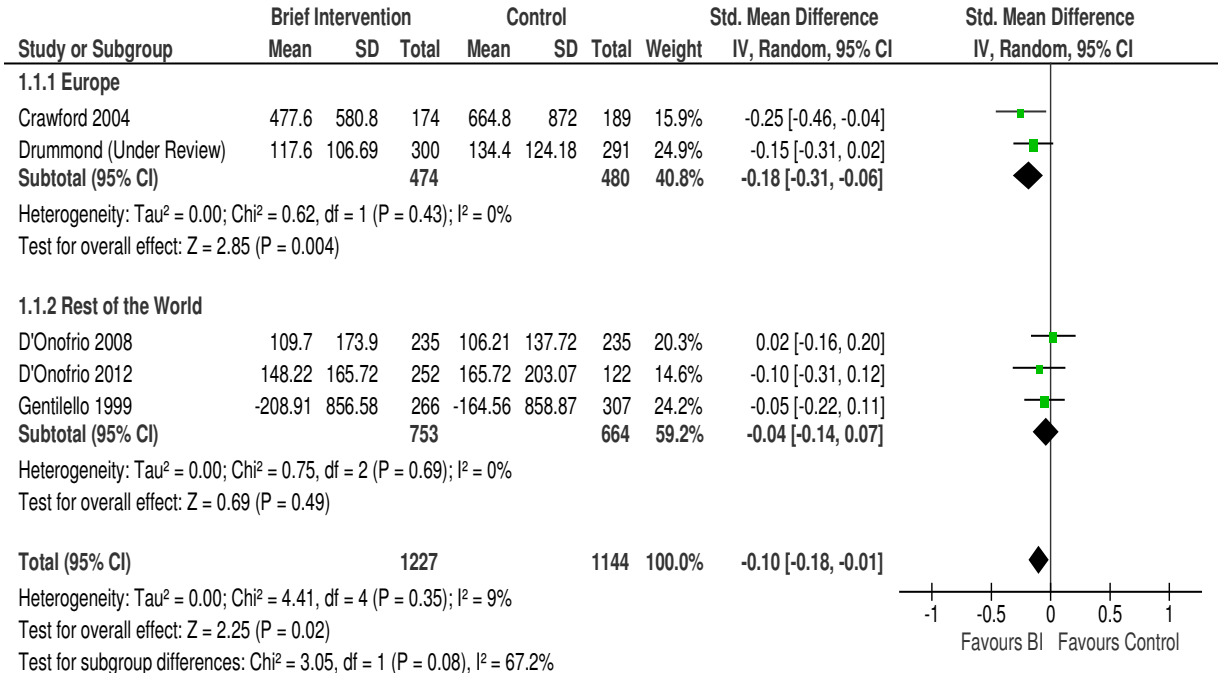
When the European data sets for brief alcohol intervention in emergency department settings at 6 month follow-up were pooled (see Figure 3), a small effect size was observed for reduction in grams of alcohol per week in favour of the active intervention group, which was significant (SMD = -0.18; Z=85; *P* = 0.004). The level of heterogeneity between the pooled European trials (I^2 = 0%) was not significant. Combining all the available data sets for trials conducted in the rest of the world showed a small effect size for brief interventions at 6 months follow-up though this was not significant (SMD = -0.04; Z=0.69; *P* = 0.49). At 6 months, the test for subgroup differences between Europe and the rest of the world was non-significant (P = 0.08) and there was a moderate level of heterogeneity (I^2 = 67.2%). The value of heterogeneity observed for trials conducted in the rest of the world was unlikely to be important (I^2 = 0%). Overall, the meta-analysis results at 6 month follow-up for both Europe and the rest of the world combined indicated that participants receiving brief intervention drank less alcohol per week than those who were allocated to the control condition (SMD =-0.10; Z = 2.25), and this difference was statistically significant (*P* = 0.02).

12 Month outcomes

For the European trials, the meta-analysis showed a non-significant effect size for brief alcohol intervention in emergency department settings at 12 month follow-up for reduction in grams of alcohol consumed per week (SMD = -0.09; Z = 1.86; *P* = 0.06)(see Figure 4). The value of heterogeneity observed for trials conducted in Europe was unlikely to be important (I^2 = 0%). The meta-analysis results showed a significant effect for brief alcohol interventions at 12 months in trials conducted in the rest of the world (SMD: -0.13; Z = 2.30; *P* = 0.02). The value of heterogeneity observed for trials conducted in the rest of the world was non-significant and considered unlikely to be important (I^2 = 7%). The test for subgroup differences for effects on the outcomes of brief alcohol interventions between Europe and the rest of the world at 12 months was not statistically significant. The degree of heterogeneity for all trials combined was small (I^2 =0%) and statistically non-significant (p=0.56). The overall effect for brief alcohol interventions in reducing grams of alcohol consumed per week at 12 month follow-up was statistically significant (SMD = -0.11; Z = 2.99; *P*= 0.0008).

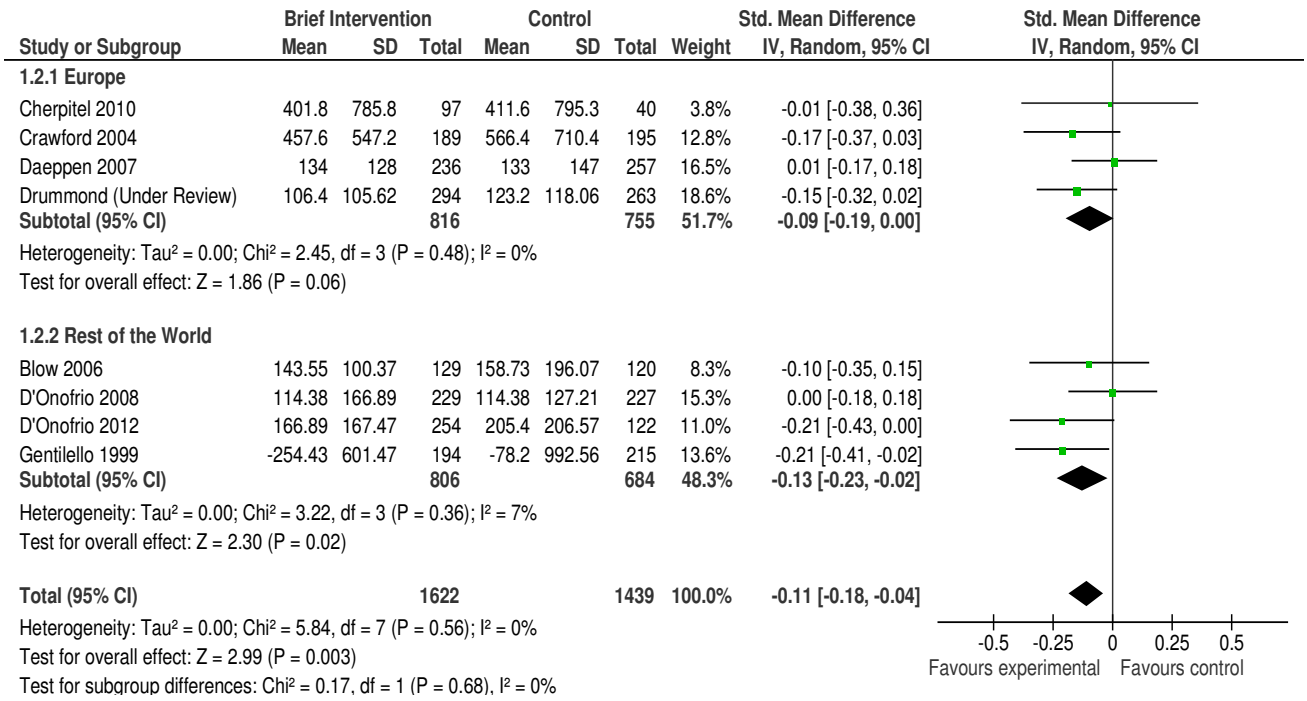
4.3.4 Forest plot of standardised mean difference in alcohol consumption at 6 months

Figure 3. Forest plot taken from emergency department meta-analysis. Estimated standardised mean difference (with standard deviation) of final quantity value for alcohol consumption in grams per week at 6 months follow-up between brief intervention and control groups in included trials for the Europe region and the rest of the world.



4.3.5 Forest plot of standardised mean difference in alcohol consumption at 12 months

Figure 4. Forest plot taken from emergency department meta-analysis. Estimated standardised mean difference (with standard deviation) of final quantity value for alcohol consumption in grams per week at 12 months follow-up between brief intervention and control groups in included trials for the Europe region and the rest of the world.



4.4 Discussion

The results presented here show that brief intervention in emergency departments are significantly more effective than control. There was no significant difference between the pooled outcomes of brief intervention for trials conducted emergency department settings in Europe compared to the rest of the world (US) at 6 and 12 month follow-up.

In the European trials at six month follow-up, there was a significant effect for brief intervention when compared to the control group in hazardous and harmful drinkers. There was no significant heterogeneity detected in the European trials at six months, which were both conducted in the UK. Both trials included subjects of both sexes, and the majority were white middle-aged men. The three trials included for the rest of the world at six month follow-up were conducted in the United States. No level of heterogeneity was detected between these trials, and the effect observed for the brief intervention versus control group was not significant. The majority of subjects included in the US trials at six month follow-up were white, middle-

aged males. The test for subgroup differences between European and the US trials was not significant, though the overall effect for all trials combined favoured brief intervention compared to the control group at six month follow-up.

As no statistically significant heterogeneity between the European trials was detected, a somewhat more meaningful interpretation can be drawn regarding the estimate of the effect. In the European trials at 12 month follow-up, a significant effect in the reduction of alcohol consumption was observed for the brief intervention group when compared to the control group. However, despite including subjects of both sexes, the majority of subjects in the four European trials were middle-aged white males. A low level of statistical heterogeneity was detected in the trials conducted in the rest of the world at 12 month follow-up. All trials were conducted in the United States, and the overall effect size of brief intervention was significant. Similar to the European findings at 12 month follow-up, the overwhelming majority of subjects included in the US trials were white, middle-aged males. The test for subgroup differences between European and the US trials at 12 month follow-up was not significant.

4.4.1 Limitations

Heather (1995; 2002) suggests that brief interventions delivered naturalistic settings are likely to show smaller effects than efficacy studies indicate. In all cases, it seems some of the purported benefits of brief interventions could be lost when translated from a special research condition to the natural conditions of typical clinical practice. Indeed, a common criticism of brief intervention trials is that they are efficacy studies (optimizing internal validity) rather than pragmatic trials. Therefore, as Drummond et al., (2009) point out, a more appropriate methodology for evaluating effectiveness might be to involve a pragmatic balance between internal and external to provide a better indication of 'naturalistic effectiveness'.

There are often systematic biases particularly associated with the population under study. In this case, across both the European trials and the trials conducted in the US, the majority focused on middle-aged, male drinkers with other groups under-represented. Overall pooled findings of outcomes for males and females might result in more weight being accorded to the trial, but is unlikely to result in any major differences (Kaner et al., 2007). In addition, most of the results were generated from self-report data, which if collected using validated methods has been regarded as appropriate for research purposes, as well as being less intrusive for participants (Babor et al., 2000). Further statistical heterogeneity between trials exists possibly on account of the screening instruments used, the populations included and the types of assessments and brief interventions delivered to the experimental and control groups. Additionally, as the optimal intensity of brief alcohol intervention for clinical trials is currently unclear, this was reflected in the variability of brief intervention included trials. However, the recent Cochrane review (Kaner *et al*. 2007) found no significant additional benefits of longer brief intervention compared to shorter brief interventions as did the SIPS ED trial which was specifically designed to test the relative effectiveness of different intensities of brief

intervention in a pragmatic trial (Drummond et al., under review). Finally, the difficulty in blinding participants is a potential source of bias.

4.5 Summary

This meta-analysis indicates the following:

- Firstly, in emergency department setting, the overall effects of brief intervention on hazardous and harmful drinkers, when compared to a control group at 6 and 12 month follow-up, for trials conducted in both Europe and the United States, are significant.

- Secondly, the subgroup differences of the effects of brief intervention on hazardous and harmful drinkers, when compared to a control group at 6 and 12 month follow-up, between trials conducted in Europe versus the United States, are not significant.

5. Meta-analysis of specialist treatments for alcohol use disorders

5.1 Introduction

Due to the considerable amount of research that has been conducted and the inherent differences in psychological approaches to the treatment and management of harmful drinking, Cognitive-Behavioural Therapy (CBT) and Motivational Techniques (MT) were selected to focus on for the purposes of this report. MT are patient centred clinical techniques, which aim to resolve a person's ambivalence towards engaging in treatment and stopping their harmful use/dependence of alcohol. CBT is a type of talking therapy through which clients work towards being able to recognise how their patterns of thoughts and/or behaviours are associated with how they feel and how these thoughts/behaviours can be modified to reduce the severity of target symptoms and problems that they are experiencing. The AMPHORA workpackage 6 Report on the mapping of European need and service provision for early diagnosis and treatment of alcohol use disorders has shown that there are significant differences in specialist treatment availability and accessibility across European countries (Wolstenholme et al., 2013). These variations are likely to extend to other countries outside of Europe and may result in differences in treatment effectiveness.

It has been suggested that there is a difference in the severity of alcohol dependence on entry into treatment for studies conducted in Europe compared to the US (Garbutt et al., 2009) and this may have an impact on the efficacy of acamprosate and naltrexone (Monterosso et al., 2001; NICE, 2011; Richardson et al., 2008). It has been noted that the majority of studies that have assessed the efficacy of acamprosate have taken place in Europe, whereas those that have assessed the efficacy of naltrexone have taken place mainly in the US (Rösner et al., 2008). These differences may impact on the study outcomes and the perceived efficacy of the medications.

5.2 Methods

5.2.1 Aims and objectives

This meta-analysis aims to;

1. Examine whether there are differences in the outcome of MT and CBT between studies conducted in Europe and those conducted in the Rest of the World.

2. Examine whether there are differences in the outcome of the pharmacological therapies, naltrexone and acamprosate, between studies conducted in Europe compared to the Rest of the World.

These aims will be achieved by conducting a sub-group analysis using the data presented in the meta-analyses published in the National Institute for Health and Clinical Excellence (NICE) Guideline on Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (NICE, 2011) updated specifically for this study. The original NICE systematic review did not include a comparison between studies conducted in Europe and the rest of the world.

5.2.2 Search strategy

A systematic search of the literature on psychological and pharmacological interventions for the treatment and management of harmful use and dependence on alcohol was conducted for the development of the NICE Guideline on Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (NICE, 2011). Searches were conducted in June 2008 and run 6 monthly until 1st March 2010 and a final search using an identical search strategy was conducted by us on the 8th August 2012 using the electronic databases Cochrane, CINAL, EMBASE, Medline and PsycINFO. No language or date restrictions were applied. Other search methods included 1) Scanning the reference lists of eligible papers for further relevant papers, 2) Sending lists of eligible papers to experts in the subject area for consideration of completeness with the request of any further relevant published or unpublished studies that were known, 3) Searching for references that may have been missed by the electronic searches by checking the contents tables of key journals, 4) Tracking key references in the Science Citation Index. Subsequent to the publication of the NICE guidelines the PREDICT study has been completed (Mann et al., 2012). This is a large study conducted in Germany, which based its methodology on the US COMBINE study (Anton et al., 2006) and examined the efficacy of both naltrexone and acamprosate. This study was also included in the current meta-analyses.

5.2.3 Selection criteria

The inclusion criteria for psychological and pharmacological therapies included;

1. Randomised Controlled Trial
2. Adults (aged >18)
3. At least 80% of the sample meet the criteria for alcohol dependence or harmful alcohol use (clinical diagnosis or drinking >30 drinks per week)
4. Minimum sample size of 10 per arm of the study

Studies which included pregnant women were excluded from the meta-analyses.

The review of evidence for a psychological therapy aimed to assess the benefit or detriment of a psychological therapy in comparison with another the absence of pharmacological treatment. In addition to the inclusion criteria outlined above, studies were deemed eligible for inclusion if treatment was planned,

patients in the study were treatment seeking, the therapy was manual based or well-defined and structured and if the therapy was ethical and safe.

The review of evidence for the pharmacological therapies acamprosate and naltrexone aimed to assess the efficacy of these treatments (in comparison to placebo) in the prevention of relapse or the reduction of alcohol consumption, either alone or in combination with psychological therapies. In addition to the inclusion criteria outlined above, studies were only considered if they used preparations that were licensed for use in the UK. Studies assessing the efficacy of naltrexone were only included if they used the oral preparation due to the lack of available evidence for usage of the extended release and subcutaneous implantation varieties of the drug.

5.2.4 Types of participants

See section 5.2.3.

5.2.5 Identification of included studies

After each search, references were downloaded to the electronic bibliographic management software Reference Manager and duplicates removed. References were screened against the inclusion criteria and quality appraised, eligibility was confirmed by at least one other member of the review group. The methodological quality of each study was assessed using a checklist which has been adapted from the validated instrument SIGN (2001). Each question in the checklist covers an aspect of research methodology and was rated using the scale;

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed
- Not reported
- No applicable

5.2.6 Statistical methods

Data was extracted from research papers deemed to be eligible for inclusion using a Microsoft Word-Based form. On occasions where more than 50% of the number of participants randomised for a given outcome was lost to follow-up, the data were excluded from the analysis. The only exception for this is for the outcome ‘leaving the study early’. An intention-to-treat analysis was used wherever possible. If there was insufficient data the 50% rule was not applied and evidence was downgraded due to risk of bias. Early withdrawals were included in both the numerator and denominator in circumstances where it was likely that participants discontinuing treatment had an unfavourable outcome. Data was extracted independently by two

different members of the research group where possible or cross-checked by another member if not. Any disagreements in data extraction were resolved by discussion between two members of the review group or if consensus could not be reached a third member of the review group was consulted. Some of the studies included in the meta-analyses had multiple arms. To avoid double counting, the number of participants in a treatment arm used more than once was divided by half for a three-arm trial and by three in a four-arm trial.

Data was extracted from the NICE meta-analyses for outcome variables deemed to have enough data to justify subgroup analysis comparing Europe to the Rest of the World (at least two studies in each sub-group). Data was entered into Review Manager (RevMan, 2012), and then cross-checked for accuracy by another member of the research team. Two sub-groups were created one for studies conducted in Europe and the other for studies conducted outside of Europe or 'the Rest of the World'. All outcome variables were dichotomous and analysed as Relative Risk (RR) with the associated 95% Confidence Interval (CI). A RR of 1 indicates that there is no difference between the experimental and control groups. A RR of less than 1 indicates a decreased risk and a RR greater than 1 indicates an increased risk in the experimental group relative to the control group. To check for the consistency of effects across studies heterogeneity was measured using I^2 and the chi^2 test of heterogeneity. The I^2 statistic was interpreted in the following way based on Higgins and Green (2011);

- 0 to 40%: Might not be important
- 30 to 60%: May represent moderate heterogeneity
- 50 to 90%: May represent substantial heterogeneity
- 75 to 100%: Considerable heterogeneity

A random-effects model using the Mantel-Haenszel method for this meta-analysis was used. A random-effects model was deemed more appropriate for this analysis than a fixed-effects model as it does not assume that all studies included in the analysis are functionally equivalent and takes into consideration that studies were conducted independently.

5.3 Results

5.3.1 Excluded studies

The main reasons for exclusion from the meta-analysis for psychological therapies included not meeting the drinking quantity/diagnostic criteria, treatment was opportunistic rather than planned, the study was not directly relevant to the review question or no relevant outcome measures were available. Similar reasons for exclusion of studies were found for pharmacological intervention studies, including not providing an acceptable diagnosis of alcohol dependence, not being an RCT, having fewer than 10 participants in each arm of the trial, not being double blind and not reporting any relevant outcomes.

5.3.2 Studies by country

A total of six studies were included for the meta-analysis assessing the efficacy of the psychological therapy MT (Table 3 section 5.3.3) half of which were conducted in the USA, one was conducted in New Zealand, one in Australia and one in the UK. Data from thirteen studies was included in the meta-analysis for the efficacy of CBT in the treatment of harmful use/dependence on alcohol (Table 4 section 5.3.3). The majority (8/13) of the studies were conducted in the USA, two were conducted in Australia and the remaining three were conducted in Europe (Norway, Sweden and the Netherlands)

Nineteen studies were identified that met inclusion criteria for the meta-analysis assessing the efficacy of acamprosate compared to placebo. The majority of these studies were conducted in European countries (Table 5 section 5.3.3) and of those studies conducted outside of Europe, just one was conducted in the US, one in Korea, one in Australia and one in Brazil. Twenty seven studies were included in the review for naltrexone versus placebo. In contrast to the acamprosate studies, the majority of these studies were conducted outside of Europe, predominantly in the USA (Table 6 section 5.3.3)

5.3.3 Description of characteristics of subjects

The characteristics of the studies found to be eligible for inclusion in the meta-analysis can be found in the tables in this section.

Table 3 Study characteristics for studies assessing Motivational Techniques in comparison to other psychological therapies

Study	**Country**	**Sex**	**Number of Cases**
Europe			
UKATT Research team, 2005 (UKATT2005)	UK	Male/female	MET= 422 SBNT = 320
Rest of the World			

Davidson et al., 2007 (Davidon2007)	US	Male/female	MET = 76 BST = 73
Project MATCH Research Group, 1997 (MATCH1997)	US	Male/female	MET = 577 CBT = 567 TSF = 582
Sellman et al., 2001 (Sellman2001)	New Zealand	Male/female	MET = 42 NDFL = 40
Shakeshaft et al., 2002 (Shakeshaft2002)	Australia	Male/female	FRAMES = 147 CBT = 148
Sobell et al., 2002 (Sobell2002)	US	Male/female	MET = 414 Bibliotherapy/drinking guidelines = 411

NB: MET = Motivational Enhancement Therapy, SBNT = Social Behaviour and Network Therapy, BST = Broad Spectrum Treatment, CBT = Cognitive Behavioural Therapy, TSF = Twelve Step Facilitation, NDFL = Non-Reflective Directive Listening

Table 4: Study characteristics for studies assessing Cognitive Behavioural Therapies in comparison to other psychological therapies

Study	**Country**	**Sex**	**Number of Cases**
Europe			
Eriksen et al., 2007 (Eriksen2007)	Norway	Male/female	SST = 12 Group Counselling = 12
Sandahl et al., 1998 (Sandahl1998)	Sweden	Male/female	RP = 24 PSYDYN = 25
Vedel et al., 2008 (Vedel2008)	Netherlands	Male/female	CBT = 34 BCT = 30
Rest of the World			

Connors et al., 2001 (Connors2001)	US	Male/female	CS+LS+NOR = 39 CS+PSY+INT = 41 CS+LS+INT = 33 CS+PSY+NOR = 31
Davidson et al.. 2007 (Davidson2007)	US	Male/female	MET = 76 BST = 73
Easton et al., 2007 (Easton2007)	US	Male	CBT = 40 TSF = 38
Lam et al., 2009 (Lam2009)	US	Male	CS = 10 BCT + Parenting Skills = 10 BCT = 10
Litt et al., 2003 (Litt2003)	US	Male/female	CS = 69 Group Counselling = 59
Project Match Research Group, 1997 (MATCH1997)	US	Male/female	CBT = 567 MET = 577 TSF = 582
Morgenstern et al., 2007 (Morgenstern2007)	US	Male	CS + MET = 47 MET = 42
Shakeshaft et al., 2002 (Shakeshaft2002)	Australia	Male/female	CBT = 148 FRAMES = 147
Sitharthan et al., 1997 (Sitharthan1997)	Australia	Male/female	CBT = 20 CE = 22
Walitzer et al., 2009 (Walitzer2009)	US	Male/female	CS = 58 TSF (directive) + CS = 58

N.B: CS = Coping Skills, LS = Life Skills, NOR = Normal Intensity, INT = Intensive, BST = Broad Spectrum Treatment, SST = Social Skills Training, BCT = Block Clearance Therapy, MET = Motivational Enhancement Therapy, CBT = Cognitive Behavioural Therapy, PSYDYN = Psychodynamic Psychotherapy, CE = Cue Exposure

Table 5 Study characteristics for studies assessing acamprosate compared to placebo

Study	Country	Sex	Age of sample	Number of Cases	Outcome measure
Europe					
Barrias et al., 1997 (Barrias1997)	Portugal	Male/female	Mean age: 40 Age range: 21 - 64	Acamprosate = 150 Placebo = 152	• Lapsed (individuals returning to any drinking at 6 month follow-up)
Besson et al., 1998 (Besson1998)	Switzerland	Male/female	Mean age: 42 Age range: 18 - 65	Acamprosate = 55 Placebo = 55	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Chick et al., 2000a (Chick2000a)	UK	Male/female	Mean age: 43 Age range: 18-65	Acamprosate = 289 Placebo = 292	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Geerlings et al., 1997 (Geerling1997)	Belgium/Luxemburg/ Netherlands	Male/Female	Mean age = 41 Age range = 18-65	Acamprosate = 128 Placebo = 134	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Gual et al., 2001 (Gual2001)	Spain	Male/female	Mean age = 41 Age range = 18-65	Acamprosate = 141 Placebo = 147	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)

Kiefer et al., 2003 (Kiefer2003)	Germany	Male/female	Mean age = 46 Age range = 18-65	Acamprosate = 40 Placebo = 40	• Discontinued treatment (leaving the study early)
Ladewig et al., 1993 (Ladewig1993)	Switzerland	Male/female	Mean age = 47 Age range = 28-70	Acamprosate = 29 Placebo = 32	• Lapsed (individuals returning to any drinking at 6 month follow-up)
Paille et al., 1995 (Paille1995)	France	Male/female	Mean age = 43 Age range = 18-65	Acamprosate = 173 Placebo = 177	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Pelc et al., 1992 (Pelc1992)	Belgium/France	Male/female	Mean age = 43 Age range = 23-64	Acamprosate = 55 Placebo = 47	• Lapsed (individuals returning to any drinking at 6 month follow-up)
Pelc et al., 1997 (Pelc1997)	Belgium/France	No information	Age range 18-65	Acamprosate = 63 Placebo = 62	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Poldrugo et al., 1997 (Poldrugo1997)	Italy	Male/female	Mean age = 44 Age range = 18-65	Acamprosate = 122 Placebo = 124	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Roussaux et al., 1996 (Roussaux1996)	Belgium	Male/female	Mean age = 42 Age range = 23-64	Acamprosate = 63 Placebo = 64	• Lapsed (individuals returning to any drinking at 6 month follow-up)
Sass et al., 1996 (Sass1996)	Germany	Male/female	Mean age = 41	Acamprosate = 136 Placebo = 136	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any

					drinking at 6 month follow-up)
Tempesta et al., 2000 (Tempesta2000)	Italy	Male/female	Mean age = 46 Age range = 18-65	Acamprosate = 164 Placebo = 166	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Whitworth et al., 1996 (Whitworth1996)	Austria	Male/female	Mean age = 42 Age range =18-65	Acamprosate = 224 Placebo = 224	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)
Rest of the World					
Anton et al., 2006 (Anton2006)	US	Male/female	Median age = 44	Acamprosate = 152 Placebo = 153 Acamprosate + CBI = 151 Placebo + CBI =156	• Discontinued treatment (leaving the study early)
Baltieri et al., 2003 (Baltieri2003)	Brazil	Males	Mean age = 44 Age range = 18-59	Acamprosate = 40 Placebo = 35	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)

Morley et al., 2006 (Morley2006)	Australia	Male/female	Mean age = 45 Age range = 18-65	Acamprosate = 55 Placebo = 61	• Discontinued treatment (leaving the study early)
Namkoong et al., 2003 (Namkoong2003)	Korea	Male/female	Mean age = 44 Age range = 21-65	Acamprosate = 72 Placebo = 70	• Discontinued treatment (leaving the study early) • Lapsed (individuals returning to any drinking at 6 month follow-up)

N.B: CBI = Cognitive Behavioural Intervention

Table 6 Study characteristics for studies assessing naltrexone compared to placebo

Study	**Country**	**Sex**	**Age of sample**	**Number of Cases**	**Outcome measure**
Europe					
Balldin et al., 2003 (Balldin2003)	Sweden	Male/female	Mean age: 49	Naltrexone + CS = 25 Placebo + CS = 30 Naltrexone + SP = 31 Placebo + SP = 30	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Chick et al., 2000b (Chick2000b)	UK	Male/female	Mean age: 48 Age range: 18 - 65	Naltrexone = 90 Placebo = 85	• Discontinued treatment (leaving the study early

					• Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Gastpar et al., 2002 (Gastpar2002)	Germany	Male/female	Mean age: 43	Naltrexone = 87 Placebo = 84	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Guardia et al., 2002 (Guardia2002)	Spain	Male/Female	Mean age = 42 Age range = 18-60	Naltrexone = 101 Placebo = 101	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Heinala et al., 2001 (Heinala2001)	Finland	Male/female	Mean age = 45 Age range = 21-65	Naltrexone +CS = 34 Placebo + CS = 33 Naltrexone + SP = 29 Placebo + SP = 25	• Relapse to heavy drinking (3 month follow-up)

Kiefer et al., 2003 (Kiefer2003)	Germany	Male/female	Mean age = 46 Age range = 18-65	Naltrexone = 40 Placebo = 40	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Mann et al., 2012 (Mann2012)	Germany	Male/female	Mean age = 45.3	Naltrexone = 169 Placebo = 85	• Relapse to heavy drinking (3 month follow-up)
Rest of the World					
Ahmadi et al., 2002 (Ahmadi2002)	Iran	Male	Mean age = 43 Age range = 23-56	Naltrexone = 58 Placebo = 58	• Discontinued treatment (leaving the study early
Anton et al., 1999 (Anton1999)	US	Males	Mean age = 44 Age range = 18-59	Naltrexone = 68 Placebo = 63	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)

Anton et al., 2005 (Anton2005)	US	Male/female	Mean age = 45 Age range = 18-65	Naltrexone + MET = 41 Placebo + MET = 39 Naltrexone + CS = 39 Placebo + CS = 41	• Discontinued treatment (leaving the study early • Relapse to heavy drinking (3 month follow-up)
Anton et al., 2006 (Anton2006)	US	Male/female	Mean age = 44 Age range = 21-65	Naltrexone = 154 Placebo = 153 Naltrexone + CBI = 155 Placebo + CBI = 156	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Relapse to heavy drinking (3 month follow-up)
Baltieri et al., 2008 (Baltieri2008)	Brazil	Male	Mean age = 44 Age range = 18-65	Naltrexone = 49 Placebo = 54	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up)
Huang et al., 2005 (Huang2005)	Taiwan	Male	Mean age = 41 Age range =20-60	Naltrexone = 20 Placebo =20	• Discontinued treatment (leaving the study early • Relapse to heavy drinking (3 month follow-up)
Killeen et al., 2004 (Killeen2004)	US	Male/female	Mean age = 37	Naltrexone = 51 Placebo = 36	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Relapse to heavy drinking (3 month follow-

					up)
Kranzler et al., 2000 (Kranzler2000)	US	Male/female	Mean age = 40 Age range = 18-60	Naltrexone = 61 Placebo = 63	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Krystal et al., 2001 (Krystal2001	US	Male/female	Mean age = 49 Age range = 18-	Naltrexone = 378 Placebo = 187	• Discontinued treatment (leaving the study early • Relapse to heavy drinking (3 month follow-up)
Latt et al., 2002 (Latt2002)	Australia	Male/female	Mean age = 45 Age range = 18-70	Naltrexone = 56 Placebo = 51	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Relapse to heavy drinking (3 month follow-up)
Lee et al., 2001 (Lee2001)	Singapore	Male	Mean age = 45 Age range = 21-65	Naltrexone = 35 Placebo = 18	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)

Monti et al., 2001 (Monti2001)	US	Male/female	Mean age = 39	Naltrexone = 64 Placebo = 64	• Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Morley et al., 2006 (Morley2006)	Australia	Male/female	Mean age = 45 Age range = 18-65	Naltrexone = 53 Placebo = 61	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Morris et al., 2001 (Morris2001)	Australia	Male	Mean age = 47 Age range = 18-65	Naltrexone = 55 Placebo = 56	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
O'Malley et al., 1992 (Omalley1992)	US	Male/female	Mean age = 41 Age range = 18-665	Naltrexone = 29 Placebo = 25 Naltrexone + SP = 23 Placebo + SP = 27	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up)
O'Malley et al., 2003 (Omalley2003)	US	Male/female	Mean age = 44 Age range = 18-65	Naltrexone + PCM = 26 Placebo + PCM =27	• Discontinued treatment (leaving the study early

				Naltrexone + CS = 30 Placebo + CS = 30	• Leaving due to adverse events
O'Malley et al., 2008 (Omalley2008)	US	Male/female	Mean age = 40 Age range = 18-65	Naltrexone = 34 Placebo = 34	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Oslin et al., 1997 (Oslin1997)	US	No information	Mean age = 58 Age range = 50-70	Naltrexone = 21 Placebo = 23	• Discontinued treatment (leaving the study early • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Oslin et al., 2008 (Oslin2008)	US	Male/female	Mean age = 43 Age range = 18-	Naltrexone = 120 Placebo = 120	• Discontinued treatment (leaving the study early
Volpicelli et al., 1992 (Volpicelli1992)	US	Male/female	Mean age = 43 Age range = 21-65	Naltrexone = 35 Placebo = 35	• Discontinued treatment (leaving the study early • Leaving due to adverse events

					• Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)
Volpicelli et al., 1997 (Volpicelli1997)	US	Male/female	Mean age = 38 Age range = 21-65	Naltrexone = 48 Placebo = 49	• Discontinued treatment (leaving the study early • Leaving due to adverse events • Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) • Relapse to heavy drinking (3 month follow-up)

N.B: CS = Coping Skills, SP = Supportive Psychotherapy, MET = Motivational Enhancement Therapy, CBI = Combined Behavioural Intervention, PCM = Primary Care Management.

5.3.4 Results for studies assessing the efficacy of psychological therapies

The meta-analyses conducted by the NICE guidelines development group for MT assessed the effects (beneficial or detrimental) of MT in the treatment of harmful use of alcohol or alcohol dependence in comparison to another active intervention. Other active interventions included counselling, CBT, Twelve Step Facilitation (TSF), Social Behaviour and Network Therapy (SBNT), FRAMES, and bibliotherapy/drinking guidelines or a combination of these therapies. As reported in section 5.3.2, there were was only one study conducted in Europe, this resulted in there being insufficient data available for further analysis to assess the effectiveness of MT in Europe versus the Rest of the World. There were also significant differences in the methodologies employed by the studies, including differences in the primary and secondary outcome measures. Furthermore, studies measured the same outcome measure in different ways. For example, four of the six studies included in the meta-analysis measured the amount of alcohol consumed after completion of the treatment period but it was measured as drinks per drinking day or drinks per week and at different periods of follow-up (post-treatment, 3 months, 6 months, 9 months, 12 months and 15 months).

Thirteen studies were included in the meta-analysis conducted by NICE assessing the efficacy of CBT in the treatment of harmful use or dependence on alcohol, in comparison to other active interventions (including MET, TSF, group counselling, Block Clearance Therapy (BCT), Parental skills training, Psychodynamic therapy, FRAMES, cue exposure, psychoeducation, or in combination). As described in section 5.3.2 and presented in Table 4 in section 5.3.3, the majority of studies were conducted in the USA with few conducted in Europe. The studies that met inclusion criteria for the meta-analysis that assessed the efficacy of CBT were heterogeneous with significant differences in the methodologies used and the primary and secondary outcome measures reported. There was a variation in the way that individual studies measured specific outcomes, an example of this would again be the outcome measure for Amount of Alcohol Consumed. Seven of the 13 studies reported data on Amount of Alcohol Consumed subsequent to the completion of treatment. This variable was measured using various methods (Weekly consumption at hazardous/harmful levels, Binge consumption (at least 12 binge episodes in the past 30 days), any binge consumption (at least one binge episode in the previous 30 days, units of alcohol per week, drinks per drinking day, alcohol consumption (:cl pure alcohol), grams of absolute alcohol per drinking day) and at different time points (post treatment, 6 month follow-up, 5 month follow-up, 12 month follow-up, 9 month follow-up and 15 month follow-up). The result of this was that there was not a sufficient number of studies to be able to conduct further statistical analysis for the sub-groups Europe and the Rest of the World.

5.3.5 Results for studies assessing the efficacy of pharmacological therapies.

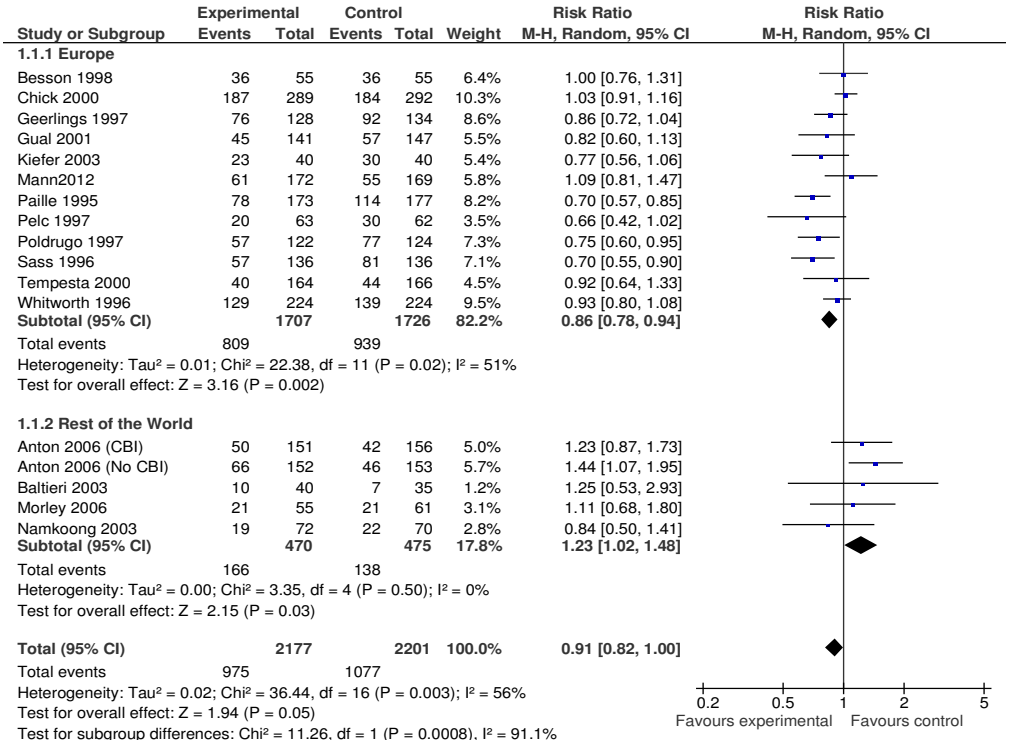
Acamprosate

A meta-analysis was conducted to compare the efficacy of acamprosate versus placebo for all published randomised controlled trials conducted in Europe compared to the Rest of the World. Due to the

low number of studies conducted outside of Europe with comparable data (see Table 5 section 5.3.3) only two variables could be analysed to compare Europe and the Rest of the World. These variables were 1) Discontinued treatment (leaving the study early) and 2) lapsed (individuals returning to any drinking at 6 months follow-up).

Of the total 19 eligible studies, 16 reported data for the variable for discontinuation of treatment and 12 were conducted in a European country, Figure 5 presents the results of the meta-analysis for this variable. There was a significant difference in risk of discontinuing treatment between those in the acamprosate and placebo groups, with a 14% decreased risk for participants in the acamprosate group for studies conducted in Europe. Significant, moderate heterogeneity was present for this analysis. The opposite was true for those studies conducted in the Rest of the World with participants in the acamprosate group having a 23% increased risk of leaving the study early, and heterogeneity between studies was found not to be significant. In a subgroup analysis the difference in findings for discontinuation of treatment for studies conducted in Europe and the Rest of the World was statistically significant.

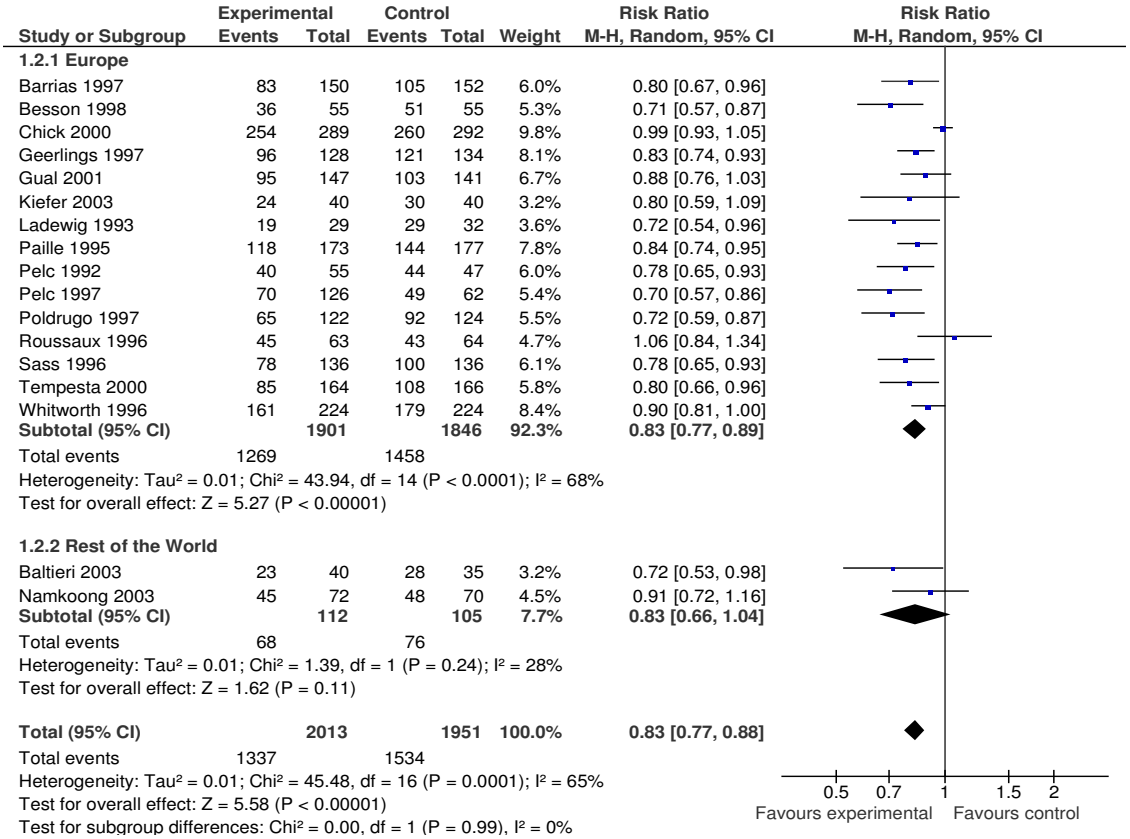
Figure 5: Forest plot for the comparison of treatment with acamprosate and placebo for the outcome Discontinued Treatment (Leaving the Study Early), Europe versus the Rest of the World.



Sub-group analysis of the second variable (lapsed) found that participants in the acamprosate group had a 17% decreased risk of returning to alcohol at 6 months follow-up compared to the placebo group for those studies conducted in Europe (Figure 6) but heterogeneity was significant and substantial. This result was

not replicated in the studies conducted in the Rest of the World. Seventeen of the 19 eligible studies reported data for this variable, just two of which were conducted in a non-European country resulting in a small sample size for the Rest of the World sub-group. The risk ratios for Europe and the Rest of the World, were identical in magnitude. Heterogeneity was small and not significant for this analysis. The difference in relative risk was not statistically significant between the sub-groups Europe and the Rest of the World. However the pooled effect of acamprosate on drinking was significant for all studies combined.

Figure 6: Forest plot for the comparison of treatment with acamprosate and placebo for the outcome Lapsed (individuals returning to any drinking at 6 month follow-up), Europe versus the Rest of the World.

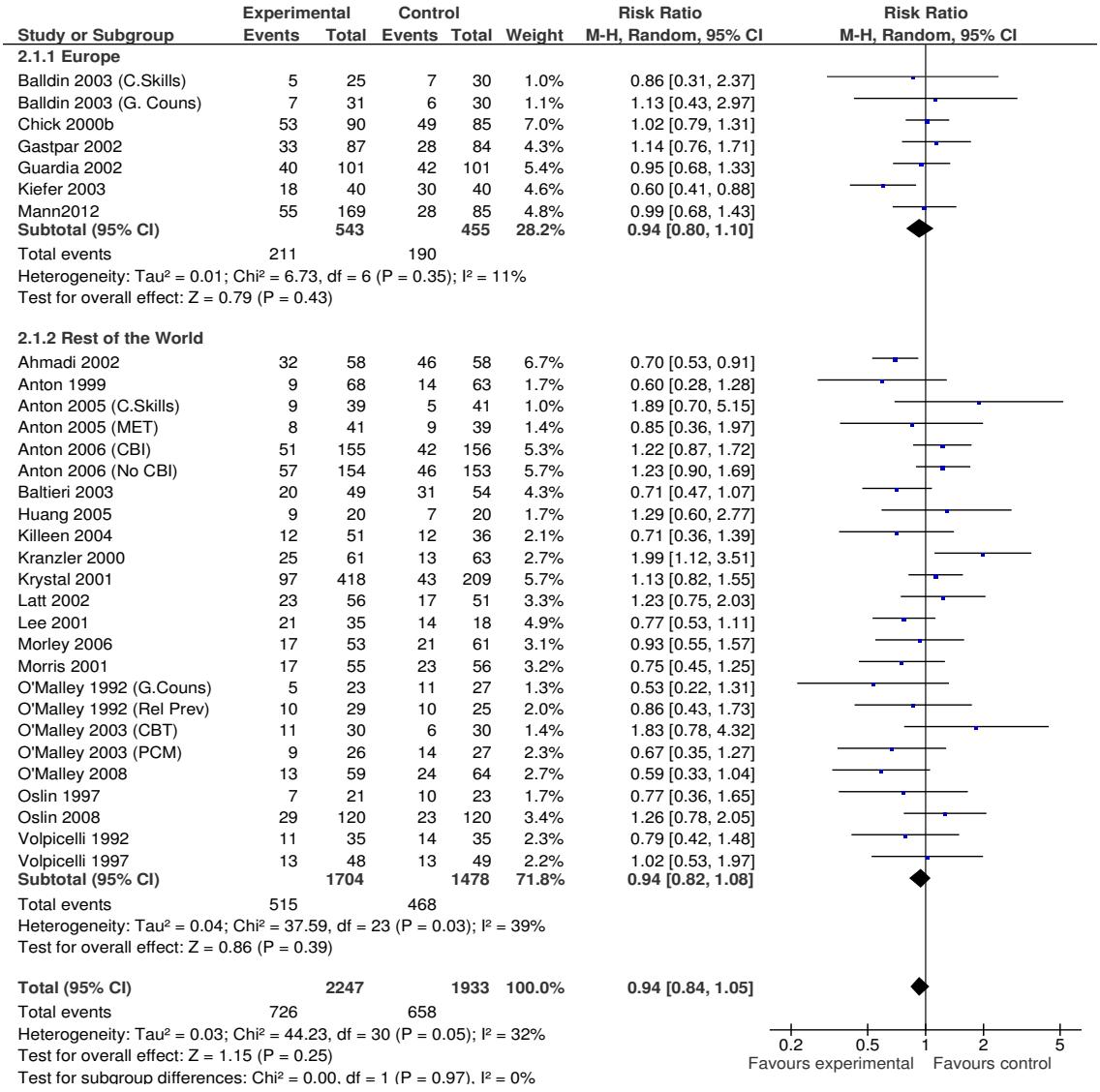


Naltrexone

Twenty seven studies met inclusion criteria for the meta-analysis comparing the efficacy of naltrexone versus placebo. On consideration of the outcome variables reported for these studies it was decided that just four had sufficient data to enable further analysis for Europe versus the Rest of the World, these variable were; 1) Discontinued treatment (leaving the study early) 2) Leaving due to adverse events 3) Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up) 4) Relapse to heavy drinking (3 month follow-up).

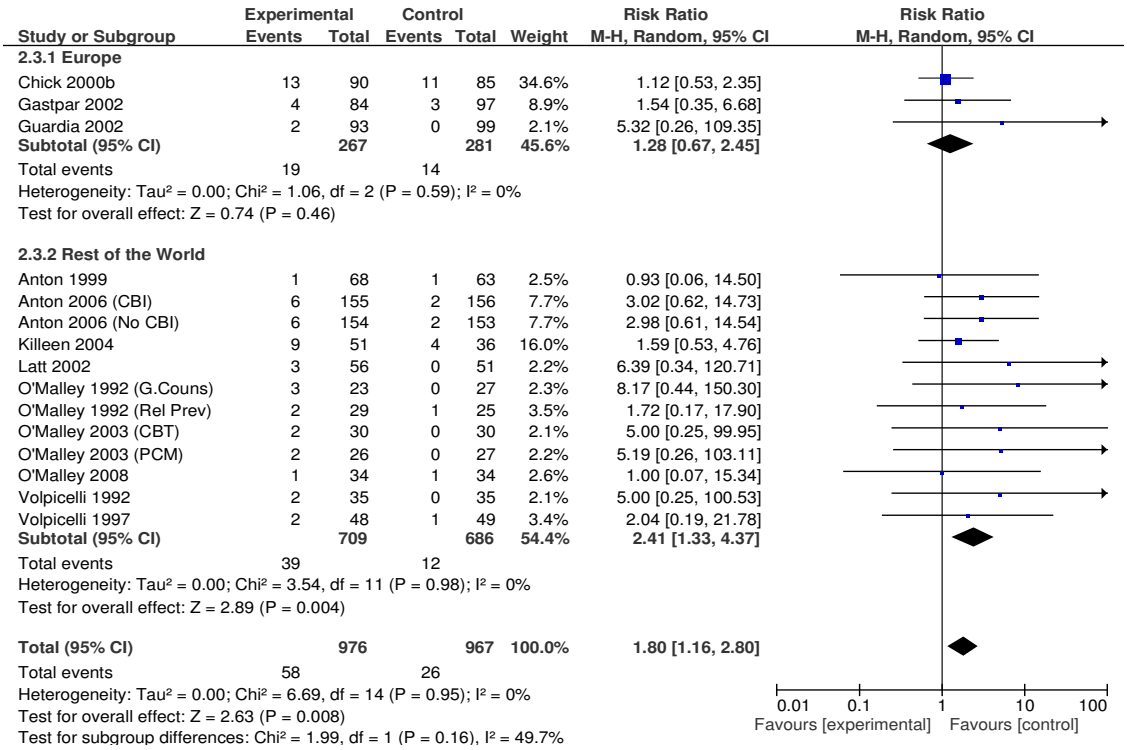
Twenty-four studies were included in the meta-analysis for the variable Discontinued Treatment, 6 of which were conducted in Europe. There were no statistically significant differences in the risk ratio (RR) of discontinuation of treatment when comparing participants in the naltrexone and placebo groups for studies conducted in Europe or the Rest of the World. There was also no statistically significant difference in RR between the sub-groups Europe and the Rest of the World. There was significant, moderate heterogeneity for the Rest of the World analysis but heterogeneity was not significant for Europe. The results for this analysis are presented in Figure 7.

Figure 7: Forest plot for the comparison of treatment with naltrexone and placebo for the outcome Discontinued Treatment (Leaving the Study Early), Europe versus the Rest of the World.



Twelve studies reported data for the variable leaving due to adverse events, only three of these studies were conducted in Europe. The results of the analysis for this variable are presented in Figure 8. There was no statistically significant difference between participants in the naltrexone group compared to the placebo group when considering the variable for leaving the study early due to adverse events in the European studies with no significant heterogeneity. However, the results of the analysis that included only those studies conducted outside of Europe found that those in the naltrexone group were at a 2.41 times greater risk of leaving the study early due to adverse events compared to participants in the placebo group. No significant heterogeneity was found for this analysis. The difference in RR between the sub-group analysis for Europe and the Rest of the World was not statistically significant.

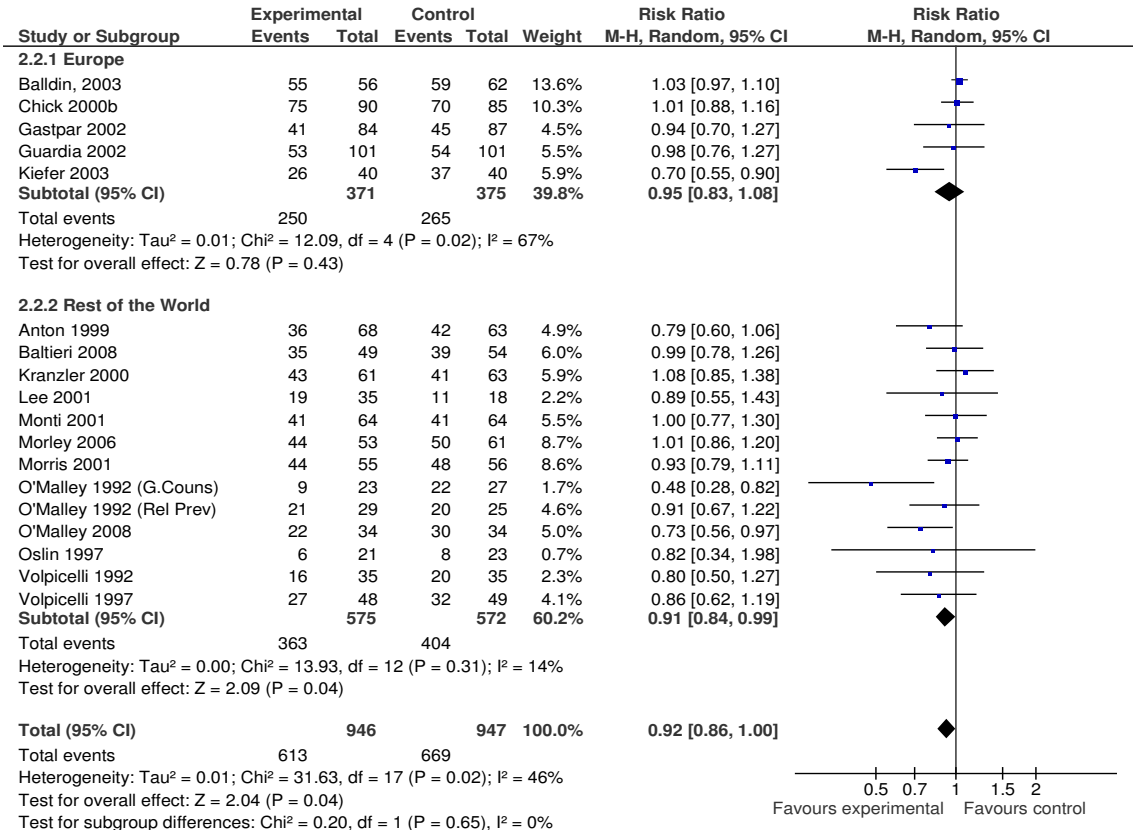
Figure 8: Forest plot for the comparison of treatment with naltrexone and placebo for the outcome Leaving due to adverse events, Europe versus the Rest of the World.



Meta-analysis of the third variable (lapsed – individuals drinking any alcohol at 12-16 weeks) found that there was no statistically significant difference between participants in the placebo group and those in the naltrexone group for this variable. However, there was significant, substantial heterogeneity present (Figure 9). The meta-analysis for the Rest of the World found that there was a small but significant 9% decrease in risk of relapse to any alcohol consumption at 12-16 week follow-up for the experimental group compared to the control group. There was no significant heterogeneity present. The RR for the two subgroups was similar with

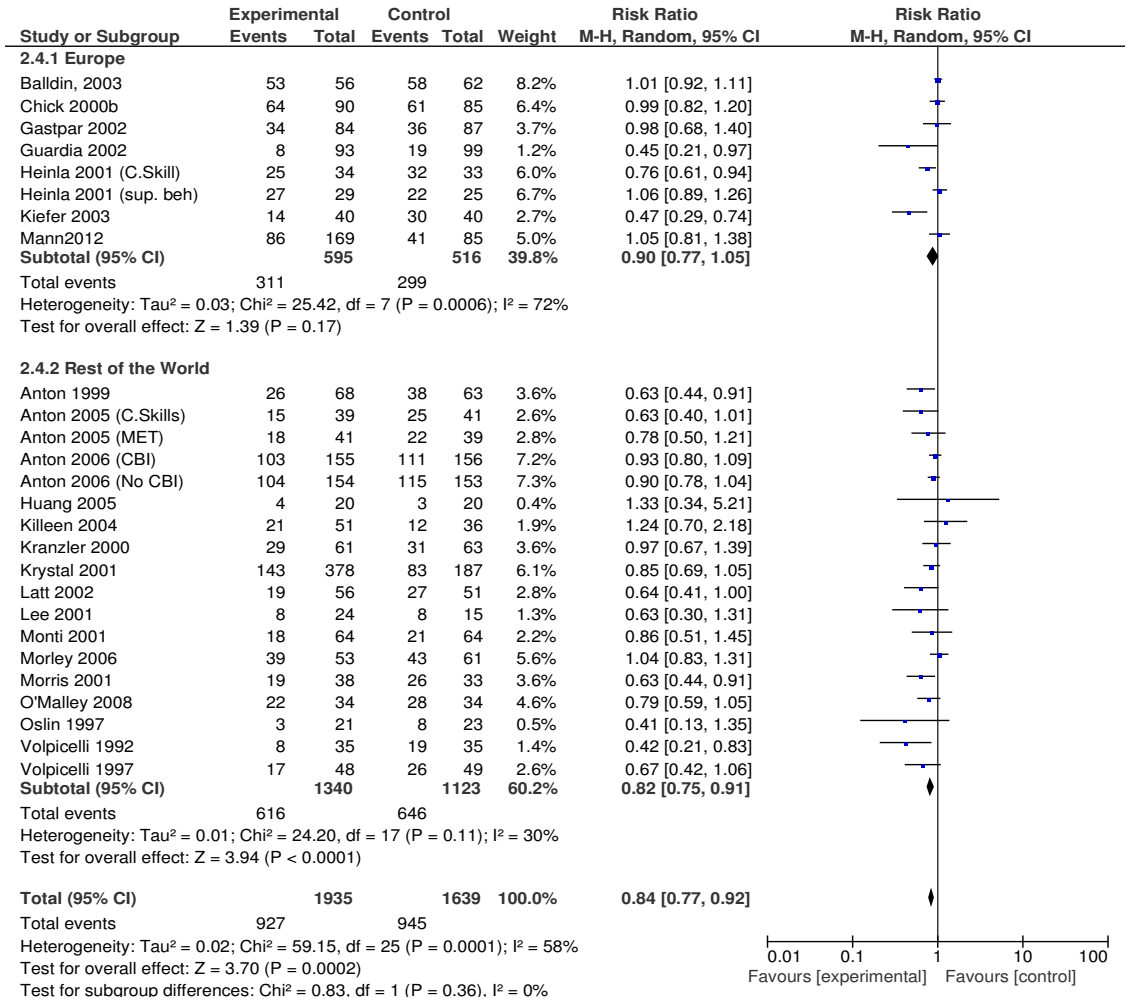
no statistically significant difference between the estimates. Seventeen studies reported data for this variable, a greater proportion of which were conducted outside of Europe (12 studies).

Figure 9: Forest plot for the comparison of treatment with naltrexone and placebo for the outcome Lapsed (individuals drinking any alcohol at 12-16 weeks follow-up), Europe versus the Rest of the World.



The final meta-analysis for the variable lapsed to heavy drinking at 3 months found that there was no significant difference between participants in the naltrexone and placebo groups for studies conducted in Europe but heterogeneity for this variable was statistically significant and substantial (Figure 10). For those studies conducted in the Rest of the World, there was a 16% decrease in risk of relapse to heavy drinking at 3 months for the naltrexone group compared to the placebo group with no significant heterogeneity. The relative risk estimate for the two sub-groups was not significantly different. Twenty three studies reported data for this variable, the majority of which were conducted in the Rest of the World (16 studies).

Figure 10: Forest plot for the comparison of treatment with Naltrexone and placebo for the outcome Relapse to heavy drinking (3 month follow-up), Europe versus the Rest of the World.



5.4 Discussion

There has been a considerable amount of research conducted worldwide investigating the efficacy of psychological therapies for the treatment of harmful use or dependence on alcohol (NICE, 2011). Despite the availability of this research, comparison between studies using meta-analysis has proven difficult due to the heterogeneous nature of the trials in this area. This report focused on CBT and MT, but found that there were considerable differences in the measurement of outcomes and the overall methodologies employed. These differences resulted in there being insufficient data to conduct subgroup analysis for studies conducted in Europe and the Rest of the World. This lack of consensus on how the impact of psychological therapies is measured in RCT's has created an obstacle to evaluating the effect of psychological therapies within and between different countries.

The available literature that has assessed the efficacy of acamprosate is methodologically heterogeneous. This resulted in it only being feasible to conduct analyses according to the subgroups Europe and the Rest of the World for two outcome variables. The meta-analysis found that there was a decreased risk of leaving the study early for participants in the acamprosate group compared to the placebo group for studies conducted in Europe but the opposite effect was true for studies conducted in the Rest of the World. It has been suggested that acamprosate is more effective in clients with a greater severity of symptoms experiencing tolerance and withdrawal symptoms (Anton et al., 2006; Mann et al., 2009) although a meta-regression conducted by NICE was inconclusive (NICE, 2011). European studies may include participants with greater symptom severity as they are often recruited via treatment services compared to research conducted in the US where participants are more often recruited via advertisement. Therefore, if the studies conducted in Europe had a greater proportion of participants with a more severe presentation, response to treatment may be greater leading to a decreased risk of disengaging with treatment. This hypothesis is supported a significant decrease in risk of lapsing at 12-16 week follow-up in those in the experimental group in those studies conducted in Europe but not for studies conducted in the Rest of the World. However, the RR was identical for both sub-groups but only two studies were included in the analysis for the Rest of the World with a small sample size, which may go some way in explaining the lack of consistent findings. Mann et al. (2012) reported the results of the PREDICT study, a RCT conducted in Germany the methodology of which was based on the COMBINE study (Anton et al., 2006). The PREDICT study assessed the efficacy of both acamprosate and naltrexone both individually and combined versus placebo and the results were compared with those of the COMBINE study. It was found that the European based PREDICT study included participants with a greater severity of harmful alcohol use compared to the US based COMBINE study but neither study found acamprosate to be effective (measured using the time to first heavy drinking).

Subgroup analysis was possible for only four variables for studies conducted assessing the efficacy of naltrexone. In contrast to the studies for acamprosate, there were no differences between the naltrexone group and placebo group for risk of discontinuation of treatment (leaving the study early) for either studies conducted in Europe or the Rest of the World. Risk of lapsing at 12-16 week follow-up was decreased in the experimental group for the studies conducted in the Rest of the World. However, this result was not found for those conducted in Europe. The overall RR was very similar for both subgroups with no statistically significant difference. However, heterogeneity was much greater for those studies conducted in Europe. A comparable result was found for relapse to heavy drinking (at 3 month follow-up), with substantial heterogeneity present for those studies conducted in Europe. The AMPHORA workpackage 6 Report on the mapping of European need and service provision for early diagnosis and treatment of alcohol use disorders has found significant variation in the organisation and provision of alcohol interventions across European countries (Wolstenholme et al., 2013). Pharmacological therapies are usually prescribed in conjunction with other care-planned treatment, and therefore differences in the care-planned treatment, for example the intensity, duration and type of treatment, may go some way to explain the heterogeneity present. Participants in the naltrexone group were at a greater risk of leaving the study early due to adverse events for studies conducted in the Rest

of the World but not in Europe. It is unlikely that this inconsistency between Europe and the Rest of the World can be explained by the dose of naltrexone administered as this was administered to participants at a standard dose of 50mg/day for all studies with the exception of the COMBINE study conducted by Anton et al., (2006), where a dose of 100mg was used.

5.5 Summary

There was not enough data available to conduct sub-group analyses for psychological therapies comparing trials conducted in Europe and the Rest of the World. The lack of data is not due to a lack of research but due to an absence of consistency in the methodologies used and the measurement and reporting of study outcome measures.

There was a statistically significant difference in the risk of discontinuing (leaving the study early) between the sub-groups, Europe and the Rest of the World, for studies assessing the efficacy of acamprosate. A decreased risk of disengagement was found for those in the experimental (acamprosate) group for European studies and an increased risk for those in the experimental group compared to controls for those studies conducted in the Rest of the World. This difference might be due to greater symptom severity of participants taking part in studies conducted in Europe, and this warrants further investigation. No other significant differences were found between the two subgroups.

6. Cost-effectiveness of brief interventions and specialist treatments

6.1 Introduction

Cost-effectiveness refers to the joint difference in costs and effects between interventions/therapies and can be assessed by the calculation of incremental cost effectiveness ratios over a given period of time. An intervention or treatment can be considered more cost-effective than an comparator if; i) it is less costly and more effective, ii) it is more costly and more effective, and the additional cost per extra unit of effectiveness is considered worth paying by decision-makers, and iii) it is less costly and less effective and the additional cost per extra unit of effectiveness for the alternative intervention is not considered worth paying (Barrett et al., 2006). There are only a few studies dedicated to understanding the economic benefits of alcohol interventions (McCollister & French, 2003). Financial constraints and scarce health care resources point towards cost-effectiveness analyses as increasingly important as clinical effectiveness analyses. Indeed, health care utilisation varies greatly across European countries, as does the nature of services (European Commission, 2004). The cost effectiveness differences between European countries are not typically distinguished from cost-effectiveness analyses compared to the rest of the world. Such differences could have important implications of public health policy in Europe as distinct from the rest of the world.

6.2 Methods

6.2.1 Aims and objectives

The aim is to have an estimate of the typical cost effectiveness of interventions in Europe based on published clinical research. The objective is to examine more closely the similarities and differences in outcomes between cost-effectiveness analyses conducted in different European countries. These aims will be achieved by conducting a sub-group analysis using the data presented in the cost-effectiveness analyses of psychological and pharmacological therapies published in the National Institute for Health and Clinical Excellence (NICE) Guideline on Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (NICE, 2011).

6.2.2 Quality criteria for selected studies

The quality of all economic papers eligible for inclusion were appraised using the methodology checklist for economic evaluations recommended by NICE (NICE, 2009). Checklist for economic evaluations was also applied to the economic models developed specifically by NICE (NICE, 2011).

6.2.3 Types of participants

To be included, the population of interest had to be identified as hazardous or harmful drinkers, or designated as having alcohol dependence requiring specialist treatment.

6.2.4 Included studies

Cost-effective analyses that compared only costs between two or more interventions were included. In the case of pharmacological therapies, studies were included that reported i) the dosage and route of administration, ii) the duration of treatment and the types of health professionals involved, and iii) the frequency and duration of treatment in the case of psychological interventions.

6.2.5 Costs and outcomes

The economic evaluation compares the costs and consequences of each therapy in comparison to a standard care package. The main outcome measured was the QALY.

6.3 Results

6.3.1 Economic outcomes of brief interventions in Europe

Table 7: Economic outcomes of brief interventions in Europe

Study	Country	Study Type	Costs	Results
Brief Interventions in Primary Care				
Europe				
Tariq et al., (2009)	**Holland**	Cost-Effectiveness Analysis	Health care costs included are the costs of opportunistic screening, costs of brief intervention, the costs of alcohol related diseases and costs of diseases unrelated to alcohol in life years gained	56,000 QALYs were gained at an additional cost of €298,000,000 due to providing alcohol SBI in the target population. This resulted in a cost-effectiveness ratio of €5,400 per QALY gained.

Rest of the World				
Fleming et al., (2002)	**US**	Cost-Benefit Analysis Comparators: Brief advice in general practice for drinking over threshold limits versus no treatment (general health information booklet)	Clinic costs for screening, assessment, primary visit, a follow up visit for patients, training costs, wider economic costs from a societal perspective, including patient and health care costs and consequences, and cost savings to the legal system following treatment. Patient costs included travel and lost work time.	Total economic benefit of the brief intervention to be $423,519 (95% CI $35,947-$884,848), the results being significantly positive although the 95% confidence interval is particularly large. Total savings of $228,071 failed to satisfy significance testing.

Brief Interventions in Emergency Department Settings			
<u>Europe</u>			
Barrett et al., UK (2006)	Cost-Effectiveness Analysis Screening in A&E followed by brief	Costs included all health services used, criminal justice resources and lost productivity.	65% probability that referral to an AHW is the more cost-effective strategy in reducing the consumption of alcohol among A&E attendees with a hazardous level of drinking, compared to an information only control group. The brevity of the treatment, its low cost (£6 per patient for each brief intervention) and

	intervention by hospital alcohol health worker (AHW) in alcohol misusing patients in A&E versus information only		short term efficacy adds to its case for selection.
Rest of the World			
Gentilello et al., US (2005)	Cost Benefit Analysis	Direct injury-related medical costs only.	The net cost savings of the intervention was $89 per patient screened, or $330 for each patient offered an intervention. The benefit in reduced health expenditures resulted in savings of $3.81 for every $1.00

				spent on screening and intervention

6.3.2 Economic outcomes of pharmacological therapies in Europe

Table 8: Economic outcomes of pharmacological therapies in Europe

Study	Country	Study Type	Costs	Results
Europe				
Annemans *et al.* (2000)	**Belgium**	Cost-analysis – based on Markov model Comparators: acamprosate (12 months) compared with placebo	Direct medical costs including hospital and ambulatory costs, that is GP, psychiatry and psychologist/psychotherapy consultations, biochemistry tests and drug costs	The total expected cost of the acamprosate strategy was €5,255 over the 2-year time horizon compared with €5,783 in the no treatment arm. Despite the higher drug acquisition costs, acamprosate was found to be a cost-saving intervention in terms of a reduction in hospitalisations due to alcohol-related complications.

Slattery et al., (2003)	**UK**	Cost-effectiveness analysis based on adapted Schadlich and Brecht (1998) model	Costs: costs of drugs, laboratory tests, medicals, key worker visits, GP consultations and visits to Alcohol Problems Treatment Unit. Service user travel time, and cost of seven disease points	Acamprosate resulted in net savings of £68,928 whilst naltrexone and disulfiram resulted in net economic costs of £83,432 and £153,189, respectively, in comparison with standard care amongst a hypothetical cohort of 1000 patients.
Palmer et al., (2000)	**Germany**	Cost-effectiveness analysis Markov model Comparators: acamprosate as adjuvant therapy + standard counselling therapy versus standard counselling therapy alone	Costs: direct medical costs including hospitalisations, rehabilitation costs, drug acquisition costs and psychosocial support	Adjuvant acamprosate therapy was shown to be the dominant strategy, as it was more effective and cheaper than standard therapy

Schadlich & Brecht (1998)	**Germany**	Cost-effectiveness analysis Comparators: acamprosate placebo + standard care (routine counselling/psychotherapy) in both	Direct medical costs. Treatment costs in acamprosate arm = 7,333,131 DM and 10,090,681 DM in the standard care group	Costs in standard care arm 26% higher than acamprosate arm The cost effectiveness ratio of acamprosate was -2602 DM. Acamprosate was the dominant treatment
Rychlik et al., (2003)	**Germany**	Cost-effectiveness analysis Comparators: acamprosate and standard care. Plus some form of psychosocial rehabilitation programme.	Direct medical costs including all physician visits, emergency treatments, diagnostic tests, lab tests, drugs, non-medical treatments, nursing, hospitalisation, cures and treatment of undesirable effects and side effects.	Acamprosate shown to dominate standard care because it is cheaper and more effective.
Parrot et al., (2006)	**UK**	Cost-utility analysis and cost-effectiveness analysis. Comparators: a detoxification service	Direct medical costs (also costs to criminal justice system and public/social services) Outcomes: QALYs in the cost-utility analysis; QALYs were calculated using the	In the cost-effectiveness analysis, the cost per unit reduction in alcohol was £1.87 in the Smithfield sample The cost for a reduction of one drink per day

		carried out at the Smithfield Centre in Manchester: open 24 hours per day, 365 days per year. The 10-day detoxification service comprised a 22-bed facility staffed by mental health nurses with 24-hour support from a local GP. versus no treatment	EQ-5D scores obtained by questionnaires given to the individuals who participated in the study.	was £92.75 at the Smithfield Centre. The cost per percentage point reduction in drinking was £30.71 at the Smithfield Centre The cost per QALY gained was £65,454 (£33,727 when considering only treatment costs) at the Smithfield Centre
Rest of the World				
Pettinati et al., (1999)	**US**	Cost-effectiveness analysis Comparators: inpatients versus outpatient addiction treatment services – both services followed multimodal clinical approach based on 12-step programme of AA	Costs: direct treatment costs – educational and therapy sessions, AA support group attendances, family educational programmes	Average costs of successfully completing treatment: inpatient: $9,014 (SD $2,986) outpatient: $1,420 (SD $619) Cost-effectiveness ratio was calculated by dividing treatment costs by the probability of returning to significant drinking. For treatment responders, the inpatient:outpatient cost-effectiveness ratio was calculated for the 3-

				month follow-up at 4.5:1, at the 6-month follow-up at 5.3:1, and at the 12-month follow-up at 5.6:1.
Zarkin et al., (2008)	**US**	Cost-effectiveness analysis Comparators: 1) Medical management + placebo 2) Medical management + naltrexone 100 mg per day for 16 weeks 3) Medical management + acamprosate 3 g per day 4) Medical management + placebo + combined behavioural intervention 5) Medical management + acamprosate + naltrexone 6) Medical management + naltrexone + combined behavioural intervention 7) Medical management + acamprosate + combined behavioural intervention 8) Medical management + naltrexone	Direct medical costs Social costs utilised were the sum of treatment costs and the economic costs of healthcare utilisation, arrests, and motor vehicle accidents. The costs of treatment include pharmaceutical, labour, and laboratory and non-laboratory assessment costs	On the basis of the mean values of cost and effectiveness, three interventions were shown to be cost-effective options relative to the other interventions for all three outcomes: medical management with placebo ($409 per patient), medical management plus naltrexone therapy ($671 per patient), and medical management plus combined naltrexone and acamprosate therapy ($1,003 per patient).

	+ acamprosate + combined behavioural intervention 9) Combined behavioural intervention only		
Zarkin et al., US (2010)	Comparators: 1) Medical management + placebo 2) Medical management + naltrexone 100 mg per day for 16 weeks 3) Medical management + acamprosate 3 g per day 4) Medical management + placebo + combined behavioural intervention 5) Medical management + acamprosate + naltrexone 6) Medical management + naltrexone + combined behavioural intervention 7) Medical management + acamprosate + combined behavioural intervention 8) Medical management + naltrexone	Direct medical costs Social costs utilised were the sum of treatment costs and the economic costs of healthcare utilisation, arrests, and motor vehicle accidents. The costs of treatment include pharmaceutical, labour, and laboratory and non-laboratory assessment costs.	At 3 years, median costs of MM plus acamprosate, MM plus naltrexone, MM plus acamprosate plus naltrexone, and MM plus acamprosate plus CBI were significantly lower than the median cost for MM plus placebo. Median cost differences ranged from $2500 to $3800 less than the median costs of MM and placebo.

	+ acamprosate + combined behavioural intervention 9) Combined behavioural intervention only		
Assessment & Delivery			
Europe			
Drummond et al., (2009)	UK	Cost-utility analysis Comparators: Stepped care – sequential series of interventions according to need and response after each successive step Minimal intervention –	Interventions and training, other healthcare, social care, criminal justice services. Outcomes: QALYs – calculated using EQ-5D utility scores obtained from questionnaires completed by study participants.	Intervention: mean total costs were £5,692 at baseline and £2,534 at 6 months. Mean QALY gain of 0.3849 Control: mean total costs were £6,851 at baseline and £12,637 at 6 months Mean QALY gain of 0.3876 Probability of intervention being cost-effective

	5-minute directive advice session		at UK £20–30,000 threshold: 98%
Parrott et al., UK (2006)	Cost-utility analysis and cost-effectiveness analysis. Comparators: a partial hospitalisation programme that was performed at Plummer Court, a NHS facility. Patients underwent 3-day inpatient detoxification, if required, followed by attendance at a day programme at the Newcastle service versus no treatment	Direct medical costs (also costs to criminal justice system and public/social services) Outcomes: QALYs in the cost-utility analysis; QALYs were calculated using the EQ-5D scores obtained by questionnaires given to the individuals who participated in the study.	The cost per unit reduction in alcohol was 1.66 among patients admitted to Plummer Court. The cost for a reduction of one drink per day was 22.56 at Plummer Court. The cost per percentage point reduction in drinking was 45.06 at Plummer Court. The cost per QALY gained was and 131,750 (90,375 when considering only treatment costs) at Plummer Court
Psychological Treatments			

Europe			
Slattery et al., (2003) UK	Cost-effectiveness analysis based on adapted Schadlich and Brecht (1998) model Comparators: coping-/social-skills training versus control intervention	A cost per attendee was calculated based on the staff requirements, accommodation (non-residential, that is hiring a hall), administration costs and manual. It also included patient travel costs and the costs of a consultation with a clinical psychologist. Total cost per person: £385. Costs of seven disease endpoints also included	Net healthcare savings over 20 years = -£274,008 (negative costs are a cost saving). The number of additional patients abstinent = 122. The costs per additional abstinent patient = -£2,252 Sensitivity analysis range = -4,441 to 54,923
Slattery et al., (2003) UK	Cost-effectiveness analysis based on adapted Schadlich and Brecht (1998) model Comparators: BSCT versus	A cost per attendee was calculated based on the staff requirements, accommodation (non-residential, that is hiring a hall), administration costs and manual. It also included patient travel costs and the costs of a consultation with	Net healthcare savings over 20 years = -£80,452 (negative costs are a cost saving) The number of additional patients abstinent = 86 The costs per additional abstinent patient = -£936

	control intervention	a clinical psychologist. Total cost per person: £385. Costs of seven disease endpoints also included	Sensitivity analysis range = -3,467 to 146,018
Slattery et al., (2003) UK	Cost-effectiveness analysis based on adapted Schadlich and Brecht (1998) model Comparators: MET versus control intervention	A cost per attendee was calculated based on the staff requirements, accommodation (non-residential, that is hiring a hall), administration costs and manual. It also included patient travel costs and the costs of a consultation with a clinical psychologist. Total cost per person: £385. Costs of seven disease endpoints also included	Net healthcare savings over 20 years = -£151,723 (negative costs are a cost saving) The number of additional patients abstinent = 99 The costs per additional abstinent patient = -£1,531 Sensitivity analysis range = -3,256 to 68,964
Slattery et al., (2003) UK	Cost-effectiveness analysis based on adapted Schadlich and Brecht (1998) model Comparators:	A cost per attendee was calculated based on the staff requirements, accommodation (non-residential, that is hiring a hall), administration costs and manual. It also included patient travel	Net healthcare savings over 20 years = -£183,795 (negative costs are a cost saving). The number of additional patients abstinent = 105 The costs per additional abstinent patient = -

		marital/family therapy versus control intervention	costs and the costs of a consultation with a clinical psychologist. Total cost per person: £385. Costs of seven disease endpoints also included	£1,759 Sensitivity analysis range = -3217 to 16,577
UKATT Research Team, (2005)	**UK**	Cost-effective analysis Comparators: MET versus SNBT	Costs: treatment costs; costs of hospitalisation, a hospital day visit, a hospital outpatient visit, a GP for home visit and in-surgery consultation, a prescription, a home visit by a CPN, a detoxification episode in primary care, rehabilitation and consultation in an alcohol agency, social service contact and court attendance Outcomes: QALYs, assessed using the EQ-5D questionnaire that was completed by clients at baseline and at 3 and 12 months. The QALYs were calculated using UK population norms for the evaluation of health states and linear interpolation to identify the areas under the QALY curve	Incremental QALYs were reported. After adjusting for baseline differences in the analysis, the SNBT group achieved 0.0113 QALYs less than the motivational group, but the difference was not statistically significant (bias corrected 95% CI: 0.0532 fewer to 0.0235 more). An incremental analysis was performed. MET had an incremental cost-effectiveness ratio of £18,230 in comparison with social therapy.

Rest of the World			
Mortimer & Segal, (2005)	**Australia**	Cost-effectiveness analysis and cost utility analysis –based on Markov model Comparators: MOCE versus BSCT Emphasis on controlled drinking	Clinical psychologist and psychiatric nurse training and trainee (clinical psychologist), consumables, lab investigations, phone calls, treatment sessions	BSCT dominated MOCE (cheaper and more effective). The cost per QALY gained was estimated at AU$2,145 in a predominantly male population with moderate dependence.

Mortimer & Segal, (2005)	**Australia**	Cost-effectiveness analysis and cost utility analysis –based on Markov model Comparators: MET versus no further counselling after initial assessment	Clinical psychologist and psychiatric nurse training and trainee (clinical psychologist), consumables, lab investigations, phone calls, treatment sessions	The incremental cost per changer = -AU$26.5 per changer; MET dominates no further counselling In the cost utility analysis: MET is estimated to deliver 0.116 QALYs gained per completer as compared to no further counselling. The incremental cost per completer of MET as compared to no further counselling was estimated at AU$389 and was assumed to reflect the incremental cost over the entire evaluation period. The cost per QALY gained is estimated at AU$3,366
Mortimer & Segal, (2005)	**Australia**	Cost-effectiveness analysis and cost utility analysis –based on Markov model Comparators: NDRL (subjects talked about anything they wanted, with no attempt to	Clinical psychologist and psychiatric nurse training and trainee (clinical psychologist), consumables, lab investigations, phone calls, treatment sessions	The Markov model was also used to estimate QALYs gained per person for NRDL compared to no further counselling The NDRL was inferior to the no further counselling based on the proportion remaining within national guidelines at 6-months follow-up. Given that the NDRL is also more costly

		steer towards alcohol problem). Four sessions over 6 weeks versus no further counselling after initial assessment and feedback/ education		than the no further counselling; the modelled cost-utility analysis has the no further counselling dominating the NDRL.
Holder et al., (2000)	**US**	Cost-analysis Comparators: 12-session CBT versus 4-session MET versus 12-session TSF	Costs: direct healthcare costs – treatments, inpatient care and outpatient care Total monthly mean costs (post-treatment): CBT: $186 MET: $176 TSF: $225	No formal incremental analysis presented by authors. Authors concluded that MET had potential for health-care cost savings after matching patients in each group for clinical prognosis
Fals-Stewart et al., (2005)	**US**	Cost-effectiveness analysis Comparators: BRT – 18 scheduled sessions over 12 weeks	Costs: treatment programme expenditures (for example, counsellor time, equipment); patient travel time Total mean treatment costs: BRT: $897 (SD $312) S-BCT: $1,294 (SD $321)	Authors calculated mean change in percentage of days of heavy drinking over 12 months divided by mean cost of treatment delivery (in $100 units) – higher ratios indicate greater cost-effectiveness Mean ratios:

	versus S-BCT – 24 sessions over 12 weeks versus IBT – 18 scheduled sessions over 12 weeks versus PACT – 18 scheduled sessions over 12 weeks	IBT: $840 (SD $200) PACT: $884 (SD $297)	BRT: 4.61 (SD 1.54) S-BCT: 3.30 (SD 1.61) IBT: 3.68 (SD 1.59) PACT: 3.48 (SD 1.70)

6.2 Summary

The lack of health economic data is not due to a lack of research but due to an absence of consistency in the methodologies used and the measurement and reporting of study outcome measures. Presenting a meaningful comparison and summary of the health economic evidence is difficult on account of the methodological differences across studies such as the comparator treatments considered, the study populations, and the costs and outcomes analysed. Many studies mainly presented economic analyses based on short-term time horizons. Additionally, the utilised costs arising from cost-effective analyses from regions in the rest of the world, dominantly the United States, may not be directly applicable to the European region. Therefore there are concerns about generalising from such trials to treatment settings across Europe.

Despite the limited number of studies available, existing evidence for cost-effectiveness served to highlight the following : i) there is insufficient evidence from which to suggest a preferred method of brief intervention to reduce hazardous and harmful alcohol consumption in primary health care settings, in terms of both clinical and cost effectiveness, (taking into consideration the benefits/adverse effects); ii) one study suggested there was a 65% probability that the preferred method of screening and brief intervention to reduce hazardous and harmful alcohol consumption in emergency department settings, in terms of both clinical and cost effectiveness (taking into consideration the benefits/adverse effects would be referral to an alcohol health worker in comparison to standard care. However, at present the evidence base for this finding is sparse; iii) from the studies included here, it was unclear which was the preferred method of pharmacological intervention aimed at attenuation of drinking/maintenance of abstinence for people who are alcohol dependent or harmful drinkers in residential and inpatient settings, in terms of both clinical and cost effectiveness (taking into consideration the benefits/adverse effects) as the findings reviewed are too methodologically heterogeneous to support a single pharmacological treatment over any other; iv) one study reported that there was a 98% probability that the preferred combined method of psychological and psychosocial intervention aimed at attenuation of drinking/maintenance of abstinence for people who are alcohol dependent or harmful drinkers in residential and inpatient settings, in terms of both clinical and cost effectiveness (taking into consideration the benefits/adverse effects) was a stepped care approach. However, at present the evidence base for this finding is sparse

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9. Annexes

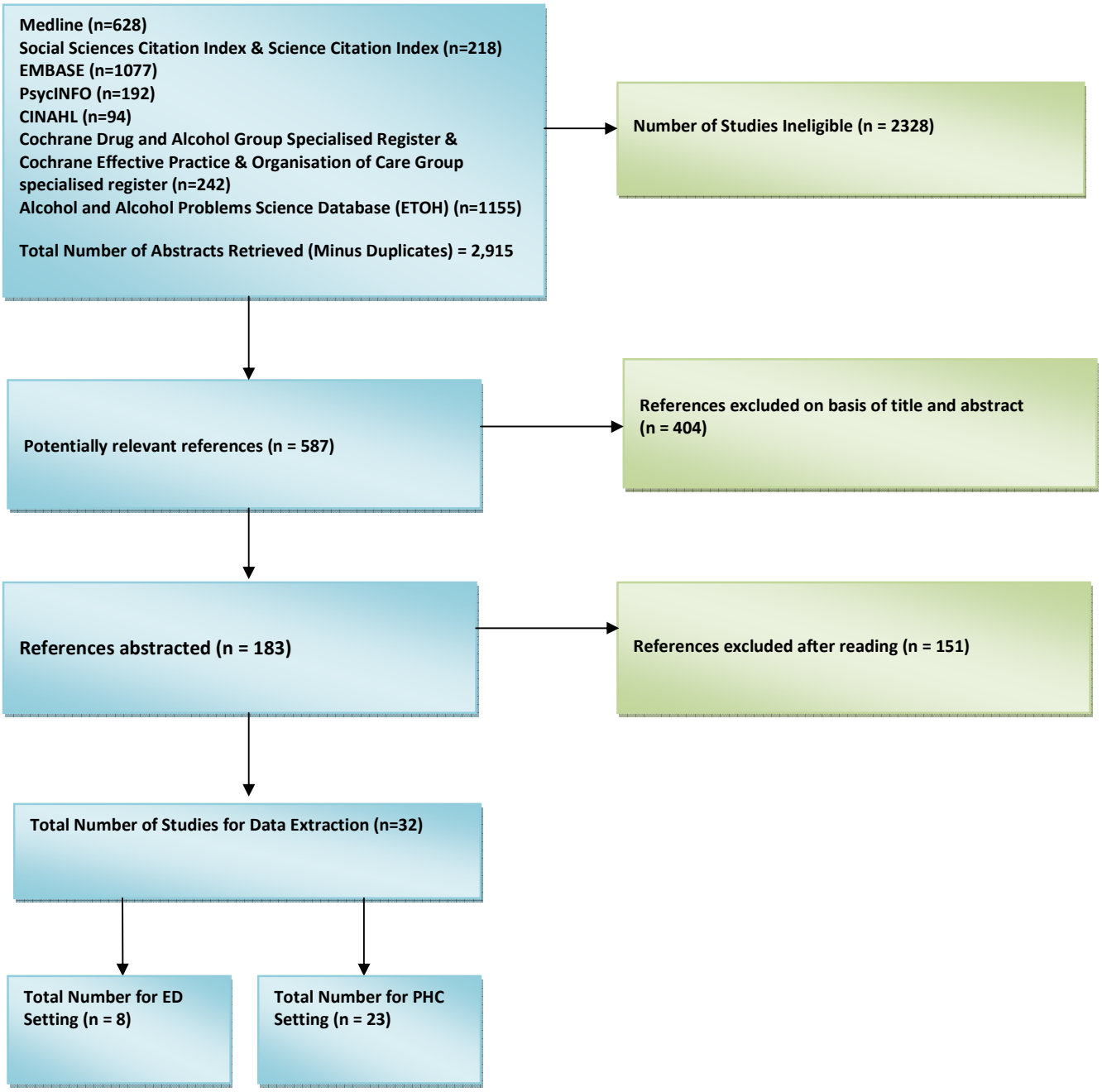
9.1 Search Strategy

1. family practice/
2. family pract$.tw.
3. general practice.sh.
4. general pract$.tw.
5. primary health care/
6. primary care/
7. community health services/
8. Community Care/
9. shared care.mp.
10. Patient Care/ or patient care team.mp.
11. family medicine/
12. family physician/
13. family phys$.tw.
14. emergency department.sh.
15. emergency care/
16. accident and emergency/
17. emergency physician/
18. emergency phys$.tw.
19. exp alcohol/
20. alcohol$.tw.
21. 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
22. 19 or 20
23. 21 and 22
24. alcohol reduction.mp.
25. brief intervention.mp.
26. early intervention.mp.
27. minimal intervention.mp.
28. alcohol therapy.mp.
29. harm reduction,.mp.
30. screening.mp.
31. (counseling or counselling).mp.
32. controlled drinking.mp.
33. (brief counseling or brief counselling).mp.

34. physician based intervention.mp.
35. general practitioner intervention.mp.
36. secondary prevention.mp.
37. general practitioner's advice.mp.
38. brief physician-delivered counseling.mp.
39. brief nurse-delivered counseling.mp.
40. identification.mp.
41. intervention.mp.
42. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. (alcohol or alcohol consumption).mp.
44. 42 and 43
45. 44 and 23
46. randomized controlled trial.mp.
47. controlled clinical trial.mp.
48. randomized controlled trials.mp.
49. random allocation.mp.
50. double blind method.mp.
51. single blind method.mp.
52. or/46-51
53. (animal not human).mp.
54. 52 not 53
55. clinical trial.mp.
56. exp clinical trials/
57. (clin$ adj2 trial$).ti,ab.
58. ((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab.
59. placebos.mp.
60. placebo$.ti,ab.
61. random$.ti,ab.
62. research design.mp.
63. or/55-62
64. 63 not 53
65. 64 not 54
66. comparative study.mp.
67. exp evaluation studies/
68. follow up studies.mp.
69. prospective studies.mp.
70. (control$ or prospectiv$ or volunteer$).ti,ab.
71. or/66-70

72. 71 not 53
73. 71 not (54 or 65)
74. 54 or 65 or 73
75. 74 and 45

9.2 Quality of Reporting Chart



9.3 Conversion Table

Study	Alcohol Measures	Conversion Factor	Source of Conversion
PHC			
Europe			
Aalto *et al.*, 2000	grams/week	1	**N/A**
Altisent *et al.*, 1997	units/week	8	**Altisent *et al.*, 1997**
Beich *et al.*, 2007	drinks/week	12	**Beich *et al.*, 2007**
Chang *et al.*, 1997	drinks/week	11.671	**Miller *et al.*, 1991; Kaner *et al.*, 2007**
Cordoba *et al.*, 1998	units/week	8	**Cordoba *et al.*, 1998**

Curry *et al.*, 2003	drinks/week	11.671	**Miller *et al.*, 1991; Kaner *et al.*, 2007**
Diez *et al.*, 2002	units/week	8	**Diez *et al.*, 2002**
Fernandez *et al.*, 1997	units/week	10	**Miller *et al.*, 1991; Kaner *et al.*, 2007**
Heather *et al.*, 1987	units/month	8 x (12/52)	**Heather *et al.*, 1987; Kaner *et al.*, 2007**
Huas *et al.*, 2002	units/week	10	**Heather *et al.*, 2006; Kaner *et al.*, 2007**
Israel *et al.*, 1996	drinks/month	13.456 x (12/52)	**Miller *et al.*, 1991; Kaner *et al.*, 2007**
Kunz *et al.*, 2004	drinks/week	11.671	**Miller *et al.*, 1991; Kaner *et al.*, 2007**

Lock *et al.,* 2006	drinks/week	8	**Miller *et al.,* 1991; Kaner *et al.,* 2007**
Romelsjo *et al.,* 1989	grams/day	1 x 7	**N/A**
Rubio *et al.,* 2010	drinks/week	12.8	**Rubio *et al.* 2010**
Scott & Anderson 1991	units/week	8	**Miller *et al.,* 1991**
Wallace *et al.,* 1988	units/week	8	**Miller *et al.,* 1991; Kaner *et al.*, 2007**
Rest of the World			
Chang *et al.,* 1997	drinks/week	11.671	**Miller *et al.,* 1991; Kaner *et al.,* 2007**
Curry *et al.,* 2003	drinks/week	11.671	**Miller *et al.,* 1991; Kaner *et***

			***al.,* 2007**
Fleming *et al.,* 1997	drinks/week	12	**Fleming *et al.,* 1997**
Fleming *et al.,* 1999	drinks/week	12	**Fleming *et al.,* 1999**
Fleming *et al.,* 2004	drinks/month	11.671 x (12/52)	**Miller *et al.,* 1991; Kaner *et al.,* 2007**
Maisto *et al.,* 2001	drinks/month	11.671 x (12/52)	**Miller *et al.,* 1991; Kaner *et al.,* 2007**
Ockene *et al.,* 1999	drinks/week	12.8	**Ockene *et al.,* 1999**
Richmond *et al.,* 1995	drinks/week	10	**Richmond *et al.,* 1995**
Senft *et al.,* 1997	drinks/3 months	11.671 x (4/52)	**Miller *et al.,* 1991; Kaner *et al.,* 2007**

ED			
Europe			
Cherpitel *et al.,* 2010	drinks/week	14	**Correspondence with Author**
Crawford *et al.,* 2004	units/week	8	**Miller *et al.,* 1991; Kaner *et al.,* 2007**
Daeppen *et al.,* 2007	drinks/week	10	**Correspondence with Author**
Drummond *et al.,* (Under review)	drinks/week	8	**Correspondence with Author**
Rest of the World			
Blow *et al.,* 2006	drinks/week	11.671	**Miller *et al.,* 1991**

D'Onofrio *et al.*, 2008	drinks/week	11.671	**Miller *et al.*, 1991**
D'Onofrio *et al.*, 2012	drinks/week	11.671	**Miller *et al.*, 1991**
Gentilello *et al.*, 1999	drinks/week	11.671	**Miller *et al.*, 1991: Kaner *et al.*, 2007**