Multistate life table model for estimating the long-term cost-effectiveness of the Alcohol Dependence and Adherence to Medications (ADAM) interventions.

Background

ADAM (Alcohol Dependence and Adherence to Medications) was a randomised controlled trial comparing standard support (SS) for post detox relapse prevention medication with SS plus pharmacy-based medicine management (SS+MM) or SS plus pharmacy-based medicine management with contingency management SS+MM+CM (financial reinforcement of uptake of pharmacist support sessions). A preliminary review of the modelling literature in 2015 did not identify any publicly available models at that time that would be appropriate to estimate the impact of treatment of severe alcohol dependence. Therefore, we undertook to build a de novo patient level, multistate life table model using published risk equations[1,2] to extrapolate trial outcomes beyond the trial time horizon.

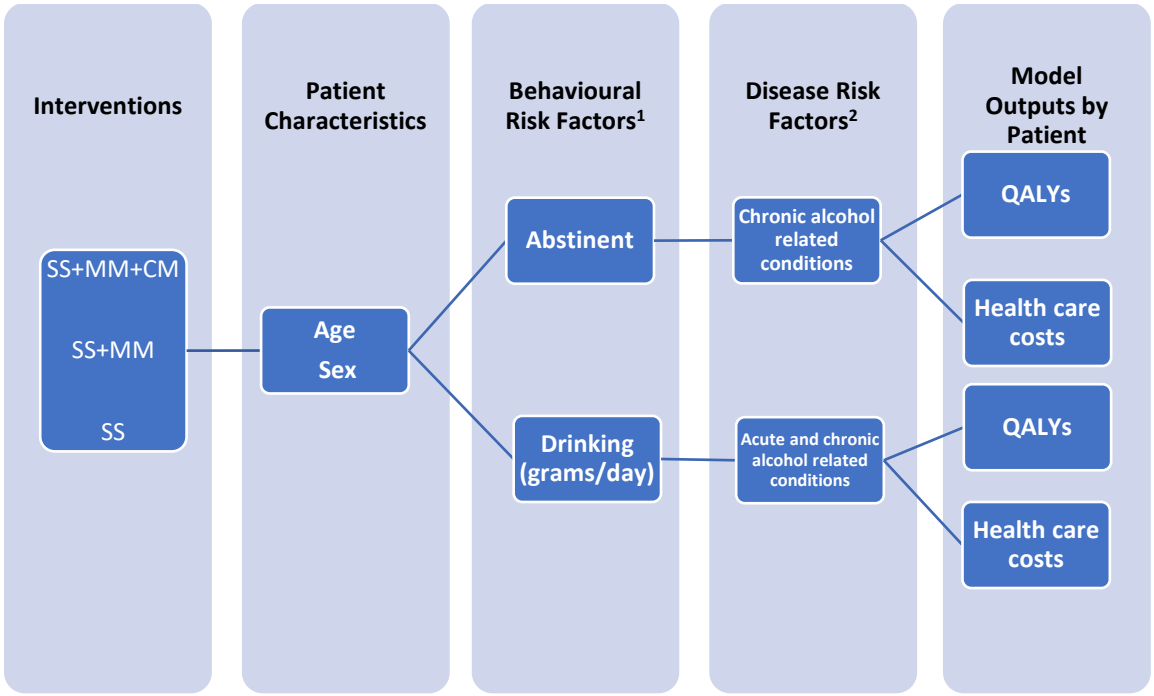
Aims

To calculate the expected costs and QALYs over a 20-year time horizon for each participant in the ADAM RCT based on age, sex, drinking status (alcohol consumption), and quality of life (EQ-5D-3L) at the end of the ADAM trial (12 months post-randomisation). QALYs were calculated using the EQ-5D-3L to be consistent with decrement values which were taken from a published EQ-5D-3L value set[3]. To estimate incremental cost effectiveness ratios (ICERs) for each ADAM intervention group compared to treatment as usual (SS alone) based on trial costs and QALYs combined with modelled long-term costs and QALYs. To estimate uncertainty around the ICERs using probabilistic sensitivity analysis (PSA). To estimate the probability of cost-effectiveness for each option compared to SS alone using cost effectiveness acceptability curves.

Methods

We built a multistate life table model[4] which quantified the effect of changing alcohol consumption (grams of alcohol per day) on morbidity (QALY decrements), mortality and condition-related costs from 31 alcohol-related conditions and events using parallel life tables using published risk equations[1,2] to estimate long-term costs and quality-adjusted life-years (QALYs) conditioned on age, sex, and end of trial health-related quality-of-life (EQ-5D-3L) and alcohol consumption (figure 1).

Figure 1 The ADAM CE conceptual model



1. Allowed to change over time to account for relapse/remission

2. Sixteen Chronic long term conditions and 15 acute conditions and events listed in Table 1

Data sources

The principal data sources outside of the ADAM trial were:

i) for the calculation of relative risks of chronic alcohol related conditions - the Sheffield Model (2), and the NICE Return on Investment (ROI) model[1]

ii) for the calculation of relative risks of acute alcohol related conditions - -- NHS digital for alcohol-related admissions in England[5], ONS population estimates for England[5] and the NICE ROI model for prevalence of acute conditions[1]

iii) QALY decrements by condition - catalogue of EQ-5D scores for the UK[3]

iv) costs by condition - the NICE ROI model[1]

v) mortality - ONS life tables[5] and standardised mortality rates[6,7]

vi) relapse and remission[8]

Model software

The model was built in Microsoft Excel and consists of the following worksheets:

i) Parameters values for the probabilistic sensitivity analysis

ii) Patient data - individual patient dataset

iii) Parameters + assumptions - individual patient data input

iv) Risk tables - condition and sex specific lifetables

v) Calculation - QALY + cost calculations

vi) Included conditions - list

vii) Chronic conditions - relative risks

viii) Acute conditions - relative risks

ix) Population - England

x) Hospital Admissions - alcohol attributable admissions

xi) Life Table - death rates by age + sex for England

xii) Drinking patterns - by age + sex for England

xiii) Relapse and remission - by age

xiv) GDP deflator - uprating costs

xv) References

A copy of the Excel model is available on request.

Simulation

The long-term costs and QALYs for each of the 739 participants in the ADAM trial were simulated using a hypothetical cohort of 1,000 alcohol dependent people with the same age, sex, drinking status at the end of the ADAM trial (abstinent/drinking), alcohol consumption at the end of the ADAM trial and EQ-5D-3L utility weight at the end of the ADAM trial. In each 12-month cycle, a proportion of the survivors in the simulated cohort accrued costs and EQ-5D-3L decrements according to the annualised risk of alcohol-related health conditions and events conditioned by sex, age and drinking profile. We assumed that the risks of alcohol-related conditions and events (apart from death) were independent and therefore the cost and QALY consequences of each condition could be summed over each simulation time horizon. The total costs and QALYs were then divided by 1,000 to yield the expected costs and QALYs for each ADAM participant which were added then to the trial 12-month costs and QALYs.

Cycle length & discounting

A cycle length of 12 months was based on the annual risk estimates available for alcohol-related health conditions and events. Costs and QALYs were discounted from the first year at 3.5% because these occurred after the ADAM twelve-month trial period.

Alcohol consumption

Daily alcohol consumption in grams for each Patients was entered into the model using the most recent time life follow back (TLFB) data from the ADAM trial. For 393 patients this was the average units per day at the 12-month follow-up, for 125 patients this was the average units per day at the 6-month follow-up and for 221 patients this was the average units per day at baseline. Grams per day were calculated by multiplying reported units by eight. One unit equals 10ml or 8g of pure alcohol, which is around the amount of alcohol the average adult can process in an hour[9].

Drinking status

Patients were categorised as either abstinent or drinking based on their most recent TLFB data from the ADAM trial. Abstinent patients were assumed not to be at risk from acute alcohol-related conditions, to have the same risk as the general population for chronic alcohol-related conditions and to be at lower risk of mortality than those who continued to drink.

Relapse & remission

Estimates of relapse to drinking from abstinence, and remission to abstinence from drinking by age reported in the literature were entered as life tables in the Risk Tables worksheet[8]. The risk for each alcohol-related acute condition by sex and age in the Risk Tables worksheet was multiplied by the corresponding relapse rate for abstinent patients, or remission rate for continued drinkers, and then this product was added to the risk for abstinent drinkers or taken off from the risk for continued drinkers. The Standardised Mortality Ratio (SMR) was adjusted in a similar fashion in the Calculation worksheet.

Costs

The initial distribution of undiscounted total 12-month costs at the start of the model were derived from the clinical trial with missing data imputed using the model. For 393 patients, this was the total costs over the 12-month follow-up, for 125 patients this was the total costs over the 6-month follow-up plus six months of costs projected by the model based on their age, sex and drinking status and for 221 patients this was the total costs for the six months prior to baseline plus six months of costs projected by the model based on their age, sex and drinking status. Condition-related costs were

based on 2009 costs used in the NICE Return on Investment tool for prevention of alcohol-use disorders and uprated to 2019 prices[1]. Condition-related costs will be revised if new data becomes available. Annual costs for each chronic or acute condition were multiplied by the number of the surviving simulation cohort at risk of the chronic or acute condition in the Calculation Worksheet. At each cycle, the costs were discounted, divided by 1,000 to reflect the expected individual patient cost, summed over 20 cycles and then added to the trial-based costs.

QALYs

The initial distribution of undiscounted total 12-month QALYs at the start of the model were derived from the clinical trial with missing data imputed by the model. For 393 patients, this was the total QALYs over the 12-month follow-up, for 125 patients this was the total QALYs over the 6-month follow-up plus six months of QALYs projected by the model based on their age, sex, drinking status and EQ-5D-3L utility at 6 months and for 221 patients this was the total QALYs for the six months prior to baseline plus six months of QALYs projected by the model based on their age, sex, drinking status and EQ-5D-3L utility at baseline. Annual QALY decrements for each chronic or acute condition were multiplied by the number of the surviving simulation cohort at risk of the chronic or acute condition in the Calculation Worksheet. At each cycle, the QALY decrements were discounted, divided by 1,000 to reflect the expected individual patient QALY loss, subtracted from the individual patient QALY estimated over the 12-month ADAM trial period, summed over 20 cycles and added to the trial-based QALYs.

Mortality

The model simulated all-cause mortality according to age and sex by using life tables (Office of National Statistics, England Interim Lifetables 2013-2015 www.ons.gov.uk accessed 8/5/17)) and then applied standardised mortality ratios (SMRs) for heavy drinkers (defined as drinking more than 75 grams of alcohol per day). Standardised mortality ratios compare the number of observed deaths in a population with the number of expected deaths assuming the age-specific death rates are the same as the general population. The SMR for all-cause mortality for patients with a primary alcohol use disorder registered with the South London and Maudsley Case Register in 2008 was 4.04 (95%CI[3.53,4.61]) (6). This SMR is applied in the model to those who continue to drink. People in treatment for alcohol use disorders or who stop drinking, have less than half the risk of dying compared to those who continue with heavy drinking (OR 0.41 (95% CI[0.34-0.50]) (10). To reflect this, an estimated SMR of 1.97 (95%CI[1.93,2.01]) based on a meta-analysis of 32 cohort studies (7) is applied to ADAM participants who have managed to stop drinking. Mortality associated with chronic

and acute alcohol-related problems is assumed to be included in the standardised mortality ratios and is not considered further in the model.

At the beginning of each cycle, the size of the surviving cohort in the Calculation Worksheet was reduced by multiplying the number of survivors in the previous cycle by the corresponding life table transition probability of death from the Risk Tables Worksheet. This assumes that all deaths occurred at the beginning of each cycle.

Chronic conditions

The annual relative risk of 16 chronic conditions (Table S1) dependent on alcohol consumption was calculated using published equations[2] and stored in the Chronic Conditions Worksheet. These equations used daily alcohol consumption in grams for each participant at the end of the ADAM trial from the Patient Data Worksheet adjusted for age and sex in the Risk Tables Worksheet to the surviving cohort in the Calculation Worksheet to estimate the number in each cycle expected to experience the condition. Age and sex weighting is estimated from alcohol attributed hospital admissions for each chronic condition in the Hospital Admissions Worksheet. Abstinent participants who reported 0 grams of alcohol at the 12-month follow up of the ADAM study were assumed to have the same general population risk for each chronic condition. The chronic condition-related costs and QALY decrements were then added up over each annual cycle on the assumption that risks were independent. The results were divided by 1000 to provide expected results for a typical cohort member of the same age, sex, drinking pattern and EQ-5D-3L profile.

Table 1: Health conditions included in the ADAM model

Chronic	The risk of occurrence changes with long term exposure to alcohol
	It is assumed that the risk of occurrence starts at age 55 except for epilepsy, and liver disease
Acute	The risk of occurrence changes with acute exposure to alcohol including intoxication
	It is assumed there is zero risk of occurrence during periods of abstinence

Chronic conditions	**ICD-10**	**Notes**
Oral cancer	C00-C14	
Oesophagus cancer	C15	
Colon cancer	C18	

Rectum cancer	C20	
Liver cancer	C22	
Larynx cancer	C32	
Breast (female)	C50	
Diabetes II	E11	Excluded following Knott et al 2015
Epilepsy (males)	G40-G41	
Epilepsy (female)	G40-G41	
Hypertension	I10-I15	
Ischaemic Heart Disease (males)	I20-I25	Excluded as no protective effect following Roerecke & Rehm 2010
Ischaemic Heart Disease (females)	I20-I25	
Arrythmias	I47-I48	
Haemorrhagic Stroke	I60-I62, 169.0-169.2	
Ischaemic Stroke	I66, I69.3, I 69.4	
Varices	I85	
Liver cirrhosis	K70.3	
Acute conditions and events	**ICD-10**	**Notes**
Behavioural & mental disorders	F10	
Alcoholic liver disease	K70	
Toxic effects	T51	
Degeneration of nervous system	G31.2	
Polyneuropathy	G62.1	
Myopathy	G72.1	
Cardiomyopathy	I42.6	
Gastritis	K29.2	
Pancreatitis (chronic + acute)	K86, K85	Includes both wholly attributable and partially attributable hospital admissions
Poisoning	T51.0	
Traffic accidents - pedestrian	V90-V94	
Falls	W00-W19	
Other unintentional accidents	V01-V99 W20-W99, X10-X59, Y40-Y89	
Self harm	X60-X84, Y87.0 (excl X65)	

Assault	X85-Y09, Y87.1

Acute conditions

Relative risk equations for most of the fifteen acute alcohol-related conditions and events listed in Table S1 were not available and instead these were calculated by dividing the number of hospital admissions by sex for each condition by the estimated number of dependent drinkers by sex in the UK. It was assumed that prevalence of acute conditions among heavy drinkers also reflects the probability of contracting the disease. These were further adjusted for age in the Risk Tables Worksheet and then applied to the surviving cohort in the Calculation Worksheet to estimate the number in each cycle expected to experience the condition. The acute condition-related costs and QALY decrements were then added up over each annual cycle on the assumption that risks were independent. The results were divided by 1000 to provide expected results for a typical cohort member of the same age, sex, drinking pattern and EQ-5D-3L profile. This approach overestimates the prevalence because each hospital admission is assumed to be a unique individual, but it also underestimates the prevalence of acute conditions that do not lead to a hospital admission (i.e., A&E, primary care, outpatient and other secondary care).

Validation

The model was validated through an internal Quality Assurance (QA) process, feedback from ADAM trial co-investigators and independent external review. We conducted a series of one-way sensitivity analyses changing key parameter values in order to confirm the model produced results in the expected direction. A summary of results appears in the One Way Sensitivity Analyses Worksheet.

Probabilistic Sensitivity Analysis (PSA)

Computational limitations restricted the number of parameters that could be feasibly varied in the PSA. Input variables were selected based on their relative impact on costs and QALYs for a 60-year-old female drinking 150 grams of alcohol a day given that older female heavy drinkers were at highest additional risks compared to all other groups. The selected variables were: mortality (heavy drinkers, treated drinkers); the prevalence, costs and QALY decrements associated with oesophageal cancer, breast cancer, hypertension in ischemic heart disease, arrythmia, acute alcohol-related mental disorders and relapse and remission rates across all age groups.

It was not practical to run a full PSA based on the individual patient data because it took 50 days for a networked PC running continuously to produce 1,000 simulations. We are presently exploring

alternative methods of propagating uncertainty based on a cohort approach, slimming down the model to key parameters, and bootstrapping as proposed by Oppe et al (2021)[12].

Structural sensitivity analysis

Structural sensitivity analyses are ongoing and will be finalised prior to journal publication of the results of the work. The method of estimating baseline trial costs and QALYs (locf+modelling) will be compared to a complete case analysis limited to the 393 participants followed-up at 12 months and an analysis which multiply imputes missing values for missing baseline costs and QALYs.

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