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RISK FACTOR STUDY

How to Reduce the Burden of Harm from Poor Nutrition, Tobacco Smoking, Physical Inactivity and Alcohol Misuse: Cost-Utility Analysis of 6 Interventions to Promote Safe Use of Alcohol

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The content of the report remans the responsibility of the study team.

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Introduction to Risk Factor Project

The risk factor project was commissioned by the Department of Health and Ageing, Population Health Division to determine how best to reduce the burden of harm on the Australian community attributable to physical inactivity, poor nutrition, alcohol misuse and tobacco smoking. The research objective was to establish which interventions are most effective and cost-effective and thus able to make the greatest contribution to harm reduction for resources allocated. This is a technical analysis, focused on health, measured by mortality and quality of life as the primary objective of health policy. While there may be other objectives and other issues relevant to policy decisions, these have not been incorporated into the analysis, due largely to their more subjective nature.

The project has been completed in several stages. It commenced with a literature review of evidence concerning interventions designed to modify these four lifestyle behaviours (Segal, Dalton, Robertson et al 2003). The primary purpose of this task was to identify a set of interventions for economic analysis that met nominated selection criteria related to quality of evidence etc. In practice, in order to achieve comprehensiveness, interventions were also included that did not meet the quality of evidence criteria. The interventions selected through this process for economic analysis are listed in Table 1. We identified 35 interventions for assessment and have been able to report 29 cost-utility (C-U) analyses; 22 based on models developed by the research team, 3 based on published models, 2 'scenario analyses', whilst 2 interventions were dominated. The results of these analyses are reported in 6 volumes; an Executive Report, plus 5 technical volumes covering each of the 4 risk factors, plus one for multiple risk factor interventions.

The relationship between the intervention, behaviour and health outcomes are complex and not necessarily directly observable. We have thus adopted a 2-staged approach to measuring economic performance that distinguishes the impact on behaviour from the consequent impact on health. We have in most cases generated an 'intermediate' measure of performance, a *cost-effectiveness ratio,* in which interventions are analysed in terms of the cost to achieve an observed change in lifestyle, based on trial results. Interventions that target the same lifestyle behaviour can then be directly compared, without having to understand the relationship between behaviour and health. This technique is applicable where behaviour is consistently and simply described. It is less useful where the life style attribute is complex, such as nutrition or physical activity. It also cannot be used to compare interventions which target several behaviours or that address different behaviours. The ultimate approach to performance measurement is the *cost-utility analysis* which we have conducted wherever data allowed.

We have, where data allows, estimated QALYs from observed impact on health outcomes, otherwise using published relationships between lifestyle behaviours and health or clinical parameters and health. In short we draw on a combination of trial evidence and pertinent epidemiological and other data in a standard cost-utility analysis. Most use a markov model structure, with the primary input the probability of moving control and intervention cohorts between pertinent health states. Full details of each model and the assumptions adopted are described in the chapters of this Executive Report and the five Technical Reports, one for each risk factor and are summarised in Table 2. Where possible, consistent assumptions have been used for all interventions. The impact of alternative assumed values for uncertain parameters have been explored via univariate sensitivity analysis or probabilistic sensitivity analysis where data quality allows.

Table 1 Interventions selected for economic evaluation

MULTI-FACTORIAL (Chapter 1-9)

Research Paper 2

Adult Interventions	**School-based Interventions**
▪ Fighting Fit, Fighting Fat Media Campaign	▪ Student TV viewing and obesity
▪ Stanford 5 City media/community Project	▪ Interdisciplinary student intervention and obesity
▪ GutBusters Workplace Program	▪ Cardiovascular disease risk factors in children
▪ Workplace prevention of heart disease *	▪ Cardiovascular disease risk reduction in children
▪ Oxcheck – Primary care nurse health checks	

PHYSICAL ACTIVITY (Chapter 1-4)

Research Paper 3

▪ Australian GP Active Script *	▪ General practice exercise referral for cardiovascular disease risk factors
▪ New Zealand GP Active Script	▪ Physical activity program and individualised advice for over 60 year olds
▪ Community based exercise for over 65 year olds	

NUTRITION (Chapter 1-8)

Research Paper 4

▪ Nutritional counselling in general practice *	▪ Orlistat plus diet for obesity
▪ Mediterranean diet in those with previous myocardial infarction	▪ Lifestyle changes to prevent type 2 diabetes
▪ Reduced fat diet for those with impaired glucose intolerance	▪ Talking computer for nutrition *
	▪ Nurse nutritional counselling in general practice
	▪ Multi-media '2 fruit 5 veg' campaign

SMOKING (Chapter 1-5)

Research Paper 5

▪ US mass media smoking campaign – Massachusetts Tobacco Control Program	▪ Meta-analysis of 34 trials evaluating minimal to intensive advice in general practice
▪ Australian mass media campaign – Phase 1 National Tobacco Campaign	▪ Meta-analysis of 86 trials comparing brief intervs, NRT and behavioural interventions *
▪ Meta-analysis of 16 Bupropion SR trials	▪ Phone counselling as adjuvant therapy for NRT

ALCOHOL (Chapter 1-6)

Research Paper 6

▪ US mass media alcohol campaign *	▪ MOCE and BSCT for moderately dependent drinkers
▪ Meta-analysis of 8 trials evaluating brief interventions in primary care for problem drinking	▪ MET and NDRL for mildly to moderately dependent drinkers
▪ Brief interventions for heavy drinkers	▪ Meta-analysis of 7 trials evaluating Naltrexone and psychosocial therapy

Notes

* Cost-utility analysis not completed due to insufficient evidence, interventions too complex or resource and time constraints.

NRT: Nicotene replacement therapy; MOCE: Moderation-Orientated Cue Exposure. BSCT: Behavioural Self-Control Training.

MET: Motivational Enhancement Therapy. NDRL: Non-directive Reflective Listening.

Table 2 Key assumptions underlying the economic modelling

Description	Details
Base case	
Discount rate	5% for costs and benefits.
Cycle length	1 year for all Markov models except the diabetes Gutbusters model of 5 years and the alcohol model with cycles 3 or 6 months.
Time horizon	Chosen to match the disease process, age of participants and reflecting available evidence; ranging between 5 years & life expectancy.
Evidence of treatment effect	Ideally drawn from meta-analyses or if unavailable from key RCTs.
Length of intervention benefit	Generally in the base case the length of intervention benefit is not extended beyond the duration of the trial evidence.
Direct costs of intervention	Estimated in Australian dollars 2003, based on described resource use or published costs adjusted by health price index and exchange rate.
Indirect costs	Indirect costs such as transportation, waiting times, costs to careers and productivity losses have not been included.
Comparator	Usual care, current practice, placebo or no intervention. If the comparator was inappropriate, an own-control comparison was made of intervention group, comparing final outcomes and baseline values.
Downstream costs	Excluded in base case analysis.
Model structure- Examples	
Smoking interventions	Markov model, containing ex-smoker tunnel sequence. Cohort initially distributed across smoker states according to prevalence in Australian population. Mortality differential commences from age 25 years.
Alcohol interventions	Tunnel sequences used to delay the health effects of moving from one state to another, quality of life gain directly attributable to alcohol moderation varies depending on severity of alcohol problems.
Hypothetical scenario analysis	Was performed for selected multi-factorial school based interventions given gap in key effectiveness data.
Modification of published model	Where a sound published model was available Australian costs were applied, and in some cases model assumptions were modified.
Sensitivity analysis - examples	
Discount rate	0%,3% and 7%
Downstream costs	Included for interventions targeted at specific disease such as diabetes or heart disease. Otherwise a threshold analyses was performed to show the downstream cost offset associated with intervention dominance.
External effects	Health effects for family members are considered for alcohol interventions
Other variables frequently varied	Time horizon, length of intervention benefit, utilities, costs, treatment effect, characteristics of starting population, relapse rates.

1. Mass media interventions for alcohol problems

1.1 Description

Intervention type

Mass media intervention for unsafe alcohol consumption aimed at the entire population.

References/sources of evidence

This review is based on the meta-analysis carried out by Treno, A.J., and Holder, H.D. (1997) Community mobilization: Evaluation of an environmental approach to local action. *Addiction*, 92(Suppl. 2), S173-S187.

1.2 Quality of evidence

Due to an absence of quantifiable outcomes, the Treno and Holder (1997) study of the US mass media campaign is excluded from further consideration and no attempt has been made to derive estimates of cost effectiveness or cost utility for this intervention.

2. Brief interventions for alcohol problems: a meta analysis

2.1 Description

Intervention type

This meta-analysis attempts to assess the clinical effectiveness of Brief Interventions (BI) for alcohol use disorders when compared to control.

References/sources of evidence

This review is based on the meta-analysis carried out by Wilk et al. (Wilk, A. I., Jensen, N. M. and Havighurst, T. C. (1997) *Journal of General Internal Medicine.,* 12**,** 274-83)

Intervention description

Recruitment and target population: Brief interventions were defined for the purposed of this analysis as those studies not involving more than 1 hour of counselling or more than 4 sessions.

Searches were made of MEDLINE and PsycLIT for studies published between 1966 to 1995.

Inclusion/exclusion criteria

Criteria for inclusion are outlined below:

- Clear focus on alcohol abuse or dependence or on heavy drinking
- Focus on intervention and outcome
- Publication in English
- Subjects aged 19 years or older
- Prospective clinical trial
- Control group that receives no alcohol-related treatment or intervention
- Sample size greater than 30
- "Brief intervention that is motivational with a self-help orientation"

A total of 5,896 articles were initially identified by electronic search and follow up of cited references. Of these, 99 were considered for inclusion in the meta-analysis. Of this sub-group, only 12 (n= 3,948) studies were finally included in the meta-analysis. 38 were excluded because they compared BI to other interventions and did not have a non-intervention control group, 21 studies had no control group and 15 studies incorporated other more intensive treatment with brief interventions. The remaining 13 articles were excluded for varying reasons including being unrandomised or being of a retrospective nature.

2.2 Quality of evidence

Evaluation description

Design:

The aim of the study was to obtain pooled data on the efficacy of brief interventions in alcohol use disorders.

The meta-analysis calculated study specific and overall Odds Ratios for moderation of drinking, which were also analysed by covariate. The covariates chosen were gender, intensity of counselling and clinical setting.

Analysis:

All studies were first assessed for quality using the Chalmers' Scoring System. Odd Ratios and 95% confidence intervals were calculated, where possible, for individual trials. Odds Ratios were only able to be calculated for 8 of the 12 trials. Individual Odds Ratios were combined into a overall Odds Ratio using the One-Step (Peto) method. The results were checked using the Mantel-Haenszel method. Heterogeneity between studies was assessed using a chi-square test. A z-statistic was also used to check for heterogeneity between the different sub-groups analysed.

Outcome measures:

There was a single primary outcome: achievement of alcohol moderation 6 or 12 months after the intervention and the inclusion criteria for trials into the Wilk et al (1997) meta-analysis required a clear focus on alcohol abuse or dependence or on heavy drinking. Eight of the 12 trials excluded patients with consumption of less than 20 drinks/week. That said, "the definition of excessive or problem drinking is imprecise and often depends on not only quantity and frequency of alcohol consumed but also individual characteristics such as gender, age, weight and comorbid conditions" (p.2). Wilk et al (1997) also caution that "generalizability of results must be limited to less severely affected drinkers who exhibit little or no alcohol dependence" (p5) and argue that "more severely affected individuals with evidence of loss of control, tolerance, or withdrawal symptoms would be at risk of withdrawal or failure if brief intervention were the sole treatment" (p5). We therefore operationalise the outcome of alcohol moderation as a move from unsafe drinking as per NHMRC Guidelines to safe drinking as per NHMRC Guidelines[1].

Assessment

Sources of bias:

A limitation of the study was the fact that in only included published studies written in English. There may well have been publication bias, resulting in overstatement of the effects of the intervention.

A major shortcoming of the trials included in the meta analysis was the short follow up duration. Effect sizes are only measured up to 12 months and another meta-analysis of brief interventions has noted that the effect sizes are largest at the earliest follow-up points "suggesting decay in intervention effects over time" (Moyer et al., 2002). No studies included follow ups of greater than one year. The authors stress that future studies must endeavour to address the lack of evidence on long term efficacy of brief interventions and their effects on morbidity and mortality.

As in most meta-analyses, the variety of intervention methods within the meta-analysis was somewhat diverse, especially regarding the intensity of the intervention. Some studies involved no follow up sessions, others had up to 3.

2.3 Outcomes – as reported

The outcome measure was achievement of alcohol moderation 6 or 12 months after the intervention.

Heterogeneity statistics were also calculated and reported. Full details can be seen in Tables 2.1 and 2.2 below.

[1] Current NHMRC Guidelines for 'low risk alcohol consumption' (NHMRC, 2001) are intended to place the majority of the population within the range of 'safe' exposures. For a low risk of harm over the long-term in adult males, the NHMRC recommends up to 28 standard drinks/week with not more than 6 standard drinks in any one day and one or two alcohol-free days per week. In adult females, the NHMRC recommends up to 14 standard drinks/week with not more than 4 standard drinks in any one day and one or two alcohol-free days per week.

Table 2.1 Percentage moderation and odds ratios for brief interventions versus control

Study	Treatment Group Drinking Moderation (%)	Control Group Drinking Moderation (%)	Sample size	Odds Ratio	95% CI
Wallace	201/448 (45%)	122/459 (27%)	909	2.22	1.69-2.91
Anderson and Scott	14/80 (18%)	4/74 (5%)	154	3.2	1.2-8.54
Scott and Anderson	9/33 (27%)	10/39 (26%)	72	1.09	0.38-3.09
Babor and Grant	391/758 (52%)	134/361 (37%)	1119	1.79	1.39-2.3
Heather et al	9/59 (15%)	3/32 (9%)	104	1.66	0.47-5.89
Antti-Poika et al	22/49 (45%)	8/40 (20%)	120	3.01	1.25-7.25
Chick et al	34/69 (49%)	20/64 (31%)	156	2.1	1.05-4.19
Richmond et al	34/136 (25%)	13/61 (21.3%)	378	1.22	0.6-2.48

Table 2.2 Benefit of brief interventions versus control by subgroup

Subgroups	Number of studies	Treatment Group Drinking Moderation (%)	Control Group Drinking Moderation (%)	Odds Ratio	95% CI	Heterogeneity (x^2, p)
All trials	8	714/1632 (43.8%)	314/1130 (27.8%)	1.95	1.66-2.3	6.23, 0.51
Quality trials	6	658/1514 (43.5%)	286/1026 (27.9%)	1.91	1.61-2.27	5.19, 0.51
Gender						
Female	3	158/317 (49.8%)	66/241 (27.4%)	2.42	1.7-3.45	4.16, 0.12
Male	5	513/1120 (45.8%)	232/796 (29.1%)	1.9	1.57-2.31	5.64, 0.23
Intensity of Counselling						
1 session	5	457/999 (45.7%)	171/570 (30%)	1.83	1.46-2.8	2.42, 0.66
>1 session	3	257/633 (40.6%)	143/560 (26%)	2.12	1.66-2.7	3.04, 0.22
Clinical setting						
Outpatient	6	658/1514 (43.5%)	286/1026 (27.9%)	1.91	1.61-2.27	5.19, 0.53
Inpatient	2	56/118 (47.5%)	28/104 (26.9%)	2.41	1.4-4.15	0.4, 0.53

Behaviour change and clinical parameters

The findings of this meta analysis that covers 12 studies demonstrated that overall problem drinker receiving brief interventions were nearly twice as likely to moderate their drinking when compared to control. There was no difference in outcomes when subgroups were analysed by gender, intensity of counselling or clinical setting. Sensitivity analysis varying the participants involved by the quality of the trial did not show any great difference in outcomes.

Adherence to treatment: The meta analysis does not give evidence of adherence to treatment.

Mortality

Mortality and alcohol related morbidity outcomes are not reported in the study.

2.4 Program costs

As reported by trial

Based on resource use

Research costs were not mentioned in this study. The cost items described in Tables 2.3 to 2.5 are the estimated cost to deliver BI in Australia today at three different intensities. Costs incurred purely as a result of research activity, rather than in the administration of the intervention, have been excluded. As the viewpoint taken is that of the Department of Health and Ageing, costs to the participant have not been included.

Brief interventions were defined for the purposed of this analysis as those studies not involving more than 1 hour of counselling or more than 4 sessions.

Costs have been calculated using the spectrum of interventions identified in the Saunders studies on brief interventions. The descriptions of the interventions were based on the following material:

- Saunders, J.B., Hanratty, S.J., Burns, F.H., Douglas, A., Clarke, J.I. & Reznik, R.B. 1991. Successful early intervention for harmful alcohol consumption: Results from the WHO randomised controlled trial. *Proceedings of the Autumn School for Studies in Alcohol and Drugs*. May, 1991: 183-192.
- Wutzke, S.E., Conigrave, K.M., Saunders, J.B. & Hall, W.D. 2002. The long term effectiveness of brief interventions for unsafe alcohol consumption: A 10 years follow up. *Addiction*. Vol 97: 665-675.

Table 2.3 Simple advice (5 mins total)

	Cost	Time	Number required	Total cost	Cost per person
Consultation with GP 5 minutes added to consultation	$13.58	5 minutes	1		$13.58
Information leaflet	$940.00 for 1000 [i]		705	$940.00	$1.33
Total					$14.91

Table 2.4 Brief counselling (20 mins total)

	Cost	Time	Number required	Total cost	Cost per person
Consultation with GP 20 minutes added to consultation	$27.15 [ii]	20 minutes	1		$27.15
Information leaflet	$940.00 for 1000		705	$940.00	$1.33
Diary card	$345 for 300		~530	~$1.15	$1.15
Total					$29.63

Table 2.5 Extended counselling (60 mins total)

	Cost	Time	Number required	Total cost	Cost per person
Consultation with GP 20 minutes at 3 separate sessions	$87.55	60 minutes	1		$87.55
Information leaflet	$940.00 for 1000		705	$940.00	**$**1.33
Diary card	$345 for 300 [iii]		~530	~$1.15	$1.15
Total					$90.03

Costs associated with consulting premises and administration are assumed to be accounted for in the professional fee schedule so have not been included as a separate component.

The studies for which raw data is available (8 of 12) have been analysed to establish which intervention type they fall into in order to produce a mean weighted cost (see Table 2.6 below).

Table 2.6 Intensity of intervention by study

Study	Simple advice (n)	Brief counselling (n)	Extended counselling (n)
1			909
2		154	
3		72	
4		1119	
5		104	
6			378
7			120
8			156

Using the figures above a mean weighted cost per person can be derived thus:
Percentage of participants falling into each category:
Simple advice 0%
Brief counselling 48.1%
Extended counselling 51.9%

Therefore, using the previously derived costs for each type of interventions, mean weighted cost will be: 0.481 x $29.63 + 0.519 x $90.03= $60.98

[i] Design and Print Centre, University of Melbourne 2003
[ii] Figures from MBS Schedule November 2003
[iii] Design and Print Centre, University of Melbourne 2003

2.5 Performance

Within-trial cost effectiveness

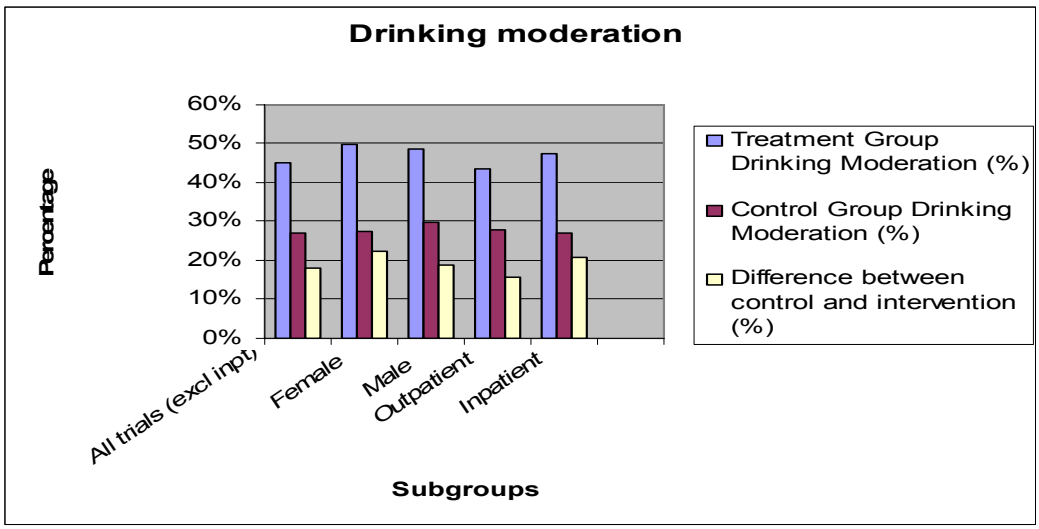
Cost-effectiveness ratios (costs per changer) have been calculated for all trials and for selected subgroups. Clinically significant differences between intervention and control by subgroup are summarised again in Table 2.7 and Figure 2.1 below. To avoid selection bias, trials involving inpatients have been isolated from others and outcomes calculated separately. The inpatients in at least one of the studies were injured patients who would be expected to have a greater impetus to change as they had already experienced a significant health effect i.e. injury from their drinking. Subgroup analysis was also performed on participants who received single interventions and those who received more than one session. We did not complete cost-effectiveness analysis for different levels of BI intensity because many studies allowed additional sessions at the discretion of the therapist and this would bias more severely affected participants towards the greater than one session group. Table 2.8 reports estimates of cost per changer for all trials and for selected subgroups.

Table 2.7 Clinically significant treatment effects by subgroup

	Treatment Group Drinking Moderation	Treatment Group Drinking Moderation (%)	Control Group Drinking Moderation	Control Group Drinking Moderation (%)	Difference between control & intervention (%)
All trials (excluding inpatient trials)	646/1427	45%	122/459	27.0%	18.00%
Gender					
Female	158/317	49.8%	66/241	27.4%	22.4%
Male	445/915	48.6%	199/671	29.7%	18.9%
Clinical setting					
Outpatient	658/1514	43.50%	286/1026	27.90%	15.60%
Inpatient	56/118	47.5%	28/104	26.9%	20.6%

Of interest, the findings above support the very recent systematic review on brief interventions performed by the U.S Preventive Services Task Force in which the proportion of participants drinking at safe levels was 10%-19% greater compared to control. [iv]

Figure 2.1 Clinically significant treatment effects by subgroup



[iv] Whitlock, E. P., M. R. Polen, et al. (2004). "Behavioural Counseling Interventions in Primary Care to Reduce Risky/Harmful Alcohol Use by Adults: A Summary of the Evidence for the U.S. Preventive Services Task Force." Ann Int Med **140**(7): 557-568.)

Table 2.8 Cost per changer

	Simple Advice	Brief Counselling	Extended Counselling	Mean weighted cost
Cost per participant	$14.91	$29.63	$90.03	$60.98
Cost per changer: All trials (18%)	$82.83	$164.61	$500.17	$338.78
Cost per changer: Subgroup analyses				
Cost per changer: Female (22.4%)	$66.56	$132.28	$401.92	$272.23
Cost per changer: Male (18.9%)	$78.89	$156.77	$401.92	$322.65
Cost per changer: Inpatient (20.6%)	$72.38	$143.83	$437.04	$296.02
Cost per changer: Outpatient (15.6%)	$95.51	189.94	$577.12	$390.90

Modelled cost-utility analysis

Pooled data from the Wilk et al (1997) trials comparing the intermediate outcome of moderation in alcohol consumption indicate a treatment effect in favour of the brief interventions. Due to differences in pooled estimates of treatment effect for men as compared to women and the availability of supporting data by age and sex band, the modelled cost-utility analysis is run for men and women separately. While the magnitude of the treatment effect for men and women differed sufficiently to justify separate models (OR: 1.9 versus OR: 2.42), there were no differences in the direction of effect or with respect to statistical significance (95%CI: 1.57-2.31, 95%CI: 1.7-3.45).

Because intermediate outcomes represent an imperfect proxy for the impact of an intervention on quality and quantity of life, we translate the results of the Wilk et al (1997) meta-analysis in cost/QALY ratios. A crude cost-utility analysis is presented based on the assumptions and parameter values specified below. At this stage, the difference in per person direct treatment costs is assumed to reflect the incremental cost over the entire evaluation period. More specifically, external effects beyond the family unit (such as the cost of alcohol-related road trauma) and downstream healthcare costs have been excluded from the modelled cost-utility analysis. It is likely that the inclusion of these line-items will serve to further reduce the cost/QALY ratio. Assuming that appropriate supporting data can be identified, downstream costs and broader external effects will be included at a later date.

A Markov model with seven non-absorbing (alcproblem1, alcproblem2, alcproblem3, moderate1, moderate2, moderate3, dependence) and one absorbing state (dead) was used to estimate QALYs gained per person for brief intervention as compared to control. In men aged 30 years brief intervention is estimated to deliver 0.091 QALYs gained per person if external effects are assumed away. In men aged 30 years of age the brief intervention is estimated to deliver 0.243 QALYs gained per person if within-family external effects are included. In women aged 30 years brief intervention is estimated to deliver 0.125 QALYs gained per person if external effects are assumed away. In women aged 30 years of age brief intervention is estimated to deliver 0.330 QALYs gained per person if within-family external effects are included. The average cost of brief intervention was estimated at 60.98 AUD and is assumed to reflect the incremental cost over the entire evaluation period. Therefore, the cost per QALY gained is estimated at less than 671 AUD in men aged 30 years and less than 490 AUD in women aged 30 years. Table 2.9 summarises findings from the modelled cost-utility analysis.

Table 2.9 Summary of cost utility of brief alcohol interventions according to the modelled cost-utility analysis (discount rate= 5%)

	Male	Male + within-family external effects	Female	Female + within-family external effects
QALYs gained/person	0.091	0.243	0.125	0.330
Extra cost/person AUD	$60.98	$60.98	$60.98	$60.98
Cost/QALY gained AUD	**$671**	**$251**	**$490**	**$185**

Health states and the Markovian assumption:

A Markov model with just three non-absorbing (problem drinking, 'moderate' or 'safe' drinking, and dependence) and one absorbing state (dead) could be used to estimate QALYs gained per person for each intervention as compared to its comparator. There is no 'tee-total' state because all subjects in the pooled sample were problem drinkers on entry to the trials and the only outcome measure is a moderation of consumption rather than abstinence. The dependence state is included to reflect the differential rate at which problem drinkers might progress to dependence in the absence of intervention or where treatment has been ineffective. Because brief interventions are ineffective in treating alcohol dependence, there is no possibility of recovery from 'dependence' to either 'problem' or 'moderate'.

Note that transitions from each state in the model are assumed to be independent of the path that a cohort or patient has followed to reach that state (ie, the Markovian assumption). Due to this memory-less structure of Markov-type models, transition probabilities are *not* permitted to vary with the number of cycles spent in the current disease state, or to reflect more distant medical history. Clearly, this memory-less feature of the model is a fairly strong assumption in describing the long-term health consequences of alcohol abuse. In particular, the literature suggests that the risk of relapse and death may decline for second and subsequent cycles spent in the moderate drinking state and may increase for second and subsequent cycles spent in the problem drinking state.

In principle, we can side step the Markovian assumption by simply increasing our number of disease states. The 'moderate' disease state could be split into N temporary disease states: 'moderate1', 'moderate2', 'moderate3' and so on. Temporary states are "defined as having transitions only to other states and not to themselves. This guarantees that the patient can spend, at most, one cycle in that state" (Sonnenberg & Beck, 1993 p. 326). Patients are not required to transition through all N moderate states (ie. patients can return to 'problem' after any number of cycles), but 'moderate3' can *only* be reached after first cycling through both 'moderate2' and 'moderate1'[2]. This gives us a fixed sequence of temporary states known as a tunnel sequence (Briggs & Sculpher, 1998). Values and onward transition probabilities for 'moderate2' and 'moderate3' can then be adjusted to reflect the cumulative effect of a return to a 'safe' consumption pattern.

In a similar vein, a tunnel-sequence is employed to model the risk of death and payoffs for problem drinkers. Certainly, we might expect the health state utility to be lower for long-term problem drinkers than for those who have recently made the transition to unsafe consumption patterns. The impact on family cohesion, employment prospects and the HRQoL of significant others might also be expected to lag behind the initial transition to unsafe consumption patterns. However, the lag is likely to be much less than one year and the cycle length should be set to reflect this fact.

Cycle length:

A crucial assumption in defining any Markov process is to specify the cycle length at which the model updates. The length of the Markov cycle must be a constant increment of time and should reflect the timing of relevant events in the disease process (Kuntz & Weinstein, 2001). A cycle length as short as one-quarter (3 months) might be appropriate in evaluating the interventions for alcohol abuse because a period of problem drinking less than 3 months might be expected to have relatively little

[2] In other words, transition to 'moderate2' would *only* be permitted from 'moderate1', and transition to 'moderate3' would *only* be permitted from 'moderate2'.

effect on employment prospects, health status and family cohesion. However, second and subsequent cycles as a problem drinker are likely to carry a relatively high risk of death and a potentially severe reduction in quality of life. Note, however, that the follow-up in the Wilks et al (1997) trials was between 6 and 12 months and problem drinkers can reasonably be assumed to have entered their current state more than 3 months previous. A cycle length of 6 months is therefore assumed when modelling the alcohol interventions. Nonetheless, it should be fairly obvious that transitions cannot routinely be assumed to occur at the end of each cycle. A half-cycle correction is therefore applied to initial and final payoffs to adjust the stepwise survival curve traced by the model to more closely approximate the continuous survival curve that operates in the real-world.

Termination condition:

The Markov model terminates when the following condition is satisfied: _stage > 40 & (_stage > 140 | _stage_eff < .001). In other words, the model terminates after 140 cycles (70 years) *or* when the reward accumulated in any given cycle falls below 1/1000 of a QALY and at least 40 cycles or 20 years have been completed.

Payoffs (private plus external):

The modelled cost-utility analysis has taken a societal perspective such that *all* costs and consequences arising in intervention and comparator arms would ideally be identified, measured and valued. External health effects such as the HRQoL impact on each patient's family are included in the denominator. Similarly, the cost of alcohol-related trauma on those outside the family unit would ideally have been included to more accurately reflect the benefits of moving to safe consumption patterns. At this stage, however, external effects are limited to within-family effects due to difficulties in obtaining supporting data as to the risk of road-trauma by alcohol consumption. To account for the full treatment effect, a weight for 'own HRQoL' *plus* a weight for external HRQoL effects has been applied for each cycle that an individual resides in a given health state.

External effects within the family unit are calculated for the average number of persons per household. While the average number of persons per household might plausibly be expected to vary according to alcohol consumption, evidence from the 1995 National Nutrition Survey (ABS, 1995) identified only trivial differences (see below). The average family unit is therefore assumed to comprise the treated individual plus an average of two other persons with a maximum possible annual HRQoL weight of 3.0 in the event of full health for all three individuals.

Table 2.10 Family size by total alcohol consumption (weighted) from 1995 NNS

Alcohol consumption in last 24 hrs: N (%)		Family size			
		Minimum	Maximum	Mean	SD
Alcohol-free	9,128,719 (68%)	1	9	3.02	1.441
Moderate (1-6 drinks)	3,526,035 (26%)	1	9	2.94	1.382
Excessive (>6 drinks)	805,281 (6%)	1	7	2.95	1.437
Total	13,460,035 (100%)	1	9	2.99	1.426

Various plausible assumptions might be applied to calculate external HRQoL effects within the family unit. It seems unlikely that persons co-habiting with a problem drinker could plausibly be assumed to approach full health. The children of alcoholics are subject to an increased risk of hyperactivity, psychomotor delays, short attention and 'acting out' (Aronson et al, 1985; Hansen, 1985; Rydelius, 1997). An increased incidence of child abuse and neglect has been observed in families where there is evidence of alcohol abuse (Haugland et al, 1987; Reich, Earls & Powell, 1988). Velleman & Orford (1999) found that the children of problem drinkers were significantly more likely than a comparison group to have "experienced disharmony, often involving domestic violence, in their families of upbringing" (Velleman & Templeton, 2003 p105). Velleman & Orford (1999) suggested that because of family disharmony, the "children of parents with a drinking problem are at significant risk of a range of emotional, conduct and learning problems whilst they are living at home and in contact with the problem drinking parent" (Velleman & Templeton, 2003 p105). This conclusion is in broad agreement

with findings reported elsewhere in the literature (eg. Drake & Vaillant, 1988; Bush, Baillard & Fremouw, 1995; Christoffersen & Soothill, 2003). More generally, "family members of all age groups (children, partners, siblings, parents and other close relatives) are often negatively affected. The result is that family members commonly develop problems in their own right, often developing high levels of physical and psychological symptoms" (Velleman & Templeton, 2003, p108).

It is recognised that calculating the external HRQoL impact of problem drinking within families is a difficult task. The absence of dose-response relationships, the importance of various moderating variables and the sheer range of outcome measures reported in the literature would make the task prohibitively complex for the purposes of the current study. Here, we assume that the HRQoL weight applicable to the problem drinker is also applicable to each person in the family unit. In other words, the impact of alcohol abuse on the individual is used as a proxy for the external effects of alcohol abuse within the family unit. Table 2.11 below summarises disability weights at different levels of alcohol abuse taken from the Australian Burden of Disease study.

The target population in the Wilk et al (1997) trials is limited to "less severely affected drinkers who exhibit little or no alcohol dependence" (p5). The external HRQoL effects are therefore likely to be relatively mild in comparison to the external HRQoL effects in individuals exhibiting alcohol dependence. Applying a disability weight of 0.110 (equivalent to a quality weight of 0.890) to all persons in the family unit would give us 2.67 QALYs per year and an annual QALY gain of 0.33 = 3.0 - 2.67 for every problem drinker who successfully moderates his/her consumption. It is, however, less likely that such effects will persist into adulthood. Velleman & Orford (1999) argue that "the adulthood risks run by offspring of parents with drinking problems have been over-emphasised in the past, and the resilience of the majority of such offspring overlooked" (Velleman & Templeton, 2003 p106). The external effects within each family unit are therefore limited to an arbitrary 15 years period, ceasing at 45 years of age irrespective of success/failure in moderating alcohol consumption.

Table 2.11 Disability weights from AusBODI

Assumption/parameter value	Rx	Control	Source/ rationale
Alcoholic	0.550	0.550	Dutch weight for manifest alcoholism
Dependent	0.330	0.330	Average of Dutch weight for problem drinking and manifest alcoholism
Problem	0.110	0.110	Dutch weight for problem drinking
Moderate or safe consumption	0.000	0.000	By assumption
Dead	1.000	1.000	Anchor point

Time-invariance:

A Markov process that can be described by the equation: $X(t+1) = A\,X(t)$, is a special case known as a Markov chain. Markov chains assume a 'stationary' transition matrix, wherein transition probabilities are fixed and independent of time (Simon & Blume, 1994). Time-invariance simplifies the model and allows algebraic solution, but it also restricts our ability to capture key features of the disease process. "For all but the shortest time periods, it would be fallacious to assume that risk of death is constant" (Briggs & Sculpher, 1998 p. 401). Removing the restriction of time-invariance requires evaluation via either cohort or Monte Carlo simulation. Both transition probabilities and values (eg. estimates of health outcome, cost or net benefit attached to each Markov state) can then be represented as some function of time (ie. the number of Markov cycles since commencement).

For the modelled cost-utility analysis TPr_Death is time-dependent but all other probabilities and payoffs are invariant with respect to time. Payoffs and the likelihood of relapse and recovery are dependent on history (see Section 1.2) rather than time per se. For example, to account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'moderate1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'alc_problem3' state. Transition to 'moderate1' does, however, result in an immediate improvement

in first-person HRQoL such that the individual is immediately raised to full-health. Subsequent transition from 'moderate1' to 'moderate2' adds an improvement in external HRQoL effects but risk of death remains as for the 'alc_problem3' state. A reduction in risk of death is finally added upon transition from 'moderate2' to the 'moderate3' state such that the tunnel sequence amounts to a accumulation of benefits made of (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 6 months, and (iii) reduction in risk of death at 18 months. A converse accumulation of payoffs and risks is specified for the problem-drinker tunnel sequence.

Initial probabilities:

Initial probabilities are used to distribute a cohort (or to designate the status of an individual) over the relevant health states. All subjects in the pooled sample were problem drinkers on entry to the trials. For the purposes of the modelled cost-utility analysis, all individuals are assumed to be in steady-state and to have accumulated the full age/sex adjusted effects of their alcohol consumption. In other words, all persons commence in the 'AlcProblem3' state.

Start age:

For each of the Wilk et al (1997) trials, subjects were aged 19 years or older. However, Wilk et al (1997) fail to provide any indication as to the average age of the pooled sample. For the purposes of the modelled cost-utility analysis, we assume an average start age of 30 years.

Quit rates:

Quit rates are taken directly from the meta-analysis but with the intermediate outcome of alcohol moderation operationalised as a move from unsafe drinking as per NHMRC Guidelines to safe drinking as per NHMRC Guidelines. Due to differences in pooled estimates of treatment effect for men as compared to women and the availability of supporting data by age and sex band, the modelled cost-utility analysis is run for men and women separately. Because follow-up in the Wilks et al (1997) trials varied between from 6-months to 12-months, we must assume a period referent for the absolute risks given below. In another meta-analysis of brief interventions, Moyer et al (20020) noted that effect sizes are largest at the earliest follow-up points "suggesting decay in intervention effects over time" (pX). It is therefore quite unlikely that an overestimation of the long-term treatment effect will result from assuming that the absolute risks given below relate to a 6-months follow-up.

In the absence of local supporting data as to autonomous changes in drinking behaviour, we assume that the absolute risk of moderation in the control group designates the likelihood of recovery from the problem drinker state in the absence of intervention (ie. for all subsequent cycles of the model).

Table 2.12 Benefit of brief interventions versus control by gender

Subgroups	Number of studies	Treatment Group Drinking Moderation (%)	Control Group Drinking Moderation (%)	Odds Ratio	95% CI	Heterogeneity (x^2, p)
Female	3	158/317 (49.8%)	66/241 (27.4%)	2.42	1.7-3.45	4.16, 0.12
Male	5	513/1120 (45.8%)	232/796 (29.1%)	1.9	1.57-2.31	5.64, 0.23

Relapse rates:

The assumptions made with respect to relapse rates depend on the length of follow-up and the validity of outcome measurement in each trial. In another meta-analysis of brief interventions, Moyer et al (2002) noted that effect sizes are largest at the earliest follow-up points "suggesting decay in intervention effects over time" (pX). It is recognised that the quit rates applied to the initial cycle are an average for 6-months and 12-months follow-ups. The rate of relapse in the subsequent 6-months period might therefore be somewhat lower than would otherwise be expected. We take the differential between 6-months and 12-months effect sizes in the Wilk et al (1997) trials as an indication of per cycle relapse rates for the second 6 months cycle and all subsequent cycles. In the

absence of supporting data, we assume that the risk of progressing from alc_problem3 to dependence is approximately equal to the risk of relapse. The risk of progressing from alc_problem2 and alc_problem1 to dependence is assumed to be zero.

Table 2.13 Benefit of brief interventions versus control by length of follow-up

Subgroups	Number of studies	Treatment Group Drinking Moderation (%)	Control Group Drinking Moderation (%)	Odds Ratio	95% CI
6-month	3	422/866 (48.7%)	145/433 (33.5%)	1.5	1.16-1.83
12-month	5	292/766 (38.1%)	169/697 (24.2%)	1.6	1.26-1.96
Risk difference		0.051	0.056		0.01-0.09 0.01-0.10

Death rates:

Current NHMRC Guidelines for 'low risk alcohol consumption' (NHMRC, 2001) are intended to place the majority of the population within the range of 'safe' exposures[3]. For a low risk of harm over the long-term in adult males, the NHMRC recommends up to 28 standard drinks/week[4] with not more than 6 standard drinks in any one day and one or two alcohol-free days per week. In adult females, the NHMRC recommends up to 14 standard drinks/week with not more than 4 standard drinks in any one day and one or two alcohol-free days per week. Because death rates are not typically available by alcohol disorder (eg, for problem drinkers or manifest alcoholism), death rates by level of consumption have been mapped to the relevant health states *without regard to the precise clinical criteria*. For example, problem drinkers are assumed to exceed the NHMRC Guidelines for low risk alcohol consumption but to "exhibit little or no alcohol dependence" (Wilk et al, 1997 p5). In practice, measures of alcohol dependence or of alcohol consumption pattern are not typically available and we are forced to rely on death rates for those with average weekly consumption exceeding the NHMRC recommendations (ie. men: 4-6 drinks/day, women: 2-4 drinks/day). For dependent drinkers, we rely on death rates for those exceeding NHMRC recommendations for peak consumption (ie. >6 drinks/session, women: >4 drinks/session) on a regular basis. For recovered drinkers, we rely on death rates for past problem drinkers where past problem drinking is defined as having ≥5 drinks on a weekly basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983. While mapping from consumption to health states provides intuitively plausible estimates of transition probabilities for males in all age bands, small cell sizes and measurement error may have contributed to the much less plausible estimates of transition probabilities for females. For example, the relative risk of death for a dependent drinker on >4 drinks/day is substantially less than that for a past problem drinker or for a light drinker on just 0-1 drinks/day but with occasional heavy drinking. It is possible that the relationship between alcohol consumption and risk of death will differ between men and women but it is unlikely that gender differences observed in the supporting data can be attributed to a real interaction between alcohol consumption and sex. A number of approaches were considered in minimising the influence of error in the supporting data on the output of the model. In the end, we simply discarded the relative risks of death calculated for females and applied the relative risk of death for males to the absolute risk of death by age and sex for Australia based on 2002 data.

[3] While the NHMRC provides the most appropriate guide in the Australian context, a number of other organisations have published guidelines that designate 'safe' levels of consumption. Even though the majority of published guidelines are evidence-based, 'safe' levels vary from the <10-20g/day recommended by the Medical Research Council of Sweden to the <40-60g/day recommended by the Alcohol Advisory Council of New Zealand (NHMRC, 2001).

[4] An Australian Standard Drink contains 10 grams of alcohol, equivalent to a 285ml glass of full strength beer (4.9% Alc./Vol), a 30ml shot of spirits (40% Alc./Vol) or a 100ml glass of wine (12% Alc./Vol). Note that the alcohol content of full strength beer and wine vary considerably.

Tables 2.14 to 2.15 summarise the relative risk of all-cause mortality for each health state as compared to abstinence. Tables 2.16 to 2.17 summarise the relative risk of all-cause mortality for each health state as compared to safe levels of consumption. Table 2.18 summarises deaths per 1000 persons by age and sex band for Australia based on 2002 data. Tables 2.19 to 2.21 summarise the probability of all-cause mortality by age and sex band for each health state.

Table 2.14 Relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.93 (0.39, 2.21)	**≥6 drinks/day *vs* lifetime abstinent**	**2.29 (1.17, 4.48)**	2-4 drinks/day *vs* lifetime abstinent	0.73 (0.39, 1.37)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.97 (0.30, 3.09)	≥4 drinks/day *vs* lifetime abstinent	1.06 (0.26, 4.34)	1-2 drinks/day *vs* lifetime abstinent	0.81 (0.42, 1.56)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.96 (1.26, 3.05)	Past problem drinking[#] *vs* lifetime abstinent	1.64 (0.98, 2.76)	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.84 (0.98, 3.44)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.77 (0.86, 3.64)	Past problem drinking[#] *vs* lifetime abstinent	2.18 (1.12, 4.24)	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.25 (0.17, 9.14)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

Table 2.15 Relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* 2-4 drinks/day	1.27 (0.53, 3.03)	≥6 drinks/day *vs* 2-4 drinks/day	**3.14 (1.60, 6.14)**	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.20 (0.37, 3.81)	≥4 drinks/day *vs* 1-2 drinks/day	1.31 (0.32, 5.36)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.68 (1.73, 4.18)	Past problem drinking[#] *vs* 2-4 drinks/day(a)	2.25 (1.34, 3.78)	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.52 (1.34, 4.71)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.19 (1.06, 4.49)	Past problem drinking[#] *vs* 1-2 drinks/day	2.69 (1.38, 5.23)	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.54 (0.21, 11.28)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

(a) Death rate for recovered.

Table 2.16 Adjusted relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.90 (0.38, 2.14)	≥6 drinks/day *vs* lifetime abstinent	2.14 (1.08, 4.23)	2-4 drinks/day *vs* lifetime abstinent	0.78 (0.41, 1.47)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.89 (0.28, 2.88)	≥4 drinks/day *vs* lifetime abstinent	0.94 (0.23, 3.86)	1-2 drinks/day *vs* lifetime abstinent	0.77 (0.40, 1.51)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.93 (1.23, 3.02)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.62 (0.86, 3.07)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.65 (0.79, 3.41)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.08 (0.15, 7.93)	Rehm, Greenfield and Rogers (2001)

Table 2.17 Adjusted relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day (a) *vs* 2-4 drinks/day	1.15 (0.49, 2.74)	≥6 drinks/day *vs* 2-4 drinks/day (b)	2.74 (1.38, 5.42)	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.16 (0.36, 3.74)	≥4 drinks/day *vs* 1-2 drinks/day	1.22 (0.30, 5.01)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with pas heavy drinking *vs* 2-4 drinks/day	2.47 (1.58, 3.87)	Past problem drinking[#] *vs* 2-4 drinks/day	NR	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.08 (1.10, 3.94)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with pas heavy drinking *vs* 1-2 drinks/day	2.14 (1.03, 4.43)	Past problem drinking[#] *vs* 1-2 drinks/day	NR	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.40 (0.19, 10.30)	Rehm, Greenfield and Rogers (2001)

(a) Death rate for problem drinker.
(b) Death rate for 'dependant'.

Table 2.18 Age-specific TPr_Death by alcohol status: Safe

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males	5.5	0.3	0.1	0.2	0.6	0.9	1.0	1.1	1.3	1.7	2.6	3.6	5.8	10.0	16.5	28.8	48.8	80.8	167.4
Females	4.7	0.2	0.1	0.1	0.3	0.3	0.4	0.5	0.7	1.0	1.5	2.4	3.7	6.0	9.6	16.2	28.9	54.2	135.4

Table 2.19 Age-specific TPr_Death by alcohol status: Problem3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.00633	0.00035	0.00012	0.00023	0.00069	0.00104	0.00115	0.00127	0.00150	0.00196	0.00299	0.00414	0.00667	0.01150	0.01898	0.03312	0.05612	0.09292	0.19251
Upper	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Lower	0.00270	0.00015	0.00005	0.00010	0.00029	0.00044	0.00049	0.00054	0.00064	0.00083	0.00127	0.00176	0.00284	0.00490	0.00809	0.01411	0.02391	0.03959	0.08203
Females																			
Mid	0.00541	0.00023	0.00012	0.00012	0.00035	0.00035	0.00046	0.00058	0.00081	0.00115	0.00173	0.00276	0.00426	0.00690	0.01104	0.01863	0.03324	0.06233	0.15571
Upper	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Lower	0.00230	0.00010	0.00005	0.00005	0.00015	0.00015	0.00020	0.00025	0.00034	0.00049	0.00074	0.00118	0.00181	0.00294	0.00470	0.00794	0.01416	0.02656	0.06635

Men's RR: 4-6 drinks/day *vs* 2-4 drinks/day= 1.15 (0.49, 2.74) applied to both men and women. For comparison women's RR: 2-4 drinks/day *vs* 1-2 drinks/day=1.16 (0.36, 3.74)

Table 2.20 Age-specific TPr_Death by alcohol status: Dependent3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Upper	0.02981	0.00163	0.00054	0.00108	0.00325	0.00488	0.00542	0.00596	0.00705	0.00921	0.01409	0.01951	0.03144	0.05420	0.08943	0.15610	0.26450	0.43794	0.90731
Lower	0.00759	0.00041	0.00014	0.00028	0.00083	0.00124	0.00138	0.00152	0.00179	0.00235	0.00359	0.00497	0.00800	0.01380	0.02277	0.03974	0.06734	0.11150	0.23101
Females																			
Mid	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Upper	0.02547	0.00108	0.00054	0.00054	0.00163	0.00163	0.00217	0.00271	0.00379	0.00542	0.00813	0.01301	0.02005	0.03252	0.05203	0.08780	0.15664	0.29376	0.73387
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685

Men's RR: >6 drinks/day *vs* 2-4 drinks/day= 2.74 (1.38, 5.42) applied to both men and women. For comparison, women's RR: >4 drinks/day *vs* 1-2 drinks/day=1.22 (0.30, 5.01)

Table 2.21 Age-specific TPr_Death by alcohol status: Recovered

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01238	0.00068	0.00023	0.00045	0.00135	0.00203	0.00225	0.00248	0.00293	0.00383	0.00585	0.00810	0.01305	0.02250	0.03713	0.06480	0.10980	0.18180	0.37665
Upper	0.02079	0.00113	0.00038	0.00076	0.00227	0.00340	0.00378	0.00416	0.00491	0.00643	0.00983	0.01361	0.02192	0.03780	0.06237	0.10886	0.18446	0.30542	0.63277
Lower	0.00737	0.00040	0.00013	0.00027	0.00080	0.00121	0.00134	0.00147	0.00174	0.00228	0.00348	0.00482	0.00777	0.01340	0.02211	0.03859	0.06539	0.10827	0.22432
Females																			
Mid	0.01058	0.00045	0.00023	0.00023	0.00068	0.00068	0.00090	0.00113	0.00158	0.00225	0.00338	0.00540	0.00833	0.01350	0.02160	0.03645	0.06503	0.12195	0.30465
Upper	0.01777	0.00076	0.00038	0.00038	0.00113	0.00113	0.00151	0.00189	0.00265	0.00378	0.00567	0.00907	0.01399	0.02268	0.03629	0.06124	0.10924	0.20488	0.51181
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685

Men's RR: Past problem drinking *vs* 2-4 drinks/day= 2.25 (1.34, 3.78) applied to both men and women. For comparison, women's RR: Past problem drinking *vs* 1-2 drinks/day=2.69 (1.38, 5.23)

Sensitivity analysis

The modelled cost-utility analysis is based on data taken from the Wilk et al (1997) meta-analysis, our own calculation of incremental program costs as described in Section 2.4, together with supporting data and assumptions as outlined above. Note, for example, that the estimate of QALYs gained from the modelled cost-utility analysis has been derived from a number of data sources with varying levels of error and uncertainty. More specifically, uncertainty in the estimate of QALYs gained is a function of sampling error in the trial-based measure of surrogate outcome (behaviour change), uncertainty as to the persistence of any behaviour change (relapse rates), and uncertainty in the relationship between a surrogate outcome such as behaviour change and a final outcome such as QALYs gained (with respect to both utility weights and life-years gained).

In an effort to identify key drivers and to evaluate robustness of estimates as to cost per QALY gained, univariate sensitivity analyses were conducted by varying parameters such as start_age, HRQoL weights in the alcproblem tunnel sequence and the dependence state, discount rate, initial rate of relapse (in the moderate1 state), the relative risk of death, response rates from the Wilk et al (1997) meta-analysis, and our estimates of incremental costs. Variation in each uncertain parameter produced intuitively plausible variations in cost per QALY ratios. Results of the sensitivity analyses for men and women are summarised in Tables 2.23 and Table 2.24, respectively.

The following details should be kept in mind for the interpretation of the sensitivity analyses.

- Recall that the base case assumed termination of the model at age=100 yrs. For the sensitivity analyses, the termination condition was adjusted to preserve termination at age=100 yrs irrespective of start_age. Note that varying start_age from 20 to 70 years produces only relatively minor changes in cost per QALY ratios for both men and women.
- The 95%CI for treatment effect is derived by calculating the 95%CI around the relative risk of transition from 'problem' to 'moderate'. Upper and lower estimates for the absolute risk of transition from 'problem' to 'moderate' in the BI group are then derived assuming that the absolute risk for the control group is as for the base case analysis. Table 2.22 below summarises these calculations.
- The cost per life-year gained is derived by setting the HRQoL weight to 1.0 for each of the seven non-absorbing health states (alcproblem1, alcproblem2, alcproblem3, moderate1, moderate2, moderate3, dependence). In other words, adjustment for HRQoL in health states other than death is removed for this analysis. Estimates of cost per life-year gained varied between 2,988 AUD in males when within-family external effects are included and 10,549 AUD in females when only 1st-person effects are included.

Table 2.22 Calculating 95%CI for treatment effect

	AR Rx (Base Case)	AR Placebo	RR (95%CI)	AR Rx (Low)	AR Rx (High)
Males	513/1120=0.458	232/796=0.291	1.57 (1.39, 1.78)	0.4039	0.5194
Females	158/317=0.498	66/241=0.274	1.82 (1.44, 2.30)	0.3947	0.6294

Table 2.23 Cost/QALY estimates according to the sensitivity analysis, males

	1st-Person Effects	1st-Person + Within-Family Effects
start_age=20	$676	$237
start_age=30	$671	$251
start_age=40	$660	$308
start_age=50	$645	$456
start_age=60	$635	$382
start_age=70	$663	$344
Q_All=1.00	$9,112	$2,988
discount=0.00	<$437	<$174
discount=0.05	$671	$251
discount=0.07	$892	$321
Initial relapse=0.056	$671	$251
Initial relapse=0.10	$682	$256
Initial relapse=0.20	$709	$266
Initial relapse=0.40	$785	$297
Lower 95%CL	$701	$266
Mean RR_Death: Taylor (2002)	$671	$251
Upper 95%CL	$625	$229
Lower 95%CL	$993	$372
Mean Treatment Effect	$671	$251
Upper 95%CL	$491	$184
Half Best Estimate	$336	$126
Best Estimate Incremental Cost	$671	$251
Twice Best Estimate	$1343	$503

Table 2.24 Cost/QALY estimates according to the sensitivity analysis, females

	1st-Person Effects	1st-Person + Within-Family Effects
start_age=20	$489	$173
start_age=30	$490	$185
start_age=40	$482	$232
start_age=50	$472	$358
start_age=60	$460	$303
start_age=70	$470	$264
Q_All=1.00	$10,549	$3,448
discount=0.03	$319	$129
discount=0.05	$490	$185
discount=0.07	$648	$235
Initial relapse=0.056	$490	$185
Initial relapse=0.10	$498	$188
Initial relapse=0.20	$519	$197
Initial relapse=0.40	$577	$220
Lower 95%CL	$502	$191
Mean RR_Death: Taylor (2002)	$490	$185
Upper 95%CL	$385	$134
Lower 95%CL	$909	$343
Mean Treatment Effect	$490	$185
Upper 95%CL	$309	$117

	1st-Person Effects	1st-Person + Within-Family Effects
Half Best Estimate	$245	$93
Best Estimate Incremental Cost	$490	$185
Twice Best Estimate	$979	$370

Threshold analysis

Recall that downstream cost offsets have not been included in the modelled cost-utility analysis (but would only serve to further reduce the cost/QALY ratio). While the complex modelling task of attributing downstream cost offsets to intervention and control groups is beyond the scope of this study, we have quantified the minimum downstream cost offset that would be required in order for brief interventions plus counselling to be cost saving. Table 2.25 specifies the minimum per cycle downstream cost offset in the moderate3 state for brief intervention to dominate the comparator.

When interpreting the threshold analysis, it should be remembered that downstream cost offsets are likely to be age/sex dependent and accrue in an episodic (rather than constant) manner. In an attempt to incorporate some of this complexity, no downstream cost offsets accrue during the initial 2 cycles in the moderate state. This is consistent with assumptions made elsewhere in the model with respect to the differential risk of death in problem and moderate states[5]. Aside from this relatively crude adjustment for duration of time spent in the moderate state, downstream cost offsets are incorporated in the simplest way possible. The dollar-value of downstream cost offsets is invariant with respect to _stage and age such that the same downstream cost offset accrues to a moderate drinker after 3 cycles as after 30 cycles. It is left to the decision-maker to determine whether a 30 years old female adopting moderate drinking behaviour is likely to average $75 per 6-months cycle in downstream cost offsets over the remaining 40 to 50 years of her lifespan or whether a 30 years old male adopting moderate drinking behaviour is likely to average $105 per 6-months cycle in downstream cost offsets over the remaining 40 to 50 years of his lifespan.

Table 2.25 Minimum downstream cost offset for BI to dominate, (discount rate= 5%)

Model	QALYs gained/person	Downstream cost offset	Incremental cost/person	Cost/QALY gained
Males				
1st-Person Effects	0.09084	$103.50	$0.00	BI dominates
1st-Person + Within-Family	0.24252	$103.50	$0.00	BI dominates
Females				
1st-Person Effects	0.124543	$74.55	$0.00	BI dominates
1st-Person + Within-Family	0.329530	$74.55	$0.00	BI dominates

[5] A reduction in risk of death is added upon transition from 'moderate2' to the 'moderate3' state such that the 'moderate' tunnel sequence amounts to a accumulation of benefits made of (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 6 months, and (iii) reduction in risk of death at 18 months.

3. Brief Interventions

3.1 Description

Intervention type

The study was a randomised controlled trial with 4 arms conducted in an outpatient setting. The primary aim of the trial was to study the effect of early, brief interventions on the non-physically dependant problem drinker. The intervention was based on the provision of brief advice, with the addition of counselling in some groups, to subjects engaged in hazardous levels of drinking but without physical dependence on alcohol. Early intervention was originally instigated to investigate secondary prevention of alcoholism in problem drinkers, rather than tertiary intervention in specialist detoxification units.

References/sources of evidence

This study was the Australian component of the global WHO Cross National Trial of Brief Interventions with Heavy Drinkers. The descriptions of the intervention and its effectiveness were based on the following material:

- Saunders, J.B., Hanratty, S.J., Burns, F.H., Douglas, A., Clarke, J.I. & Reznik, R.B. 1991. Successful early intervention for harmful alcohol consumption: Results from the WHO randomised controlled trial. *Proceedings of the Autumn School for Studies in Alcohol and Drugs*. May, 1991: 183-192.
- Saunders, J.B., Conigrave, K.M. & Gomel, M.K. 1998. Preventative Approaches to Alcohol and Drug Problems. In Jenkins, R.A. & Ustun, B. (editors), Preventing Mental Illness: Mental Health Promotion in Primary Care, pp405-419. John Wiley, New York.
- Wutzke, S.E., Conigrave, K.M., Saunders, J.B. & Hall, W.D. 2002. The long term effectiveness of brief interventions for unsafe alcohol consumption: A 10 years follow up. *Addiction*. Vol 97: 665-675. This paper provided details of the original study that were not provided in the proceedings paper.
- The results of the global study were reported by the WHO Brief Intervention Study Group. WHO Brief Intervention Study Group. 1996. A Cross National Trial of Brief Interventions with Heavy Drinkers. *American Journal of Public Health*. Vol 86(7): 948-955.

For the purposes of economic analysis, it was decided to present only the Australian component of the study. Methodologies were described in greater detail in the global report, so it will be assumed that the Australian collaborating centres followed the procedures laid down for the global study.

Intervention description

Recruitment and target population:

The collaborative centre was in Sydney and subjects were recruited principally from the metropolitan area. A significant minority of patients were recruited from Darwin.

Clients were recruited for the study from the following sites:

- Medical and surgical outpatients in the Royal Prince Alfred Hospital (RPAH)
- Physical rehabilitation services within the RPAH
- RPAH Emergency Department
- Medicheck, a multiphasic health screening and counselling program based in Sydney
- Twelve GP clinics in Sydney
- Royal Darwin Hospital Early Intervention Unit

8542 participants were initially screened for inclusion. A total of 705 participants aged 17-70 were enrolled in the study, of whom 118 were recruited from Darwin. The Australian study was required to recruit 360 participants for the global study, however they continued to recruit in the Sydney area until they had 554 subjects. Analysis of the study outcomes was carried out only on the 554 participants enrolled from the Sydney centres.

Inclusion/exclusion criteria:

Subjects were primarily recruited based on a hazardous level of alcohol consumption.

Inclusion:

- Subjects must drink to a hazardous level (350g+ of alcohol per week (men) or 225g+ (women)).
- Drink to intoxication at least once per month (drinks in a single session: ≥10 for men, ≥6 for women)
- Express concern about their drinking and/or want to cut down

Exclusion:

Subjects must not:

- Have an average weekly alcohol intake exceeding 840g (men) and 560g (women)
- Be physically dependent on alcohol
- Have any concurrent psychiatric disorders
- Be pregnant
- Be using major psychotropic drugs
- Be under medical advice to completely abstain from alcohol
- Have been admitted to hospital for alcohol related problems
- Be residentially unstable (more than 2 address changes in the previous 6 months)
- Have limited literacy in English

Of the 8542 subjects screened, 961 did not complete the initial questionnaire for various reasons (422 not English literate, 214 in pain, 155 visitors to Sydney, 83 called to consultation, 87 declined to participate). Of the 7581 subjects who completed the initial questionnaire, 988 met the inclusion criteria. However, 274 of these also met the exclusion criteria leaving 714 eligible to participate. In 136 cases the therapist was not available before the patient had to leave and so they were not recruited. A further 24 participants declined any further involvement, leaving a final cohort of 554 patients (6.5% of total screened and 77.5% of eligible subjects).

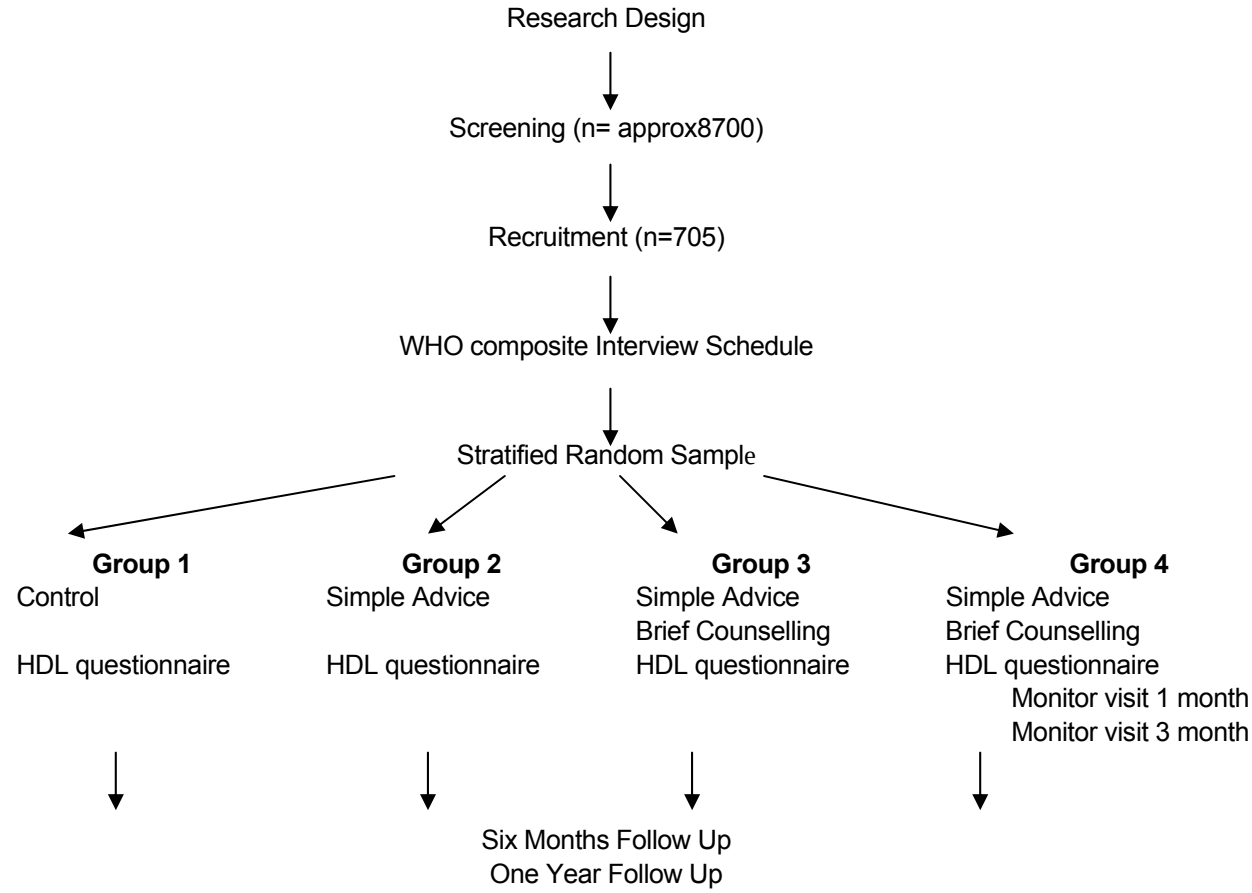
Characteristics of the cohort:

- 351 men and 203 women
- Mean age at baseline 40.1 year (13.0 SD)
- Those participants recruited through GP clinics were younger than the other groups (36 years, 11.2 SD) ($p<0.001$)
- There were no significant differences in alcohol consumption between the intervention groups and the control group.

Study Procedure:

The recruitment and randomization of participants is described in Figure 3.1.

Figure 3.1 Recruitment and randomization of participants



Subjects were randomised to one of four groups:

- Control group
- Simple advice lasting 5 minutes
- Simple advice followed by brief counselling and problem solving strategies (20 minutes)
- Simple advice and counselling followed by two "booster" sessions including feedback of laboratory results (120-150 minutes)

Simple advice:

This component was essentially a strategy to induce motivation to change drinking behaviour. The content of the 5 minute interview, namely the level of alcohol consumption, the risks associated with this intake, and any evidence of physical of psychological harm, was relayed back to the participant. Comparisons were made with the general population, and the participant was told that their drinking fell within the hazardous range. A target drinking level (different levels for men and women) was suggested and the goal of the therapist/interviewer was to reach agreement with the participant that the goal was both necessary and achievable.

Brief counselling:

This session began with an identification of situations that would place the individual at higher risk of drinking heavily. These might be locations, situations (eg meeting friends) or mood states (boredom, frustration, anger). Alternatives to drinking were explored in the session and advice was given. The patient was given reasons for reducing consumption and it was suggested that participants enlist the aid of a helper. Participants were asked to complete a drinking diary and were supplied with a self help manual which covered the essentials of the intervention. Sessions lasted 20 minutes.

Brief counselling/monitoring:
Participants in this group attended the brief counselling as described above, but also attended 2 further sessions at 1 and 3 months respectively. At these extra sessions, the drinking diary was reviewed and situations that led to heavy drinking were examined. Techniques for dealing with similar situations in the future were suggested by the therapist. Results of laboratory tests were made available and discussed.

Control:
The control group consisted of those participants randomly assigned to receive no further counselling or advice after the WHO composite interview.

Follow up:
Of the 551 participants in the Sydney trial, 483 (89%) were followed up at 6 months and at 12 months after completing the intervention. Further follow up was undertaken in a second study at 10 years after the original intervention. 433 (78.6%) of subjects were contacted for the 10 years interview, 370 (67.2%) of the original cohort completed the 10 years interview. Of the 181 participants who failed to complete the 10 years follow up, 38 (6.9%) refused and 25 (4.5%) had died. The remaining 118 (21.4%) participants remain unaccounted for.

3.2 Quality of evidence

Evaluation description

Design:
The study was a part of an international trial conducted in 10 countries by the WHO. It was a randomised controlled trial with 4 arms conducted in an outpatient setting.

Further follow up was undertaken in a second study at 10 years after the original intervention.

Analysis:
The initial study data was analysed using multiple regression analysis with median weekly alcohol consumption at follow up as the dependent variable and consumption at recruitment, age range, sex, site of recruitment, recruitment criteria and treatment condition as independent variables.

The 10 years follow up study analysed date using SPSS for Windows Version9.01. Categorical outcomes were analysed using chi-square tests (Fisher's exact test or McNemar's test for repeated measures). Normally distributed continuous data were analysed with paired t-tests (or ANOVA for variables in three or more groups). Non-normally distributed data were transformed into a normal distribution before testing. A sensitivity analysis was conducted with changes made to a single variable: change in alcohol consumption, for those lost to follow up.

Outcome measures:
The two main outcome variables in the initial follow up of the trial were median weekly alcohol consumption and prevalence of drinking to intoxication.

Outcome measures at the 10 years follow up were:
- Drinking behaviour
- Biochemical markers of alcohol use- GGT,AST,ALT
- Diagnosable alcohol use disorders
- Experience of alcohol related physical, psychological or social harm
- Mortality
- Time to death

Assessment

Sources of bias:

Selection bias:
The randomization step was effective as there were no significant differences in age, gender, or alcohol intake across the treatment groups. The only differences between individuals were between recruitment site. Those patients recruited in the GP clinics were significantly younger (36.0 vs. 41.2 SD 13.2, $p<0.001$) and more likely to be women (56.3% vs. 31.7%, $p<0.001$) than the participants in the other groups (Hospital and MediCheck).

Measurement bias:
Subjects in the control group may have become concerned about their drinking levels after completing the questionnaire and have voluntarily cut back on drinking. There was about a 10% reduction in the median weekly alcohol consumption in the control group. Note also that the literature reports a strong decline in heavy drinking after the age of 50. At the 10 years follow up the median age of participants was 49 years. This may have reduced the power of the study to detect a significant treatment effect, independent of the effects of aging.

Attrition bias:
Although there was significant loss to follow up there does not appear to be a significant difficulty with attrition bias. Long term follow up rates were comparable with other studies on alcohol use disorders. Baseline characteristics of subjects lost to follow up were not significantly different from the general cohort. Mortality rates for those lost to follow up were calculated through use of the State Deaths Registry. The only minor concern is that younger people were more likely to be lost to follow-up. These subjects may have allowed a better measure of the effectiveness of the intervention as they would not have been as subject to the age-related decline in drinking noted in the medical literature.

Reporting:
While there do not appear to be any major limitations with the design of the Sydney study, there do appear to be variations in the reporting of methods and results between the different sources. The proceedings paper refers to a sample size of 551 participants, whereas the 10 years follow up refers to 554. The proceedings paper refers to session times ranging from 5 minutes (simple advice) to 60 minutes (monitored counselling). The 10 years follow up paper reports session times ranging from 5 minutes to 40 minutes (this may be a simple misprint as the paper also mentions 60 minutes). The mental health proceedings paper also mentions that sessions ranged from 5 minutes to 40 minutes. Additionally the proceedings paper mentioned that recruitment was carried out in 12 GP clinics whereas the 10 years follow up paper mentions recruitment in only 6 GP clinics. Also the inclusion/exclusion criteria vary between the reports. In the global report and the proceedings paper, inclusion criteria are described as consuming 350g per week for males and 225g of alcohol per week for females, whereas in the mental health proceedings report, the figures are 300g (males) and 180g (females).

3.3 Outcomes – as reported

Behaviour change and clinical parameters

Adherence to treatment:
There was a significant overall treatment effect. Results of the analysis indicate a positive treatment effect from the intervention in the short term that was *not* sustained at the 10-years follow-up.

At initial follow up:

- Median weekly alcohol consumption decreased by a combined total of 26% in the groups receiving simple advice, brief counselling and the booster sessions, compared to 10% in the control group.
- The reduction in median weekly alcohol consumption in the brief counselling group was significant compared to the control ($p<0.002$)
- The reduction in median weekly alcohol consumption in the brief counselling with monitoring group was significant compared to the control ($p<0.05$)
- The reduction in median weekly alcohol consumption in the simple advice group was marginally significant compared to the control ($0.05<p<0.10$)
- The simple advice group recorded a net reduction in the prevalence of drinking to intoxication by 44% compared to 10% in the control group ($p<0.05$)
- The findings that even a simple 5 minute advice session was capable of producing a significant reduction in consumption as well as intoxication is important because it supports the implementation of early intervention techniques within general practice.
- The results from the Australian trial were consistent with the results from trials in the other collaborating centres around the world.

At 10-years follow up:

- Median weekly alcohol consumption was not statistically significantly different between intervention and control groups
- Proportion of subjects drinking at hazardous levels was not statistically significantly different between intervention and control groups
- Reduction in proportion of unsafe drinkers was not statistically significantly different between intervention and control groups
- Prevalence of alcohol use disorders was not statistically significantly different between intervention and control groups
- Prevalence of physical, psychological or social problems was not statistically significantly different between intervention and control groups
- Mortality rates were not statistically significantly different between intervention and control groups

i.e. there was no evidence of any positive benefit of intervention at long term follow up.

Table 3.1 Adjusted average weekly alcohol intake at recruitment and initial follow up*

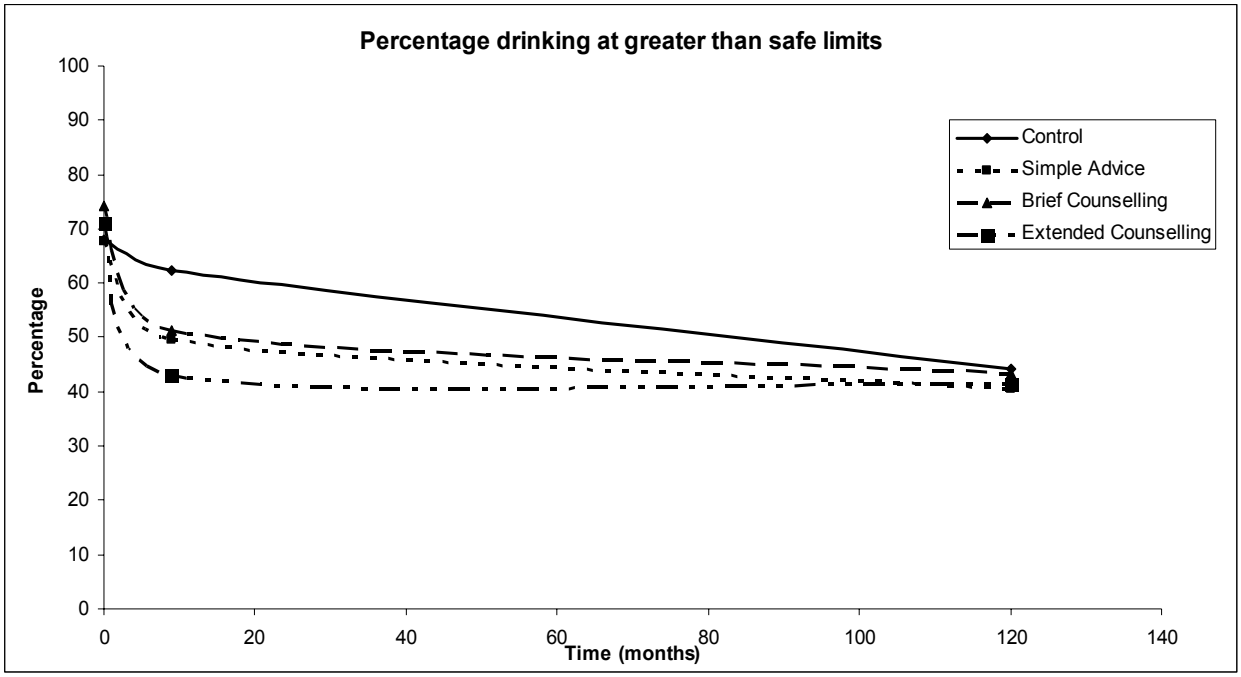
Intervention	Intake at recruitment (g)	Intake at follow up (g)	Reduction (%)	*p*
Control	402	402	0	NS
Simple Advice	424	307	27.5	<0.05
Advice and Counselling	480	341	29.0	<0.05
Extended Counselling	460	285	38.0	<0.05

* adjusted for age, intervention, sex, site of recruitment, mean alcohol intake at recruitment and follow up

Table 3.2 Drinking behaviour and outcomes by intervention at 9 months and 10 years follow-up

	Control	Simple advice	Brief counselling	Extended counselling	All interventions	p-value
Median weekly alcohol consumption						
Baseline	308.9	282.8	336.3	348.2	317.7	0.725
9 months	262.9	220.9	230.1	195.6	233.8	0.112
10 years	158.0	150.1	181.8	204.0	173.7	0.405
Drinking >safe limits (%)						
Baseline	67.9	67.7	74.2	71.0	70.1	0.594
9 months	62.2	49.6	51.2	43.1	52.6	0.049
10 years	44.2	40.5	43.4	41.5	42.4	0.965
Drinking to intoxication > monthly (%)						
10 years	51.0	53.5	54	55.9	53.4	0.937
ICD-10 alcohol dependence syndrome (%)						
10 years	10.1	8.0	6.9	10.1	8.6	0.819

Figure 3.2 Percentage drinking at greater than safe limits



Mortality

Mortality at 10 years was not significantly different between the intervention groups and controls. Alcohol related morbidity was not statistically significantly different between the intervention groups and controls.

3.4 Program costs

As reported by trial

Based on resource use

The cost to deliver simple advice, brief counselling and extended counselling is calculated in Table 3.3. Costs incurred purely as a result of research activity, rather than in the administration of the

intervention, have been excluded. As the viewpoint taken is that of the Department of Health and Ageing, costs to the participant have not been included.

These costings assume that a self-administered questionnaire would be completed by those waiting for their GP appointment as part of baseline data collected on all patients. Thus, in most cases, there would be an insignificant use of the GP's time in identifying eligible patients.

It has been assumed that about half those who required simple advice about their drinking would then be pushed into a higher billing category by the extra time taken. Level B consultations have been taken as the standard as they comprise over 86% of standard GP consultations. A sensitivity analysis assesses the impact of higher and lower numbers of patients requiring longer sessions with their GP, resulting in higher charges to Medicare.

Costs associated with consulting premises and administration are assumed to be accounted for in the professional fee schedule so have not been included as a separate component.

Table 3.3 Treatment costs

	Cost	Time	Number	Total cost	Cost/person
Control					
Consultation with GP	$0 (no difference to standard consultation fee)				$0
Total				No additional cost	
Simple Advice (5 mins total)					
Consultation with GP 5 minutes added to consultation	$13.58 (difference between level B & C consultation for 50% of patients) [v]	5 minutes	1		$13.58
Information leaflet	$940.00 for 1000 [vi]		705	$940.00	$1.33
Total					$14.91
Brief Counselling (20 mins total)					
Consultation with GP 20 minutes added to consultation	$27.15 (difference between level B & C consultation) (Wutzke et al., 2001) [vii]	20 minutes	1		$27.15
Information leaflet	$940.00 for 1000		705	$940.00	$1.33
Diary card	$345 for 300		~530	~$1.15	$1.15
Total					$29.63
Extended Counselling (60 mins total)					
Consultation with GP x3 @ 20minutes per consult	$87.55 [viii] (difference between level B & C consultation) (Wutzke et al., 2001) + 2 Level B consultations	60 minutes	1		$87.55
Information leaflet	$940.00 for 1000		705	$940.00	$1.33
Diary card	$345 for 300 [ix]		~530	~$1.15	$1.15
Total					$90.03

[v] Nearly all patients would be pushed up to a Level C category by the 20 minute counselling required. Figures from MBS Schedule November 2003
[vi] Design and Print Centre, University of Melbourne 2003
[vii] Figures from MBS Schedule November 2003
[viii] Figures from MBS Schedule November 2003
[ix] Design and Print Centre, University of Melbourne 2003

3.5 Within-trail CEA

The changes in each group over time (defined as those not drinking above national guidelines) have been compared to the control group and the excess effect plotted in Figure 3.3 below. A dose-effect response can be clearly seen, more marked at early review and declining towards baseline at 10 years.

Figure 3.3 Change in %drinking above safe limits after adjusting for control group changes

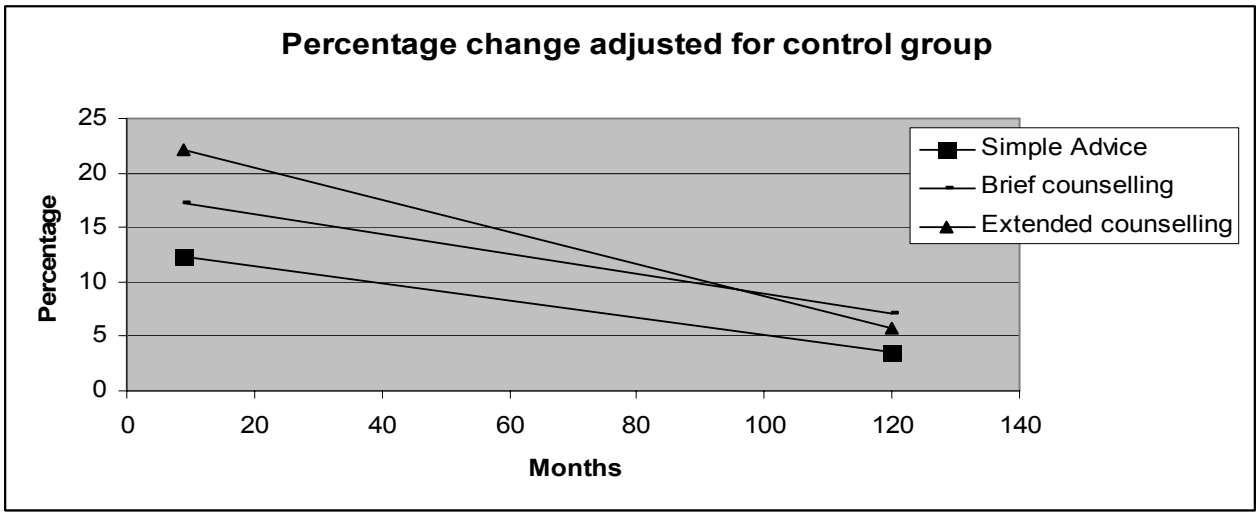


Table 3.4 Change in %drinking above safe limits after adjusting for control group changes

	Simple Advice	Brief Counselling	Extended Counselling
%improvement at 9 months	12.4	17.3	22.2
%improvement at 120 months	3.5	7.1	5.8

The excess effect for each treatment arm is summarised in Table 3.4 above. This excess effect has been used to calculate the ratio of treatment costs per additional changer given in Table 3.5 below.

Table 3.5 Within-trial cost-effectiveness analysis

	Simple Advice	Brief Counselling	Extended Counselling
Cost per enrolled	$14.91	$29.63	$90.03
Cost per completer	$14.91	$29.63	$90.03
Cost per changer at 9 months	$120.24	$171.27	$405.54
Cost per changer at 10 years	$426	$417.32	$1,552.24

Table 3.6 summarises results from one-way sensitivity analysis varying the proportion of patients requiring Level C consults in the simple advice arm.

Table 3.6 Sensitivity analysis varying average cost of GP consults for simple advice

	Simple advice cost of consultation	Cost per changer at 9 months	Cost per changer at 10 years
25% patients convert to Level C	$8.12	$65.48	$232
75% patients convert to Level C	$21.69	$174.92	$619.71

A calculation of the number of additional “safe drinking” years produced over the ten year follow-up period has also been made using the difference in percentage changes in the groups over time. This has been done to try and assess the degree of benefit available over the 10 years period that may not be reflected by the end of the period where the effect curves begin to coincide.

To calculate the cost incurred to produce each safe drinking month the following formulae have been used:

Cost of simple advice for 100 people = 100 x $14.91 = $1491
Cost of brief counselling for 100 people = 100 x $$29.63 = $2963
Cost of extended counselling for 100 people = 100 x $90.03 = $9003

Number of additional "safe drinking" months produced by giving simple advice for 100 people = percentage greater than control drinking safely at 120 month x 111 (i.e. 120-9) + percentage greater than control drinking safely at 7 months x 55.5 (i.e. 120-9 /2)
= 882.45 months or 73.54 years
Cost per additional "safe drinking" year = $20.27

Number of additional "safe drinking" months produced by giving brief counselling to100 people = percentage greater than control drinking safely at 120 month x 111 (i.e. 120-9) + percentage greater than control drinking safely at 7 months x 55.5 (i.e. 120-9 /2)
= 1354.2 months or 112.85 years
Cost per additional "safe drinking" years = $26.28

Number of additional "safe drinking" months produced by giving extended counselling to 100 people = percentage greater than control drinking safely at 120 month x 111 (i.e. 120-9) + percentage greater than control drinking safely at 7 months x 55.5 (i.e. 120-9 /2)
= 1554 months or 129.5 years
Cost per additional "safe drinking" year = $69.48

3.6 Modelled CUA

The model that was used to estimate QALYs gained per person for brief interventions as compared to control in Chapter 2 was adapted to the Australian component of the WHO Cross-National Trial of Brief Interventions with Heavy Drinkers. Estimates of effect sizes and relapse rates for each of the four arms of the WHO trial were substituted into the Chapter 30 model. Parameters such as start_age, death rates and background quit rates were then corrected in line with patient characteristics in the Australian component of the WHO trial. For example, a weighted average of male and female death rate was calculated for each age band with the weights corresponding to the proportion of males and females in the trial population (63.4% males, 36.6% females). Details of the model structure and of key assumptions and parameter values are specified below.

A Markov model with seven non-absorbing (alcproblem1, alcproblem2, alcproblem3, moderate1, moderate2, moderate3, dependence) and one absorbing state (dead) was used to estimate QALYs gained per person for (i) brief intervention of simple advice plus extended counselling, (ii) brief intervention of simple advice plus brief counselling, and (iii) brief intervention of simple advice alone as compared to (iv) a no intervention control. Based on quit rates from the trial, the brief intervention of simple advice alone is estimated to deliver up to 0.397 QALYs gained per treated person as compared to a no intervention control in an Australian population aged 40 years. More intensive intervention produced additional QALY gains, with the potential to deliver up to 0.757 QALYs gained per treated person as compared to a no intervention control in an Australian population aged 40 years.

Incremental cost per person for each of the brief interventions and the no intervention control is summarised below. At this stage, the difference in per person direct treatment costs is assumed to reflect the incremental cost over the entire evaluation period. More specifically, external effects beyond the family unit (such as the cost of alcohol-related road trauma) and downstream healthcare costs have been excluded from the modelled cost-utility analysis. It is likely that the inclusion of these costs will serve to further reduce the cost/QALY ratio. The cost per QALY gained is estimated at well under $1,000 for initiation or escalation of the brief interventions evaluated in the WHO trial. Tables

3.7 to 3.10 summarise findings from the modelled cost-utility analysis with different assumptions as to the characteristics of the intervention, comparator and treatment effects.

Table 3.7 Summary of cost utility of brief alcohol interventions according to the modelled cost-utility analysis (discount rate= 5%): V1, 1st-person effects only

	QALYs gained/person	Incremental cost/person AUD	**Cost/QALY gained AUD**
Advice alone *vs* Nil	0.181	$14.91	$82.38
Advice+brief *vs* Nil	0.251	$29.63	$118.05
Advice+extended *vs* Nil	0.319	$90.03	$282.23
Advice+brief *vs* Advice alone	0.070	$14.72	$210.29
Advice+extended *vs* Advice+brief	0.068	$60.40	$888.24
Advice+extended *vs* Advice alone	0.138	$75.12	$544.35

Table 3.8 Summary of cost utility of brief alcohol interventions according to the modelled cost-utility analysis (discount rate= 5%): V1, 1st-person plus within-family external effects

	QALYs gained/person	Incremental cost/person AUD	**Cost/QALY gained AUD**
Advice alone *vs* Nil	0.358	$14.91	$41.65
Advice+brief *vs* Nil	0.496	$29.63	$59.74
Advice+extended *vs* Nil	0.632	$90.03	$142.45
Advice+brief *vs* Advice alone	0.138	$14.72	$106.67
Advice+extended *vs* Advice+brief	0.135	$60.40	$447.41
Advice+extended *vs* Advice alone	0.274	$75.12	$274.16

Table 3.9 Summary of cost utility of brief alcohol interventions according to the modelled cost-utility analysis (discount rate= 5%): V2, 1st-person effects only

	QALYs gained/person	Incremental cost/person AUD	**Cost/QALY gained AUD**
Advice alone *vs* Nil	0.225	$14.91	$66.27
Advice+brief *vs* Nil	0.326	$29.63	$90.89
Advice+extended *vs* Nil	0.406	$90.03	$221.75
Advice+brief *vs* Advice alone	0.102	$14.72	$144.31
Advice+extended *vs* Advice+brief	0.079	$60.40	$764.56
Advice+extended *vs* Advice alone	0.181	$75.12	$415.03

Table 3.10 Summary of cost utility of brief alcohol interventions according to the modelled cost-utility analysis (discount rate= 5%): V2, 1st-person plus within-family external effects

	QALYs gained/person	Incremental cost/person AUD	**Cost/QALY gained AUD**
Advice alone *vs* Nil	0.421	$14.91	$35.42
Advice+brief *vs* Nil	0.606	$29.63	$48.89
Advice+extended *vs* Nil	0.757	$90.03	$118.93
Advice+brief *vs* Advice alone	0.185	$14.72	$795.68
Advice+extended *vs* Advice+brief	0.152	$60.40	$397.37
Advice+extended *vs* Advice alone	0.336	$75.12	$223.57

Cycle length

Follow-up in the WHO trials was at 9 months and 10 years. A cycle length of 6 months is assumed when modelling the brief alcohol interventions evaluated by the WHO. Quit rates at 9 months and at 10 years are adjusted to per cycle transition probabilities as per Miller and Homan (1994). A half-cycle correction is applied to initial and final payoffs to adjust the stepwise survival curve traced by the model to more closely approximate the continuous survival curve that operates in the real-world.

Termination condition

The Markov model terminates when the following condition is satisfied: _stage > 20 & (_stage > 120 | _stage_eff < .001). In other words, the model terminates after 120 cycles (60 years) *or* when the reward accumulated in any given cycle falls below 1/1000 of a QALY and at least 20 cycles or 10 years have been completed.

Payoffs (private plus external)

First-person and within-family external HRQoL effects are calculated as for the Chapter 2 models. However, external effects within each family unit are limited to an arbitrary 5 years period, ceasing at 45 years of age irrespective of success/failure in moderating alcohol consumption. The reduction in the persistence of external effects from 15 years to 5 years reflects the older start_age of participants in the WHO trial.

Time-invariance

For the modelled cost-utility analysis TPr_Death is time-dependent but all other probabilities and payoffs are invariant with respect to time. Payoffs and the likelihood of relapse and recovery are dependent on history rather than time per se. For example, to account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'moderate1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'problem3' state. Transition to 'moderate1' does, however, result in an immediate improvement in first-person HRQoL such that the individual is immediately raised to full-health. Subsequent transition from 'moderate1' to 'moderate2' adds an improvement in external HRQoL effects but risk of death remains as for the 'problem3' state. A reduction in risk of death is finally added upon transition from 'moderate2' to the 'moderate3' state such that the tunnel sequence amounts to an accumulation of benefits comprising (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 6 months, and (iii) reduction in risk of death at 18 months. A converse accumulation of payoffs and risks is specified for the problem-drinker tunnel sequence.

Initial probabilities

Initial probabilities are used to distribute a cohort (or to designate the status of an individual) over the relevant health states. All subjects were required to drink to a hazardous level but not be physically dependent on alcohol such that the target population can be characterised as problem drinkers. For the purposes of the modelled cost-utility analysis, all individuals are assumed to be in steady-state and to have accumulated the full age/sex adjusted effects of their alcohol consumption. In other words, all persons commence in the 'AlcProblem3' state.

Start age

Mean age at baseline for the Australian component of the WHO trial was 40.1 years (13.0 SD). For the purposes of the modelled cost-utility analysis, we therefore assume an average start age of 40 years.

Quit rates

Quit rates are taken directly from the trial but with the intermediate outcome of alcohol moderation operationalised as a move from unsafe drinking as per NHMRC Guidelines to safe drinking as per

NHMRC Guidelines. Because follow-up in the WHO trial was at 9 months and 10 years, we must convert quit rates to per cycle transition probabilities as per Miller and Homan (1994). Two versions of the model are run. The first version calculates cost/QALY gains under the assumption that the 9-months treatment effect is evenly distributed over the first two cycles before reverting to the background quit rate calculated from the 10 years follow-up. For example, the 9-montsh reduction in the share of controls drinking above safe drinking limits would be converted to a per cycle risk via the formula: $1 - (1- 0.057)^{2/3} = 0.0384$. The second version assumes that the 10-years treatment effect is unevenly distributed over a 10-years period, with the 9-months treatment effect distributed over the first two cycles and the remainder of the 10-years treatment effect distributed over the remaining 18 cycles before reverting to the background quit rate calculated from the 10 years follow-up calculated from the 10 years follow-up. Table 3.11 summarises the treatment effect relating to time intervals bounded by 9 months and 10 years follow-ups. In the absence of local supporting data as to autonomous changes in drinking behaviour, we assume that the absolute risk of moderation in the control group at 10 years follow-up designates the likelihood of recovery from the problem drinker state in the absence of intervention (ie. for all subsequent cycles of the model).

Table 3.11 Percentage reduction in % drinking >safe limits

	Control	Simple Advice	Advice plus brief counselling	Advice plus extended counselling
Baseline to 9 months	5.7	18.1	23.0	27.9
Baseline to 120 months	23.7	27.2	30.8	29.5
9 to 120 months	18.0	9.1	7.8	1.6

Relapse rates

On first inspection the WHO trial would seem to provide a rare opportunity to calculate long-term treatment effects due to an attempt to follow-up the study sample some 10 years after entry to the initial trial. Of the 551 participants in the Australian component of the WHO trial, 433 (78.6%) were contacted for the 10 years follow-up and 370 (67.2%) completed the 10 year interview. Of the 181 participants who failed to complete the 10 years follow up, 38 (6.9%) refused and 25 (4.5%) had died. The remaining 118 (21.4%) participants remain unaccounted for. That said, no statistically significant differences were observed between treatment and control groups at 10 years follow-up. This would suggest a relatively high rate of relapse. Under the assumption that the 10-years risk of relapse approaches unity, the per cycle risk of relapse would equal approximately 0.206 (much greater than the per cycle risk of relapse of 0.056 assumed for the Chapter 2 models). Unfortunately, the 10 years follow-up is confounded by the age-gradient in alcohol consumption and our estimate of the per cycle risk of relapse likely to be inflated as a result. Moreover, it should be noted that small differences on some outcome measures persist at the 10 years follow-up and that the trial was not powered to detect treatment effects after 10 years of decay. For example, 44.2% of the control group were drinking at levels above the safe limit at the 10 years follow-up as compared to 42.4% of the intervention groups.

For our base case, risks of relapse and progression from ‘problem3’ to ‘dependence’ are as per the Chapter 2 models for cycles subsequent to follow-up from the trial. Because quit rates are net of relapse from baseline to follow-up, risk of relapse is set to zero for all cycles within the trial period (2 cycles in V1, 20 cycles in V2). Risk of relapse calculated from the 10 years follow-up will be within the range of values employed in sensitivity analysis.

Death rates

Risk of death is calculated as for the Chapter 2 models but are then combined to obtain a weighted average of the male and female death rate for each age band. Weights correspond to the proportion of males and females in the trial population (63.4% males, 36.6% females) under the assumption that they approximate the proportion of males and females in the target population.

Table 3.12 Relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.93 (0.39, 2.21)	≥6 drinks/day *vs* lifetime abstinent	2.29 (1.17, 4.48)	2-4 drinks/day *vs* lifetime abstinent	0.73 (0.39, 1.37)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.97 (0.30, 3.09)	≥4 drinks/day *vs* lifetime abstinent	1.06 (0.26, 4.34)	1-2 drinks/day *vs* lifetime abstinent	0.81 (0.42, 1.56)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.96 (1.26, 3.05)	Past problem drinking[#] *vs* lifetime abstinent	1.64 (0.98, 2.76)	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.84 (0.98, 3.44)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.77 (0.86, 3.64)	Past problem drinking[#] *vs* lifetime abstinent	2.18 (1.12, 4.24)	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.25 (0.17, 9.14)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

Table 3.13 Relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* 2-4 drinks/day	1.27 (0.53, 3.03)	≥6 drinks/day *vs* 2-4 drinks/day	3.14 (1.60, 6.14)	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.20 (0.37, 3.81)	≥4 drinks/day *vs* 1-2 drinks/day	1.31 (0.32, 5.36)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.68 (1.73, 4.18)	Past problem drinking[#] *vs* 2-4 drinks/day (a)	2.25 (1.34, 3.78)	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.52 (1.34, 4.71)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.19 (1.06, 4.49)	Past problem drinking[#] *vs* 1-2 drinks/day	2.69 (1.38, 5.23)	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.54 (0.21, 11.28)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.
(a) Death rate for recovered.

Table 3.14 Adjusted relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.90 (0.38, 2.14)	≥6 drinks/day *vs* lifetime abstinent	2.14 (1.08, 4.23)	2-4 drinks/day *vs* lifetime abstinent	0.78 (0.41, 1.47)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.89 (0.28, 2.88)	≥4 drinks/day *vs* lifetime abstinent	0.94 (0.23, 3.86)	1-2 drinks/day *vs* lifetime abstinent	0.77 (0.40, 1.51)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.93 (1.23, 3.02)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.62 (0.86, 3.07)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.65 (0.79, 3.41)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.08 (0.15, 7.93)	Rehm, Greenfield and Rogers (2001)

Table 3.15 Adjusted relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day (a) *vs* 2-4 drinks/day	1.15 (0.49, 2.74)	≥6 drinks/day *vs* 2-4 drinks/day (b)	2.74 (1.38, 5.42)	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.16 (0.36, 3.74)	≥4 drinks/day *vs* 1-2 drinks/day	1.22 (0.30, 5.01)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.47 (1.58, 3.87)	Past problem drinking[#] *vs* 2-4 drinks/day	NR	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.08 (1.10, 3.94)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.14 (1.03, 4.43)	Past problem drinking[#] *vs* 1-2 drinks/day	NR	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.40 (0.19, 10.30)	Rehm, Greenfield and Rogers (2001)

(a) Death rate for problem drinker.
(b) Death rate for 'dependant'.

Table 3.16 Age-specific deaths/1000 by alcohol status: Safe

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males	5.5	0.3	0.1	0.2	0.6	0.9	1.0	1.1	1.3	1.7	2.6	3.6	5.8	10.0	16.5	28.8	48.8	80.8	167.4
Females	4.7	0.2	0.1	0.1	0.3	0.3	0.4	0.5	0.7	1.0	1.5	2.4	3.7	6.0	9.6	16.2	28.9	54.2	135.4
Persons	5.21	0.26	0.10	0.16	0.49	0.68	0.78	0.88	1.08	1.44	2.20	3.16	5.03	8.54	13.97	24.19	41.52	71.06	155.69
TPr_M	0.0055	0.0003	0.0001	0.0002	0.0006	0.0009	0.0010	0.0011	0.0013	0.0017	0.0026	0.0036	0.0058	0.0100	0.0165	0.0288	0.0488	0.0808	0.1674
TPr_F	0.0047	0.0002	0.0001	0.0001	0.0003	0.0003	0.0004	0.0005	0.0007	0.0010	0.0015	0.0024	0.0037	0.0060	0.0096	0.0162	0.0289	0.0542	0.1354
TPr_P	0.0052	0.0003	0.0001	0.0002	0.0005	0.0007	0.0008	0.0009	0.0011	0.0014	0.0022	0.0032	0.0050	0.0085	0.0140	0.0242	0.0415	0.0711	0.1557

Proportion of men and women: 63.4% males, 36.6% females

Table 3.17 Age-specific TPr_Death by alcohol status: Problem3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.00633	0.00035	0.00012	0.00023	0.00069	0.00104	0.00115	0.00127	0.00150	0.00196	0.00299	0.00414	0.00667	0.01150	0.01898	0.03312	0.05612	0.09292	0.19251
Upper	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Lower	0.00270	0.00015	0.00005	0.00010	0.00029	0.00044	0.00049	0.00054	0.00064	0.00083	0.00127	0.00176	0.00284	0.00490	0.00809	0.01411	0.02391	0.03959	0.08203
Females																			
Mid	0.00541	0.00023	0.00012	0.00012	0.00035	0.00035	0.00046	0.00058	0.00081	0.00115	0.00173	0.00276	0.00426	0.00690	0.01104	0.01863	0.03324	0.06233	0.15571
Upper	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Lower	0.00230	0.00010	0.00005	0.00005	0.00015	0.00015	0.00020	0.00025	0.00034	0.00049	0.00074	0.00118	0.00181	0.00294	0.00470	0.00794	0.01416	0.02656	0.06635
Persons																			
Mid	0.00599	0.00030	0.00012	0.00019	0.00056	0.00078	0.00090	0.00101	0.00124	0.00166	0.00253	0.00363	0.00579	0.00982	0.01607	0.02782	0.04774	0.08172	0.17904
Upper	0.01427	0.00072	0.00027	0.00045	0.00134	0.00186	0.00214	0.00241	0.00296	0.00396	0.00602	0.00866	0.01379	0.02339	0.03829	0.06628	0.11376	0.19472	0.42659
Lower	0.00255	0.00013	0.00005	0.00008	0.00024	0.00033	0.00038	0.00043	0.00053	0.00071	0.00108	0.00155	0.00247	0.00418	0.00685	0.01185	0.02034	0.03482	0.07629

Men's RR: 4-6 drinks/day *vs* 2-4 drinks/day= 1.15 (0.49, 2.74). Women's RR: 2-4 drinks/day *vs* 1-2 drinks/day=1.16 (0.36, 3.74). Proportion of men and women: 63.4% males, 36.6% females

Table 3.18 Age-specific TPr_Death by alcohol status: Dependent3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Upper	0.02981	0.00163	0.00054	0.00108	0.00325	0.00488	0.00542	0.00596	0.00705	0.00921	0.01409	0.01951	0.03144	0.05420	0.08943	0.15610	0.26450	0.43794	0.90731
Lower	0.00759	0.00041	0.00014	0.00028	0.00083	0.00124	0.00138	0.00152	0.00179	0.00235	0.00359	0.00497	0.00800	0.01380	0.02277	0.03974	0.06734	0.11150	0.23101
Females																			
Mid	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Upper	0.02547	0.00108	0.00054	0.00054	0.00163	0.00163	0.00217	0.00271	0.00379	0.00542	0.00813	0.01301	0.02005	0.03252	0.05203	0.08780	0.15664	0.29376	0.73387
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01427	0.00072	0.00027	0.00045	0.00134	0.00186	0.00214	0.00241	0.00296	0.00396	0.00602	0.00866	0.01379	0.02339	0.03829	0.06628	0.11376	0.19472	0.42659
Upper	0.02822	0.00143	0.00054	0.00089	0.00266	0.00369	0.00423	0.00477	0.00586	0.00783	0.01191	0.01713	0.02727	0.04627	0.07574	0.13110	0.22502	0.38517	0.84383
Lower	0.00719	0.00036	0.00014	0.00023	0.00068	0.00094	0.00108	0.00121	0.00149	0.00199	0.00303	0.00436	0.00694	0.01178	0.01928	0.03338	0.05729	0.09807	0.21485

Men's RR: >6 drinks/day *vs* 2-4 drinks/day= 2.74 (1.38, 5.42). Women's RR: >4 drinks/day *vs* 1-2 drinks/day=1.22 (0.30, 5.01). Proportion of men and women: 63.4% males, 36.6% females

Table 3.19 Age-specific TPr_Death by alcohol status: Recovered

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01238	0.00068	0.00023	0.00045	0.00135	0.00203	0.00225	0.00248	0.00293	0.00383	0.00585	0.00810	0.01305	0.02250	0.03713	0.06480	0.10980	0.18180	0.37665
Upper	0.02079	0.00113	0.00038	0.00076	0.00227	0.00340	0.00378	0.00416	0.00491	0.00643	0.00983	0.01361	0.02192	0.03780	0.06237	0.10886	0.18446	0.30542	0.63277
Lower	0.00737	0.00040	0.00013	0.00027	0.00080	0.00121	0.00134	0.00147	0.00174	0.00228	0.00348	0.00482	0.00777	0.01340	0.02211	0.03859	0.06539	0.10827	0.22432
Females																			
Mid	0.01058	0.00045	0.00023	0.00023	0.00068	0.00068	0.00090	0.00113	0.00158	0.00225	0.00338	0.00540	0.00833	0.01350	0.02160	0.03645	0.06503	0.12195	0.30465
Upper	0.01777	0.00076	0.00038	0.00038	0.00113	0.00113	0.00151	0.00189	0.00265	0.00378	0.00567	0.00907	0.01399	0.02268	0.03629	0.06124	0.10924	0.20488	0.51181
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01172	0.00059	0.00023	0.00037	0.00110	0.00153	0.00176	0.00198	0.00243	0.00325	0.00494	0.00711	0.01132	0.01921	0.03144	0.05442	0.09341	0.15989	0.35030
Upper	0.01968	0.00100	0.00038	0.00062	0.00185	0.00257	0.00295	0.00333	0.00408	0.00546	0.00831	0.01195	0.01902	0.03227	0.05282	0.09143	0.15693	0.26862	0.58850
Lower	0.00705	0.00036	0.00014	0.00022	0.00066	0.00092	0.00105	0.00119	0.00146	0.00195	0.00297	0.00427	0.00680	0.01153	0.01887	0.03265	0.05606	0.09602	0.21060

Men's RR: Past problem *vs* 2-4 drinks/day= 2.25 (1.34, 3.78). Women's RR: Past problem *vs* 1-2 drinks/day=2.69 (1.38, 5.23). Proportion of men and women: 63.4% males, 36.6% females

Sensitivity analysis

The modelled cost-utility analysis is based on data taken from the Saunders et al (1991) meta-analysis, our own calculation of incremental program costs as described in Section 3.4, together with supporting data and assumptions as outlined above. Note, for example, that the estimate of QALYs gained from the modelled cost-utility analysis has been derived from a number of data sources with varying levels of error and uncertainty. More specifically, uncertainty in the estimate of QALYs gained is a function of sampling error in the trial-based measure of surrogate outcome (behaviour change), uncertainty as to the persistence of any behaviour change (relapse rates), and uncertainty in the relationship between a surrogate outcome such as behaviour change and a final outcome such as QALYs gained (with respect to both utility weights and life-years gained).

In an effort to identify key drivers and to evaluate robustness of estimates as to cost per QALY gained, univariate sensitivity analyses were conducted by varying parameters such as start_age, HRQoL weights in the 'problem' tunnel sequence and the dependence state, discount rate, initial rate of relapse (in the moderate1 state), the relative risk of death, response rates from the Saunders et al (1991) meta-analysis, and our estimates of incremental costs. Variation in each uncertain parameter produced intuitively plausible variations in cost per QALY ratios. Results of the sensitivity analyses are summarised in Table 3.22.

In order to keep the task manageable, sensitivity analyses were conducted for the V1 model with 1st person effects only. The base case analyses summarised in Tables 3.7 to 3.11 adequately demonstrate the change in cost per QALY ratios due to inclusion of within-family external effects and due to variation in the quit rate from 9 months through to 10 years.

The following details should be kept in mind for the interpretation of the sensitivity analyses.

- Recall that the base case assumed termination of the model at age=100 yrs. For the sensitivity analyses, the termination condition was adjusted to preserve termination at age=100 yrs irrespective of start_age. Note that varying start_age from 20 to 70 years produces only relatively minor changes in cost per QALY ratios.
- Recall that the V1 model calculates cost/QALY gains under the assumption that the 9-months treatment effect is evenly distributed over the first two cycles before reverting to the background quit rate calculated from the 10 years follow-up. For example, the 9-months reduction in the share of controls drinking above safe drinking limits would be converted to a per cycle risk via the formula: $1 - (1- 0.057)^{2/3} = 0.0384$. The 95%CI for treatment effect is derived by calculating the 95%CI around the relative risk of transition from 'problem' to 'moderate' over the initial 9 months follow-up. In order to calculate relative risks, we assumed that the 483 patients remaining in the study at 9 month follow-up were equally distributed across the four trial-arms. Upper and lower estimates for the absolute risk of transition from 'problem' to 'moderate' in BI groups are then derived assuming that the absolute risk for the Nil group is as for the base case analysis. Table 3.20 summarises these calculations. Note that the upper and lower limits on the absolute risk of transition from 'problem' to 'moderate' over the initial 9 months follow-up must be converted to per cycle risks as per Miller & Homan (1994). Table 3.21 summarises the conversion from 9 months risks to per cycle risks.
- The cost per life-year gained is derived by setting the HRQoL weight to 1.0 for each of the seven non-absorbing health states (problem1, problem2, problem3, moderate1, moderate2, moderate3, dependence). In other words, adjustment for HRQoL in health states other than death is removed for this analysis. Estimates of cost per life-year gained for the BI *vs* Nil comparison (based on 1st-person effects only) varied between 760 AUD and 2,655AUD depending on the characteristics of the brief intervention.

Table 3.20 Calculating 95%CI for Treatment Effect on 9 months follow-up data

Comparison	AR BIs (Base Case)	AR Nil	RR (95%CI)	AR BIs (Low)	AR BIs (High)
Advice alone *vs* Nil	22/121 ≈ 0.181	7/121 ≈ 0.057	3.14 (1.39, 7.08)	0.0807	0.4097
Advice+brief *vs* Nil	28/121 ≈ 0.230	7/121 ≈ 0.057	4.00 (1.82, 8.80)	0.1051	0.5094
Advice+extended *vs* Nil	34/121 ≈ 0.279	7/121 ≈ 0.057	4.86 (2.24, 10.53)	0.1297	0.6090

Table 3.21 Converting 9 months risks to per cycle risks

Comparison	AR BIs (Low)	Convert to per cycle AR (Low)	AR BIs (High)	Convert to per cycle AR (High)
Advice alone *vs* Nil	0.0807	$1 - (1- 0.0807)^{2/3}=0.0546$	0.4097	$1 - (1- 0.4097)^{2/3}=0.2963$
Advice+brief *vs* Nil	0.1051	$1 - (1- 0.1051)^{2/3}=0.0714$	0.5094	$1 - (1- 0.5094)^{2/3}=0.3780$
Advice+extended *vs* Nil	0.1297	$1 - (1- 0.1297)^{2/3}=0.0885$	0.6090	$1 - (1- 0.6090)^{2/3}=0.4653$

Table 3.22 Cost/QALY estimates according to the sensitivity analysis: V1, 1st-person effects only

	Advice alone *vs* Nil	Advice+brief *vs* Nil	Advice+extended *vs* Nil
start_age=20	$84.88	$121.86	$290.91
start_age=30	$84.16	$120.83	$288.46
start_age=40	$82.38	$118.05	$282.23
start_age=50	$79.48	$114.11	$271.84
start_age=60	$76.69	$110.21	$263.21
start_age=70	$79.77	$114.61	$273.06
Q_All=1.00	$760.44	$1,104.36	$2,653.80
discount=0.00	<$56.32	<$80.88	<$193.12
discount=0.05	$82.38	$118.05	$282.23
discount=0.07	$110.03	$157.94	$376.96
Initial relapse=0.056	$82.38	$118.05	$282.23
Initial relapse=0.10	$83.54	$119.90	$286.10
Initial relapse=0.20	$86.60	$124.16	$295.96
Initial relapse=0.40	$93.54	$133.80	$318.18
Lower 95%CL	$86.78	$124.59	$296.65
Mean RR_Death: Taylor (2002)	$82.38	$118.05	$282.23
Upper 95%CL	$75.50	$108.51	$259.18
Lower 95%CL	$214.14	$210.77	$425.43
Mean Treatment Effect	$82.38	$118.05	$282.23
Upper 95%CL	$15.20	$23.98	$60.93
Half Best Estimate	$41.14	$59.06	$140.99
Best Estimate Incremental Cost	$82.38	$118.05	$282.23
Twice Best Estimate	$164.55	$236.24	$563.98

Threshold Analysis

Recall that downstream cost offsets have not been included in the modelled cost-utility analysis (but would only serve to further reduce the cost/QALY ratio). While the complex modelling task of attributing downstream cost offsets to intervention and control groups is beyond the scope of this

study, we have quantified the minimum downstream cost offset that would be required in order for brief interventions plus counselling to be cost saving. Table 3.23 specifies the minimum per cycle downstream cost offset in the moderate3 state for BI at various intensities to dominate the comparator.

When interpreting the threshold analysis, it should be remembered that downstream cost offsets are likely to be age/sex dependent and accrue in an episodic (rather than constant) manner. In an attempt to incorporate some of this complexity, no downstream cost offsets accrue during the initial 2 cycles in the moderate state. This is consistent with assumptions made elsewhere in the model with respect to the differential risk of death in problem and moderate states[6]. Aside from this relatively crude adjustment for duration of time spent in the moderate state, downstream cost offsets are incorporated in the simplest way possible. The dollar-value of downstream cost offsets is invariant with respect to _stage and age such that the same downstream cost offset accrues to a moderate drinker after 3 cycles as after 30 cycles. It is left to the decision-maker to determine whether a 40 years old adopting moderate drinking behaviour is likely to average $45 per 6-months cycle in downstream cost offsets over the remaining 30 to 40 years of his/her lifespan.

Table 3.23 Minimum downstream cost offset for BIs to dominate: V1, 1st-person effects only (discount rate = 5%)

Model	QALYs gained/person	Downstream cost offset	Incremental cost/person	Cost/QALY gained
Advice alone *vs* Nil	0.181223	$13.15	$0.00	BI dominates
Advice+brief *vs* Nil	0.250842	$18.85	$0.00	BI dominates
Advice+extended *vs* Nil	0.31927	$44.95	$0.00	BI dominates

[6] A reduction in risk of death is added upon transition from 'moderate2' to the 'moderate3' state such that the 'moderate' tunnel sequence amounts to a accumulation of benefits made of (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 6 months, and (iii) reduction in risk of death at 18 months.

4 Moderation oriented cue exposure

4.1 Description

Intervention type

This analysis of Moderation Oriented Cue Exposure (MOCE) is based on a randomized controlled trial (RCT) conducted in an outpatient setting. This intervention is based on a controlled drinking method, aimed at moderating alcohol consumption rather than inducing total abstinence.

The primary aim of the study was to compare the effectiveness of MOCE with Behavioral Self Control Training (BSCT). It was also hypothesized that MOCE would be more effective than BSCT amongst more severe problem drinkers who were aiming at moderation rather than abstinence.

References/sources of evidence

The analysis is based on the article by Heather et al. (Heather, N., Brodie, J., Wale, S., Wilkinson, G., Luce, A., Webb E. & McCarthy, S. 2000. A Randomized Control Trial of Moderation-Oriented Cue Exposure. *Journal of Studies on Alcohol*. Vol 61 (4): 561-570.).

Research suggests that severely alcohol dependant individuals are more likely to recover with programs based on abstinence where more moderately dependant subjects (as defined by a score of less than 30 on the Severity of Alcohol Dependence Questionnaire (SADQ)) are able to recover with programs based on a reduction in drinking. This study was aimed at moderately dependant drinkers as well as more severely dependant drinkers than would normally be treated with moderation-oriented treatments.

Previous literature has suggested that a particularly important cue for heavy drinking is the effect of low to moderate doses of alcohol on increasing cravings. Clinical experience with problem drinkers has suggested that impaired control over consumption occurs after the ingestion of a few drinks Animals studies suggest that intake of small amounts of alcohol become a precondition for the acceptance of larger doses. On this basis, it is thought that if patients can be “primed” with small doses of alcohol and then taught to resist the subsequent cravings, this may prevent them going on to consume much larger amounts of alcohol.

MOCE is thus a form of extinction procedure where patients are given the priming dose of alcohol, and are then asked to resist further drinking despite the cravings they will probably experience. The expectation is that the cravings will gradually diminish over successive exposures.

MOCE is compared to the standard method of moderation-oriented treatment, Behavioural Self Control Training (BSCT). BSCT is supported by a large number of positive trials and is widely used in countries where moderation-oriented treatment is accepted.

Intervention description

Recruitment and target population:

Participants were recruited over a one year period from Newcastle and surrounding areas in the north of England).

Most participants were self-referred through local newspaper advertising (58 of 173 subjects.) Other sources of referrals included alcohol treatment agencies, general practitioners and “other sources of formal referral”.

One-hundred and seventy-three participants were initially screened for inclusion. Of these, 40 failed to attend the screening interview, 16 attended the screening interview but failed to attend the pre-treatment assessment and 9 were ineligible for the trial, leaving 108 subjects who were judged

eligible for entry to the trial. Figure 4.1 summarises recruitment and randomization of participants to the trial.

Inclusion/exclusion criteria:

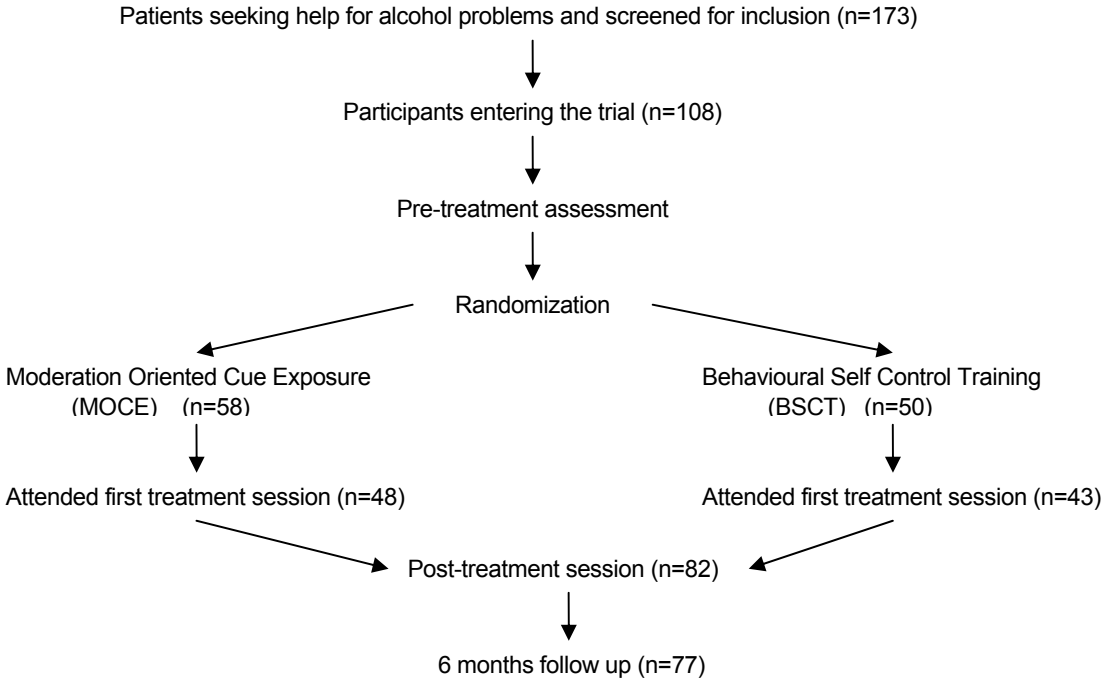
Participants were excluded from the study if they:

- Did not express a preference for moderation rather than total abstinence
- Had alanine transferase (ALT) levels above 60 (unless cleared for participation by a subsequent medical examination)
- Continued alcohol consumption at a level contraindicated on medical grounds eg total abstinence advised due to severe co-existing morbidity
- Severe psychiatric disturbance (unless cleared for participation by a subsequent psychiatric evaluation)
- Severe cognitive impairment
- Current dependence on other substances excluding cannabis and nicotine. However, polydrug users were allowed to participate if alcohol was judged to be their most important dependence problem
- Pregnancy or client planning to become pregnant during the lifetime of the trial

Further conditions of inclusion were:

- Written consent to random allocation
- Physical ability to attend the research centre for treatment sessions
- Willing to suspend involvement in any other therapeutic intervention for the duration of the trial
- Willingness to have all sessions audio-taped

Figure 4.1 Recruitment and randomization of participants



Intervention:

Pre-treatment assessment:

This assessment was scheduled 1 week after the screening interview and lasted for approximately 60 minutes.

Several questionnaires were completed for each participant

- A modified version of the Form 90 questionnaire from Project MATCH on alcohol consumption, called Form 60 in this study which detailed alcohol consumption over the previous two months.
- Severity of Alcohol Dependence Questionnaire C (SADQC)
- Alcohol Problems Questionnaire (APQ)

Treatment:
Sessions were delivered by 2 male therapists - a clinical psychologist and a psychiatric nurse, both with extensive experience in the treatment of alcohol problems. Therapists were trained in both general cognitive - behavioural alcohol therapy and in the two specific treatment therapies. Therapists treated 20 subjects each with one treatment modality before changing over to the alternative therapy to treat the remaining patients.

Participants received up to 16 weeks of treatment (Heather et al.).

MOCE
The mean length of sessions was 88 minutes with a mode of 90 minutes. The mean number of sessions attended was 7.67 and ranged from 1 to 16.

BSCT
The mean length of sessions was 63.49 minutes, with a mode of 60 minutes. The mean number of sessions attended was 6.56 and ranged from 1 to 16.

Post treatment assessment:
This session took place as soon as possible after the final treatment session. It involved repeating the pre treatment questionnaires.

Follow up:
Follow up was carried out by interview 6 months after participants completed the post-treatment assessment. Follow up was completed by a research assistant who was blinded to the treatment type completed by each participant. Participants were asked not to reveal what type of treatment they had. Follow up consisted of repeating the initial questionnaires and a finger prick blood sample for quantification of ALT and GGT (liver enzymes commonly elevated in alcohol dependant patients)
When participants were unable to be contacted for interviews, they were sent questionnaires by post (if addresses were available). If no response was obtained within 2 months, follow up data was assumed to be missing.

4.2 Quality of evidence

Evaluation description

Design:
This was a randomized controlled trial conducted in an outpatient setting. It was unblinded apart from the research assistant conducting follow up interviews. Blinding of participants and therapists would have been impossible to achieve.

Recruitment:
Overall the recruitment process was sound. The inclusion/exclusion criteria were rigorous enough to encompass only those alcohol dependant subjects who were suited to these methods of treatment. Unlike many other studies, many polydrug users were accepted, which is a better reflection of the patient population.

Methodology:
Participants were not included in the intention to treat analysis unless they had attended at least one session of therapy.

Analysis:
Non normally distributed variables were log or square root transformed. If transformations failed to achieve an approximately normal distribution, non parametric tests were used in the analysis. All tests were two-tailed.

Normally distributed study data were analysed with repeated measures ANOVA. Skewed data were analysed using the Wilcoxon Signed Rank Test (PDA was a skewed variable). Difference in PDA between intake and follow up was a normally distributed variable, and was analysed with simple factorial ANOVA.

Outcome measures:
The two main outcome variables in the trial were drinks per drinking day (DDD) and percent days abstinent (PDA). Data for these variables were collected during pre-treatment and post-treatment session and at the 6 months follow-up.

Assessment

Sources of bias:

Attrition bias:
Randomized clients that failed to attend the first treatment session (n=17) were not included in the analysis. It is possible that this exclusion affected the randomization process and resulted in an unmatched treatment sample. The baseline characteristics of the two groups were analysed and it was found that whilst the two groups did not differ in any socio-demographic characteristics, there were significant differences in the alcohol related variables. The MOCE group had significantly higher mean DDD and APQ. The MOCE group also had a significantly greater score on the global psychopathology score than those participants in the BSCT group, indicating that the MOCE group had a higher incidence of severe psychiatric disturbance than the BSCT group. This is not considered a significant factor considering that the scores were below the inclusion/exclusion criteria cut-off.

Selection bias:
The majority of participants were self referred, so a more highly motivated group than average would be expected, resulting in better results for both the intervention and control group. Baseline characteristics of participants in the trial population and in each treatment group are summarised in Table 4.1.

Overall this study was of high quality in terms of design and implementation. The key limitation relates to the differences in the alcohol markers between the two treatment groups.

4.3 Outcomes as reported

Behaviour change and clinical parameters

Of the 108 participants that were randomized in the study, 91 completed the treatment. 82 (90%) completed the post treatment assessment and 77 (85%) of these were successfully followed up at 6 months. Two participants died during the 6 months follow up period.

Table 4.1 Baseline characteristics of clients in each treatment group

Variable	Overall (n=91) (%)	MOCE n=48) (%)	BSCT n=43) (%)	*p*<
Male (%)	68 (75)	38 (80)	30 (70)	NS
Female (%)	23 (25)	10 (20)	13 (30)	NS
Age mean (SD)	41.43±9.92	40.67±10.51	42.30±9.30	NS
Married/living together (%)	45 (53)	24 (50)	24 (57)	NS
Single (%)	23 (25)	14 (29)	9 (21)	NS
Separated/divorced (%)	19 (21)	10 (21)	9 (21)	NS
Widowed (%)	1 (1)	0 (0)	1 (1)	NS
School leaving age mean (SD)	16.19±1.33	16.26±1.30	16.12±1.40	NS
Higher/further education (%)	28 (31)	18 (37)	10 (23)	NS
Vocational education (%)	24 (26)	11 (23)	13 (30)	NS
No post school education (%)	39 (43)	19 (40)	20 (47)	NS
Employed	46 (51)	21 (44)	25 (58)	NS
Dependent on state for income	45 (49)	27 (56)	18 (42)	NS
Prior treatment for alcohol problems (%)	45 (50)	26 (54)	19 (44)	NS
Drinks per drinking day, mean (SD)	19.69±14.42	20.97±12.23	18.27±16.60	0.05
Percent Days Abstinent, mean (SD)	19.14±23.15	20.60±23.00	18.22±24.00	NS
Alcohol dependence (SADQ-C) mean (SD)	18.70±11.00	20.26±10.52	17.00±11.35	NS
Global psychopathology (BSI) mean (SD)	51.35±12.00	54.07±11.44	48.44±11.83	0.05
Alcohol related problems (APQ) mean (SD)	10.10±5.00	11.26±5.10	8.84±4.53	0.05
Liver function tests mean (SD)				
ALT	30.21±18.62	31.58±19.96	28.63±17.08	NS
GGT	82.22±175.13	87.50±224.05	76.45±99.77	NS

Participants in the MOCE group attended an average of 7.67 therapy sessions (range 1-16). Participants in the BSCT group attended an average of 6.56 therapy sessions (range 1-16). The mean number of sessions attended was not significantly different between therapy groups.

There was a significant overall 'treatment' effect in this study from the therapy sessions. (Table 4.3)

- Mean drinks per drinking day (DDD) decreased from 18.88 at intake, to 11.14 at follow up (p=0.0001)
- Mean percent days abstinent (PDA) increased from 19.83 at intake, to 37.13 at follow up (p=0.0001)
- There were no significant differences in mean DDD and mean PDA between the MOCE group and the BSCT group.

When the treatment group was stratified into high (≥30) and low (≤29) alcohol dependence (SADQ-C):

- Participants in the high dependence group showed a significantly greater reduction in mean DDD at follow up compared to those in the lower dependence group. (p=0.001)

There was also a significant interaction with treatment type.

- Those participants in the high dependence group showed a greater improvement in DDD if they received BSCT (n=4) compared to MOCE (n=6) (p=0.005). The low numbers of participants in this group should be noted.
- Those participants low in dependence, given MOCE (n=31) showed no significant change in DDD compared to those who received BSCT (n=33).
- Clients with low dependence, who were given MOCE had a significantly increased PDA compared to BSCT (p=0.02)
- Clients with high dependence, who were given BSCT (n=4) had a significantly increased PDA compared to MOCE (n=6) (p=0.02)

Table 4.2 shows that 24% of participants achieved the goal of non problem or abstinence when outcomes were stratified into abstinent, non-problem, much improved, somewhat improved or unimproved. A total of 47% were at least much improved at follow up. The two treatment types showed an identical percentage of abstinence or non problem drinking at follow up. A higher percentage of participants in the MOCE group were "much improved" (53%) compared to the BSCT group (41%). Table 4.3 summarises between-group comparisons on the mean number of drinks per drinking day and the percentage of days abstinent. These differences were not significant.

Table 4.2 Numbers (%) of clients in various categories at 6 months follow-up

Outcome Category	Total Sample n (%)	Treatment Group n (%)		Alcohol Dependence n (%)	
		MOCE	BSCT	≤29	≥30
Abstinent	6 (7)	3 (7)	3 (7)	3 (4)	3 (25)
Non problem drinker	14 (17)	7 (17)	7 (17)	12 (18)	2 (16.7)
Much improved	19 (23)	12 (29)	7 (17)	16 (23)	2 (16.7)
Somewhat improved	13(16)	6 (15)	7 (17)	11 (16)	2 (16.7)
Unimproved	30 (37)	13 (32)	17 (42)	27 (39)	3 (25)
Total	82 (100)	41 (100)	41 (100)	69 (100)	12 (100)

Table 4.3 Means (SD) of outcome variables in the follow-up sample at intake & follow-up

Outcome Variable	Total Sample (n=77)	Treatment Type		Alcohol Dependence	
		MOCE (n=39)	BSCT (n=38)	≤29 (n=65)	≥30 (n=11)
Drinks per drinking day (DDD) (SD)					
Intake	18.88 (13.65)	20.41 (12.12)	17.32 (15.10)	17.11 (12.20)	31.12 (17.50)
6 months follow-up	11.14 (9.53)	13.06 (8.91)	9.17 (9.90)	11.28 (9.53)	10.61 (10.40)
Percent days abstinent (PDA)					
Intake	19.83 (23.32)	20.34 (22.66)	19.30 (24.27)	20.00 (24.27)	15.76 (15.26)
6 months follow-up	37.13 (32.10)	40.88 (30.29)	33.38 (33.80)	32.59 (30.30)	66.17 (31.21)

Considered as a whole, this study has not demonstrated any superiority of MOCE over BSCT. The authors concede that MOCE is also considerably more expensive than BSCT when considering additional time costs and consumables and training required.

Mortality

Two deaths were reported amongst the study population, one of which was alcohol related. The numbers are too small to be statistically significant and mortality was not an outcome variable. Once again, use of longer term outcome variables is constrained by the short follow up time.

4.4 Program costs

As reported by trial

Based on resource use

Research costs were not mentioned in this study. The following costs are estimated cost to run this program in Australia today. Costs incurred purely as a result of research activity, rather than in the administration of the intervention, have been excluded. As the viewpoint taken is that of the Department of Health and Ageing, costs to the participant have not been included.

Table 4.4 Treatment costs for MOCE patients

	Cost	Time	Number	Total cost	Cost/person
Clinical psychologist training	$50/hr	10 weeks	1	$500	$8.62
Psychiatric nurse training	$38.50/hr	10 weeks	1	$385	$8.02
Trainer – clinical psychologist	$50/hr	10 weeks	10 sessions	$500	$8.62
Phone calls	$0.4	N/A	48	$19.20	$0.4
Consumables – referral form	$0.05	N/A	86.5 referral forms	$4.33	$0.05
Newspaper advertising	$150		4	$600	$12.50
Screening interview	$37.50	30-60 minutes	58	$2,175.00	$37.50
Screening questionnaires: Form60 (2 pages), SADQ-C (6 pages), APQ, trial information	Approx $700 for 300 of each		58 of each x 2 per participant	$270.66	$14.58
Pre-treatment assessment	$23.11	60 minutes	58	$1,340.38	$23.11
Treatment sessions	$75	90 minutes	48 x 7.57 (mean)	$27,252.50	$567.50
Pathology- ALT, GGT	$11.75 (HIC, 2003)		1	$681.50	$11.75
Total				**$33,457.91**	**$679.20**

Table 4.5 Treatment costs for BSCT patients

	Cost	Time	Number	Total cost	Cost/person
Clinical psychologist	$50/hr	10 weeks	1	$500	$10
Psychiatric nurse	$38.50/hr	10 weeks	1	$385.00	$6.63
Trainer - clinical psychologist	$50/hr	10 weeks	1	$500	$10
Phone calls	$0.4		50	$20	$0.4
Consumables – referral form	$0.05		86.5 referral forms	$4.33	$0.05
Screening interview	$37.50	30-60 minutes	50	$1,875.00	$37.50
Screening questionnaires: Form60, SADQ-C, APQ, trial information	Approx $700 for 300 of each		50 of each x 2 per participant	$233	$4.66
Pre-treatment assessment	$23.11	60 minutes	50	$1,155.50	$23.11
Treatment sessions	$50	60 minutes	43 x 6.56 (mean)	$14,104.00	$328.00
Pathology- ALT, GGT	$11.75		43	$587.50	$11.75
Total				**$19,344.33**	**$433.17**

4.5 Within-trial CEA

Tables 4.6 and 4.7 summarise findings from the within-trial cost-effectiveness analysis expressed as average cost per changer. Note that BSCT would dominate MOCE in a head-to-head comparison because BSCT is no less effective and cheaper than MOCE.

Table 4.6 Average cost per changer: MOCE

	As calculated	Change in cost of training to cover 100 or 200 people
Cost per enrolled	$679.20	$662.87
Cost per completer	$687.29	$662.87
Cost per changer (defined as "non-problem drinker" or "abstinent") (24%)	$2,863.71	$2,761.96

Table 4.7 Average cost per changer: BSCT

	As calculated	Change in cost of training to cover 100 or 200 people
Cost per enrolled	$433.17	416.99
Cost per completer	$438.44	$416.99
Cost per changer (defined as "non-problem drinker" or "abstinent") (24%)	$1,826.83	$1,737.46

There is a well documented body of evidence showing the alcohol abuse and dependence tends to decline naturally over time and with age. Vaillent in a review of 8 such studies in 1995, reported an average of 2% of alcohol dependant participants reverted to abstinence over any twelve month period.[x] The Saunders study reviewed in Chapter 3, showed a much sharper decline in their control group over a 6 month period of almost 6% in only 9 months.[xi] The percentage of participants moving into 'non-problem' or 'abstinent' drinkers' categories as a result of treatment has been adjusted for the natural decline in drinking over time and with age. Figure 4.2 summarises the adjustment under two scenarios: 1) natural decline of 1% over 6 months and; 2) natural decline of 3.8% over 6 months. Table 4.8 summarises average cost per changer in MOCE and BSCT groups after adjusting for the natural decline in drinking over time under each scenario.

Figure 4.2 Percentage 'non-problem' or 'abstinent' adjusted for natural decline

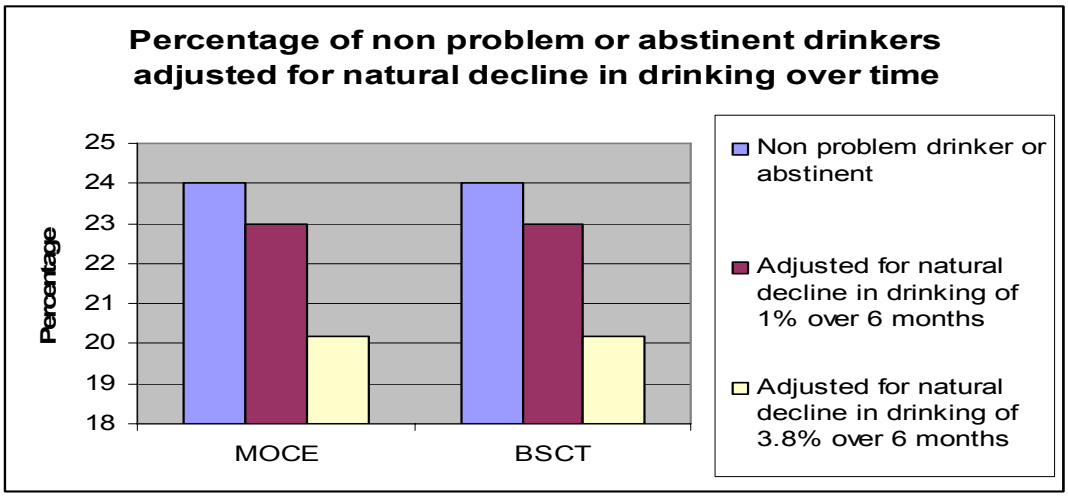


Table 4.8 Average cost per changer[#] adjusted for natural decline in drinking over time

	Base case	Taking into account natural decline in drinking of 1% over 6 months	Taking into account natural decline in drinking of 3.8% over 6 months [xii]
MOCE	$2,863.71	2,988.22	$3,402.43
BSCT	$1,826.83	$1,906.26	$2,170.49

[#] Defined as those who had not "broke[n] national guidelines at least once"

It is noted that MOCE in particular resulted in more marked improvements in the high dependence subgroup. However, the numbers are small and significance uncertain, thus costing has not been carried out for the subgroup.

4.6 Modelled CUA

When responders are defined as 'non-problem drinker' or 'abstinent', the trial fails to demonstrate any significant treatment effect. MOCE is also considerably more expensive than BSCT when considering the additional time costs and consumables and training required such that – based on the outcome of interest (ie. %responders) – the BSCT would dominate the MOCE (no less effective but cheaper). That said, there appears to be evidence for a differential effect with respect to %partial responders where partial responders are defined as 'much improved', 'non-problem drinker' or 'abstinent'.

Because the intermediate outcome of partial responders represents an imperfect proxy for the impact of an intervention on quality and quantity of life, we translate the results of the Heather et al (2000) trial into a cost/QALY ratio. A modelled cost-utility analysis was conducted based on the assumptions and parameter values specified below. At this stage, the difference in per completer direct treatment costs is assumed to reflect the incremental cost over the entire evaluation period. More specifically, external effects beyond the family unit (such as the cost of alcohol-related road trauma) and downstream healthcare costs have been excluded from the modelled cost-utility analysis. It is likely that the inclusion of these costs will serve to further reduce the cost/QALY ratio.

A Markov model with six non-absorbing (dependence1, dependence2, dependence3, recovered1, recovered2, recovered3) and one absorbing state (dead) was used to estimate QALYs gained per person for MOCE as compared to BSCT. Table 4.9 summarises results from the modelled cost-utility analysis. In a predominantly male population aged 41 years, MOCE is estimated to deliver 0.116 QALYs gained per completer as compared to BTSC if external effects are assumed away. In a predominantly male population aged 41 years, MOCE is estimated to deliver 0.244 QALYs gained per completer as compared to BTSC if within-family external effects are included. The incremental cost per completer of MOCE as compared to BSCT was estimated at 249 AUD and is assumed to reflect the incremental cost over the entire evaluation period. The cost per QALY gained is estimated at 2,145 AUD based on 1st-person effects (or 1,020 AUD if within-family external effects are included).

[x] Secretary of Health and Human Services (2000). 10th Special Report to the U.S. Congress on Alcohol and Health, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

[xi] Wutzke, S., K. Conigrave, et al. (2002). "The long-term effectiveness of brief interventions for unsafe alcohol consumption: a 10-year follow up." Addiction **97**: 665-675

[xii] Wutzke, S., K. Conigrave, et al. (2002). "The long-term effectiveness of brief interventions for unsafe alcohol consumption: a 10-year follow up." Addiction **97**: 665-675

Table 4.9 MOCE *vs* BSCT according to the modelled cost-utility analysis (discount rate= 5%)

	1st-person effects only	1st-person + within-family external effects
QALYs gained/completer	0.116	0.244
Extra cost/completer AUD	$248.80	$248.80
Cost/QALY gained AUD	**$2,144.83**	**$1,019.67**

Health states and the Markovian assumption

A Markov model with just two non-absorbing (dependence and recovered) and one absorbing state (dead) could be used to estimate QALYs gained per person for each intervention as compared to its comparator. There is no 'tee-total' state because all subjects in the trial were moderately dependent drinkers on entry to the trials and because small cell sizes preclude the use of data with respect to abstinence. Similarly, only 7 patients in each arm reached 'safe' consumption levels at 6 months follow-up. For the modelled cost-utility analysis, we combine the 'abstinent', 'non-problem drinker' and 'much improved' categories and make the conservative assumption that individuals in these categories at 6 months follow-up have achieved a minimum improvement in HRQoL and risk of death that can be characterised as transition from 'dependence' to 'recovered'. Because it is difficult to undo some of the damage done during dependence, the risk of death is elevated for persons characterised as 'recovered' (as compared to persons characterised as 'moderate' or 'problem' drinkers in the Chapter 2 and 3 models).

In order to model the cumulative effect of an 'improved' consumption pattern, the 'recovered' and 'dependence' disease states are split into temporary disease states. Temporary states are "defined as having transitions only to other states and not to themselves. This guarantees that the patient can spend, at most, one cycle in that state". (Sonnenberg & Beck, 1993 p. 326) Patients are not required to transition through the three 'recovered' states (ie. patients can return to 'dependence' after any number of cycles) but 'recovered3' can *only* be reached after first cycling through both 'recovered2' and 'recovered1'. This gives us a fixed sequence of temporary states known as a tunnel sequence (Briggs & Sculpher, 1998).

Cycle length

Follow-up in the Heather et al (2000) trial was at 6 months (with the result that data as to behaviour change refers to a time period of 6 months). A cycle length of 6 months is therefore assumed when modelling the MOCE and BSCT interventions. A half-cycle correction is applied to initial and final payoffs to adjust the stepwise survival curve traced by the model to more closely approximate the continuous survival curve that operates in the real-world.

Termination condition

The Markov model terminates when the following condition is satisfied: _stage > 18 & (_stage > 118 | _stage_eff < .001). In other words, the model terminates after 118 cycles (59 years) *or* when the reward accumulated in any given cycle falls below 1/1000 of a QALY and at least 18 cycles or 9 years have been completed.

Payoffs (private plus external)

First-person and within-family external HRQoL effects are calculated as for the Chapter 2 models. In the absence of supporting data, we make the conservative assumption that the HRQoL weight for the 'recovered' state is approximately equal to the HRQoL weight for problem drinkers. External effects within each family unit are limited to an arbitrary 4 years period, ceasing at 45 years of age irrespective of success/failure in moderating alcohol consumption. The reduction in the persistence of external effects to 4 years reflects the older start_age of participants in the Heather et al (2000) trial.

Time-invariance

For the modelled cost-utility analysis TPr_Death is time-dependent but all other probabilities and payoffs are invariant with respect to time. Payoffs and the likelihood of relapse and recovery are dependent on history rather than time per se. For example, to account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'recovered1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'alc_dependence3' state. Transition to 'recovered1' does, however, result in an immediate improvement in first-person HRQoL. Subsequent transition from 'recovered1' to 'recovered2' adds an improvement in external HRQoL effects but risk of death remains as for the 'dependence3' state. A reduction in risk of death is finally added upon transition from 'recovered2' to the 'recovered3' state such that the tunnel sequence amounts to a accumulation of benefits made of (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 6 months, and (iii) reduction in risk of death at 18 months. A converse accumulation of payoffs and risks is specified for the alc_dependence tunnel sequence.

Initial probabilities

Initial probabilities are used to distribute a cohort (or to designate the status of an individual) over the relevant health states. All subjects in the Heather et al (2000) sample were moderately or severely dependent on entry to the trials. For the purposes of the modelled cost-utility analysis, all individuals are assumed to be in steady-state and to have accumulated the full age/sex adjusted effects of their alcohol consumption. In other words, all persons commence in the 'AlcDependence3' state.

Start age

Mean age at baseline in the Heather et al (2000) trial was 41.43 years (9.92 SD). For the purposes of the modelled cost-utility analysis, we therefore assume an average start age of 41 years.

Recovery

Recovery rates are taken directly from the trial but the outcomes of 'abstinent', 'non-problem drinker' and 'much improved' are combined and operationalised as a move from 'dependence' to 'recovered'. The % recovered at 6 months follow-up is taken as the absolute risk of transition from 'dependence' to 'recovered'. While it is recognised that this data fails to control for differences in severity at baseline, this has the effect of deflating rather than inflating the treatment effect. Note, for example, that the MOCE group had significantly higher mean DDD and APQ than the BSCT group at baseline and averaged significantly greater global psychopathology scores (see Table 4.1 above). Table 4.10 summarises per cycle risk of transition from 'dependence' to 'recovered' in MOCE and BSCT groups.

There is a well documented body of evidence showing the alcohol abuse and dependence tends to decline naturally over time and with age. Vaillent (1995) in a review of 8 such studies reported an average of 2% of alcohol dependant participants reverted to abstinence over any twelve month period. The risk of recovery reported by Vaillent (1995) is taken as the background risk of transition from 'dependence' to 'recovered' and converted to a per cycle risk as per Miller & Homan (1994): $1 - (1- 0.02)^{1/2} = 0.010051$.

Table 4.10 Percentage recovered at 6 month follow-up: MOCE *vs* BSCT

MOCE Recovered (%)	BSCT Recovered (%)	Difference (95%CI)	RR (95%CI)
22/41 (53.7%)	17/41 (41.5%)	0.12 (-0.09, 0.34)	1.29 (0.82, 2.05)

Relapse rates

The risk of relapse from recovered to dependence is assumed to be equal to the risk of progression from alc_problem to dependence used in the Chapter 2 and 3 models.

Death rates

For dependent drinkers, we rely on death rates for those exceeding NHMRC recommendations for peak consumption (ie. >6 drinks/session, women: >4 drinks/session) on a regular basis. For recovered drinkers, we rely on death rates for past problem drinkers where past problem drinking is defined as having ≥5 drinks on a weekly basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983. Risk of death for males and females are calculated as for the Chapter 2 models but we then combine these risks to obtain a weighted average of the male and female death rate for each age band. Weights correspond to the proportion of males and females in the Chapter 4 trial population (75% males, 25% females) under the assumption that this approximates the proportion of males and females in the target population.

Table 4.11 Relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.93 (0.39, 2.21)	**≥6 drinks/day *vs* lifetime abstinent**	**2.29 (1.17, 4.48)**	2-4 drinks/day *vs* lifetime abstinent	0.73 (0.39, 1.37)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.97 (0.30, 3.09)	≥4 drinks/day *vs* lifetime abstinent	1.06 (0.26, 4.34)	1-2 drinks/day *vs* lifetime abstinent	0.81 (0.42, 1.56)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.96 (1.26, 3.05)	Past problem drinking[#] *vs* lifetime abstinent	1.64 (0.98, 2.76)	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.84 (0.98, 3.44)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.77 (0.86, 3.64)	Past problem drinking[#] *vs* lifetime abstinent	2.18 (1.12, 4.24)	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.25 (0.17, 9.14)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

Table 4.12 Relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* 2-4 drinks/day	1.27 (0.53, 3.03)	≥6 drinks/day *vs* 2-4 drinks/day	**3.14 (1.60, 6.14)**	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.20 (0.37, 3.81)	≥4 drinks/day *vs* 1-2 drinks/day	1.31 (0.32, 5.36)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.68 (1.73, 4.18)	Past problem drinking[#] *vs* 2-4 drinks/day (a)	2.25 (1.34, 3.78)	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.52 (1.34, 4.71)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.19 (1.06, 4.49)	Past problem drinking[#] *vs* 1-2 drinks/day	2.69 (1.38, 5.23)	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.54 (0.21, 11.28)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

(a) Death rate for recovered.

Table 4.13 Adjusted relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.90 (0.38, 2.14)	≥6 drinks/day *vs* lifetime abstinent	2.14 (1.08, 4.23)	2-4 drinks/day *vs* lifetime abstinent	0.78 (0.41, 1.47)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.89 (0.28, 2.88)	≥4 drinks/day *vs* lifetime abstinent	0.94 (0.23, 3.86)	1-2 drinks/day *vs* lifetime abstinent	0.77 (0.40, 1.51)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.93 (1.23, 3.02)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.62 (0.86, 3.07)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.65 (0.79, 3.41)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.08 (0.15, 7.93)	Rehm, Greenfield and Rogers (2001)

Table 4.14 Adjusted Relative Risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day (a) *vs* 2-4 drinks/day	1.15 (0.49, 2.74)	≥6 drinks/day *vs* 2-4 drinks/day (b)	2.74 (1.38, 5.42)	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.16 (0.36, 3.74)	≥4 drinks/day *vs* 1-2 drinks/day	1.22 (0.30, 5.01)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.47 (1.58, 3.87)	Past problem drinking[#] *vs* 2-4 drinks/day	NR	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.08 (1.10, 3.94)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.14 (1.03, 4.43)	Past problem drinking[#] *vs* 1-2 drinks/day	NR	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.40 (0.19, 10.30)	Rehm, Greenfield and Rogers (2001)

(a) Death rate for problem drinker.
(b) Death rate for 'dependant'.

Table 4.15 Age-specific deaths/1000 by alcohol status: Safe

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males	5.5	0.3	0.1	0.2	0.6	0.9	1.0	1.1	1.3	1.7	2.6	3.6	5.8	10.0	16.5	28.8	48.8	80.8	167.4
Females	4.7	0.2	0.1	0.1	0.3	0.3	0.4	0.5	0.7	1.0	1.5	2.4	3.7	6.0	9.6	16.2	28.9	54.2	135.4
Persons	5.30	0.28	0.10	0.18	0.53	0.75	0.85	0.95	1.15	1.53	2.33	3.30	5.28	9.00	14.78	25.65	43.83	74.15	159.40
TPr_M	0.0055	0.0003	0.0001	0.0002	0.0006	0.0009	0.0010	0.0011	0.0013	0.0017	0.0026	0.0036	0.0058	0.0100	0.0165	0.0288	0.0488	0.0808	0.1674
TPr_F	0.0047	0.0002	0.0001	0.0001	0.0003	0.0003	0.0004	0.0005	0.0007	0.0010	0.0015	0.0024	0.0037	0.0060	0.0096	0.0162	0.0289	0.0542	0.1354
TPr_P	0.0053	0.0003	0.0001	0.0002	0.0005	0.0008	0.0009	0.0010	0.0012	0.0015	0.0023	0.0033	0.0053	0.0090	0.0148	0.0257	0.0438	0.0742	0.1594

Proportion of men and women: 75% males, 25% females

Table 4.16 Age-specific TPr_Death by alcohol status: Problem3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.00633	0.00035	0.00012	0.00023	0.00069	0.00104	0.00115	0.00127	0.00150	0.00196	0.00299	0.00414	0.00667	0.01150	0.01898	0.03312	0.05612	0.09292	0.19251
Upper	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Lower	0.00270	0.00015	0.00005	0.00010	0.00029	0.00044	0.00049	0.00054	0.00064	0.00083	0.00127	0.00176	0.00284	0.00490	0.00809	0.01411	0.02391	0.03959	0.08203
Females																			
Mid	0.00541	0.00023	0.00012	0.00012	0.00035	0.00035	0.00046	0.00058	0.00081	0.00115	0.00173	0.00276	0.00426	0.00690	0.01104	0.01863	0.03324	0.06233	0.15571
Upper	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Lower	0.00230	0.00010	0.00005	0.00005	0.00015	0.00015	0.00020	0.00025	0.00034	0.00049	0.00074	0.00118	0.00181	0.00294	0.00470	0.00794	0.01416	0.02656	0.06635
Persons																			
Mid	0.00610	0.00032	0.00012	0.00020	0.00060	0.00086	0.00098	0.00109	0.00132	0.00175	0.00267	0.00380	0.00607	0.01035	0.01699	0.02950	0.05040	0.08527	0.18331
Upper	0.01452	0.00075	0.00027	0.00048	0.00144	0.00206	0.00233	0.00260	0.00315	0.00418	0.00637	0.00904	0.01445	0.02466	0.04048	0.07028	0.12008	0.20317	0.43676
Lower	0.00260	0.00013	0.00005	0.00009	0.00026	0.00037	0.00042	0.00047	0.00056	0.00075	0.00114	0.00162	0.00258	0.00441	0.00724	0.01257	0.02147	0.03633	0.07811

Men's RR: 4-6 drinks/day *vs* 2-4 drinks/day= 1.15 (0.49, 2.74). Women's RR: 2-4 drinks/day *vs* 1-2 drinks/day=1.16 (0.36, 3.74). Proportion of men and women: 75% males, 25% females

Table 4.17 Age-specific TPr_Death by alcohol status: Dependent3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Upper	0.02981	0.00163	0.00054	0.00108	0.00325	0.00488	0.00542	0.00596	0.00705	0.00921	0.01409	0.01951	0.03144	0.05420	0.08943	0.15610	0.26450	0.43794	0.90731
Lower	0.00759	0.00041	0.00014	0.00028	0.00083	0.00124	0.00138	0.00152	0.00179	0.00235	0.00359	0.00497	0.00800	0.01380	0.02277	0.03974	0.06734	0.11150	0.23101
Females																			
Mid	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Upper	0.02547	0.00108	0.00054	0.00054	0.00163	0.00163	0.00217	0.00271	0.00379	0.00542	0.00813	0.01301	0.02005	0.03252	0.05203	0.08780	0.15664	0.29376	0.73387
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01452	0.00075	0.00027	0.00048	0.00144	0.00206	0.00233	0.00260	0.00315	0.00418	0.00637	0.00904	0.01445	0.02466	0.04048	0.07028	0.12008	0.20317	0.43676
Upper	0.02873	0.00149	0.00054	0.00095	0.00285	0.00407	0.00461	0.00515	0.00623	0.00827	0.01260	0.01789	0.02859	0.04878	0.08008	0.13902	0.23753	0.40189	0.86395
Lower	0.00731	0.00038	0.00014	0.00024	0.00072	0.00104	0.00117	0.00131	0.00159	0.00210	0.00321	0.00455	0.00728	0.01242	0.02039	0.03540	0.06048	0.10233	0.21997

Men's RR: >6 drinks/day *vs* 2-4 drinks/day= 2.74 (1.38, 5.42). Women's RR: >4 drinks/day *vs* 1-2 drinks/day=1.22 (0.30, 5.01). Proportion of men and women: 75% males, 25% females

Table 4.18 Age-specific TPr_Death by alcohol status: Recovered

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01238	0.00068	0.00023	0.00045	0.00135	0.00203	0.00225	0.00248	0.00293	0.00383	0.00585	0.00810	0.01305	0.02250	0.03713	0.06480	0.10980	0.18180	0.37665
Upper	0.02079	0.00113	0.00038	0.00076	0.00227	0.00340	0.00378	0.00416	0.00491	0.00643	0.00983	0.01361	0.02192	0.03780	0.06237	0.10886	0.18446	0.30542	0.63277
Lower	0.00737	0.00040	0.00013	0.00027	0.00080	0.00121	0.00134	0.00147	0.00174	0.00228	0.00348	0.00482	0.00777	0.01340	0.02211	0.03859	0.06539	0.10827	0.22432
Females																			
Mid	0.01058	0.00045	0.00023	0.00023	0.00068	0.00068	0.00090	0.00113	0.00158	0.00225	0.00338	0.00540	0.00833	0.01350	0.02160	0.03645	0.06503	0.12195	0.30465
Upper	0.01777	0.00076	0.00038	0.00038	0.00113	0.00113	0.00151	0.00189	0.00265	0.00378	0.00567	0.00907	0.01399	0.02268	0.03629	0.06124	0.10924	0.20488	0.51181
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01193	0.00062	0.00023	0.00039	0.00118	0.00169	0.00191	0.00214	0.00259	0.00343	0.00523	0.00743	0.01187	0.02025	0.03324	0.05771	0.09861	0.16684	0.35865
Upper	0.02003	0.00104	0.00038	0.00066	0.00198	0.00284	0.00321	0.00359	0.00435	0.00576	0.00879	0.01247	0.01994	0.03402	0.05585	0.09696	0.16566	0.28029	0.60253
Lower	0.00715	0.00037	0.00014	0.00024	0.00071	0.00101	0.00114	0.00128	0.00155	0.00205	0.00313	0.00445	0.00711	0.01212	0.01989	0.03453	0.05901	0.09990	0.21495

Men's RR: Past problem *vs* 2-4 drinks/day= 2.25 (1.34, 3.78). Women's RR: Past problem *vs* 1-2 drinks/day=2.69 (1.38, 5.23). Proportion of men and women: 75% males, 25% females

Sensitivity Analysis

The modelled cost-utility analysis is based on data taken from the Heather et al (2000) trial, our own calculation of incremental program costs as described in Section 4.4, together with supporting data and assumptions as outlined above. Note, for example, that the estimate of QALYs gained from the modelled cost-utility analysis has been derived from a number of data sources with varying levels of error and uncertainty. More specifically, uncertainty in the estimate of QALYs gained is a function of sampling error in the trial-based measure of surrogate outcome (behaviour change), uncertainty as to the persistence of any behaviour change (relapse rates), and uncertainty in the relationship between a surrogate outcome such as behaviour change and a final outcome such as QALYs gained (with respect to both utility weights and life-years gained).

In an effort to identify key drivers and to evaluate robustness of estimates as to cost per QALY gained, univariate sensitivity analyses were conducted by varying parameters such as start_age, HRQoL weights in the alcproblem tunnel sequence and the dependence state, discount rate, initial rate of relapse (in the moderate1 state), the relative risk of death, quit rates from the Heather et al (2000) trial, and our estimates of incremental costs. Variation in each uncertain parameter produced intuitively plausible variations in cost per QALY ratios. Results of the sensitivity analyses are summarised in Table 4.20.

The following details should be kept in mind for the interpretation of the sensitivity analyses.

- Recall that the base case assumed termination of the model at age=100 yrs. For the sensitivity analyses, the termination condition was adjusted to preserve termination at age=100 yrs irrespective of start_age. Note that varying start_age from 20 to 70 years produces only relatively minor changes in cost per QALY ratios for both men and women.
- The 95%CI for treatment effect is derived by calculating the 95%CI around the relative risk of transition from 'dependence' to 'recovered' for MOCE *vs* BSCT. Upper and lower estimates for the absolute risk of transition from 'dependence' to 'recovered' in the MOCE group are then derived assuming that the absolute risk for the NFC group is as for the base case analysis. Table 4.19 below summarises these calculations.
- The cost per life-year gained is derived by setting the HRQoL weight to 1.0 for each of the six non-absorbing health states (dependence1, dependence2, dependence3, recovered1, recovered2, recovered3). In other words, adjustment for HRQoL in health states other than death is removed for this analysis. Estimates of cost per life-year gained for the MOCE *vs* BSCT comparison varied between 57,391 AUD (based on 1st-person effects) and 19,111 AUD (if within-family external effects are included).

Table 4.19 Calculating 95%CI for Treatment Effect

AR MOCE (Base)	AR BSCT	RR (95%CI)	AR MOCE (Low)	AR MOCE (High)
22/41 = 0.537	17/41 = 0.415	1.29 (0.82, 2.05)	0.3382	0.8515

Table 4.20 Cost/QALY estimates according to the sensitivity analysis

	1st-Person Effects	1st-Person + Within-Family Effects
start_age=20	$2,147	$746
start_age=30	$2,146	$759
start_age=41	$2,145	$1,020
start_age=50	$2,150	$1,896
start_age=60	$2,207	$1,750
start_age=70	$2,482	$1,735
Q_All=1.00	$57,391	$19,111
discount=0.00	<$1,760	<$863
discount=0.05	$2,145	$1,020
discount=0.07	$2,523	$1,165
Initial relapse=0.056	$2,145	$1,020
Initial relapse=0.10	$2,229	$1,063
Initial relapse=0.20	$2,455	$1,183
Initial relapse=0.40	$3,100	$1,531
Lower 95%CL	$2,175	$1,058
Mean RR_Death: Taylor (2002)	$2,145	$1,020
Upper 95%CL	$2,071	$942
Lower 95%CL	BSCT dominates	BSCT dominates
Mean Treatment Effect	$2,145	$1,020
Upper 95%CL	$599	$285
Half Best Estimate	$1,072	$510
Best Estimate Incremental Cost	$2,145	$1,020
Twice Best Estimate	$4,290	$2,039

Threshold Analysis

Recall that downstream cost offsets have not been included in the modelled cost-utility analysis (but would only serve to further reduce the cost/QALY ratio). While the complex modelling task of attributing downstream cost offsets to intervention and control groups is beyond the scope of this study, we have quantified the minimum downstream cost offset that would be required in order for MOCE to be cost saving when compared to BSCT. Table 4.21 specifies the minimum per cycle downstream cost offset in the recovered3 state for MOCE at various intensities to dominate BSCT.

When interpreting the threshold analysis, it should be remembered that downstream cost offsets are likely to be age/sex dependent and accrue in an episodic (rather than constant) manner. In an attempt to incorporate some of this complexity, no downstream cost offsets accrue during the initial 2 cycles in the recovered state. This is consistent with assumptions made elsewhere in the model with respect to the differential risk of death in dependence and recovered states[7]. Aside from this relatively crude adjustment for duration of time spent in the recovered state, downstream cost offsets are incorporated in the simplest way possible. The dollar-value of downstream cost offsets is invariant with respect to _stage and ages such that the same downstream cost offset accrues to a recovered drinker after 3 cycles as after 30 cycles. It is left to the decision-maker to determine

[7] To account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'recovered1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'alc_dependence3' state. Transition to 'recovered1' does, however, result in an immediate improvement in first-person HRQoL. Subsequent transition from 'recovered1' to 'recovered2' adds an improvement in external HRQoL effects but risk of death remains as for the 'dependence3' state. A reduction in risk of death is finally added upon transition from 'recovered2' to the 'recovered3' state.

whether a 'recovered' 41 years old is likely to average $300 per 6-months cycle in downstream cost offsets over the remaining 30 to 40 years of his/her lifespan.

Table 4.21 Minimum downstream cost offset for MOCE to dominate: 1st-person effects only (discount rate= 5%)

Model	QALYs gained/person	Downstream cost offset	Incremental cost/person	Cost/QALY gained
MOCE *vs* BSCT	0.116121	$300.65	$0.00	MOCE dominates

5. Motivational Enhancement Therapy for mild to moderate alcohol dependence

5.1 Description

Intervention type

The study was a randomised controlled trial with 3 arms conducted in an outpatient setting. The intervention was based on motivational enhancement therapy (MET) compared to 2 types of control: non-directive reflective listening (NDRL) and no further counselling (NFC), in subjects with mild to moderate physical dependence on alcohol.

MET is a brief, psychotherapeutic intervention based on the principles of motivational interviewing. The technique is "not designed to guide the client, step by step, through recovery, but instead [employ] motivational strategies to mobilise the individual's own resources". (Project MATCH Research Group, 1997)

There were 2 study questions:
- Is MET more effective than feed-back and follow-up alone?
- Is MET more effective than four sessions of NDRL?

References/sources of evidence

This analysis is based on the following study: Sellman, J.D., Sullivan, P.F., Dore, G.M., Adamson, S.J. & MacEwan, I. 2001. A Randomized control trial for Motivational Enhancement Therapy (MET) for mild to moderate alcohol dependence. *Journal of Studies on Alcohol*. Vol 62: 389-396.

Intervention description

Recruitment and target population:

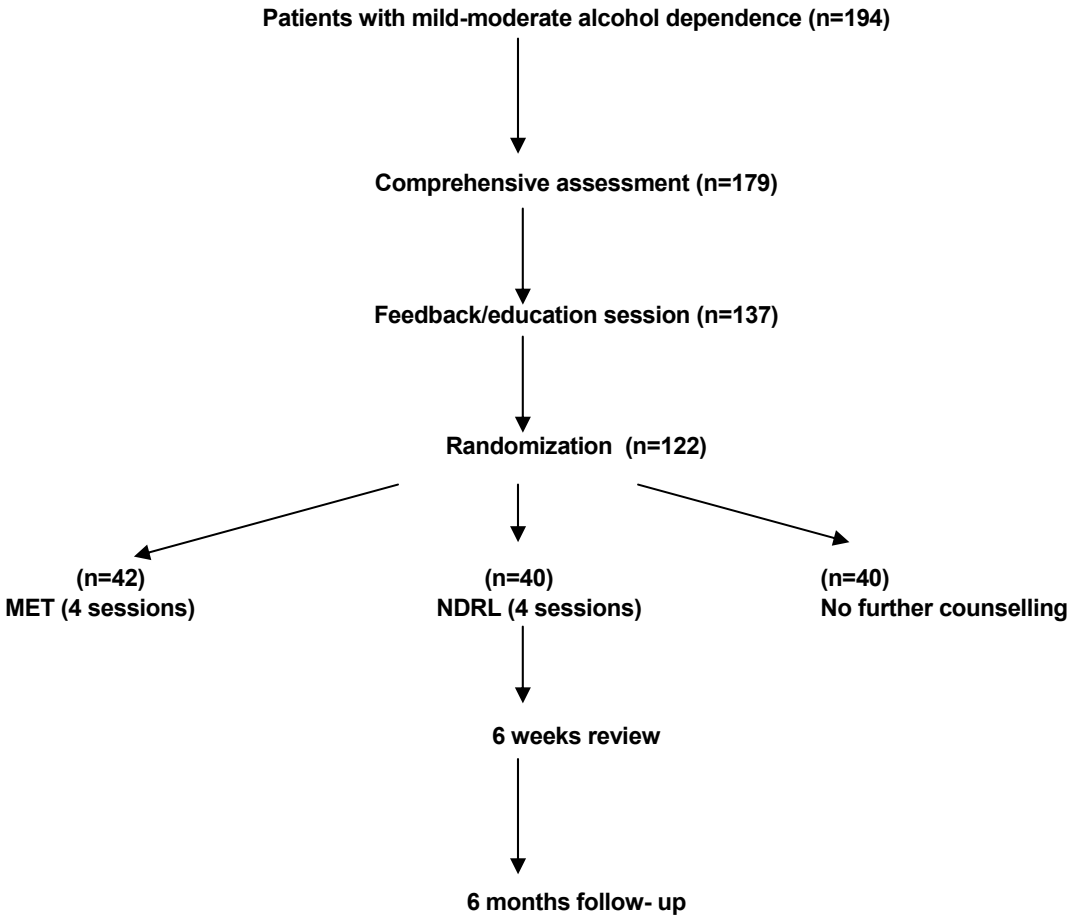
This study was carried out in Christchurch, New Zealand. Study participants ranged in age from 15-59 years. Recruitment was based on referrals to the Community Alcohol and Drug Service, Christchurch.

Inclusion Criteria:
- Able to give informed consent.
- Alcohol dependence as the principal current disorder when using the DSM-IV criteria (i.e. no psychiatric illness causing greater problems than the alcohol dependence).

Exclusion Criteria:
- Severe alcohol dependence.
- Alcohol withdrawal syndrome lasting longer than 24 hours.
- Mental or psychiatric illness such that any form of alcohol intake was considered inadvisable.
- Elevated AST or ALT.
- GGT greater than three times normal.

One-hundred and ninety-four patients with mild-moderate alcohol dependence were referred for evaluation against inclusion/exclusion criteria. Forty-two patients were excluded for not meeting the study inclusion criteria. Another 15 patients did not complete the initial assessment and a further 12 patients were excluded prior to randomization for miscellaneous reasons. Remaining participants were randomized into three groups: 42 were randomized to MET, 40 to NDRL and 40 to NFC. Figure 5.1 summarises the recruitment and randomization of participants to the trial.

Figure 5.1 Recruitment and randomization of participants



Study Protocol:

The 122 participants in the study were assessed at baseline and the following information collected for all participants:

Comprehensive Assessment:

- Diagnosis of alcohol dependence and a review of the previous 6 months drinking history using a Timeline Followback Procedure.
- Number of abstinent days.
- Number of days drinking within or above the national drinking guidelines.
- Number of days drank 10 or more standard drinks in a day.

Drinking data were checked with a 'significant other' nominated by the participant. Where there were discrepancies, negotiations took place until a consensus was reached. Liver-function tests were arranged for each participant and a second assessment session was arranged. In the second session, participants were given a structured diagnostic interview (The Diagnostic Interview for Genetic Studies). This interview covered the full range of mental disorders, as well as the Global Assessment Scale (GAS) which measures general overall functioning.

The feedback/education session: This session provided participants with details of their drinking history over the baseline 6 months. All participants were given pamphlets and information booklets on responsible drinking and encouraged to drink within national guidelines. The 'significant other' of the participant was encouraged to attend this session as well.

Randomization process: Participants were given an envelope with instructions for the next step in their treatment. These letters were the randomization step to one of the three treatment strategies described below.

Motivational Enhancement Therapy (MET):

Participants were given four sessions of MET counselling over a six-week period, with follow-up 6 months after the therapy.

MET was based around 5 key principles. These being:

- *Expressing empathy*: The MET therapist seeks to communicate great respect for the client. Communications that imply a superior/inferior relationship between therapist and client are avoided.
- *Deploying discrepancy*: Motivation for change occurs when people perceive a discrepancy between where they are and where they want to be. The MET approach seeks to enhance and focus the client's attention on such discrepancies with regard to alcohol abuse.
- *Avoiding argumentation:* The MET style explicitly avoids direct argumentation which tends to evoke resistance. No attempt is made to have the client accept or "admit" a diagnostic label.
- *Rolling with resistance*: MET strategies do not meet resistance head-on, but rather roll with the momentum, with a goal of shifting client perceptions in the process. New ways of thinking about problems are invited but not imposed.
- *Supporting self efficacy*: A person who is persuaded that he or she has a serious problem will still not move toward change unless there is hope for success. Bandura (1982) has described self-efficacy as a critical determinant of behaviour change. Self-efficacy is, in essence, the belief that one *can* perform a particular behaviour or accomplish a particular task.

Counselling was given in two main phases, Phase 1: Building motivation to change, and Phase 2: Strengthening commitment to change. All counselling sessions focused on drinking within New Zealand national guidelines. All participants in this group were reviewed after four sessions of MET over a 6-weeks period.

Counselling was provided by one of 4 specially trained therapists in 4 one-on-one sessions. The location of the sessions is unclear from the article. The comprehensive assessment and follow up sessions were at a venue of the participants choosing. It is assumed that therapy sessions were located at the offices of the Christchurch Community Alcohol and Drug Services.

Non directional reflective listening (NDRL):

For the purposes of the study, NDRL was called ‘person-centred therapy’. This was designed to test the differing content and structure of the therapy session (MET vs. NDRL).

NDRL consisted of non-strategic reflective listening sessions where subjects were invited to talk about anything they wanted (not necessarily issues about drinking). The direction of content was deliberately left to the subject to determine. All participants in this group were reviewed after four sessions of NDRL over a 6-week period.

No further counselling (NFC):

The NFC group received no further therapy after the two part comprehensive assessment and feedback/education session. All participants in this group were reviewed after a 6-weeks period. This group represented a brief intervention style group, as they received the feedback session discussing their drinking habits and encouragement to drink at levels consistent with the national drinking guidelines. Participants from all groups were asked to not to be involved in any other treatment for the 6 weeks duration of the trial but were encouraged to attend self-help group meetings.

5.2 Quality of evidence

Evaluation description

Design: The study was a randomised controlled trial with 3 arms conducted in an outpatient setting. It was unblinded apart from the research assistant conducting follow-up interviews. Blinding of participants and therapists would have been impossible to achieve.

Recruitment: Over all, the recruitment process was sound. The inclusion/exclusion criteria were designed to include only mild to moderately alcohol dependant subjects. Those with more severe dependence were excluded as they were likely to require more intensive therapy.

Randomisation: There were two randomization steps in this study. The first was concerned with the assessor/therapist combination, and the second with the type of therapy. This randomization procedure enabled a comparison between the MET group and the NDRL group, as well as between some therapy sessions.

Methodology: A third of the way through the study an external random audit, was performed by 2 independent clinicians on the audio-taped content of 8 of the therapy sessions (five MET, three NDRL). There was 100% agreement about which therapy was being given, and on a measure of the overall quality of the treatment, the mean score for MET was 4.9 and NDRL was 5 (on a 6 point scale). This suggests that therapy was given as intended.

The three groups were seen as embodying increasing doses of therapy. This helped the researchers to determine whether any effects could be contributed to MET particularly or whether positive benefits could be conferred by any type of counselling.

Analysis: Data were analysed with SPSS Version 9. Categorical variables were analysed with chi-square tests. Continuous variables were analysed with ANOVA tests. Paired samples were analysed with paired t tests and McNemar tests. Logistic regression was then employed to analyse differential treatment effects across the groups, calculated as Odds Ratios (OR).

Outcome measures:

Primary endpoints:

- Unequivocal heavy drinking defined as drinking 10 or more standard drinks six or more times in the 6 months follow-up period.
- General functioning as measured by the GAS, covering the month before 6 months follow-up.

Secondary endpoints:

- Breaking of abstinence
- Breaking national drinking guideline levels at least once in the 6 month follow-up period
- Breaking national drinking guideline levels six or more times in the 6 month follow-up period
- Drinking 10 or more standard drinks on at least one occasion in the 6 month follow-up period

Follow up period: The participants of all groups were followed up 6 months after completing therapy.

Assessment

Sources of bias:

Despite randomization, participants in the MET group were more dysfunctional, measured by GAS score at baseline than those participants randomized to NFC (p=0.03 post hoc Tukey HSD). Table 5.1 also suggests that participants in the MET group were more likely to have a current depressive disorder (p=0.08). There were no significant differences in demographic characteristics between the 3 groups.

Overall this study was of high quality in terms of design and implementation. The key limitation relates to the means for establishing pre-existing alcohol use, which relied on the recall of the participants and a significant other.

5.3 Outcomes – as reported

Outcomes were determined at follow up by a researcher who was blinded to the treatment group of each participant. Table 5.2 summarises between-group comparisons on key outcome measures at 6 months follow-up.

Table 5.1 Baseline values for participants in each therapy group

	MET (n=42)	NDRL (n=40)	NFC (n=40)	χ^2	*p*
Women (%)	45.2	45	37.5	0.64	0.73
Age, mean years (SD)	38.1 (11.5)	35.4 (8.7)	33.4 (10.3)	2.24	0.11
Maori (%)	7.1	17.5	17.5	2.46	0.29
Married (%)	40.5	32.5	30.0	1.09	0.58
Education, mean years (SD)	12.1 (3.1)	11.6 (2.8)	11.3 (2.9)	0.96	0.39
Current depressive anxiety disorder (%)	26.2	17.5	7.5	5.03	0.08
Current other substance disorder (%)	11.9	15.0	15.0	0.22	0.90
Current conduct disorder (%)	2.4	7.5	12.5	3.07	0.22
Unequivocal heavy drinking 6 times (%)	88.1	92.5	90.0	0.45	0.80
GAS score, mean (SD)*	63.2 (6.5)	65.3 (5.1)	66.5 (5.2)	3.54	0.03

* Low score means poorer overall functioning, scores ranged from 0 to 100

Table 5.2 Outcome measurements at follow up, 6 months after therapy

	MET (n=42)	NDRL (n=40)	NFC (n=40)	χ^2	*p*
Broke abstinence (%)	88.1	90.0	92.5	0.44	0.51
Exceeded national guidelines at least once (%)	64.3	77.5	72.5	0.69	0.41
Exceeded national guidelines six or more times (%)	64.3	77.5	72.5	0.69	0.41
Drank 10+ standard drinks at least once (%)	61.9	77.5	79.0	0.66	0.42
Drank 10+ standard drinks six times or more (%)	42.9	62.5	65.0	4.11	0.04
GAS score at 6 month follow up, mean adjusted (SE) *	70.2 (1.2)	69.9 (1.3)	67.6 (1.3)	1.23	0.30

* Low score means poorer overall functioning, scores ranged from 0 to 100

Behaviour change and clinical parameters

Adherence to treatment:

Of the 125 initial participants in the study, 122 completed all stages and were evaluated at 6 months follow-up. There was no significant difference in the mean number of therapy sessions attended by participants in the MET and NDRL groups (p=0.17).

Positive effects were seen in both control and treatment groups. Globally:

- Non-abstinence rates decreased from 100 to 90.2%.
- Rate of participants breaking national drinking guidelines decreased from 100 to 71.3%.
- Rate of participants drinking 10 or more standard drinks more than 6 times decreased from 90.2% to 56.5% ($p<0.001$).
- Men were more likely to show unequivocal heavy drinking than women (OR 2.42 95% CI 1.16-5.05).
- Those with current cannabis dependence were more likely to show a severe level of drinking than those without (OR=4.24, 95%CI: 1.15, 15.63).

A logistic regression was performed using the three treatment conditions, and the variables shown to be significantly different at baseline (GAS score) or correlated with outcome (gender and coexisting cannabis dependence) as co-variates. Unequivocal heavy drinking was the dependent variable.

- The odds of unequivocal heavy drinking when treated with NFC were greater than those treated with MET (OR=2.95, 95%CI: 1.10, 7.92)
- The odds of unequivocal heavy drinking when treated with NDRL were greater than those treated with MET (OR=2.62, 95%CI: 1.01, 6.85)
- There were no significant differences in unequivocal heavy drinking between those participants treated with NFC and NDRL (OR=1.12, 95%CI: 0.43, 2.96)

In summary, MET was superior to NDRL and NFC in reducing unequivocal heavy drinking at the 6 months follow-up. MET was not demonstrated to have significantly better effect than control on the other drinking outcomes at the 6 months follow-up. The study appears to have been underpowered to detect these outcomes.

Mortality

Mortality and morbidity are not reported in the study. Use of longer term outcome variables is constrained by the short follow up time.

5.4 Program costs

As reported by trial

Based on resource use

Tables 5.3 to 5.5 set out the estimated cost to run each program in Australia today. Costs incurred purely as a result of research activity, rather than in the administration of the intervention, have been excluded. As the viewpoint taken is that of the Department of Health and Ageing, costs to the participant have not been included. Costs have been taken from the intervention undertaken by Sellman et al, from the methods described in the published paper.

For the purposes of the base analysis, staff members were assumed to be salaried rather than fee for service workers and costs have been calculated for the actual number of participants taking place in the clinical trial. In the sensitivity analysis, costings have been performed for scenarios where the programs would cater for 100 participants.

Table 5.3 MET treatment costs

	Cost	Time	Number required	Total cost	Cost per person
Clinical psychologist training	$50/hr	15 hours in group	4	$3,000.00	$71.43
Trainer – clinical psychologist	$$50/hr	15 hours	1	$750	$17.86
Consumables – referral form	$0.05		1	$9.70	$0.05
Comprehensive assessment of drinking history	$28.13/hr	Assume 1 hour	1	$1,181.46	$28.13
Timeline followback questionnaire	$700 for 300		1	$98	$2.33
LFT's – AST, ALT, GGT[8]	$13.75		1	$577.50	$13.75
Feedback session (equiv to brief intervention)	$50/hr	Assume 30 minutes	1	$1,050.00	$25.00
Information booklets x 2 for feedback session	$1605 for 300 booklets	Assume 2 A5 booklets	1	$449.40	$10.70
MET counselling (4 sessions over 6 weeks)	$50/hr	1 hour	4	$12,600.00	$300.00
Total				**$19,716.06**	**$469.25**

Table 5.4 NDRL treatment costs

	Cost	Time	Number required	Total cost	Cost per person
Clinical psychologist training	$50/hr	15 hours in group	4	$3,000.00	$150
Trainer – clinical psychologist	$50/hr	15 hours	1	$750.00	$37.50
Consumables – referral form	$0.05		1	$2	$0.05
Comprehensive assessment of drinking history	$28.13/hr	Assume 1 hour	1	$1125.20	$28.13
Timeline followback questionnaire	$700 for 300		1	$93.33	$2.33
LFT's – AST, ALT, GGT	$13.75		1	$468	$13.75
Feedback session (equiv to brief intervention)	$50/hr	Assume 30 minutes	1	$2,000	$50
Information booklets x 2 for feedback session	$1605 for 300 booklets	Assume 2 A5 booklets	1	$428	$10.70
NDRL counselling (4 sessions over 6 weeks)	$50/hr	1 hour	4	$8,000.00	$200.00
Total				**$14,948.53**	**$373.71**

[8] MBS November 2003, 85% outpatient rebate

Table 5.5 NFC treatment costs

	Cost	Time	Number required	Total cost	Cost per person
Consumables – referral form	$0.05		1	$2	$0.05
Comprehensive assessment of drinking history	$28.13/hr	Assume 1 hour	1	$1125.20	$28.13
Timeline followback questionnaire	$700 for 300		1	$93.33	$2.33
LFT's – AST, ALT, GGT	$13.75		1	$468	$13.75
Feedback session (equiv to brief intervention)	$50/hr	Assume 30 minutes	1	$2,000	$50
Information leaflet for feedback session	$1605 for 300 booklets	Assume 2 A5 booklets	1	$428	$10.70
Total				**$4,198.53**	**$79.96**

5.5 Within-trial CEA

Figure 5.2 depicts between-group comparison on the key outcome: percentage drinking within national guidelines for the duration of the trial. Results of the within-trial cost-effectiveness analysis are summarised in Tables 5.6 and 5.7 below.

Figure 5.2 Percentage drinking within national guidelines: MET *vs* NDRL *vs* NFC

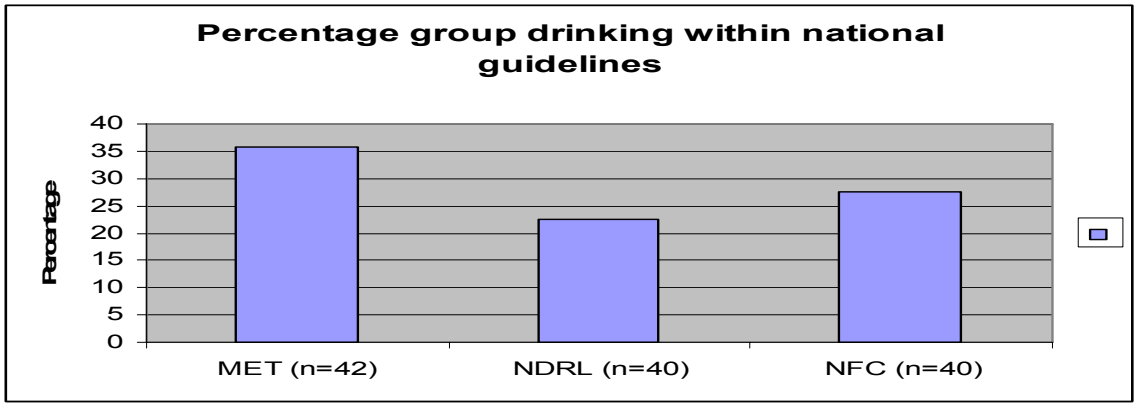


Table 5.6 Average cost per changer: MET

	As calculated	Change in cost of training to cover 100 people
Cost per enrolled	$469.25	$427.82
Cost per completer	$469.25	$427.82
Cost per changer^	$1,314.43	$1,198.38

^Defined as those who had not "broke[n] national guidelines at least once" (35.7%)

Table 5.7 Average cost per changer: NDRL

	As calculated	Change in cost of training to cover 100 people
Cost per enrolled	$373.71	$327.82
Cost per completer	$373.71	$327.82
Cost per changer^	$1,660.93	$1,456.98

^Defined as those who had not "broke[n] national guidelines at least once" (22.5%)

There is a well documented body of evidence showing the alcohol abuse and dependence tends to decline naturally over time and with age. Vaillent in a review of 8 such studies in 1995, reported an average of 2% of alcohol dependant participants reverted to abstinence over any twelve months period.[9] The Saunders study reviewed in Chapter 3, showed a much sharper decline in their control group over a 6 months period of almost 6% in only 9 months.[10] A sensitivity analysis has been performed to takes into account this natural decline and to calculate the cost effects.

Figure 5.3 Percentage drinking within national guidelines adjusted for natural decline

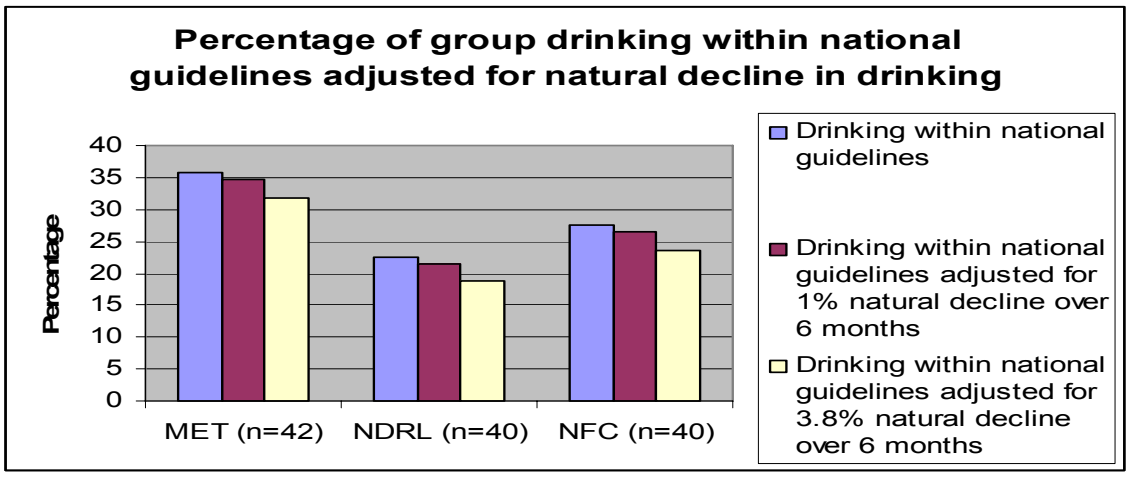


Table 5.8 Average cost/changer taking into account natural decline in drinking over time: MET

	As calculated	Taking into account natural decline in drinking of 1% over 6 months	Taking into account natural decline in drinking of 3.8% over 6 months[11]
Cost per enrolled	$469.25	$469.25	$469.25
Cost per completer	$469.25	$469.25	$469.25
Cost per changer^	$1,314.43	$1,352.31	$1,471.00

^Defined as those who had not "broke[n] national guidelines at least once"

5.6 Modelling

A Markov model with six non-absorbing (dependence1, dependence2, dependence3, recovered1, recovered2, recovered3) and one absorbing state (dead) was used to estimate QALYs gained per person for MET compared to NFC. In a predominantly male population aged 35 years, MET is estimated to deliver 0.116 QALYs gained per completer as compared to NFC if external effects are assumed away. In a predominantly male population aged 35 years, MET is estimated to deliver 0.287 QALYs gained per completer as compared to NFC if within-family external effects are included. The incremental cost per completer of MET as compared to NFC was estimated at 389 AUD and is assumed to reflect the incremental cost over the entire evaluation period. The cost per QALY gained is estimated at 3,366 AUD based on 1st-person effects or 1,359 AUD if within-family external effects are included. Table 5.9 summarises key findings from the modelled cost-utility analysis.

[9] Secretary of Health and Human Services (2000). 10th Special Report to the U.S. Congress on Alcohol and Health, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

[10] Wutzke, S., K. Conigrave, et al. (2002). "The long-term effectiveness of brief interventions for unsafe alcohol consumption: a 10-year follow up." Addiction **97**: 665-675

[11] Wutzke, S., K. Conigrave, et al. (2002). "The long-term effectiveness of brief interventions for unsafe alcohol consumption: a 10-year follow up." Addiction **97**: 665-675

Table 5.9 Summary of cost utility of brief alcohol interventions according to the modelled cost-utility analysis (discount rate= 5%)

	QALYs gained/person	Incremental cost/person AUD	**Cost/QALY gained AUD**
1st-person effects only			
MET *vs* NFC	0.1157	$389.29	$3,365.50
NDRL *vs* NFC	-0.0705	$293.75	NFC dominates
1st-person plus within-family external effects			
MET *vs* NFC	0.2865	$389.29	$1,358.62
NDRL *vs* NFC	-0.1747	$293.75	NFC dominates

The model was also used to estimated QALYs gained per person for NRDL compared to NFC. Recall that the NDRL was inferior to the NFC based on the proportion remaining within national guidelines at 6-months follow-up. Given that the NDRL is also more costly than the NFC, it is not surprising that the modelled cost-utility analysis has the NFC dominating the NDRL.

Health states and the Markovian assumption

A Markov model with just two non-absorbing (dependence and recovered) and one absorbing state (dead) could be used to estimate QALYs gained per person for each intervention as compared to its comparator. There is no 'tee-total' state because nearly all subjects in the Sellman et al (2001) sample were mildly to moderately dependent drinkers on entry to the trials and because small cell sizes preclude the use of data with respect to abstinence. For the modelled cost-utility analysis, we define responders as those who did not exceed the national guidelines even once: operationalised as a move from 'dependence' to 'recovered'. Because it is difficult to undo some of the damage done during dependence, the risk of death is elevated for persons characterised as 'recovered' as compared to persons characterised as 'moderate' or 'problem' drinkers.

In order to model the cumulative effect of an 'improved' consumption pattern, the 'recovered' and 'dependence' disease states are split into temporary disease states. Temporary states are "defined as having transitions only to other states and not to themselves. This guarantees that the patient can spend, at most, one cycle in that state" (Sonnenberg & Beck, 1993 p. 326). Patients are not required to transition through all three 'recovered' states (ie. patients can return to 'dependence' after any number of cycles), but 'recovered3' can *only* be reached after first cycling through both 'recovered2' and 'recovered1'. This gives us a fixed sequence of temporary states known as a tunnel sequence (Briggs & Sculpher, 1998).

Cycle length

Follow-up in the Sellman et al (2001) trial was at 6 months. A cycle length of 6 months is assumed when comparing the MET, NDRL and NFC interventions. A half-cycle correction is applied to initial and final payoffs to adjust the stepwise survival curve traced by the model to more closely approximate the continuous survival curve that operates in the real-world.

Termination condition

The Markov model terminates when the following condition is satisfied: _stage > 30 & (_stage > 130 | _stage_eff < .001). In other words, the model terminates after 130 cycles (65 years) *or* when the reward accumulated in any given cycle falls below 1/1000 of a QALY and at least 30 cycles or 15 years have been completed.

Payoffs (private plus external)

First-person and within-family external HRQoL effects are calculated as for the Chapter 30 models. In the absence of supporting data, we make the conservative assumption that the HRQoL weight for the 'recovered' state is approximately equal to the HRQoL weight for problem drinkers. External

effects within each family unit are limited to an arbitrary 10 year period, ceasing at 45 years of age irrespective of success/failure in moderating alcohol consumption. The reduction in the persistence of external effects to 10 years reflects the start_age of participants in the Sellman et al (2001) trial.

Time-invariance

For the modelled cost-utility analysis TPr_Death is time-dependent but all other probabilities and payoffs are invariant with respect to time. Payoffs and the likelihood of relapse and recovery are dependent on history rather than time per se. For example, to account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'recovered1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'dependence3' state. Transition to 'recovered1' does, however, result in an immediate improvement in first-person HRQoL. Subsequent transition from 'recovered1' to 'recovered2' adds an improvement in external HRQoL effects but risk of death remains as for the 'dependence3' state. A reduction in risk of death is finally added upon transition from 'recovered2' to the 'recovered3' state such that the tunnel sequence amounts to a accumulation of benefits made of (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 6 months, and (iii) reduction in risk of death at 18 months. A converse accumulation of payoffs and risks is specified for the 'dependence' tunnel sequence.

Initial probabilities

Initial probabilities are used to distribute a cohort (or to designate the status of an individual) over the relevant health states. All subjects in the Sellman et al (2001) sample were mildly to moderately dependent on entry to the trials. For the purposes of the modelled cost-utility analysis, all individuals are assumed to be in steady-state and to have accumulated the full age/sex adjusted effects of their alcohol consumption. In other words, all persons commence in the 'dependence3' state.

Start age

Mean age at baseline in the Sellman et al (2001) trial was 38.1 years (11.5 SD) in the MET arm, 35.4 years (8.7 SD) in the NDRL arm and 33.4 years (10.3 SD) in the NFC arm. For the purposes of the modelled cost-utility analysis, we therefore assume an average start age of 35 years.

Recovery

Recovery rates are taken directly from the trial with those not exceeding the national guidelines even once at 6-months follow-up classified as recovered. The percent recovered at 6 months follow-up given in Table 5.10 below is taken as the absolute risk of transition from 'dependence' to 'recovered'. While it is recognised that this data fails to control for differences in severity at baseline, this has the effect of deflating rather than inflating the treatment effect. Note, for example, that the MET group had a higher proportion of participants with depressive anxiety disorder and poorer overall functioning (as measured by GAS score) at baseline than the NDRL group. The NDRL group had a higher proportion of participants with depressive anxiety disorder and poorer overall functioning (as measured by GAS score) at baseline than the NFC group. The only measure of severity on which either the NDRL or NFC group outstripped the MET was the rate of unequivocal heavy drinking on at least 6 occasions but this difference was not statistically significant ($\chi^2 = 0.45$, p=0.80).

There is a well documented body of evidence showing the alcohol abuse and dependence tends to decline naturally over time and with age. Vaillent (1995) in a review of 8 such studies reported an average of 2% of alcohol dependant participants reverted to abstinence over any twelve months period. The background risk of recovery reported by Vaillent (1995) is then converted to a per cycle risk as per Miller & Homan (1994): $1 - (1- 0.02)^{1/2} = 0.010051$.

Table 5.10 Percent recovered at 6 month follow-up: MET *vs* NDRL *vs* NFC

MET Group Recovered (%)	NDRL Group Recovered (%)	NFC Group Recovered (%)	χ^2	p
15/42 (35.7%)	9/40 (22.5%)	11/40 (27.5%)	0.69	0.41

Relapse rates

The risk of relapse from recovered to dependence are assumed to be equal to the risk of progression from 'problem' to 'dependence' used in the Chapter 2 models.

Death rates

For dependent drinkers, we rely on death rates for those exceeding NHMRC recommendations for peak consumption (ie. men: >6 drinks/session, women: >4 drinks/session) on a regular basis. For recovered drinkers, we rely on death rates for past problem drinkers where past problem drinking is defined as having ≥5 drinks on a weekly basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983. Risk of death is calculated as for the Chapter 2 models but we then combined male and female risks to obtain a weighted average death rate for each age band. Weights correspond to the proportion of males and females in the Chapter 5 trial population (57% males, 43% females) under the assumption that this approximates the proportion of males and females in the target population.

Table 5.11 Relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.93 (0.39, 2.21)	**≥6 drinks/day *vs* lifetime abstinent**	**2.29 (1.17, 4.48)**	2-4 drinks/day *vs* lifetime abstinent	0.73 (0.39, 1.37)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.97 (0.30, 3.09)	≥4 drinks/day *vs* lifetime abstinent	1.06 (0.26, 4.34)	1-2 drinks/day *vs* lifetime abstinent	0.81 (0.42, 1.56)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.96 (1.26, 3.05)	Past problem drinking[#] *vs* lifetime abstinent	1.64 (0.98, 2.76)	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.84 (0.98, 3.44)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.77 (0.86, 3.64)	Past problem drinking[#] *vs* lifetime abstinent	2.18 (1.12, 4.24)	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.25 (0.17, 9.14)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

Table 5.12 Relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* 2-4 drinks/day	1.27 (0.53, 3.03)	≥6 drinks/day *vs* 2-4 drinks/day	**3.14 (1.60, 6.14)**	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.20 (0.37, 3.81)	≥4 drinks/day *vs* 1-2 drinks/day	1.31 (0.32, 5.36)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.68 (1.73, 4.18)	Past problem drinking[#] *vs* 2-4 drinks/day (a)	2.25 (1.34, 3.78)	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.52 (1.34, 4.71)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.19 (1.06, 4.49)	Past problem drinking[#] *vs* 1-2 drinks/day	2.69 (1.38, 5.23)	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.54 (0.21, 11.28)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.
(a) Death rate for recovered.

Table 5.13 Adjusted relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.90 (0.38, 2.14)	≥6 drinks/day *vs* lifetime abstinent	2.14 (1.08, 4.23)	2-4 drinks/day *vs* lifetime abstinent	0.78 (0.41, 1.47)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.89 (0.28, 2.88)	≥4 drinks/day *vs* lifetime abstinent	0.94 (0.23, 3.86)	1-2 drinks/day *vs* lifetime abstinent	0.77 (0.40, 1.51)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.93 (1.23, 3.02)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.62 (0.86, 3.07)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.65 (0.79, 3.41)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.08 (0.15, 7.93)	Rehm, Greenfield and Rogers (2001)

Table 5.14 Adjusted relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day (a) *vs* 2-4 drinks/day	1.15 (0.49, 2.74)	≥6 drinks/day *vs* 2-4 drinks/day (b)	2.74 (1.38, 5.42)	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.16 (0.36, 3.74)	≥4 drinks/day *vs* 1-2 drinks/day	1.22 (0.30, 5.01)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.47 (1.58, 3.87)	Past problem drinking[#] *vs* 2-4 drinks/day	NR	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.08 (1.10, 3.94)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.14 (1.03, 4.43)	Past problem drinking[#] *vs* 1-2 drinks/day	NR	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.40 (0.19, 10.30)	Rehm, Greenfield and Rogers (2001)

(a) Death rate for problem drinker.
(b) Death rate for 'dependant'.

Table 5.15 Age-specific deaths/1000 by alcohol status: Safe

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males	5.5	0.3	0.1	0.2	0.6	0.9	1.0	1.1	1.3	1.7	2.6	3.6	5.8	10.0	16.5	28.8	48.8	80.8	167.4
Females	4.7	0.2	0.1	0.1	0.3	0.3	0.4	0.5	0.7	1.0	1.5	2.4	3.7	6.0	9.6	16.2	28.9	54.2	135.4
Persons	5.16	0.26	0.10	0.16	0.47	0.64	0.74	0.84	1.04	1.40	2.13	3.08	4.90	8.28	13.53	23.38	40.24	69.36	153.64
TPr_M	0.0055	0.0003	0.0001	0.0002	0.0006	0.0009	0.0010	0.0011	0.0013	0.0017	0.0026	0.0036	0.0058	0.0100	0.0165	0.0288	0.0488	0.0808	0.1674
TPr_F	0.0047	0.0002	0.0001	0.0001	0.0003	0.0003	0.0004	0.0005	0.0007	0.0010	0.0015	0.0024	0.0037	0.0060	0.0096	0.0162	0.0289	0.0542	0.1354
TPr_P	0.0052	0.0003	0.0001	0.0002	0.0005	0.0006	0.0007	0.0008	0.0010	0.0014	0.0021	0.0031	0.0049	0.0083	0.0135	0.0234	0.0402	0.0694	0.1536

Proportion of men and women: 57% males, 43% females

Table 5.16 Age-specific TPr_Death by alcohol status: Problem3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.00633	0.00035	0.00012	0.00023	0.00069	0.00104	0.00115	0.00127	0.00150	0.00196	0.00299	0.00414	0.00667	0.01150	0.01898	0.03312	0.05612	0.09292	0.19251
Upper	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Lower	0.00270	0.00015	0.00005	0.00010	0.00029	0.00044	0.00049	0.00054	0.00064	0.00083	0.00127	0.00176	0.00284	0.00490	0.00809	0.01411	0.02391	0.03959	0.08203
Females																			
Mid	0.00541	0.00023	0.00012	0.00012	0.00035	0.00035	0.00046	0.00058	0.00081	0.00115	0.00173	0.00276	0.00426	0.00690	0.01104	0.01863	0.03324	0.06233	0.15571
Upper	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Lower	0.00230	0.00010	0.00005	0.00005	0.00015	0.00015	0.00020	0.00025	0.00034	0.00049	0.00074	0.00118	0.00181	0.00294	0.00470	0.00794	0.01416	0.02656	0.06635
Persons																			
Mid	0.00593	0.00030	0.00012	0.00018	0.00054	0.00074	0.00085	0.00097	0.00120	0.00161	0.00245	0.00355	0.00563	0.00952	0.01556	0.02689	0.04628	0.07977	0.17669
Upper	0.01413	0.00070	0.00027	0.00043	0.00129	0.00176	0.00203	0.00231	0.00286	0.00383	0.00583	0.00845	0.01342	0.02269	0.03708	0.06407	0.11027	0.19005	0.42097
Lower	0.00253	0.00013	0.00005	0.00008	0.00023	0.00031	0.00036	0.00041	0.00051	0.00069	0.00104	0.00151	0.00240	0.00406	0.00663	0.01146	0.01972	0.03399	0.07528

Men's RR: 4-6 drinks/day *vs* 2-4 drinks/day= 1.15 (0.49, 2.74). Women's RR: 2-4 drinks/day *vs* 1-2 drinks/day=1.16 (0.36, 3.74). Proportion of men and women: 57% males, 43% females

Table 5.17 Age-specific TPr_Death by alcohol status: Dependent3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Upper	0.02981	0.00163	0.00054	0.00108	0.00325	0.00488	0.00542	0.00596	0.00705	0.00921	0.01409	0.01951	0.03144	0.05420	0.08943	0.15610	0.26450	0.43794	0.90731
Lower	0.00759	0.00041	0.00014	0.00028	0.00083	0.00124	0.00138	0.00152	0.00179	0.00235	0.00359	0.00497	0.00800	0.01380	0.02277	0.03974	0.06734	0.11150	0.23101
Females																			
Mid	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Upper	0.02547	0.00108	0.00054	0.00054	0.00163	0.00163	0.00217	0.00271	0.00379	0.00542	0.00813	0.01301	0.02005	0.03252	0.05203	0.08780	0.15664	0.29376	0.73387
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01413	0.00070	0.00027	0.00043	0.00129	0.00176	0.00203	0.00231	0.00286	0.00383	0.00583	0.00845	0.01342	0.02269	0.03708	0.06407	0.11027	0.19005	0.42097
Upper	0.02795	0.00139	0.00054	0.00085	0.00255	0.00348	0.00402	0.00456	0.00565	0.00758	0.01153	0.01672	0.02654	0.04488	0.07335	0.12673	0.21812	0.37594	0.83273
Lower	0.00712	0.00035	0.00014	0.00022	0.00065	0.00089	0.00102	0.00116	0.00144	0.00193	0.00294	0.00426	0.00676	0.01143	0.01868	0.03227	0.05554	0.09572	0.21202

Men's RR: >6 drinks/day *vs* 2-4 drinks/day= 2.74 (1.38, 5.42). Women's RR: >4 drinks/day *vs* 1-2 drinks/day=1.22 (0.30, 5.01). Proportion of men and women: 57% males, 43% females

Table 5.18 Age-specific TPr_Death by alcohol status: Recovered

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01238	0.00068	0.00023	0.00045	0.00135	0.00203	0.00225	0.00248	0.00293	0.00383	0.00585	0.00810	0.01305	0.02250	0.03713	0.06480	0.10980	0.18180	0.37665
Upper	0.02079	0.00113	0.00038	0.00076	0.00227	0.00340	0.00378	0.00416	0.00491	0.00643	0.00983	0.01361	0.02192	0.03780	0.06237	0.10886	0.18446	0.30542	0.63277
Lower	0.00737	0.00040	0.00013	0.00027	0.00080	0.00121	0.00134	0.00147	0.00174	0.00228	0.00348	0.00482	0.00777	0.01340	0.02211	0.03859	0.06539	0.10827	0.22432
Females																			
Mid	0.01058	0.00045	0.00023	0.00023	0.00068	0.00068	0.00090	0.00113	0.00158	0.00225	0.00338	0.00540	0.00833	0.01350	0.02160	0.03645	0.06503	0.12195	0.30465
Upper	0.01777	0.00076	0.00038	0.00038	0.00113	0.00113	0.00151	0.00189	0.00265	0.00378	0.00567	0.00907	0.01399	0.02268	0.03629	0.06124	0.10924	0.20488	0.51181
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01160	0.00058	0.00023	0.00035	0.00106	0.00144	0.00167	0.00189	0.00234	0.00315	0.00479	0.00694	0.01102	0.01863	0.03045	0.05261	0.09055	0.15606	0.34569
Upper	0.01949	0.00097	0.00038	0.00059	0.00178	0.00243	0.00280	0.00318	0.00394	0.00529	0.00804	0.01166	0.01851	0.03130	0.05115	0.08838	0.15212	0.26219	0.58076
Lower	0.00699	0.00035	0.00014	0.00021	0.00064	0.00087	0.00100	0.00114	0.00141	0.00189	0.00288	0.00417	0.00663	0.01120	0.01830	0.03161	0.05442	0.09388	0.20821

Men's RR: Past problem *vs* 2-4 drinks/day= 2.25 (1.34, 3.78). Women's RR: Past problem *vs* 1-2 drinks/day=2.69 (1.38, 5.23). Proportion of men and women: 57% males, 43% females

Sensitivity Analysis

The modelled cost-utility analysis is based on data taken from the Sellman et al (2001) trial, our own calculation of incremental program costs as described in Section 5.4, together with supporting data and assumptions as outlined above. Note, for example, that the estimate of QALYs gained from the modelled cost-utility analysis has been derived from a number of data sources with varying levels of error and uncertainty. More specifically, uncertainty in the estimate of QALYs gained is a function of sampling error in the trial-based measure of surrogate outcome (behaviour change), uncertainty as to the persistence of any behaviour change (relapse rates), and uncertainty in the relationship between a surrogate outcome such as behaviour change and a final outcome such as QALYs gained (with respect to both utility weights and life-years gained).

In an effort to identify key drivers and to evaluate robustness of estimates as to cost per QALY gained, univariate sensitivity analyses were conducted by varying parameters such as start_age, HRQoL weights in non-absorbing health states, discount rate, initial rate of relapse in the recovered1 state, the relative risk of death, recovery rates from the Sellman et al (2004) trial, and our estimates of incremental costs. Variation in each uncertain parameter produced intuitively plausible variations in cost per QALY ratios. Results of the sensitivity analyses are summarised in Tables 5.20 and 5.21 below.

The following details should be kept in mind for the interpretation of the sensitivity analyses:

- Recall that the base case assumed termination of the model at age=100 yrs. For the sensitivity analyses, the termination condition was adjusted to preserve termination at age=100 yrs irrespective of start_age. Note that varying start_age from 20 to 70 years produces only relatively minor changes in cost per QALY ratios.
- The 95%CI for treatment effect is derived by calculating the 95%CI around the relative risk of transition from 'dependence' to 'recovered' for MET *vs* NFC and NDRL *vs* NFC. Upper and lower estimates for the absolute risk of transition from 'dependence' to 'recovered' in MET and NDRL groups are then derived assuming that the absolute risk for the NFC group is as for the base case analysis. Table 5.19 below summarises these calculations.
- The cost per life-year gained is derived by setting the HRQoL weight to 1.0 for each of the six non-absorbing health states (dependence1, dependence2, dependence3, recovered1, recovered2, recovered3). In other words, adjustment for HRQoL in health states other than death is removed for this analysis. Estimates of cost per life-year gained for the MET *vs* NFC comparison varied between 147,140 AUD (based on 1st-person effects) and 48,953 AUD (if within-family external effects are included).

Table 5.19 Calculating 95%CI for treatment effect

Comparison	AR Rx (Base Case)	AR NFC	RR (95%CI)	AR Rx (Low)	AR Rx (High)
MET *vs* NFC	15/42 = 0.357	11/40 = 0.275	1.30 (0.68, 2.48)	0.1871	0.6817
NDRL *vs* NFC	9/40 = 0.225	11/40 = 0.275	0.82 (0.38, 1.76)	0.1048	0.4831

Table 5.20 Cost/QALY estimates according to the sensitivity analysis: MET *vs* NFC

	1st-Person Effects	1st-Person + Within-Family Effects
start_age=20	$3,349	$1,122
start_age=35	$3,366	$1,359
start_age=50	$3,462	$3,325
start_age=60	$3,692	$3,306
start_age=70	$4,314	$3,589
Q_All=1.00	$147,140	$48,953
discount=0.00	<$2,796	<$1,180
discount=0.05	$3,366	$1,359
discount=0.07	$3,940	$1,533
Initial relapse=0.056	$3,366	$1,359
Initial relapse=0.10	$3,500	$1,413
Initial relapse=0.20	$3,856	$1,556
Initial relapse=0.40	$4,869	$1,957
Lower 95%CL	$3,385	$1,383
Mean RR_Death: Taylor (2002)	$3,366	$1,359
Upper 95%CL	$3,319	$1,313
Lower 95%CL	NFC dominates	NFC dominates
Mean Treatment Effect	$3,366	$1,359
Upper 95%CL	$679	$274
Half Best Estimate	$1,683	$679
Best Estimate Incremental Cost	$3,366	$1,359
Twice Best Estimate	$6,731	$2,717

Table 5.21 Cost/QALY estimates according to the sensitivity analysis: NDRL *vs* NFC

	1st-Person Effects	1st-Person + Within-Family Effects
start_age=20	NFC dominates	NFC dominates
start_age=35	NFC dominates	NFC dominates
start_age=50	NFC dominates	NFC dominates
start_age=60	NFC dominates	NFC dominates
start_age=70	NFC dominates	NFC dominates
Q_All=1.00	NFC dominates	NFC dominates
discount=0.00	NFC dominates	NFC dominates
discount=0.05	NFC dominates	NFC dominates
discount=0.07	NFC dominates	NFC dominates
Initial relapse=0.056	NFC dominates	NFC dominates
Initial relapse=0.10	NFC dominates	NFC dominates
Initial relapse=0.20	NFC dominates	NFC dominates
Initial relapse=0.40	NFC dominates	NFC dominates
Lower 95%CL	NFC dominates	NFC dominates
Mean RR_Death: Taylor (2002)	NFC dominates	NFC dominates
Upper 95%CL	NFC dominates	NFC dominates
Lower 95%CL	NFC dominates	NFC dominates
Mean Treatment Effect	NFC dominates	NFC dominates
Upper 95%CL	$1,001	$404
Half Best Estimate	NFC dominates	NFC dominates
Best Estimate Incremental Cost	NFC dominates	NFC dominates
Twice Best Estimate	NFC dominates	NFC dominates

Threshold Analysis

Recall that downstream cost offsets have not been included in the modelled cost-utility analysis (but would only serve to further reduce the cost/QALY ratio). While the complex modelling task of attributing downstream cost offsets to intervention and control groups is beyond the scope of this study, we have quantified the minimum downstream cost offset that would be required in order for MET to be cost saving when compared to NFC. Table 5.22 specifies the minimum per cycle downstream cost offset in the recovered3 state for MET to dominate NFC.

When interpreting the threshold analysis, it should be remembered that downstream cost offsets are likely to be age/sex dependent and accrue in an episodic (rather than constant) manner. In an attempt to incorporate some of this complexity, no downstream cost offsets accrue during the initial 2 cycles in the recovered state. This is consistent with assumptions made elsewhere in the model with respect to the differential risk of death in dependence and recovered states[12]. Aside from this relatively crude adjustment for duration of time spent in the recovered state, downstream cost offsets are incorporated in the simplest way possible. The dollar-value of downstream cost offsets is invariant with respect to _stage and age such that the same downstream cost offset accrues to a recovered drinker after 3 cycles as after 30 cycles. It is left to the decision-maker to determine whether a 'recovered' 35 years old is likely to average $700 per 6-month cycle in downstream cost offsets over the remaining 30 to 45 years of his/her lifespan.

Table 5.22 Minimum downstream cost offset for MET to dominate: 1st-person effects only (discount rate= 5%)

Model	QALYs gained/person	Downstream cost offset	Incremental cost/person	Cost/QALY gained
MET *vs* NFC	0.115671	$701.85	$0.00	MET dominates

[12] To account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'recovered1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'dependence3' state. Transition to 'recovered1' does, however, result in an immediate improvement in first-person HRQoL. Subsequent transition from 'recovered1' to 'recovered2' adds an improvement in external HRQoL effects but risk of death remains as for the 'dependence3' state. A reduction in risk of death is finally added upon transition from 'recovered2' to the 'recovered3' state.

6. Pharmacotherapy: Naltrexone

6.1 Description

Intervention type

This meta-analysis attempts to assess the effects of naltrexone, an opioid receptor antagonist, when used as an adjunct to psychosocial rehabilitation for alcohol dependence. Naltrexone may confer additional benefit to alcoholic patients who have undergone detoxification and have entered into a post-detoxification counselling programme. As such, costings in the paper do not include the costs of detoxification and counselling as these are assumed to be the agreed minimum standard of care for this particular group of severely dependant patients. Only the additional costs incurred by use of naltrexone in addition to usual therapies have been included.

References/sources of evidence

This review cited[13] is an Australian meta-analysis of randomized controlled trials of naltrexone therapy conducted between 1976 and 2001.

The 13 published articles (relating to 7 studies) included in the meta analysis are listed below:

- Volpicelli, J.R., Rhines, K.C., Rhines, J.S., Volpicelli, L.A., Alterman, A.I. & O'Brien, C.P. 1997. Naltrexone and alcohol dependence. Role of subject compliance. Archives of General Psychiatry. Vol 54: 737-742.
- Oslin, D., Liberto, J.G., O'Brien, J., Krois, S. & Nobeck, J. 1997. Naltrexone as an adjunctive treatment for older patients with alcohol dependence. American Journal of Geriatric Psychiatry. Vol 5: 324-332.
- Oslin, D., Liberto, J.G., O'Brien, J. & Krois, S. 1997. Tolerability of naltrexone in treating older alcohol dependent patients. American Journal of Addiction. Vol 6: 266-270.
- Anton, R.F., Moak, D.H., Waid, L.R., Latham, P.K., Malcom, R.J. & Dias, J.K. 1999. Naltrexone and cognitive behavioural therapy for the treatment of outpatient alcoholics: results of a placebo controlled trial. American Journal of Psychiatry. Vol 156: 1758-1764.
- Chick, J., Anton, R., Checinski, K., Croop, R., Drummond, C., Farmer, R., Labriola, D., Marshall, J., Morgan, M.Y., Moncrieff, J.P.T. & Ritson, B. 2000. A multicentre, double blinded placebo controlled trial of naltrexone in the treatment of alcohol dependence and misuse. Alcohol and Alcoholism. Vol 35: 587-593.
- Internal company report (DuPont Merck 393-103)
- Jaffe, A.J., Rounsaville, B., Chang, G., Schottenfeld, R.S., Meyer, R.E. & O'Malley, S.S. 1996. Naltrexone, relapse prevention and supportive therapy with alcoholics: an analysis of patient treatment matching. Journal of Consulting General Psychology. Vol 64: 1044-1053.
- O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E. & Rounsaville, B. 1992. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Archives of General Psychiatry. Vol 49: 881-887.
- O'Malley, S.S., Jaffe, A.J., Rode, S. & Rounsaville, B. 1996. Experience of a slip among alcoholics treated with naltrexone or placebo. American Journal of Psychiatry. Vol 153: 281-283.
- Volpicelli, J.R., Volpicelli, L.A. & O'Brien, C.P. 1990. Naltrexone and the treatment of alcohol dependence: initial observations. In Opioids, Bulimia, and Alcohol Abuse and Alcoholism, Reid, L.D. (editor), pp 195-214. Springer Verlag, New York.
- Volpicelli, J.R., Alterman, A.I., Hayashida, M. & O'Brien, C.P. 1992. Naltrexone in the treatment of alcohol dependence. Archives of General Psychiatry. Vol 49: 876-880.
- Volpicelli, J.R., Clay, K.L., Watson, N.T. & O'Brien, C.P. 1995. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. Journal of Clinical Psychiatry. Vol 56: 39-44.

[13] Streeton, C. & Whelan, G. 2001. Naltrexone; a relapse prevention maintenance treatment of alcohol dependence: A meta analysis of randomized controlled trials. *Alcohol & Alcoholism*. Vol 36: 544-552.

- Volpicelli, J.R., Watson, N.T., King, A.C., Sherman, C.E. & O'Brien, C.P. 1995. Effect of naltrexone on alcohol high in alcoholics. American Journal of Psychiatry. Vol 152:613-615.
- O'Brien, C.P., Volpicelli, L.A. & Volpicelli, J.R. 1996. Naltrexone in the treatment of alcoholism: a clinical review. Alcohol. Vol 13 : 35-39.

Intervention description

Recruitment and target population:

A literature search was conducted for English language articles contained in the MEDLINE, EMBASE, PschLIT and Cochrane Controlled Trials Registry databases. The manufacturers of naltrexone were also contacted for information on any unpublished studies of which they were aware. A total of 72 references were identified. Thirteen articles, reporting on 7 separate studies and involving a total of 804 participants, met the inclusion criteria for the analysis.

Studies were considered for the meta analysis if they were:

- Randomized control trials (RCT),
- Involved patients aged 18 years or over with a diagnosis of alcohol dependence or abuse as defined by the DSM III R criteria (American Psychiatric Association, 1987),
- Compared naltrexone 50mg daily with placebo (or another active drug licensed in Australia) as an adjunct to either psychosocial therapy or standard alcohol rehabilitation,
- Measured defined clinical endpoints (relapse rates, abstinence rates, percentage of patients discontinuing due to adverse events, or percentage of patients with at least one adverse events), and
- Involved an active treatment period of at least 3 months.

Additionally, all seven trials included in the meta-analysis were:

- Double-blinded trials,
- Compared naltrexone with placebo only (not another active drug),
- Conducted in outpatient specialist alcohol treatment centres,
- 12 weeks in duration, and
- Allowed for comparisons between naltrexone and placebo when used as an adjunct therapy with psychosocial therapy or alcohol rehabilitation therapy.

Patient selection criteria in each of the 7 trials were designed to produce a study population that were recently detoxified from alcohol, had no significant psychiatric disease and no co-existing substance abuse. The mean age of trial participants ranged from 39 to 59 years.

Intervention:

Naltrexone is a central opioid receptor antagonist which blocks the effects of endogenous opioids released after alcohol intake. These endogenous opioids are thought to produce some of the pleasurable effects of the drug and to be in some way related to inducing cravings for alcohol.[xiii] All studies in the meta-analysis used a daily dose of 50 mg of naltrexone over a period of 12 weeks.

Placebo was given to controls in each of the seven studies. It is not specified what form the placebo took.

Psychosocial therapy was given as adjunct to naltrexone or placebo in each of the 7 trials. Therapies varied between the 7 trials as summarized in Table 6.1.

[xiii] Therapeutic guidelines

Table 6.1 Psychosocial therapy used in adjunct to either naltrexone or placebo

Study	**Therapy**
1	Individual counselling 1st month twice a week, remaining 2 months, once a week
2	Weekly group therapy, peer support & education
3	Weekly session of manual guided individual cognitive behavioural therapy
4	Less intensive therapy treatment type and amount not constrained by the study
5	Psychosocial therapy treatment type and amount not constrained by the study protocol but some patients received intensive inpatient treatment for up to a month
6	Subjects randomized to receive on a weekly basis, either Supportive therapy, individual family or group therapy Coping skills/relapse prevention therapy
7	Alcohol rehabilitation program partial day treatment for the 1st month, followed by twice weekly group sessions for the remaining 2 months

6.2 Quality of evidence

Evaluation description

Design:
The aim of the study was to obtain pooled data on the efficacy and adverse effects of naltrexone therapy. The meta-analysis calculated pooled risk differences and pooled relative risks on various outcome data for naltrexone therapy as compared to placebo.

Methodology:
Data describing participants, settings, intervention and outcomes was extracted for each trial using a data extraction form. The soundness of the methodology for each trial was scored out of a maximum possible score of 12. The quality rating comprised 7 elements including the randomization process, loss to follow-up and reliability of outcome assessment. Quality scores for the trials ranged from 10-11, with a mean score of 10.4 across all 7 trials. Pooled risk difference and pooled relative risks were calculated using RevMan 4.1 (Cochrane Collaboration, 2000). Weighted mean difference was used for continuous variables. Results were checked for homogeneity using the Chi squared test. For categorical variables, Mantel Haenszel fixed effects modelling was used with heterogeneous data further checked using the DerSimonian and Laird random effects model. Continuous variables were modelled using the fixed effects (inverse variance methodology) and DerSimonian random effects models.

Outcome measures:
The primary outcomes were relapse and abstinence rates. The definition of relapse did vary between studies but the common element was the consumption of 5 or more drinks in a day for males and 4 or more drinks in a day for females. Participants were considered abstinent if they continued the study and consumed no alcohol for the 12-weeks duration of the trial.

Relapse rates and abstinence rates were directly reported in 4 of the 7 trials. The remaining 3 trials reported survival analysis, which was the time to first heavy drinking session (relapse) or time to first alcoholic drink (abstinence). The survival analysis data was transformed to abstinence rates and these figures were used to calculate the proportion of subjects that relapsed or remained abstinent in each treatment group.

Secondary outcomes, which were not reported in all trials, were:
- Difference in mean percentage of reported drinking days per subject,
- Difference in mean number of drinks per drinking day per subject,
- Number of subjects reporting at least one adverse event, and
- Treatment discontinuations due to adverse events.

The difference in mean percentage of reported drinking days per subject, whilst not defined in the paper, is likely to be the difference between naltrexone and placebo participants in the number of drinking days as a percentage of the total 12 weeks treatment period.

The difference in mean number of drinks per drinking day per subject, whilst not defined in the paper, is likely to be the difference between naltrexone and placebo participants in the number of drinks per drinking day over the total 12 weeks treatment period.

The number of subjects reporting at least one adverse event was not defined in the paper; however the authors mentioned specific events (pain, nausea, somnolence, abdominal pain, anorexia and vomiting) that they did analyse between the treatment groups.

Treatment discontinuations due to adverse events was not defined (adverse events was not defined) however the authors mentioned that this outcome was the number of subjects that discontinued a trial due to an adverse event.

The meta-analysis does not describe reporting of alcohol consumption and adverse events in the individual trials.

Assessment

Sources of bias:
The authors mention that, as occurs with most meta-analyses, there was significant heterogeneity amongst the study populations:

- Study 1 recruited subjects who were younger and had been drinking for fewer years on average than other studies.
- Studies 1 and 3 contained a higher proportion of employed persons.
- Study 3 had a greater number of participants who were in a stable relationship
- Study 2 participants were considerably older on average and were less likely to be in a stable relationship.
- Study 4 and 5 participants underwent a longer initial detoxification period.

The psychosocial interventions and some of the outcome definitions were also slightly different in each case, although not to the point where the researchers felt pooling of the data was unreasonable.

A major limitation of the trials included in the meta-analysis was their short duration of follow-up. Follow-up was to 12 weeks in all but one trial (trial 6, which extended to allow follow-up to 6 months after completion of pharmacotherapy). The lack of information on the sustainability of results is a major limiting factor in assessing this intervention. The one study with extended follow-up suggested that the benefits from naltrexone treatment would be lost within 6 months of discontinuing pharmacotherapy.

The small sample sizes from the individual trials may also be a limiting factor. These underpowered studies may contribute to Type II error i.e. erroneous acceptance of the null hypothesis.

Publication bias:
Publication bias is a significant problem for meta-analysis because studies with negative findings are less frequently published. This meta-analysis is less likely to suffer from this bias because both published and unpublished studies were used.

Selection bias:
Only English language trials were included.

All the included studies excluded patients with a co-existing major psychiatric illness or another type of drug addiction, which would be expected to exclude a significant proportion of the clinical

population. It would be expected that these patients would be particularly likely to relapse and this could bias the cost effectiveness studies considerably.

Attrition bias:
Significant numbers of participants were discontinued from the studies (in one study, greater than 50%). However, there did not appear to be a significant difference between the intervention and the placebo arms of the studies and the outcomes were analysed on an intention to treat basis.

6.3 Outcomes – as reported

Outcome measures were relapse rate (%) and abstinence rate (%) and alcohol consumption variables. Table 6.2 and Figure 6.1 summarise between-group comparisons from the individual trials. Table 6.3 summarises between-group comparisons based on the pooled sample included in the meta-analysis.

Table 6.2 Key outcomes: Naltrexone plus psych *vs* Placebo plus psych

Study	Number of subjects	Relapse rates (%)		Abstinence rates (%)		Mean % of drinking days per subject		Mean number of drinks per drinking day per subject	
		I	C	I	C	I	C	I	C
1	97	35	53	44	35	6.2	10.8	NR	NR
2	44	14	35	71	65	NR	NR	NR	NR
3	131	38	60	47	33	10	18	2.5	4.2
4	175	70	69	18	19	23.9	22.8	10.2	10.1
5	171	38	38	54	51	10.8	8.6	8.4	8.2
6	104	31	60	52	23	4.3	10	NR	NR
7	82	21	41	56	37	2.4	6.2	NR	NR

NR not reported I = Intervention C = Control

Figure 6.1 Abstinence rates: Naltrexone plus psych *vs* Placebo plus psych

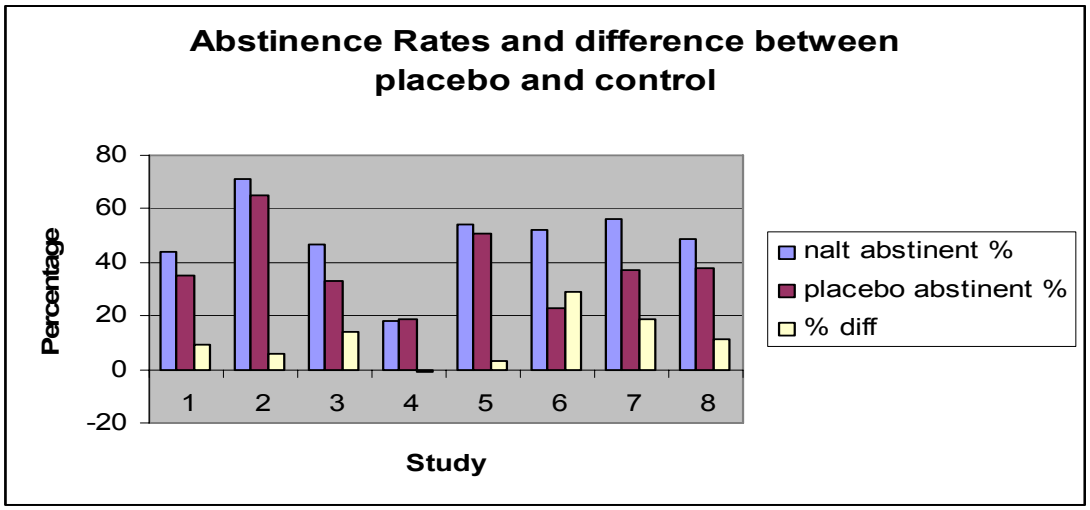


Table 6.3 Pooled risk difference for outcome measures

Outcome	Pooled risk difference^ or effect size* (95% CI)		Test for homogeneity			Pooled RR (95% CI)
	Fixed effects	Random effects	$\chi 2$	df	*p*	
Relapse Rate^ (%)	-12 (-19,-6)	-14 (-23,-5)	11.9	6	0.06	0.72 (0.55,0.94)
Abstinence Rate^ (%)	10 (3.5,16.3)	10 (2,19)	9.7	6	0.14	1.28 (1.08,1.52)
Difference in mean % of drinking days per subject (WMD)*	-3.0 (-5.4,-0.5)	-2.8 (-5.8,-0.2)	5.75	4	0.22	NR
Difference in mean no of drinks per drinking day per subject (WMD)* (%)	-1.04 (-2.0,-0.1)	-1.04 (-2.0, -0.1)	2.97	3	0.40	NR
Adverse Events (%)	1 (-6,8)	2 (-6,10)	3.63	3	0.30	1.04 (0.95,1.15)
Discontinuation due to adverse event (%)	2 (-1,5)	1 (-1,4)	4.2	6	0.65	1.43 (0.82,2.48)

WMD: weighted mean difference

Behaviour change and clinical parameters

The findings suggest that naltrexone is no different to placebo (2 studies) or more effective than placebo (5 studies). Based on a meta-analysis of 804 participants:

- Subjects randomly assigned to receive naltrexone showed significant improvement in relapse rates compared to placebo. Fourteen percent fewer participants taking naltrexone relapsed to heavy drinking compared to participants taking placebo. There was some heterogeneity (p=0.06) in relapse rates so the random effects model was used to determine the pooled risk difference for relapse rate (-14, 95%CI: –23,-5).
- Subjects assigned to take naltrexone showed significant improvement in abstinence rates compared to placebo. 10% more participants taking naltrexone remained abstinent compared to participants taking placebo. There was no heterogeneity (p=0.14) in abstinence rates so the fixed effects model was used to determine the pooled risk difference for abstinence rates (10, 95%CI: 3.5, 16.3).
- Subjects assigned to naltrexone showed a decrease in the number of drinking days compared to subjects taking placebo. Participants taking naltrexone consumed alcohol on an average fewer days compared to participants taking placebo. There was no heterogeneity (p=0.22) in drinking days so the fixed effects model was used to determine the pooled risk difference for drinking days (-3, 95%CI: –5.4,-0.5).
- Subjects randomly assigned to take naltrexone showed a decrease in the number of drinks per day compared to placebo subjects. Participants taking naltrexone consumed an average of 1 standard drink less per drinking day compared to participants taking placebo. There was no heterogeneity (p=0.40) in this variable so the fixed effects model was used to determine the pooled risk difference (-1.04, 95%CI: –2.0,-0.1).

Adherence to treatment: Naltrexone was found to be no more likely to provoke adverse events than placebo with no significant difference between naltrexone and placebo in the number of adverse events (1, 95%CI: –6, 8) and the number of discontinuations due to adverse events (2, 95%CI: –1, 5). However, the confidence intervals are wide and naltrexone use was found to be significantly associated with specific adverse events such as pain, nausea, somnolence, abdominal pain, anorexia and vomiting, when compared to placebo.

It is important to note that the effectiveness of naltrexone is dependent on treatment compliance. The meta analysis mentions nothing about treatment compliance rates amongst the participants of the 7 trials. However low compliance was a factor in Trial 4 which could not show any significant

difference between naltrexone and placebo. This may be the case with trial 5, which was also not significant, however this cannot be verified as the study is unpublished.

Mortality

Mortality and alcohol related morbidity outcomes are not reported in the study.

6.4 Program costs

As reported by trial

Based on resource use

Table 6.4 summarises the estimated cost to run this program in Australia today. Costs incurred purely as a result of research activity, rather than in the administration of the intervention, have been excluded. As the viewpoint taken is that of the Department of Health and Ageing, costs to the participant have not been included. Costs have been based on a description of the intervention given in one of the studies included in the meta-analysis.[14] Note that naltrexone may confer additional benefit to alcoholic patients who have undergone detoxification and have entered into a post-detoxification counselling programme. Costings in the paper do not include the costs of detoxification and counselling as these are assumed to be the agreed minimum standard of care for this particular group of severely dependant patients. Only the additional costs incurred by use of naltrexone in addition to usual therapies have been included.

Adverse effects were reported as not significantly different between placebo and naltrexone use but it would still be of use to have costings for these events. We did not assign costs for the treatment of adverse events in the absence of any supporting data.

Table 6.4 Cost of naltrexone therapy

	Cost	Number	Cost per person
Screening including questionnaires (eg. SADQ-C)	~$345 for 300	1	~$1
Pre-treatment assessment	$30.20 (Level B consultation)	1	$30.20
Phone call to apply for authority	$0.40	1	$0.40
Naltrexone 50mg daily for up to 12 wks	$167.30 for 30 days supply	3	$501.90
Monthly assessment	$30.20 (Level B consultation)	3	$90.60
Pathology- ALT, AST, GGT, ALP, Bilirubin monthly (McKenna & Astolfi, 2000)	$15.15	4	$60.60
Total			$684.70

Incremental cost per additional changer is calculated based on the cost calculations from Table 6.4 and the pooled effect size from Table 6.3 above. Results of the within-trial cost-effectiveness analysis are given in Table 6.5 below.

Table 6.5 Within-trial cost-effectiveness: Naltrexone plus psych *vs* Placebo plus psych

Cost per enrolled	$684.70
Cost per completer	$1048.38
Cost per additional changer^ *vs* behavioural counselling only	$4890.71

^Defined as “abstinent and completed course” (14%)

[14] Chick et al (2000). A multicentre, double blinded placebo controlled trial of naltrexone in the treatment of alcohol dependence and misuse. *Alcohol and Alcoholism*, Vol 35: 587-593.

It should be noted that in some clinical situations naltrexone therapy may be extended to a total of 6 months. However, as the meta-analysis does not describe outcomes for this group of patients, an accurate cost per changer cannot be calculated for a 6 months course.

6.6 Modelled CUA

A Markov model with six non-absorbing (dependence1, dependence2, dependence3, recovered1, recovered2, recovered3) and one absorbing state (dead) was used to estimate QALYs gained per person for naltrexone as compared to placebo. In a predominantly male population aged 41 years, naltrexone is estimated to deliver 0.0528 QALYs gained per person as compared to placebo if external effects are assumed away. In a predominantly male population aged 41 years, naltrexone is estimated to deliver 0.132 QALYs gained per person as compared to placebo if within-family external effects are included. The incremental cost per completer of naltrexone as compared to placebo was estimated at 685 AUD and is assumed to reflect the incremental cost over the entire evaluation period. The cost per QALY gained is estimated at 12,966 AUD based on 1st-person effects or 5,191 AUD if within-family external effects are included. Table 6.6 below summarises results from the modelled cost-utility analysis.

Table 6.6 Summary of cost utility of naltrexone+ *vs* placebo+ according to the modelled cost-utility analysis (discount rate= 5%)

	1st-person effects only	1st-person + within-family external effects
QALYs gained/person	0.0528	0.132
Extra cost/person AUD	$684.70	$684.70
Cost/QALY gained AUD	**$12,966**	**$5,191**

Health states and the Markovian assumption

A Markov model with just two non-absorbing (dependence and recovered) and one absorbing state (dead) could be used to estimate QALYs gained per person for each intervention as compared to its comparator. There is no 'tee-total' state because all relapse was defined as a return to consumption of 5 or more drinks in a day for males and 4 or more drinks in a day for females rather than a lapse in abstinence. For the modelled cost-utility analysis, we combine the 'abstinent' and other pre-lapsed drinkers into a single category and make the conservative assumption that individuals in these categories at 6 months follow-up have achieved a minimum improvement in HRQoL and risk of death that can be characterised as transition from 'dependence' to 'recovered'. Because it is difficult to undo some of the damage done during dependence, the risk of death is elevated for persons characterised as 'recovered' as compared to persons characterised as 'moderate' or 'problem' drinkers.

In order to model the cumulative effect of an 'improved' consumption pattern, the 'recovered' and 'dependence' disease states are split into temporary disease states. Temporary states are "defined as having transitions only to other states and not to themselves. This guarantees that the patient can spend, at most, one cycle in that state" (Sonnenberg & Beck, 1993 p. 326). Patients are not required to transition through all three 'recovered' states (ie. patients can return to 'dependence' after any number of cycles), but 'recovered3' can *only* be reached after first cycling through both 'recovered2' and 'recovered1'. This gives us a fixed sequence of temporary states known as a tunnel sequence (Briggs & Sculpher, 1998).

Cycle length

Follow-up in all but one of the 7 included trials was just 12 weeks. Follow-up in the remaining trial was 6 months after completion of the intervention. A cycle length of 3 months is therefore assumed for the modelled cost-utility analysis. A half-cycle correction is applied to initial and final payoffs to

adjust the stepwise survival curve traced by the model to more closely approximate the continuous survival curve that operates in the real-world.

Termination condition

The Markov model terminates when the following condition is satisfied: _stage > 36 & (_stage > 236 | _stage_eff < .001). In other words, the model terminates after 236 cycles (59 years) *or* when the reward accumulated in any given cycle falls below 1/1000 of a QALY and at least 36 cycles or 9 years have been completed.

Payoffs (private plus external)

First-person and within-family external HRQoL effects are calculated as for the Chapter 2 models. In the absence of supporting data, we make the conservative assumption that the HRQoL weight for the 'recovered' state is approximately equal to the HRQoL weight for problem drinkers. External effects within each family unit are limited to an arbitrary 4 years period, ceasing at 45 years of age irrespective of success/failure in moderating alcohol consumption. The reduction in the persistence of external effects to 4 years reflects the start_age of participants in the model.

Time-invariance

For the modelled cost-utility analysis TPr_Death is time-dependent but all other probabilities and payoffs are invariant with respect to time. Payoffs and the likelihood of relapse and recovery are dependent on history rather than time per se. For example, to account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'recovered1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'dependence3' state. Transition to 'recovered1' does, however, result in an immediate improvement in first-person HRQoL. Subsequent transition from 'recovered1' to 'recovered2' adds an improvement in external HRQoL effects but risk of death remains as for the 'dependence3' state. A reduction in risk of death is finally added upon transition from 'recovered2' to the 'recovered3' state such that the tunnel sequence amounts to a accumulation of benefits made of (i) first-person HRQoL effects on adoption of safe drinking behaviours, (ii) external HRQoL effects at 3 months, and (iii) reduction in risk of death at 6 months. A converse accumulation of payoffs and risks is specified for the dependence tunnel sequence.

Note that accumulation of benefits for the Chapter 6 model is accelerated as compared to the accumulation of benefits in other models of alcohol interventions (Chapter 2-5). This approach limits the multiplication of health states in the tunnel sequences and the error associated with an accelerated accumulation of benefits is expected to be quite small because participants had already undergone detoxification on entry to the trials.

Initial probabilities

Initial probabilities are used to distribute a cohort (or to designate the status of an individual) over the relevant health states. All subjects in the pooled sample from the Streeton et al (2001) meta-analysis were dependent but recently detoxified on entry to the trials. It is not clear how these patients should be classified for the purposes of the modelled costs-utility analysis. It seems unlikely that recently detoxified persons can be assumed to have undone the accumulated age/sex adjusted effects of their past alcohol consumption. We therefore assume that all persons commence in the 'recovered1' state.

Start age

The mean age of participants in the 7 included trials ranged from 39 to 59 years but the average age of the pooled sample is not reported. Dependent drinkers undergoing detoxification and naltrexone therapy are likely to be at the moderate to severe end of the severity spectrum but without concomitant psychiatric disease or poly-drug substance abuse. This closely approximates the target

population for the Chapter 4 intervention and, for the purposes of the modelled cost-utility analysis; we assume that the characteristics of the Chapter 4 and Chapter 6 models are identical. Mean age at baseline in the Heather et al (2000) trial was 41.43 years (9.92 SD). We therefore assume an average start age of 41 years for both the Chapter 4 and Chapter 6 models.

Recovery

There is a well documented body of evidence showing the alcohol abuse and dependence tends to decline naturally over time and with age. Vaillent (1995) in a review of 8 such studies reported an average of 2% of alcohol dependant participants reverted to abstinence over any twelve month period. The background risk of recovery reported by Vaillent (1995) is then converted to a per cycle risk as per Miller & Homan (1994): $1 - (1- 0.02)^{1/4} = 0.005037944$ for use in the modelled cost-utility analysis.

Relapse rates

Relapse rates are taken directly from the trial but the outcomes but are operationalised as a move from 'recovered' to 'dependence'. The % relapsed at follow-up is taken as the annual absolute risk of transition from 'recovered' to 'dependence' during the treatment period. The annual risk of relapse during the treatment period is then converted to a per cycle risk as per Miller & Homan (1994): $1 - (1-\text{annual risk})^{1/4}$, for use in the model. This gives us a per cycle risk of relapse for the initial cycle equal to 0.123159199 for the treatment group and 0.171945141 for the control group. It is recognised that this derivation fails to control for any differences in severity at baseline and ignores heterogeneity between the seven included trials.

Table 6.7 Percentage relapsed at follow-up: Naltrexone+ *vs* Placebo+

Number of studies	Treatment Group Relapsed (%)	Control Group Relapsed (%)	Risk difference	95%CI
7	166/406 (40.887%)	213/402 (52.985%)	-0.14	-0.24, -0.05

The only study with extended follow up to be included in the Streeton et al (2001) meta-analysis suggested that the benefits from naltrexone treatment would be lost within 6 months of discontinuing pharmacotherapy. We therefore assume that both groups revert to a background relapse rate at 6-months following treatment (_stage=3). The relapse rate in the first 6 months following treatment (_stage=1-2) is calculated by interpolation between the background relapse rate and the relapse rate applicable during the intervention. The background risk of relapse from recovered to dependence was assumed equal to the risk of progression from 'problem' to 'dependence' used in the Chapter 2 models. We then converted this 6-months risk to a per cycle risk as per Miller and Homan (1994): $1 - (1- 0.056)^{1/2} = 0.028403376$, for use in the model.

Death rates

For dependent drinkers, we rely on death rates for those exceeding NHMRC recommendations for peak consumption (ie. >6 drinks/session, women: >4 drinks/session) on a regular basis. For recovered drinkers, we rely on death rates for past problem drinkers where past problem drinking is defined as having ≥5 drinks on a weekly basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983. Risk of death is calculated as for the Chapter 2 models but are then combined to obtain a weighted average of the male and female death rate for each age band. Weights correspond to the proportion of males and females in the Chapter 4 trial population (75% males, 25% females) under the assumption that this approximates the proportion of males and females in the target population[15].

[15] Dependent drinkers undergoing detoxification and naltrexone therapy are likely to be at the moderate to severe end of the severity spectrum but without concomitant psychiatric disease or poly-drug substance abuse. This closely approximates the target population for the Chapter 4 intervention and, for the purposes of the modelled cost-uility analysis; we assume that the characteristics of the Chapter 4 and Chapter 6 models are identical.

Table 6.8 Relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.93 (0.39, 2.21)	**≥6 drinks/day *vs* lifetime abstinent**	**2.29 (1.17, 4.48)**	2-4 drinks/day *vs* lifetime abstinent	0.73 (0.39, 1.37)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.97 (0.30, 3.09)	≥4 drinks/day *vs* lifetime abstinent	1.06 (0.26, 4.34)	1-2 drinks/day *vs* lifetime abstinent	0.81 (0.42, 1.56)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.96 (1.26, 3.05)	Past problem drinking[#] *vs* lifetime abstinent	1.64 (0.98, 2.76)	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.84 (0.98, 3.44)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.77 (0.86, 3.64)	Past problem drinking[#] *vs* lifetime abstinent	2.18 (1.12, 4.24)	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.25 (0.17, 9.14)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.

Table 6.9 Relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* 2-4 drinks/day	1.27 (0.53, 3.03)	≥6 drinks/day *vs* 2-4 drinks/day	**3.14 (1.60, 6.14)**	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.20 (0.37, 3.81)	≥4 drinks/day *vs* 1-2 drinks/day	1.31 (0.32, 5.36)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.68 (1.73, 4.18)	Past problem drinking[#] *vs* 2-4 drinks/day (a)	2.25 (1.34, 3.78)	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.52 (1.34, 4.71)	Rehm, Greenfield and Rogers (2001)
RR adjusted for age & ethnicity (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.19 (1.06, 4.49)	Past problem drinking[#] *vs* 1-2 drinks/day	2.69 (1.38, 5.23)	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.54 (0.21, 11.28)	Rehm, Greenfield and Rogers (2001)

[#]Past problem drinking defined as having ≥5 drinks on a weeks basis or by having felt that their drinking was no longer under control in any year between 1973 and 1983.
(a) Death rate for recovered.

Table 6.10 Adjusted relative risk of all-cause death by alcohol disorder vs lifetime abstainers

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day *vs* lifetime abstinent	0.90 (0.38, 2.14)	≥6 drinks/day *vs* lifetime abstinent	2.14 (1.08, 4.23)	2-4 drinks/day *vs* lifetime abstinent	0.78 (0.41, 1.47)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* lifetime abstinent	0.89 (0.28, 2.88)	≥4 drinks/day *vs* lifetime abstinent	0.94 (0.23, 3.86)	1-2 drinks/day *vs* lifetime abstinent	0.77 (0.40, 1.51)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.93 (1.23, 3.02)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-2 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.62 (0.86, 3.07)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* lifetime abstinent	1.65 (0.79, 3.41)	Past problem drinking[#] *vs* lifetime abstinent	NR	0-1 drinks/day with occasional heavy drinking *vs* lifetime abstinent	1.08 (0.15, 7.93)	Rehm, Greenfield and Rogers (2001)

Table 6.11 Adjusted relative risk of all-cause death by alcohol disorder vs safe drinkers (men: 2-4 drinks/day, women: 1-2 drinks/day)

Measure	Sample	Group 1		Group 2		Group 3		Source
		Definition	all-cause mortality	Definition	all-cause mortality	Definition	all-cause mortality	
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	4-6 drinks/day (a) *vs* 2-4 drinks/day	1.15 (0.49, 2.74)	≥6 drinks/day *vs* 2-4 drinks/day (b)	2.74 (1.38, 5.42)	2-4 drinks/day *vs* 2-4 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	2-4 drinks/day *vs* 1-2 drinks/day	1.16 (0.36, 3.74)	≥4 drinks/day *vs* 1-2 drinks/day	1.22 (0.30, 5.01)	1-2 drinks/day *vs* 1-2 drinks/day	1.00	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US men: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 2-4 drinks/day	2.47 (1.58, 3.87)	Past problem drinking[#] *vs* 2-4 drinks/day	NR	0-2 drinks/day with occasional heavy drinking *vs* 2-4 drinks/day	2.08 (1.10, 3.94)	Rehm, Greenfield and Rogers (2001)
RR adjusted for confounders (95%CI)	US women: aged 18+, white, black or hispanic	Current abstinent with past heavy drinking *vs* 1-2 drinks/day	2.14 (1.03, 4.43)	Past problem drinking[#] *vs* 1-2 drinks/day	NR	0-1 drinks/day with occasional heavy drinking *vs* 1-2 drinks/day	1.40 (0.19, 10.30)	Rehm, Greenfield and Rogers (2001)

(a) Death rate for problem drinker.
(b) Death rate for 'dependant'.

Table 6.12 Age-specific deaths/1000 by alcohol status: Safe

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males	5.5	0.3	0.1	0.2	0.6	0.9	1.0	1.1	1.3	1.7	2.6	3.6	5.8	10.0	16.5	28.8	48.8	80.8	167.4
Females	4.7	0.2	0.1	0.1	0.3	0.3	0.4	0.5	0.7	1.0	1.5	2.4	3.7	6.0	9.6	16.2	28.9	54.2	135.4
Persons	5.30	0.28	0.10	0.18	0.53	0.75	0.85	0.95	1.15	1.53	2.33	3.30	5.28	9.00	14.78	25.65	43.83	74.15	159.40
TPr_M	0.0055	0.0003	0.0001	0.0002	0.0006	0.0009	0.0010	0.0011	0.0013	0.0017	0.0026	0.0036	0.0058	0.0100	0.0165	0.0288	0.0488	0.0808	0.1674
TPr_F	0.0047	0.0002	0.0001	0.0001	0.0003	0.0003	0.0004	0.0005	0.0007	0.0010	0.0015	0.0024	0.0037	0.0060	0.0096	0.0162	0.0289	0.0542	0.1354
TPr_P	0.0053	0.0003	0.0001	0.0002	0.0005	0.0008	0.0009	0.0010	0.0012	0.0015	0.0023	0.0033	0.0053	0.0090	0.0148	0.0257	0.0438	0.0742	0.1594

Proportion of men and women: 75% males, 25% females

Table 6.13 Age-specific TPr_Death by alcohol status: Problem3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.00633	0.00035	0.00012	0.00023	0.00069	0.00104	0.00115	0.00127	0.00150	0.00196	0.00299	0.00414	0.00667	0.01150	0.01898	0.03312	0.05612	0.09292	0.19251
Upper	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Lower	0.00270	0.00015	0.00005	0.00010	0.00029	0.00044	0.00049	0.00054	0.00064	0.00083	0.00127	0.00176	0.00284	0.00490	0.00809	0.01411	0.02391	0.03959	0.08203
Females																			
Mid	0.00541	0.00023	0.00012	0.00012	0.00035	0.00035	0.00046	0.00058	0.00081	0.00115	0.00173	0.00276	0.00426	0.00690	0.01104	0.01863	0.03324	0.06233	0.15571
Upper	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Lower	0.00230	0.00010	0.00005	0.00005	0.00015	0.00015	0.00020	0.00025	0.00034	0.00049	0.00074	0.00118	0.00181	0.00294	0.00470	0.00794	0.01416	0.02656	0.06635
Persons																			
Mid	0.00610	0.00032	0.00012	0.00020	0.00060	0.00086	0.00098	0.00109	0.00132	0.00175	0.00267	0.00380	0.00607	0.01035	0.01699	0.02950	0.05040	0.08527	0.18331
Upper	0.01452	0.00075	0.00027	0.00048	0.00144	0.00206	0.00233	0.00260	0.00315	0.00418	0.00637	0.00904	0.01445	0.02466	0.04048	0.07028	0.12008	0.20317	0.43676
Lower	0.00260	0.00013	0.00005	0.00009	0.00026	0.00037	0.00042	0.00047	0.00056	0.00075	0.00114	0.00162	0.00258	0.00441	0.00724	0.01257	0.02147	0.03633	0.07811

Men's RR: 4-6 drinks/day *vs* 2-4 drinks/day= 1.15 (0.49, 2.74). Women's RR: 2-4 drinks/day *vs* 1-2 drinks/day=1.16 (0.36, 3.74). Proportion of men and women: 75% males, 25% females

Table 6.14 Age-specific TPr_Death by alcohol status: Dependent3

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01507	0.00082	0.00027	0.00055	0.00164	0.00247	0.00274	0.00301	0.00356	0.00466	0.00712	0.00986	0.01589	0.02740	0.04521	0.07891	0.13371	0.22139	0.45868
Upper	0.02981	0.00163	0.00054	0.00108	0.00325	0.00488	0.00542	0.00596	0.00705	0.00921	0.01409	0.01951	0.03144	0.05420	0.08943	0.15610	0.26450	0.43794	0.90731
Lower	0.00759	0.00041	0.00014	0.00028	0.00083	0.00124	0.00138	0.00152	0.00179	0.00235	0.00359	0.00497	0.00800	0.01380	0.02277	0.03974	0.06734	0.11150	0.23101
Females																			
Mid	0.01288	0.00055	0.00027	0.00027	0.00082	0.00082	0.00110	0.00137	0.00192	0.00274	0.00411	0.00658	0.01014	0.01644	0.02630	0.04439	0.07919	0.14851	0.37100
Upper	0.02547	0.00108	0.00054	0.00054	0.00163	0.00163	0.00217	0.00271	0.00379	0.00542	0.00813	0.01301	0.02005	0.03252	0.05203	0.08780	0.15664	0.29376	0.73387
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01452	0.00075	0.00027	0.00048	0.00144	0.00206	0.00233	0.00260	0.00315	0.00418	0.00637	0.00904	0.01445	0.02466	0.04048	0.07028	0.12008	0.20317	0.43676
Upper	0.02873	0.00149	0.00054	0.00095	0.00285	0.00407	0.00461	0.00515	0.00623	0.00827	0.01260	0.01789	0.02859	0.04878	0.08008	0.13902	0.23753	0.40189	0.86395
Lower	0.00731	0.00038	0.00014	0.00024	0.00072	0.00104	0.00117	0.00131	0.00159	0.00210	0.00321	0.00455	0.00728	0.01242	0.02039	0.03540	0.06048	0.10233	0.21997

Men's RR: >6 drinks/day *vs* 2-4 drinks/day= 2.74 (1.38, 5.42). Women's RR: >4 drinks/day *vs* 1-2 drinks/day=1.22 (0.30, 5.01). Proportion of men and women: 75% males, 25% females

Table 6.15 Age-specific TPr_Death by alcohol status: Recovered

	0	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Males																			
Mid	0.01238	0.00068	0.00023	0.00045	0.00135	0.00203	0.00225	0.00248	0.00293	0.00383	0.00585	0.00810	0.01305	0.02250	0.03713	0.06480	0.10980	0.18180	0.37665
Upper	0.02079	0.00113	0.00038	0.00076	0.00227	0.00340	0.00378	0.00416	0.00491	0.00643	0.00983	0.01361	0.02192	0.03780	0.06237	0.10886	0.18446	0.30542	0.63277
Lower	0.00737	0.00040	0.00013	0.00027	0.00080	0.00121	0.00134	0.00147	0.00174	0.00228	0.00348	0.00482	0.00777	0.01340	0.02211	0.03859	0.06539	0.10827	0.22432
Females																			
Mid	0.01058	0.00045	0.00023	0.00023	0.00068	0.00068	0.00090	0.00113	0.00158	0.00225	0.00338	0.00540	0.00833	0.01350	0.02160	0.03645	0.06503	0.12195	0.30465
Upper	0.01777	0.00076	0.00038	0.00038	0.00113	0.00113	0.00151	0.00189	0.00265	0.00378	0.00567	0.00907	0.01399	0.02268	0.03629	0.06124	0.10924	0.20488	0.51181
Lower	0.00649	0.00028	0.00014	0.00014	0.00041	0.00041	0.00055	0.00069	0.00097	0.00138	0.00207	0.00331	0.00511	0.00828	0.01325	0.02236	0.03988	0.07480	0.18685
Persons																			
Mid	0.01193	0.00062	0.00023	0.00039	0.00118	0.00169	0.00191	0.00214	0.00259	0.00343	0.00523	0.00743	0.01187	0.02025	0.03324	0.05771	0.09861	0.16684	0.35865
Upper	0.02003	0.00104	0.00038	0.00066	0.00198	0.00284	0.00321	0.00359	0.00435	0.00576	0.00879	0.01247	0.01994	0.03402	0.05585	0.09696	0.16566	0.28029	0.60253
Lower	0.00715	0.00037	0.00014	0.00024	0.00071	0.00101	0.00114	0.00128	0.00155	0.00205	0.00313	0.00445	0.00711	0.01212	0.01989	0.03453	0.05901	0.09990	0.21495

Men's RR: Past problem *vs* 2-4 drinks/day= 2.25 (1.34, 3.78). Women's RR: Past problem *vs* 1-2 drinks/day=2.69 (1.38, 5.23). Proportion of men and women: 75% males, 25% females

Sensitivity Analysis

The modelled cost-utility analysis is based on data taken from the Streeton et al (2001) meta-analysis, our own calculation of incremental program costs as described in Section 6.4, together with supporting data and assumptions as outlined above. Note, for example, that the estimate of QALYs gained from the modelled cost-utility analysis has been derived from a number of data sources with varying levels of error and uncertainty. More specifically, uncertainty in the estimate of QALYs gained is a function of sampling error in the trial-based measure of surrogate outcome (behaviour change), uncertainty as to the persistence of any behaviour change (relapse rates), and uncertainty in the relationship between a surrogate outcome such as behaviour change and a final outcome such as QALYs gained (with respect to both utility weights and life-years gained).

In an effort to identify key drivers and to evaluate robustness of estimates as to cost per QALY gained, univariate sensitivity analyses were conducted by varying parameters such as start_age, HRQoL weights in non-absorbing health states, discount rate, initial rate of relapse (in the recovered1 state to _stage=3), the relative risk of death, recovery rates from the Streeton et al (2001) meta-analysis, and our estimates of incremental costs. Variation in each uncertain parameter produced intuitively plausible variations in cost per QALY ratios. Results of the sensitivity analyses are summarised in Table 6.17.

The following details should be kept in mind for the interpretation of the sensitivity analyses.

- Recall that the base case assumed termination of the model at age=100 yrs. For the sensitivity analyses, the termination condition was adjusted to preserve termination at age=100 yrs irrespective of start_age. Note that varying start_age from 20 to 70 years produces only relatively minor changes in cost per QALY ratios.
- The 95%CI for treatment effect is derived by calculating the 95%CI around the relative risk of relapse from 'recovered' to 'dependence'. Upper and lower estimates for the absolute risk of relapse from 'recovered' to 'dependence' in the naltrexone group are then derived assuming that the absolute risk for the placebo group is as for the base case analysis. Table 6.16 below summarises these calculations.
- The cost per life-year gained is derived by setting the HRQoL weight to 1.0 for each of the six non-absorbing health states (dependence1, dependence2, dependence3, recovered1, recovered2, recovered3). In other words, adjustment for HRQoL in health states other than death is removed for this analysis. Estimates of cost per life-year gained varied between 682,820 AUD (based on 1st-person effects) and 225,536 AUD (if within-family external effects are included).

Table 6.16 Calculating 95%CI for treatment effect

AR Rx (Base Case)	AR Placebo	RR (95%CI)	AR Rx (Low)	AR Rx (High)
0.12	0.17	0.72 (0.55, 0.94)	0.0935	0.1598

Table 6.17 Cost/QALY estimates according to the sensitivity analysis

	1st-Person Effects	1st-Person + Within-Family Effects
start_age=20	$12,962	$4,258
start_age=30	$12,963	$4,276
start_age=41	$12,966	$5,191
start_age=50	$12,997	$12,079
start_age=60	$13,160	$11,188
start_age=70	$13,977	$10,268
Q_All=1.00	$682,820	$225,536
discount=0.00	<$9,717	<$4,176
discount=0.05	$12,966	$5,191
discount=0.07	$16,252	$6,183
Initial Rx relapse=0.12	$12,966	$5,191
Initial Rx relapse=0.20	$105,238	$48,932
Initial Rx relapse=0.40	placebo dominates	placebo dominates
Initial C relapse=0.17	$12,966	$5,191
Initial C relapse=0.20	$9,935	$3,957
Initial C relapse=0.40	$3,725	$1,468
Lower 95%CL	$13,045	$5,267
Mean RR_Death: Taylor (2002)	$12,966	$5,191
Upper 95%CL	$12,728	$4,977
Lower 95%CL	$9,688	$3,859
Mean Treatment Effect	$12,966	$5,191
Upper 95%CL	$22,281	$9,047
Half Best Estimate	$6,483	$2,596
Best Estimate Incremental Cost	$12,966	$5,191
Twice Best Estimate	$25,932	$10,382

Threshold Analysis

Recall that downstream cost offsets have not been included in the modelled cost-utility analysis (but would only serve to further reduce the cost/QALY ratio). While the complex modelling task of attributing downstream cost offsets to intervention and control groups is beyond the scope of this study, we have quantified the minimum downstream cost offset that would be required in order for naltrexone plus counselling to be cost saving when compared to placebo plus counselling. Table 6.18 specifies the minimum per cycle downstream cost offset in the recovered3 state for naltrexone plus to dominate placebo plus.

When interpreting the threshold analysis, it should be remembered that downstream cost offsets are likely to be age/sex dependent and accrue in an episodic (rather than constant) manner. In an attempt to incorporate some of this complexity, no downstream cost offsets accrue during the initial 2 cycles in the recovered state. This is consistent with assumptions made elsewhere in the model with respect to the differential risk of death in dependence and recovered states[16]. Aside from this relatively crude adjustment for duration of time spent in the recovered state, downstream cost offsets are incorporated in the simplest way possible. The dollar-value of downstream cost offsets is

[16] To account for the cumulative effect of a return to a 'safe' consumption pattern we assume that transition to 'recovered1' fails to deliver any reduction in risk of death and fails deliver any improvement in external effects within the family unit. That is, the risk of death and the external HRQoL weight is as for the 'dependence3' state. Transition to 'recovered1' does, however, result in an immediate improvement in first-person HRQoL. Subsequent transition from 'recovered1' to 'recovered2' adds an improvement in external HRQoL effects but risk of death remains as for the 'dependence3' state. A reduction in risk of death is finally added upon transition from 'recovered2' to the 'recovered3' state.

invariant with respect to _stage and age such that the same downstream cost offset accrues to a recovered drinker after 3 cycles as after 30 cycles. It is left to the decision-maker to determine whether a 'recovered' 41 years old is likely to average $750 per 3-months cycle in downstream cost offsets over the remaining 30 to 40 years of his/her lifespan.

Table 6.18 Minimum downstream cost offset for naltrexone plus to dominate: 1st-person effects only (discount rate= 5%)

Model	QALYs gained/person	Downstream cost offset	Incremental cost/person	Cost/QALY gained
Naltrexone+ *vs* Placebo+	0.131904	$752.10	$0.00	Naltrexone+ dominates

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