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Cost-effectiveness analysis of EFAR-FVG: A randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website

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Cost-effectiveness analysis of EFAR-FVG: A randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website

Authors:

Rachael Hunter[1], Paul Wallace[1], Pierluigi Struzzo[2-4], Roberto Della Vedova[3], Francesca Scafuri[2], Costanza Tersar[4], Charilaos Lygidakis[5], Richard McGregor[6], Emanuele Scafato[7], Nick Freemantle[1]

Institutional affiliations:

[1]Department of Primary Care and Population Health, University College London, London, UK

[2]Regional Centre for Training in Primary Care, Monfalcone (GO) Italy

[3] CSeRMEG, Centro Studi e Ricerche in Medicina Generale, Italy

[4] University of Trieste, Life Sciences Department, Italy

[5] Institute for Health and Behaviour - Research Unit INSIDE, Université du Luxembourg, Luxembourg

[6] Codeface Ltd, Hove, UK

[7] Istituto Superiore di Sanità, WHO Collaborating Centre for Research and Health Promotion on Alcohol and Alcohol-Related Health Problems,

Corresponding author: Rachael Hunter, Department of Primary Care and Population Health, University College London, London, UK r.hunter@ucl.ac.uk, tel: +44 (0)20 830 2338

Collaborative group list-The EFAR Study Team:

Giosué Acampora, Maria Angela Bravo, Chiara Bregant, Gianna Bunello, Leonardo Butà, Lucia Casatta, Castellarin, Egidio Chamouni, Moshé Benyamin, Maria Pia Cisilin, Clemente Condello, Nelly Drigani, Tiziano Ermacora, Alessandro Falcidia, Adriana Fasiolo, Angelo Florio, Mauro Gubiani, Gianni Iacuzzo, Edi Ietri, Giuseppe Latella, Guglielmo Lucca, Ciro Mamolo, Carmelo Matera, Lucia Mei, Francesca Melon, Emilio Mezzasalma, Isabella Milan, Carlo Miotti, Gian Franco Panizzo, Francesca Pighin, Raffaela Principato, Pierina Revignas, Antonella Rolff, Ivana Rupalti, Rosanna Sellibara, Michela Sereni, Gianfranco Silverii, Giuseppe Taglialatela, Chiara Toffoletti, Massimo Toffolo, Laura Ivana Tonelli, Simone Trevisani, Roberto Troisi, Gianni Tubaro, Roberto Vallini, Elisabetta Zappalà, Antonio Zappi.

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Abstract

Objectives: To evaluate the 12 month costs and quality adjusted life years (QALYs) gained to the Italian National Health Service (INHS) of facilitated access to a website for hazardous drinkers compared to a standard face-to-face brief intervention (BI).

Design: Randomised 1:1 non-inferiority trial.

Setting: Practices of 58 General Practitioners (GPs) in Italy.

Participants: Of 9080 patients (>18yrs old) approached to take part in the trial 4529 (49·9%) logged on to the website and 3841 (84·8%) undertook online screening. 822 (21.4%) screened positive and 763 (19·9%) were recruited to the trial.

Interventions: Patients were randomised to receive either a face-to-face BI or to to access via their GP to an alcohol reduction website (facilitated access).

Primary and secondary outcome measures: The primary outcome is the cost per QALY gained of facilitated access compared to face-to-face. A secondary analysis includes total costs and benefits per 100 patients, including number of hazardous drinkers prevented at 12 months.

Results: The average time required for the face-to-face BI was 8 minutes (95% confidence interval (CI) 7.5 minutes to 8.6 minutes). Assuming facilitated access takes ~2 minutes, face-to-face is an additional 6 minutes: equivalent to having time for another GP appointment for every two patients referred to the website. Complete case analysis adjusting for baseline the difference in QALYs for facilitated access is 0.002 QALYs per patient (95% CI -0.007 to 0.011). Facilitated access dominated face-to-face with more QALYs and lower cost.

Conclusions: Facilitated access to a website to reduce hazardous drinking costs less than a face-to-face BI given by a GP, with better outcomes, although not significantly so. The lower cost of facilitated access, particularly in regards to investment of time, may facilitate the increase in provision of brief interventions for hazardous drinking in Italy.

Trial Registration: ClinicalTrials.org NCT: 01638338

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The cost-effectiveness analysis uses individual patient data to evaluate the short term costs and benefits of a way to increase the implementation of brief interventions for hazardous and harmful drinkers in Primary Care.
- Follow up rates exceeded 90% at 3 months and 80 % at 12 months
- Limited data was collected as part of the trial on time taken in standard Italian GP appointments and cost of a GP in Italy so assumptions based on data from the literature were required.
- The results were extrapolated to the English National Health Services (NHS), hence caution should be exercised interpreting these findings given differences between the Italian and English NHS.
- The results of the analysis are dependent on assumptions made regarding the number of patients that receive a face-to-face brief intervention or the number of patients that access the website.

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Introduction

Consumption of alcohol is a risk factor for premature mortality[1], with growing evidence of the significant negative health impact of alcohol consumption, including increased risk of cancer[2]. The World Health Organisation (WHO) has identified the European region as having the highest rates of alcohol related ill health across the globe[2]. Brief interventions have been found to be effective in reducing alcohol consumption in Primary Care populations[3] leading to recommendations for their implementation in Primary Care, including in the Italian National Guidelines[4]. Delivering a face-to-face standard brief intervention alongside screening the Italian population for hazardous drinking is potentially cost-effective to the Italian National Health Service (INHS), with the potential to prevent 7,200 alcohol related deaths over 30 years and 91,700 alcohol related hospitalisations[5]. Despite strong evidence of their potential benefit, the implementation of brief interventions in Primary Care across Europe has been limited[6]. This may be due to the significant upfront investment required to deliver face-to-face brief interventions in the form of GP or other Primary Care staff time, of which there is finite availability.

As a result an alternative approach may be required to deliver brief interventions in Primary Care, one that is less of a burden on GP and other clinical staff time and is easier to implement. Facilitated access to a website for alcohol reduction has the potential to provide similar benefits to a face-to-face brief intervention but potentially with a lower upfront investment in time and hence cost. Although there is evidence regarding the potential impact of brief interventions on reducing alcohol consumption and hence anticipated long term health benefits, there is less evidence for their impact on short term costs and health related quality of, particularly in an Italian primary health care setting[5]. This information is required to identify strategies to improve the implementation of brief interventions in the INHS.

The aim of this health economic evaluation is to evaluate the short term cost savings and potential additional short term benefits to the INHS of facilitated access to a website for hazardous and harmful drinkers compared to a standard face-to-face brief intervention (BI) over 12 months. Hazardous drinkers are defined as people with an alcohol consumption level that is potentially detrimental to their health and is measured using the Alcohol Use Disorders Identification Test (AUDIT)[7]. A secondary analysis of the potential cost savings to the English National Health System (NHS) is also included.

Methods

EFAR Trial

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EFAR-FVG is a randomised 1:1 trial, with the primary aim of testing for non-inferiority of a face-to-face brief intervention for hazardous and harmful drinkers delivered by a GP (face-to-face BI) compared to facilitated access to an interactive website for reducing hazardous and harmful drinking (facilitated access). GPs from the region of Northern Italy, Friuli-Venezia, were recruited via the official register for the region. Patients aged 18 years and over and who did not meet any of the exclusion criteria for the trial were recruited to the trial by being given a trial brochure and encouraged by their GP to access a healthy lifestyle website. Patients that accessed the website were asked to complete the short Alcohol Use Disorders Identification test (AUDIT-C)[8 9]. The AUDIT-C is comprised of three questions to identify probable hazardous or harmful drinking, with a lower threshold score of 5 for men and 4 for women. Patients scoring at the threshold and above on the AUDIT-C were advised of their risk via a personalised message from their GP and advised to enter the study. Following consent to the study patients completed baseline questionnaires and were randomised to face-to-face brief intervention or facilitated access to a version of the Down Your Drink Website (www.downyourdrink.org.uk) adapted for an Italian audience. Further details of the EFAR FVG trial[10] (Wallace et al in this issue) and Down Your Drink website[11] can be found elsewhere.

Costs

The aim of this analysis is to assess the short term resource impact of facilitated access to a website. There is unlikely to be a significant immediate health benefit to patients as a result of reductions in alcohol consumption given the long term impact and health risk of hazardous and harmful drinking. As a result the only resource use collected as part of the trial was time spent by GPs delivering the standard face-to-face brief intervention as this is likely to be the main source of cost-savings. GPs indicated if the face-to-face brief intervention took less than 5 minutes, 5 to 10 minutes or greater than 10 minutes. The cost per minute of a GP appointment was then multiplied by 5, 10 or 15 minutes for each patient to obtain the cost per patient of the face-to-face intervention. The time and cost of screening was not included given that it was assumed to be the same in both groups. GPs were also asked to report how long it took them to refer patients to the website.

Limited information is routinely collected in the INHS on the costs of health care services and as a result UK sources are commonly used as they contain more detailed information[5]. The cost of a GP appointment was taken from the Italian study published by Gerzeli et al (2014)[12] and was estimated at €11 an appointment for 2010 costs. No health care cost inflation index for Italy could be located so instead the UK health care cost inflation index was applied to bring the cost to 2013/2014 values[13] at €12 an appointment. Assuming an average appointment length of 11 minutes, this results in a

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cost per minute of €1.09. This value is also similar to the value used by Angus et al (2014)[5] of €1.07 per minute in 2008.

The primary analysis for costs is from the Italian health care perspective. A secondary analysis evaluating the potential cost-savings for the UK National Health Service (NHS) costs has also been conducted to provide hypothetical information on the probability the intervention is cost-effective in the UK. As reported in the PPSRU[13] the average duration of a GP appointment in the UK is 11 minutes at a cost of £46.

All GPs attended a 1 day training session for the delivery of a face-to-face brief intervention for hazardous and harmful drinking using motivational interviewing, with an average cost per GP participant of €51 for the cost of trainers, resources and room hire. The cost of an honorarium and travel costs for experts leading the training (€10 971), and cost of the GP's time attending the training (at €458 per GP per day) was also included in the cost of training.

The cost of adapting the website was collected as part of the trial at a total cost of €35 000. GPs were asked to familiarise themselves with use of the website prior to start of the trial at a cost per GP of €65.

Quality Adjusted Life Years (QALYs)

Implementation of new interventions into a health care system tends to require investment in terms of the cost of implementation and/or the additional cost of the intervention. To help decision makers decide which interventions represent value for money and hence should be invested in there needs to be an equitable and standardised way to compare costs and the potential health benefits of new interventions across programmes of work and disease areas. The standard approach in most developed countries with a publicly financed health care system is to calculate the additional quality adjusted life years (QALYs) generated from the new intervention compared to the status quo. QALYs represent a measure of mortality and morbidity over time, anchored at 1 for perfect health and 0 for death, with 1 year spent in perfect health equal to 1 QALY. The cost of the new intervention compared to status quo is divided by the additional QALYs generated to calculate the cost per QALY gained, with a lower cost to QALY ratio being preferable, or the new intervention dominating the status quo by resulting in more QALYs for less cost. The EuroQol EQ-5D[14] and its associated preference based tariff[15] is the most common way to calculate QALYs in most developed countries.

Euroqol EQ-5D 5 level (EQ-5D-5L)[16] was administered to all patients in the trial to complete at baseline, 3 months and 12 months. Patients were asked to complete questionnaires online in the first instance, but for some patients questionnaires were completed over the phone following

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multiple attempts to contact the patient to complete the questionnaire online. The 5-level version of the EQ-5D was chosen given recent evidence of a reduced ceiling effect compared to the 3-level[17]. Time-trade off values for the EQ-5D-5L were used to calculate patient level utility tariffs. As no Italian weights are currently available in the cross-walk or time-trade off value sets for the EQ-5D-5L, the time-trade off algorithm for the UK was applied[18].

Patient level QALYs were calculated from baseline, 3 month and 12 month patient level utility scores, adjusting for timing of follow-ups to calculate the area under the curve. Adjustments though were not patient specific, and were counted specifically as 3 months and 12 months regardless of when the patient actually completed the questionnaire so as not to introduce bias from delayed responses. As responses at all three time points are required to calculate QALYs, values reported are for complete case analysis (patients that have complete EQ-5D-5L responses for all 3 time points). The mean QALYs per patient reported have been adjusted for baseline values using regression analysis[19]. Confidence intervals are from 1000 bootstrap replications.

Cases of hazardous or harmful drinking prevented

As hazardous drinkers also include a generally healthy population, with potential QALY losses occurring in the far future as a result of future chronic alcohol related health problems, the EQ-5D has been found to be insensitive to changes in hazardous drinking at the point of behaviour change for risk reduction[20]. As a result additional analyses of costs versus cases of hazardous or harmful drinking prevented have been included. Patients completed the 10 question version of the AUDIT (AUDIT-10) at baseline, 3 months and 6 months, with hazardous or harmful drinking defined as a score ≥8. Cases of hazardous or harmful drinking prevented at 12 months have been calculated using the data from the main paper for the trial using AUDIT-10 data at 12 months (Wallace et al in this issue). This was converted to cases prevented per 1000 patients by calculating the percentage of patients that are hazardous or harmful drinkers at 12 months in the face-to-face intervention, changing this to a rate per 1000 patient years and applying the odds ratio reported in the main clinical paper (Wallace et al in this issue) for 12 months.

Sensitivity analysis: missing data

It was assumed that data at follow-up time points was missing at random. Additional analyses have been conducted using alternative ways to account for missing data in QALYs. This includes an available case analysis using all data collected, not just complete cases to calculate QALYs and calculating QALYs imputing missing data using chained equations as recommended in Hunter et al (2015)[21].

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Cost effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

Results from the bootstrapped, complete case, QALYs were used to populate the CEP and CEAC.

To represent the uncertainty in costs the average duration of the appointment was calculated using the proportion of patients that had appointments of different lengths and the Dirichlet process[22]. The cost was varied using a random number generated in Excel and the gamma distribution assuming that the standard error is equal to the mean cost of an appointment (€12 for IHNS and £46 in the UK). An average cost per appointment was then generated for each of the 1000 simulated iterations and for Italian and UK costs.

No discount rate was applied to the analysis given the 12 month time horizon.

Hypothesis testing

Given the hypothesis of non-inferiority between the two groups as the primary analysis for the trial, it was assumed that there would be no difference in QALYs or cases of hazardous or harmful drinking between the two groups. Instead the analysis focuses on the potential benefit per 1000 patients with facilitated access to the alcohol reduction website compared to a brief face-to-face intervention. As no information of the average GP appointment duration in Italy is available it has been assumed that the average appointment duration in Italy is similar to that of the UK of 11 minutes.

Results

Patient numbers and loss to follow-up for the trial are reported in Figure 1. Further patient demographics can be found in the main trial findings paper (Wallace et al in this issue).

Costs

Of the 416 patients allocated to the face to face BI group, 304 (73%) received the intervention from their GP. Information on the duration of each BI was recorded by the GPs using a questionnaire with 3 options: less than 5 minutes, 5-10 minutes, more than 10 minutes. The percentage of patients for each recorded appointment duration is reported in Table 1. The average time required for the face-to-face intervention is 8 minutes (95% confidence interval 7.5 minutes to 8.6 minutes). GPs reported that the time spent facilitating access to the website was negligible as it required handing over a leaflet only and providing a quick description of what was involved, with the maximum time spent of 2 minutes. Based on this we made the conservative estimate that facilitated access required 2

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minutes of a GP's time. The difference of 6 minutes between the two groups is equivalent to having time for another appointment for every two patients referred to the website.

Table 1. Recorded duration of appointments for face to face (n= 304)

Duration	Number of patients	Percentage
Less than 5 minutes	171	56.3%
5 to 10 minutes	87	28.6%
Greater than 10 minutes	46	15.1%

The average cost per patient of a face-to-face BI, including patients randomised to face-to-face BI but who did not receive the face-to-face appointment was €6,98 per patient (95% CI €6,44 to €7,53). If patients who did not receive the face-to-face BI are excluded from the analysis the average cost is €9,53 per patient (95% CI €9,03 to €10,03).

The average cost per GP of training to deliver the face-to-face BI was €698. The cost per patient of training for face-to-face BI is dependent on how many interventions each GP delivers. Assuming that GPs could have provided a face-to-face BI to patients in either group, the total number of interventions they could have provided was 763, or 13 patients per GP resulting in an average cost per patient of €54 for training for face-to-face BI.

Assuming 763 patients would also receive facilitated access the total cost per patient of updating the website and GPs familiarising themselves with the website is €61. Arguably an unlimited number of patients could access the website. This would reduce the cost per patient to €5 if the cost of the GP familiarisation with the website only is included.

In the most conservative scenario of €6,98 per face-to-face appointment, 2 minutes for facilitated access and an additional cost per patient of updating the website compared to training of €7, facilitated access costs an additional €2,20 per patient. Assuming €9,53 per patient for a face-to-face appointment and that the cost to update the website is included as either a sunk cost or considered negligible as a per patient cost due to the potential for unlimited access, facilitated access results in a cost saving of €57 per patient.

Utility scores and QALYs

The results for mean complete case analysis for utility scores and QALYs are reported in Table 2.

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There was no significant difference in QALYs between facilitated access to the website and the face-to-face BI. Complete case analysis and adjusting for baseline the difference in QALYs for facilitated access minus face-to-face BI was 0.002 per patient (95% confidence interval (CI) -0.007 to 0.011). At a willingness to pay (WTP) of €25 000 per QALY gained, as recommended by the INHS[23], facilitated access could cost an additional €50 per patient on average compared to face to face BI and be considered cost-effective. At the lower end of the CI where facilitated access results in a QALY decrement of -0.007 QALYs over 1 year facilitated access would need to save €175 per patient to be cost-effective. The difference in utility scores and QALYs is described in table 3.

QALYs calculated using available cases (using all values regardless of if a patient has a missing value at a follow-up point) and using multiple imputation for missing values results in marginally smaller QALY gains compared to complete case analysis (Table 3).

Table 2. Utility scores and QALYs (complete case analysis adjusting for baseline differences in utility scores for QALY calculation)

Time period	Face to face	Facilitated Access
Number (complete case)	n=331	n=275
Baseline mean (STD)	0.919 (.09)	0.916 (.10)
3 months mean (STD)	0.942 (.08)	0.944 (.08)
12 months mean (STD)	0.941 (.08)	0.941 (.08)
QALYs (baseline adjusted) mean (SE)	0.938 (.003)	0.940 (.003)

STD = standard deviation SE= standard error

Table 3. Difference in health utility at 3 months and 12 months and adjusted difference in QALYs (complete case analysis)

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Complete Case				
3 month EQ-5D-5L	0.003	-0.010	0.013	0.658
12 month EQ5D 5L	-0.0003	-0.013	0.012	0.960
QALYS (adjusted)	0.002	-0.007	0.01	0.622
Available Case				
3 month EQ-5D-5L	0.0006	-0.011	0.012	0.914
12 month EQ5D 5L	0.0004	-0.013	0.013	0.955
QALYS (from means)	0.0003			

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Multiple Imputation				
3 month EQ-5D-5L	0.0006	-0.010	0.012	0.913
12 month EQ5D 5L	0.0005	-0.012	0.013	0.935
QALYS (adjusted)	0.0006	-0.009	0.01	0.901

Cost effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

Results of the CEP and CEAC are reported in Figure 2. At a willingness to pay for a QALY of 25,000 (Euros and British Pounds) there is a 72% probability that facilitated access is cost-effective compared to face-to-face BI for GP appointment costs only, 70% if the cost of training for face-to-face BI and updating the website is included and 86% if the cost of training for face-to-face BI is included but it is assumed the cost of updating the website is a sunk cost or becomes zero as an unlimited number of patients can access the website. There is a 78% probability that the website is cost-effective compared to face-to-face BI if UK NHS costs are used and appointment costs only are included.

Benefits per 1000 patients referred

The results from the AUDIT analysis are reported in the clinical paper (Wallace et al in this issue). At 12 months there was no significant difference between two groups in the number of hazardous or harmful drinkers with an odds ratio of 0.94 (95% CI 1.432 to 0.621). At 12 months of the patients randomised to face-to-face BI 26.3% were hazardous or harmful drinkers (AUDIT-10 ≥ 8) or 263 patients per 1000. Change this to a rate of 263 patients per 1000 patient years and applying an odds ratio of 0.94, 18 patients per 1000 patient years are prevented from hazardous or harmful drinking if they were given facilitated access instead of a face-to-face BI. This is in addition to time for an additional 545 appointments and 2 QALYs gained (95% CI -7 to 11).

Question 10 in the AUDIT-10 asks patients if a health care professional has recommended that they reduce their drinking. Potentially as a result of the nature of the intervention (a GP discussing their drinking with them) this was the question most frequently with a score above 0 compared to other questions on the AUDIT. In the face-to-face group 40% of patients answered greater than 0 to question 10 and 31% in the intervention group at 12 months. If this is taken into account and a lower threshold of 7 for hazardous drinking applied, 16% of patients fall above the threshold for risky drinking in the face-to-face group and 18% in the facilitated access group with an odds ratio of 1.9 (95% CI 1 to 3.7). This equates to 158 additional hazardous or harmful drinkers per 1000 patient years for facilitated access compared to face-to-face BI. Facilitated access also results in a cost-

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saving in the cost of GP time of €7180 or €45 per additional hazardous or harmful drinker. This saving is likely to be significantly less than the lifetime cost of a hazardous or harmful drinker to the INHS.

Discussion

Our findings indicate that in the INHS system, the chance that facilitated access to a website to reduce hazardous drinking is cost-effective compared to a face-to-face BI delivered by a GP is between 70% and 86%. This could be as high as 78% in the UK NHS, given the greater cost per GP appointment. However these numbers are dependent on assumptions made about the number of patients given facilitated access versus those given a face-to-face BI given the high up-front costs of website modification or training, respectively. The costs per patient decrease as more patients access each treatment.

Although no data on the long term benefits was included as part of this trial other modelling studies in Italy have looked at the potential long term benefits of BIs. Angus et al (2014)[5] modelled screening of the adult Italian population and providing a standard brief intervention for those identified as hazardous drinkers over 10 years. They estimated that 32% of population receive the intervention at a cost of €411 million, with a potential cost saving of €370 million and a QALY gain of 75,200. This translates to an incremental cost-effectiveness ration (ICER) of 550 per QALY gained. Given that facilitated access to a website costs significantly less than the standard brief intervention across a whole population it is likely that population level screening for hazardous drinking and a facilitated access to a website is potentially cost-saving. The lower cost in terms of time required of facilitated access compared to face-to-face may also increase the probability that brief interventions are implemented in the INHS.

Strengths and weaknesses

Limited resource use data was collected as part of the trial. In particular there was no data on what impact access to the website had on follow-up GP appointments. If patients had concerns about the information they accessed on the website it is the possible that they went to see their GP for additional advice, representing an additional cost that was not included in this analysis. Conversely, any cost savings as a result of prevention of alcohol related admissions were not captured as part of this study. If the wider costs to society beyond health care are considered the cost to the economy of productivity losses as a result of alcohol related days off work and loss of productivity were also not considered. A trial of an online brief intervention implemented in the work place found that the intervention group were less likely to have sick leave and for less days in total, although not

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significantly so[24]. This though represents an important consideration for inclusion for trials in this area and population group.

Obtaining high quality information on the cost of GP time in Italy was challenging, with availability only of limited information on GP time and costs and no published national costs[5]. As a result there is limited information to use for costing. However, the two sources used to cost GP time resulted in a similar value per minute of GP time suggesting consistency in the way GP time is costed in Italy.

We have used data from the English NHS to estimate the potential cost-effectiveness of the intervention in a UK Primary Care population. Previous trials of online interventions for reducing hazardous drinking in the UK have found it challenging to achieve high enough rates of follow-up to enable reliable measurement of effectiveness and cost-effectiveness.[20] There is no evidence that there would be a similar level of effectiveness of facilitated access compared to face-to-face BI in the UK, but the cost savings are likely to be similar to those projected here if GPs take a similar amount of time to conduct a brief intervention.

The use of the AUDIT-10 as an outcome measure to measure the effectiveness of treatments for hazardous or harmful drinking is questionable. This is due to the problem with question 10 in the AUDIT which asks whether a health care professional has suggested reducing drinking. This is more likely to receive a positive response for patients screened for hazardous drinking and provided with any form of intervention – face-to-face BI or facilitated access. Advice is potentially more memorable at face-to-face BI and hence the reversal of results when this question was removed. This is discussed further in the main clinical paper (Wallace et al in this issue)

Conclusions

There is a high probability that facilitated access to a website to reduce alcohol consumption could deliver more benefits for fewer resources given that it costs less than the standard face-to-face BI. Additional benefits may also include an increase in the rates of delivery of brief intervention via facilitated access given the lower time requirement for GPs compared to face-to-face BI.

Word Count: 4,164

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Contributors:

PW, PS and RDV conceived the study and together with NF developed the design. PS, PW, RDV, CT, CL and RMcG were responsible for the development of the website, and PS, FS, RDV, CT were responsible for follow up of patients. RH was responsible for the analysis with the oversight of NF. RH wrote the first draft, and authors PW, PS, PDV, FS, CT, CL RMcG, ES and NF contributed to its revision and final approval.

Declaration of interests:

PW has intellectual property rights for www.downyourdrink.org.uk, is Chief Medical Advisor to the UK charity Drinkaware and has provided private consultancy on the topic of screening and brief interventions to several agencies. CL is the cofounder and Chief Executive Officer at Lumos Medica Srl, which provides software solutions for clinical trials. The other authors declare no competing interests.

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Ethics Approval:
Ethical Committee of the Azienda Sanitaria 4 Medio Friuli,Udine, IT. The protocol was approved on 14 June 2012 by the Independent Local Ethics Committee for Clinical Research of the Health Services Agency No 2 Isontina, Italy.

Data Sharing Agreement:
Anonymised trial data is held on secure servers at University College London. For access to the data please contact the corresponding author. Access will be granted subject to approval by the steering committee.

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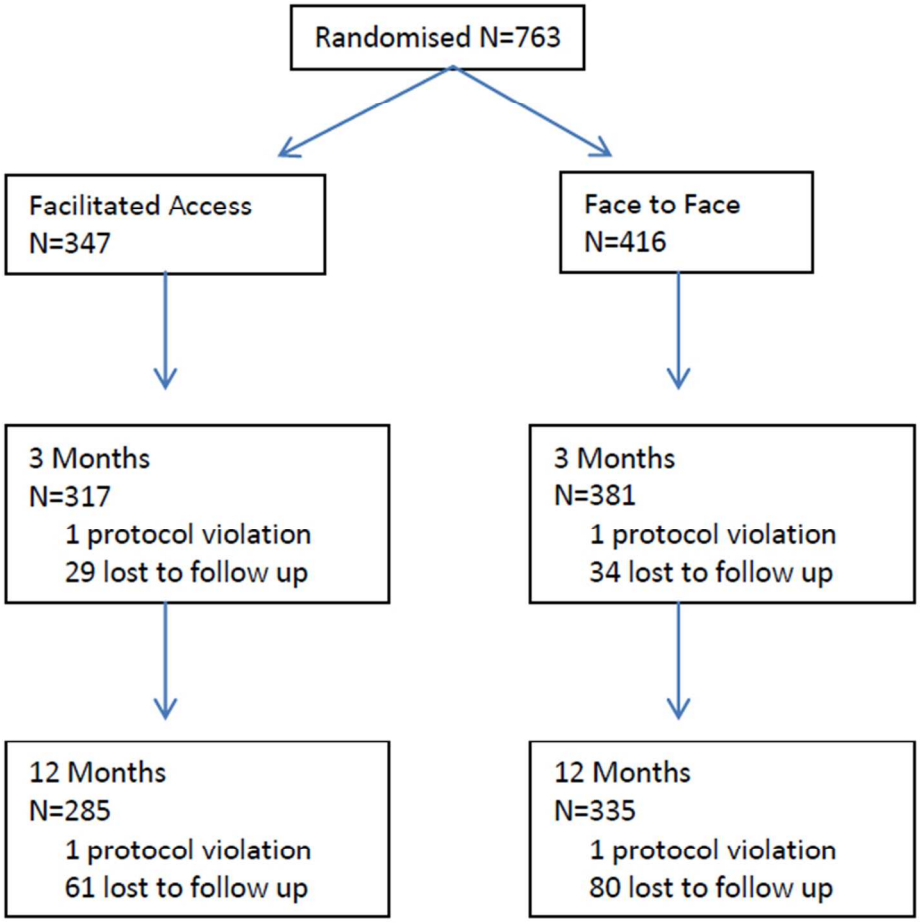

Figure 1: Patient progress through trial for the primary outcome

242x232mm (72 x 72 DPI)

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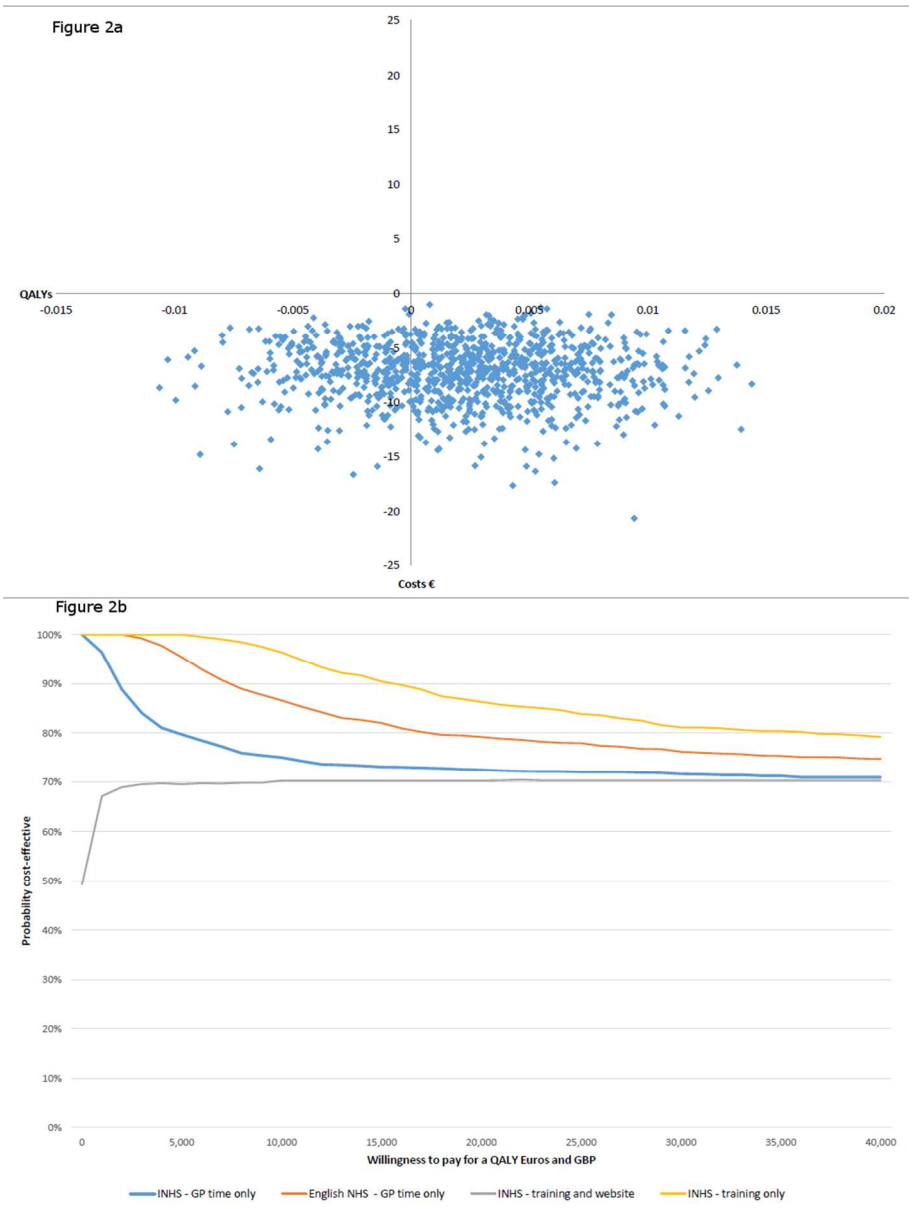

Figure 2: Cost-effectiveness plane of INHS GP costs only (2a) and cost-effectiveness acceptability curves (2b).

372x493mm (72 x 72 DPI)

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The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

BJOG: An International Journal of Obstetrics and Gynaecology
BMC Medicine 2013; 11:80
BMJ 2013;346:f1049
Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)
Cost Effectiveness and Resource Allocation 2013 11:6.
The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
International Journal of Technology Assessment in Health Care
Journal of Medical Economics 2013 Mar 25. [Epub ahead of print]
Pharmacoeconomics 2013 Mar 26. [Epub ahead of print]
Value in Health 2013 March - April;16(2):e1-e5

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and	

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		outcomes and say why appropriate.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.

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Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

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BMJ Open

Cost-effectiveness analysis of EFAR-FVG: A randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website

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Cost-effectiveness analysis of EFAR-FVG: A randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website

Authors:

Rachael Hunter[1], Paul Wallace[1], Pierluigi Struzzo[2-4], Roberto Della Vedova[3], Francesca Scafuri[2], Costanza Tersar[4], Charilaos Lygidakis[5], Richard McGregor[6], Emanuele Scafato[7], Nick Freemantle[1]

Institutional affiliations:

[1]Department of Primary Care and Population Health, University College London, London, UK

[2]Regional Centre for Training in Primary Care, Monfalcone (GO) Italy

[3] CSeRMEG, Centro Studi e Ricerche in Medicina Generale, Italy

[4] University of Trieste, Life Sciences Department, Italy

[5] Institute for Health and Behaviour - Research Unit INSIDE, Université du Luxembourg, Luxembourg

[6] Codeface Ltd, Hove, UK

[7] Istituto Superiore di Sanità, WHO Collaborating Centre for Research and Health Promotion on Alcohol and Alcohol-Related Health Problems,

Corresponding author: Rachael Hunter, Department of Primary Care and Population Health, University College London, London, UK r.hunter@ucl.ac.uk, tel: +44 (0)20 830 2338

Collaborative group list-The EFAR Study Team:

Giosué Acampora, Maria Angela Bravo, Chiara Bregant, Gianna Bunello, Leonardo Butà, Lucia Casatta, Castellarin, Egidio Chamouni, Moshé Benyamin, Maria Pia Cisilin, Clemente Condello, Nelly Drigani, Tiziano Ermacora, Alessandro Falcidia, Adriana Fasiolo, Angelo Florio, Mauro Gubiani, Gianni Iacuzzo, Edi Ietri, Giuseppe Latella, Guglielmo Lucca, Ciro Mamolo, Carmelo Matera, Lucia Mei, Francesca Melon, Emilio Mezzasalma, Isabella Milan, Carlo Miotti, Gian Franco Panizzo, Francesca Pighin, Raffaela Principato, Pierina Revignas, Antonella Rolff, Ivana Rupalti, Rosanna Sellibara, Michela Sereni, Gianfranco Silverii, Giuseppe Taglialatela, Chiara Toffoletti, Massimo Toffolo, Laura Ivana Tonelli, Simone Trevisani, Roberto Troisi, Gianni Tubaro, Roberto Vallini, Elisabetta Zappalà, Antonio Zappi.

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Abstract

Objectives: To evaluate the 12 month costs and quality adjusted life years (QALYs) gained to the Italian National Health Service (INHS) of facilitated access to a website for hazardous drinkers compared to a standard face-to-face brief intervention (BI).

Design: Randomised 1:1 non-inferiority trial.

Setting: Practices of 58 General Practitioners (GPs) in Italy.

Participants: Of 9080 patients (>18yrs old) approached to take part in the trial 4529 (49·9%) logged on to the website and 3841 (84·8%) undertook online screening for hazardous drinking. 822 (21.4%) screened positive and 763 (19·9%) were recruited to the trial.

Interventions: Patients were randomised to receive either a face-to-face BI or access via a brochure from their GP, to an alcohol reduction website (facilitated access).

Primary and secondary outcome measures: The primary outcome is the cost per QALY gained of facilitated access compared to face-to-face. A secondary analysis includes total costs and benefits per 100 patients, including number of hazardous drinkers prevented at 12 months.

Results: The average time required for the face-to-face BI was 8 minutes (95% confidence interval (CI) 7.5 minutes to 8.6 minutes). Given the maximum time taken for facilitated access of 5 minutes, face-to-face is an additional 3 minutes: equivalent to having time for another GP appointment for every two patients referred to the website. Complete case analysis adjusting for baseline the difference in QALYs for facilitated access is 0.002 QALYs per patient (95% CI -0.007 to 0.011). .

Conclusions: Facilitated access to a website to reduce hazardous drinking costs less than a face-to-face BI given by a GP with no worse outcomes. The lower cost of facilitated access, particularly in regards to investment of time, may facilitate the increase in provision of brief interventions for hazardous drinking.

Trial Registration: ClinicalTrials.org NCT: 01638338

Funding: The study was jointly supported by the Italian Ministry of Health and by the Region Friuli-Venezia Giulia, Italy (grant number: D25E12002900003).

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The cost-effectiveness analysis uses individual patient data to evaluate the short term costs and benefits of a way to increase the implementation of brief interventions for hazardous and harmful drinkers in Primary Care.
- Follow up rates exceeded 90% at 3 months and 80 % at 12 months
- Limited data was collected as part of the trial on time taken in standard Italian GP appointments and cost of a GP in Italy so assumptions based on data from the literature were required.
- The results were extrapolated to the English National Health Services (NHS), hence caution should be exercised interpreting these findings given differences between the Italian and English NHS.
- The results of the analysis are dependent on assumptions made regarding the number of patients that receive a face-to-face brief intervention or the number of patients that access the website.

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Introduction

Consumption of alcohol is a risk factor for premature mortality[1], with growing evidence of the significant negative health impact of alcohol consumption, including increased risk of cancer[2]. The World Health Organisation (WHO) has identified the European region as having the highest rates of alcohol related ill health across the globe[2]. Brief interventions have been found to be effective in reducing alcohol consumption in Primary Care populations[3] leading to recommendations for their implementation in Primary Care, including in the Italian National Guidelines[4]. Delivering a face-to-face standard brief intervention alongside screening the Italian population for hazardous drinking is potentially cost-effective to the Italian National Health Service (INHS), with the potential to prevent 7,200 alcohol related deaths over 30 years and 91,700 alcohol related hospitalisations[5]. Despite strong evidence of their potential benefit, the implementation of brief interventions in Primary Care across Europe has been limited[6]. This may be due to the significant upfront investment required to deliver face-to-face brief interventions in the form of GP or other Primary Care staff time, of which there is finite availability.

As a result an alternative approach may be required to deliver brief interventions in Primary Care, one that is less of a burden on clinician time and is easier to implement. Facilitated access, where a clinician directs patients to a website for alcohol reduction, has the potential to provide similar benefits to a face-to-face brief intervention but potentially with a lower upfront investment in time and hence cost. Although there is evidence regarding the potential impact of brief interventions on reducing alcohol consumption and hence anticipated long term health benefits, there is less evidence for their impact on short term costs and health related quality of, particularly in an Italian primary health care setting[5]. This information is required to identify strategies to improve the implementation of brief interventions in the INHS.

The aim of this health economic evaluation is to evaluate the short term cost savings to the INHS of facilitated access to a website for hazardous and harmful drinkers compared to a standard face-to-face brief intervention (BI) over 12 months. Hazardous drinkers are defined as people with an alcohol consumption level that is potentially detrimental to their health and is measured using the Alcohol Use Disorders Identification Test (AUDIT)[7]. These will be reported alongside potential benefits. Face-to-face BI for hazardous drinking has been recommended for widespread implementation in the English National Health System (NHS), but that evidence suggests this has not happened.[6] We have therefore included a secondary analysis of the potential cost savings to the English NHS of facilitated access to a website to provide additional information to NHS policy makers.

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Methods

EFAR Trial

EFAR-FVG is a randomised 1:1 trial, with the primary aim of testing for non-inferiority of a face-to-face brief intervention for hazardous and harmful drinkers delivered by a GP (face-to-face BI) compared to facilitated access to an interactive website for reducing hazardous and harmful drinking (facilitated access). GPs from the region of Northern Italy, Friuli-Venezia, were recruited via the official register for the region. Patients aged 18 years and over and who did not meet any of the exclusion criteria for the trial were recruited to the trial by being given a trial brochure and encouraged by their GP to access a healthy lifestyle website. Patients that accessed the website were asked to complete the short Alcohol Use Disorders Identification test (AUDIT-C)[8 9]. The AUDIT-C is comprised of three questions to identify probable hazardous or harmful drinking, with a lower threshold score of 5 for men and 4 for women. Patients scoring at the threshold and above on the AUDIT-C were advised of their risk via a personalised message from their GP and advised to enter the study. Following consent to the study patients completed baseline questionnaires and were randomised to face-to-face brief intervention or facilitated access (the GP gives the patient a leaflet that directs them to the website) to a version of the Down Your Drink Website (www.downyourdrink.org.uk) adapted for an Italian audience. Further details of the EFAR FVG trial[10] (Wallace et al in this issue) and Down Your Drink website[11] can be found elsewhere.

Costs

The aim of this analysis is to assess the short term resource impact of facilitated access to a website. There is unlikely to be a significant immediate health benefit to patients as a result of reductions in alcohol consumption given the long term impact and health risk of hazardous and harmful drinking. As a result the only resource use collected as part of the trial was time spent by GPs delivering the standard face-to-face brief intervention as this is likely to be the main source of cost-savings. GPs indicated if the face-to-face brief intervention took less than 5 minutes, 5 to 10 minutes or greater than 10 minutes. The cost per minute of a GP appointment was then multiplied by 5, 10 or 15 minutes for each patient to obtain the cost per patient of the face-to-face intervention. The time and cost of screening was not included given that it was assumed to be the same in both groups. GPs were also asked to report how long it took them to refer patients to the website.

The cost of a GP appointment was taken from the Italian study published by Gerzeli et al (2014)[12] and was estimated at €11 an appointment for 2010 costs. No health care cost inflation index for Italy could be located so instead the English health care cost inflation index was applied to bring the cost

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to 2015/2016 values[13] at €12 an appointment. Assuming an average appointment length of 9 minutes[14], this equates to a cost per minute of €1.27.The primary analysis for costs is from the Italian health care perspective. A secondary analysis evaluating the potential cost-savings for the English NHS costs has also been conducted to provide hypothetical information on the probability the intervention is cost-effective in England. As reported in Hobbs[14] study of 101.8 million GP consultations carried out in English GPs, the average duration of a GP appointment in England is 9.2 minutes at a cost of £31[13]. The significantly higher cost of GP time in the English NHS compared to INHS is likely to be a result of higher salaries and overhead costs in the English NHS.

All GPs attended a 1 day training session for the delivery of a face-to-face brief intervention for hazardous and harmful drinking using motivational interviewing, with an average cost per GP participant of €51 for the cost of trainers, resources and room hire. The cost of an honorarium and travel costs for experts leading the training (€10 971), and cost of the GP's time attending the training (at €533 per GP per day) was also included in the cost of training.

The cost of adapting the website was collected as part of the trial at a total cost of €35 000. GPs were asked to familiarise themselves with use of the website prior to start of the trial at a cost per GP of €76.

Quality Adjusted Life Years (QALYs)

QALYs represent a measure of mortality and morbidity over time, anchored at 1 for perfect health and 0 for death, with 1 year spent in perfect health equal to 1 QALY. They are used to assist health care policy makers with decisions about the implementation of new interventions in health care in an equitable and standardised way. . The cost of the new intervention minus e current practice is divided by the additional QALYs generated by the new intervention to calculate the cost per QALY gained, with a lower mean cost per QALY being preferable. The new intervention might also dominate current practice by resulting in more QALYs for a lower average cost per patient. The EuroQol EQ-5D[15] and its associated preference based tariff[16] is the most common way to calculate QALYs in most developed countries.

Euroqol EQ-5D 5 level (EQ-5D-5L)[17] was administered to all patients in the trial to complete at baseline, 3 months and 12 months. Patients were asked to complete questionnaires online in the first instance, but for some patients questionnaires were completed over the phone following multiple attempts to contact the patient to complete the questionnaire online. The 5-level version of the EQ-5D was chosen given recent evidence of a reduced ceiling effect compared to the 3-level[18]. Time-trade off values for the EQ-5D-5L were used to calculate patient level utility tariffs. As no

Italian weights are currently available in the cross-walk or time-trade off value sets for the EQ-5D-5L, the time-trade off algorithm for the UK was applied[19].

Patient level QALYs were calculated from baseline, 3 month and 12 month patient level utility scores, adjusting for timing of follow-ups to calculate the area under the curve. Adjustments though were not patient specific, and were counted specifically as 3 months and 12 months regardless of when the patient actually completed the questionnaire so as not to introduce bias from delayed responses. As responses at all three time points are required to calculate QALYs, values reported are for complete case analysis (patients that have complete EQ-5D-5L responses for all 3 time points). The mean QALYs per patient reported have been adjusted for baseline EQ-5D-5L utility values using linear regression analysis and including a co-efficient for randomisation[20]. Confidence intervals (CIs) are from 1000 bootstrap replications.

Cases of hazardous or harmful drinking prevented

As hazardous drinkers also include a generally healthy population, with potential QALY losses occurring in the far future as a result of future chronic alcohol related health problems, the EQ-5D has been found to be insensitive to changes in hazardous drinking at the point of behaviour change for risk reduction[21]. As a result additional analyses of costs versus cases of hazardous or harmful drinking prevented have been included. Patients completed the 10 question version of the AUDIT (AUDIT-10) at baseline, 3 months and 12 months, with hazardous or harmful drinking defined as a score ≥8. Cases of hazardous or harmful drinking prevented at 12 months have been calculated using the data from the main paper for the trial using AUDIT-10 data at 12 months [22]. This was converted to cases prevented per 1000 patients by calculating the percentage of patients that are hazardous or harmful drinkers at 12 months in the face-to-face intervention, changing this to a rate per 1000 patient years and applying the odds ratio reported in the main clinical paper[22] for 12 months.

Sensitivity analysis: missing data

It was assumed that data at follow-up time points was missing at random. Additional analyses have been conducted using alternative ways to account for missing data in QALYs. This includes an incomplete case analysis using all data collected, not just complete cases, to calculate QALYs and calculating QALYs imputing missing data using chained equations as recommended in Hunter et al (2015)[23].

Cost effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

Results from the bootstrapped, complete case, QALYs were used to generate the CEP and CEAC.

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To represent the uncertainty in costs the average duration of the appointment was calculated using the proportion of patients that had appointments of different lengths and the Dirichlet process[24]. The cost was varied using a random number generated in Excel and the gamma distribution assuming that the standard error is equal to the mean cost of an appointment (€12 for IHNS and £31 in the UK). An average cost per appointment was then generated for each of the 1000 simulated iterations and for Italian and UK costs.

The CEAC is calculated using the formula $(\beta_1)WTP-(C_1-C_2)$, where β_1 is the beta co-efficient for the treatment effect from one of the iterations of the bootstrapped linear regressions adjusting for baseline EQ-5D-5L utility scores, WTP is the willingness to pay for a QALY gained, $C_1$is the average cost per patient of facilitated access and C_2 is cost of the average cost per patient of the face-to-face BI. The probability that facilitated access to cost-effective compared to the face-to-face BI for a given WTP for a QALY is based on the proportion of times the formula is positive from the 1000 bootstrap iterations combined with the 1000 simulated iterations.

No discount rate was applied to the analysis given the 12 month time horizon.

Hypothesis testing

Given the hypothesis of non-inferiority between the two groups as the primary analysis for the trial, it was assumed that there would be no difference in QALYs or cases of hazardous or harmful drinking between the two groups. Instead the analysis focuses on the potential benefit per 1000 patients with facilitated access to the alcohol reduction website compared to a brief face-to-face intervention. As no information of the average GP appointment duration in Italy is available it has been assumed that the average appointment duration in Italy is similar to that of the English NHSof 9 minutes.

Results

Patient numbers and loss to follow-up for the trial are reported in Figure 1. Further patient demographics can be found in the main trial findings paper[22].

Costs

Of the 416 patients allocated to the face to face BI group, 304 (73%) received the intervention from their GP. Information on the duration of each BI was recorded by the GPs using a questionnaire. For 171 patients (56.3%) the BI took less than 5 minutes, 5 to 10 minutes for 87 patients (28.6%) and

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more than 10 minutes for 46 patients (15.1%). The average time required for the face-to-face BI is 8 minutes (95% confidence interval (CI) 7.5 minutes to 8.6 minutes). The amount of time spent facilitating access to the website was less than 5 minutes. Based on this we made the conservative estimate that facilitated access required 5 minutes of a GP's time. The difference of 3 minutes between the two groups is equivalent to having time for another appointment for every three patients referred to the website.

The average cost per patient of a face-to-face BI, including patients randomised to face-to-face BI but who did not receive the face-to-face appointment was €10,16 per patient (95% CI €9,53 to €10,92). If patients who did not receive the face-to-face BI are excluded from the analysis the average cost is €11,10 per patient (95% CI €10,52 to €11,69).

The average cost per GP of training to deliver the face-to-face BI was €774. The cost per patient of training for face-to-face BI is dependent on how patients the GP delivers a face-to-face BI to. Assuming that GPs could have provided a face-to-face BI to patients in either group, the total number of interventions they could have provided was 763, or 13 patients per GP resulting in an average cost per patient of €60 for training for face-to-face BI.

The total cost of website development and piloting was €45 410. Assuming 763 patients received facilitated access, the cost per patient of the website is €60,23. Each patient was also given a leaflet from the GP directing them to the website at a total cost per patient of €0,51. In the most conservative scenario of €70 per patient for face-to-face BI (€60 for training and €10,16 for the GP time to deliver the BI) and facilitated access costs €68 per patient (5 minutes for facilitated access and an additional cost per patient of updating the website of €62) , facilitated access costs €2 less per patient compared to face-to-face BI.

In the least conservative estimate we assume that the cost of the website approaches zero given that there is no upper limit to the number of patients that could feasibly access the website. Instead the only costs for facilitated access are the cost of the leaflet (€0,51 per patient), GP time referring patients to the website (5 minutes at a cost of €6,35 per patient) and time spent familiarising themselves with the website (€5,86). In the least conservative estimate we assume that the cost per patient for face-to-face BI is €64 (€60 for training and €11,10 for the GP time to deliver the BI) and facilitated access costs €13 per patient (5 minutes for facilitated access and an additional cost of the leaflet and GPs time familiarise themselves with the website of €6,37) facilitated access results in a cost saving of €51 compared to face-to-face BI.

Utility scores and QALYs

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The results for mean complete case analysis for utility scores and QALYs are reported in Table 1.

There was no significant difference in QALYs between facilitated access to the website and the face-to-face BI. Complete case analysis and adjusting for baseline the difference in QALYs for facilitated access minus face-to-face BI was 0.002 per patient (95% CI -0.007 to 0.011). At a willingness to pay (WTP) of €25 000 per QALY gained, as recommended by the INHS[25], facilitated access could cost an additional €50 per patient on average compared to face to face BI and be considered cost-effective. At the lower end of the CI where facilitated access results in a QALY decrement of -0.007 QALYs over 1 year facilitated access would need to save €175 per patient to be cost-effective. The difference in utility scores and QALYs is described in table 2. Based on the results of the multiple imputation analysis, facilitated access can cost an additional €15 compared to face-to-face BI and be considered cost effective (95% CI -€225 to €250)

Table 1. Mean utility scores and QALYs for face-to-face and facilitated access

	Face-to-face				Facilitated Access			
	Baseline	3 months	12 months	QALYs	Baseline	3 months	12 months	QALYs
N	415	381	335	331	346	317	285	275
Mean	0.914	0.942	0.938	0.937	0.913	0.942	0.938	0.937
SE	0.004	0.004	0.004	0.004	0.005	0.004	0.005	0.004
95% CI - lower	0.905	0.934	0.93	0.929	0.903	0.934	0.929	0.929
95% CI - Upper	0.923	0.949	0.948	0.944	0.923	0.95	0.948	0.945

STD = standard deviation SE= standard error

Table 2. Difference in health utility of facilitated access compared to face-to-face BI at 3 months and 12 months and adjusted difference in QALYs

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Complete Case				
3 month EQ-5D-5L	0.003	-0.010	0.013	0.658
12 month EQ5D 5L	-0.0003	-0.013	0.012	0.960
QALYS (adjusted)	0.002	-0.007	0.01	0.622
Incomplete-Case				

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3 month EQ-5D-5L	0.0006	-0.011	0.012	0.914
12 month EQ-5D-5L	0.0004	-0.013	0.013	0.955
QALYS (from means)	0.0003			
Multiple Imputation				
3 month EQ-5D-5L	0.0006	-0.010	0.012	0.913
12 month EQ-5D-5L	0.0005	-0.012	0.013	0.935
QALYS (adjusted)	0.0006	-0.009	0.01	0.901

Cost effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

Results of the CEP and CEAC are reported in Figure 2. There is a 70% probability that the intervention is cost-effective from an INHS cost perspective when all relevant costs are included (intervention delivery, training and website development) at a willingness to pay for a QALY of €25 000. There is a 75% probability that the website is cost-effective compared to face-to-face BI if English NHS costs are used and intervention costs only are included, at a willingness to pay for a QALY of £25 000.

Benefits per 1000 patients referred

The results from the AUDIT analysis are reported in the clinical paper[22]. At 12 months there was no significant difference between two groups in the number of hazardous or harmful drinkers with an odds ratio of 0.94 (95% CI 1.432 to 0.621). At 12 months, of the patients randomised to face-to-face BI 26.3% were hazardous or harmful drinkers (AUDIT-10 ≥ 8) or 263 patients per 1000. Change this to a rate of 263 patients per 1000 patient years and applying an odds ratio of 0.94, 18 patients per 1000 patient years are prevented from hazardous or harmful drinking if they were given facilitated access instead of a face-to-face BI. Facilitated access compared to the face-to-face BI also results in time for an additional 333 appointments.

Question 10 in the AUDIT-10 asks patients if a health care professional has recommended that they reduce their drinking. Potentially as a result of the nature of the intervention (a GP discussing their drinking with them) this was the question most frequently with a score above 0 compared to other questions on the AUDIT. In the face-to-face group 40% of patients answered greater than 0 to question 10 and 31% in the intervention group at 12 months. If this is taken into account and a lower threshold of 7 for hazardous drinking applied, 16% of patients fall above the threshold for risky drinking in the face-to-face group and 18% in the facilitated access group with an odds ratio of 1.9 (95% CI 1 to 3.7). This equates to 158 additional hazardous or harmful drinkers per 1000 patient years for facilitated access compared to face-to-face BI.

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Discussion

Our findings indicate that in the INHS system, the chance that facilitated access to a website to reduce hazardous drinking is cost-effective compared to a face-to-face BI delivered by a GP is between 70% and 84%. However these numbers are dependent on assumptions made about the number of patients given facilitated access versus those given a face-to-face BI given the high up-front costs of website modification or training, respectively. The costs per patient decrease as more patients access each treatment.

Although no data on the long term benefits was included as part of this trial other modelling studies in Italy have looked at the potential long term benefits of BIs. Angus et al (2014)[5] modelled screening of the adult Italian population and providing a standard brief intervention for those identified as hazardous drinkers over 10 years. They estimated that 32% of population receive the intervention at a cost of €411 million, with a potential cost saving of €370 million and a QALY gain of 75,200. This translates to an incremental cost-effectiveness ratio (ICER) of 550 per QALY gained. Given that facilitated access to a website costs significantly less than the standard brief intervention across a whole population it is likely that population level screening for hazardous drinking and a facilitated access to a website is potentially cost-saving. The lower cost in terms of time required of facilitated access compared to face-to-face may also increase the probability that brief interventions are implemented in the INHS.

Given the low level of implementation in the English NHS and the higher cost per hour of English GPs, if the findings from the Italian study were equivalent in England, there would be an even greater probability that facilitated access is cost-effective compared to a face-to-face BI. This result though should be interpreted with caution and points to the need for additional research in this area in England.

Strengths and weaknesses

Limited resource use data was collected as part of the trial. In particular there was no data on what impact access to the website had on follow-up GP appointments. If patients had concerns about the information they accessed on the website it is the possible that they went to see their GP for additional advice, representing an additional cost that was not included in this analysis. Conversely, any cost savings as a result of prevention of alcohol related admissions were not captured as part of this study. If the wider costs to society beyond health care are considered the cost to the economy of productivity losses as a result of alcohol related days off work and loss of productivity were also not considered. A trial of an online brief intervention implemented in the work place found that the

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intervention group were less likely to have sick leave and for less days in total, although not significantly so[26]. This though represents an important consideration for inclusion for trials in this area and population group.

Obtaining high quality information on the cost of GP time in Italy was challenging, with availability only of limited information on GP time and costs and no published national costs[5]. As a result there is limited information to use for costing. However, the two sources used to cost GP time resulted in a similar value per minute of GP time suggesting consistency in the way GP time is costed in Italy. The lack of availability of an Italian tariff for the EQ-5D-5L is also a limitation of this study. An Italian tariff developed for the 3 level version of the EQ-5D found that Italian valuations were higher, particularly for more severe health states[27]. Further research would be required to evaluate the implications for studies similar to these.

We have used data from the English NHS to estimate the potential cost-effectiveness of the intervention in an English Primary Care population. Previous trials of online interventions for reducing hazardous drinking in the UK have found it challenging to achieve high enough rates of follow-up to enable reliable measurement of effectiveness and cost-effectiveness.[21] It is not possible to be sure that there would be a similar level of effectiveness of facilitated access compared to face-to-face BI in England, but the cost savings are likely to be similar to those projected here if GPs take a similar amount of time to conduct a brief intervention.

The use of the AUDIT-10 as an outcome measure to measure the effectiveness of treatments for hazardous or harmful drinking is questionable. This is due to the problem with question 10 in the AUDIT which asks whether a health care professional has suggested reducing drinking. This is more likely to receive a positive response for patients screened for hazardous drinking and provided with any form of intervention – face-to-face BI or facilitated access. Advice is potentially more memorable at face-to-face BI and hence the reversal of results when this question was removed. This is discussed further in the main clinical paper[22]

Conclusions

There is a high probability that facilitated access to a website to reduce alcohol consumption could deliver more benefits for fewer resources given that it costs less than the standard face-to-face BI. Additional benefits may also include an increase in the rates of delivery of brief intervention via facilitated access given the lower time requirement for GPs compared to face-to-face BI.

Word Count: 4,304

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Contributors:

PW, PS and RDV conceived the study and together with NF developed the design. PS, PW, RDV, CT, CL and RMcG were responsible for the development of the website, and PS, FS, RDV, CT were responsible for follow up of patients. RH was responsible for the analysis with the oversight of NF. RH wrote the first draft, and authors PW, PS, PDV, FS, CT, CL RMcG, ES and NF contributed to its revision and final approval.

Declaration of interests:

PW has intellectual property rights for www.downyourdrink.org.uk, is Chief Medical Advisor to the UK charity Drinkaware and has provided private consultancy on the topic of screening and brief interventions to several agencies. CL is the cofounder and Chief Executive Officer at Lumos Medica Srl, which provides software solutions for clinical trials. The other authors declare no competing interests.

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Ethics Approval:
Ethical Committee of the Azienda Sanitaria 4 Medio Friuli,Udine, IT. The protocol was approved on 14 June 2012 by the Independent Local Ethics Committee for Clinical Research of the Health Services Agency No 2 Isontina, Italy.

Data Sharing Agreement:
Anonymised trial data is held on secure servers at University College London. For access to the data please contact the corresponding author. Access will be granted subject to approval by the steering committee.

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Legend Figure 2b: Blue - INHS GP time only; Orange - English NHS; Grey - INHS Training and Website; Yellow - INHS Training only.

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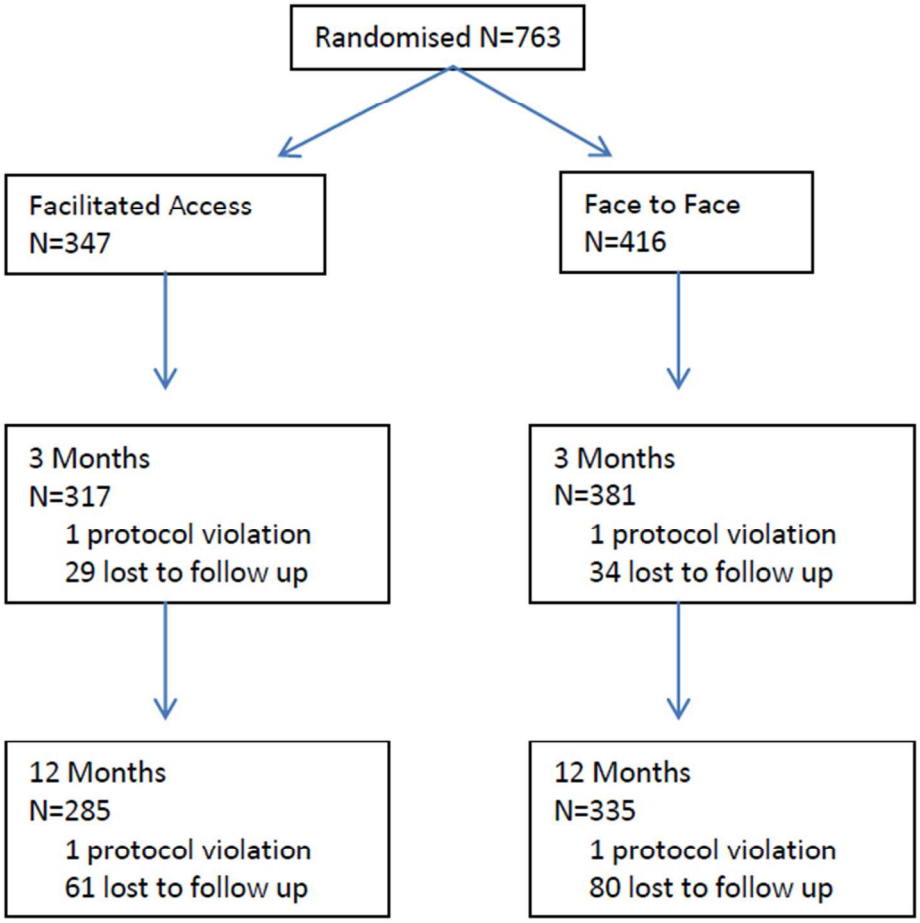

Figure 1: Patient progress through trial for the primary outcome

58x55mm (300 x 300 DPI)

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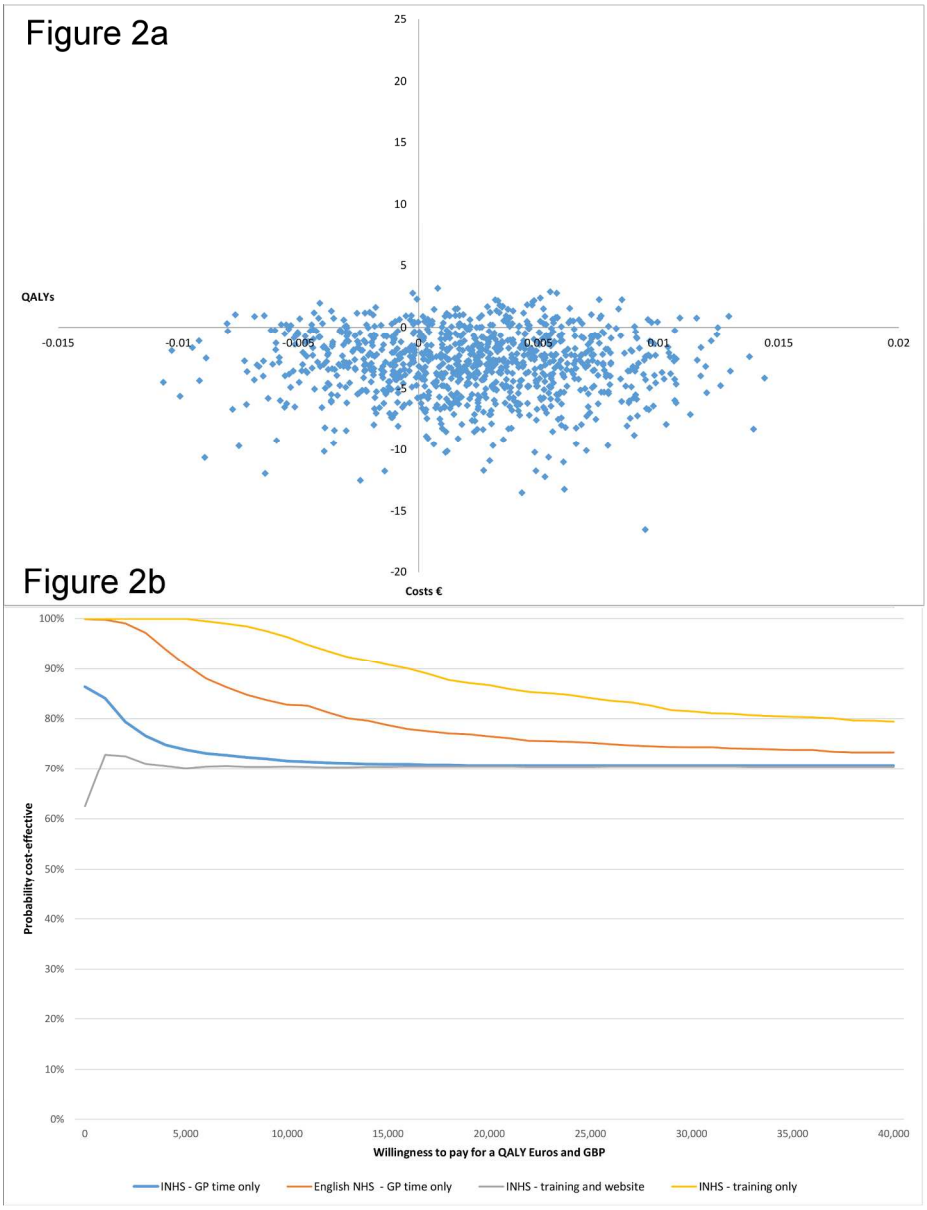

Cost-effectiveness plane of INHS GP costs only (2a) and cost-effectiveness acceptability curves (2b).

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Cost Effectiveness and Resource Allocation 2013 11:6.
The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
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Pharmacoeconomics 2013 Mar 26. [Epub ahead of print]
Value in Health 2013 March - April;16(2):e1-e5

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and	

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		outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	

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Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website: cost effectiveness analysis

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Complete List of Authors:	Hunter, Rachael; University College London, Research Dept of Primary Care and Population Health Wallace, Paul; University College London, Primary Care and Population Health; Kings College London, Primary Health and Social Care Struzzo, Pierliugio; Universita degli Studi di Trieste, Life Sciences Della Vedova, Roberto ; Centro Studi e Ricerca Medicina Generale Scafuri, Francesca Tersar, Costanza; Regional Centre for the Training in Primary Care, Region Friuli-Venezia Giuia Lygidakis, Charilaos; Universite du Luxembourg, Institute for Health and Behaviour - Research Unit INSIDE Mc Gregor, Richard; Codeface Ltd, Scafato, Emanuele; Istituto Superiore di Sanita Freemantle, Nick; University College London, Dept Primary Care and Population Health
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Randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website: cost effectiveness analysis

Authors: Rachael Hunter[1], Paul Wallace[1], Pierluigi Struzzo[2-4], Roberto Della Vedova[3], Francesca Scafuri[2], Costanza Tersar[4], Charilaos Lygidakis[5], Richard McGregor[6], Emanuele Scafato[7], Nick Freemantle[1]

Institutional affiliations:

[1]Department of Primary Care and Population Health, University College London, London, UK

[2]Regional Centre for Training in Primary Care, Monfalcone (GO) Italy

[3] CSeRMEG, Centro Studi e Ricerche in Medicina Generale, Italy

[4] University of Trieste, Life Sciences Department, Italy

[5] Institute for Health and Behaviour - Research Unit INSIDE, Université du Luxembourg, Luxembourg

[6] Codeface Ltd, Hove, UK

[7] Istituto Superiore di Sanità, WHO Collaborating Centre for Research and Health Promotion on Alcohol and Alcohol-Related Health Problems,

Corresponding author: Rachael Hunter, Department of Primary Care and Population Health, University College London, London, UK r.hunter@ucl.ac.uk, tel: +44 (0)20 830 2338

Collaborative group list-The EFAR Study Team:

Giosué Acampora, Maria Angela Bravo, Chiara Bregant, Gianna Bunello, Leonardo Butà, Lucia Casatta, Castellarin, Egidio Chamouni, Moshé Benyamin, Maria Pia Cisilin, Clemente Condello, Nelly Drigani, Tiziano Ermacora, Alessandro Falcidia, Adriana Fasiolo, Angelo Florio, Mauro Gubiani, Gianni Iacuzzo, Edi Ietri, Giuseppe Latella, Guglielmo Lucca, Ciro Mamolo, Carmelo Matera, Lucia Mei, Francesca Melon, Emilio Mezzasalma, Isabella Milan, Carlo Miotti, Gian Franco Panizzo, Francesca Pighin, Raffaela Principato, Pierina Revignas, Antonella Rolff, Ivana Rupalti, Rosanna Sellibara, Michela Sereni, Gianfranco Silverii, Giuseppe Taglialatela, Chiara Toffoletti, Massimo Toffolo, Laura Ivana Tonelli, Simone Trevisani, Roberto Troisi, Gianni Tubaro, Roberto Vallini, Elisabetta Zappalà, Antonio Zappi.

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Abstract

Objectives: To evaluate the 12 month costs and quality adjusted life years (QALYs) gained to the Italian National Health Service (INHS) of facilitated access to a website for hazardous drinkers compared to a standard face-to-face brief intervention (BI).

Design: Randomised 1:1 non-inferiority trial.

Setting: Practices of 58 General Practitioners (GPs) in Italy.

Participants: Of 9080 patients (>18yrs old) approached to take part in the trial 4529 (49·9%) logged on to the website and 3841 (84.8%) undertook online screening for hazardous drinking. 822 (21.4%) screened positive and 763 (19.9%) were recruited to the trial.

Interventions: Patients were randomised to receive either a face-to-face BI or access via a brochure from their GP, to an alcohol reduction website (facilitated access).

Primary and secondary outcome measures: The primary outcome is the cost per QALY gained of facilitated access compared to face-to-face. A secondary analysis includes total costs and benefits per 100 patients, including number of hazardous drinkers prevented at 12 months.

Results: The average time required for the face-to-face BI was 8 minutes (95% confidence interval (CI) 7.5 minutes to 8.6 minutes). Given the maximum time taken for facilitated access of 5 minutes, face-to-face is an additional 3 minutes: equivalent to having time for another GP appointment for every three patients referred to the website. Complete case analysis adjusting for baseline the difference in QALYs for facilitated access is 0.002 QALYs per patient (95% CI -0.007 to 0.011).

Conclusions: Facilitated access to a website to reduce hazardous drinking costs less than a face-to-face BI given by a GP with no worse outcomes. The lower cost of facilitated access, particularly in regards to investment of time, may facilitate the increase in provision of brief interventions for hazardous drinking.

Trial Registration: ClinicalTrials.org NCT: 01638338

Funding: The study was jointly supported by the Italian Ministry of Health and by the Region Friuli-Venezia Giulia, Italy (grant number: D25E12002900003).

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- The cost-effectiveness analysis uses individual patient data to evaluate the short term costs and benefits of a way to increase the implementation of brief interventions for hazardous and harmful drinkers in Primary Care.
- Follow up rates exceeded 90% at 3 months and 80 % at 12 months
- Limited data was collected as part of the trial on time taken in standard Italian GP appointments and cost of a GP in Italy so assumptions based on data from the literature were required.
- The results were extrapolated to the English National Health Services (NHS), hence caution should be exercised interpreting these findings given differences between the Italian and English NHS.
- The results of the analysis are dependent on assumptions made regarding the number of patients that receive a face-to-face brief intervention or the number of patients that access the website.

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Introduction

Consumption of alcohol is a risk factor for premature mortality[1], with growing evidence of the significant negative health impact of alcohol consumption, including increased risk of cancer[2]. The World Health Organisation (WHO) has identified the European region as having the highest rates of alcohol related ill health across the globe[2]. Brief interventions have been found to be effective in reducing alcohol consumption in Primary Care populations[3] leading to recommendations for their implementation in Primary Care, including in the Italian National Guidelines[4]. Delivering a face-to-face standard brief intervention alongside screening the Italian population for hazardous drinking is potentially cost-effective to the Italian National Health Service (INHS), with the potential to prevent 7,200 alcohol related deaths over 30 years and 91,700 alcohol related hospitalisations[5]. Despite strong evidence of their potential benefit, the implementation of brief interventions in Primary Care across Europe has been limited[6]. This may be due to the significant upfront investment required to deliver face-to-face brief interventions in the form of GP or other Primary Care staff time, of which there is finite availability.

As a result an alternative approach may be required to deliver brief interventions in Primary Care, one that is less of a burden on clinician time and is easier to implement. Facilitated access, where a clinician directs patients to a website for alcohol reduction, has the potential to provide similar benefits to a face-to-face brief intervention but potentially with a lower upfront investment in time and hence cost. Although there is evidence regarding the potential impact of brief interventions on reducing alcohol consumption and hence anticipated long term health benefits, there is less evidence for their impact on short term costs and health related quality of, particularly in an Italian primary health care setting[5]. This information is required to identify strategies to improve the implementation of brief interventions in the INHS.

The aim of this health economic evaluation is to evaluate the short term cost savings to the INHS of facilitated access to a website for hazardous and harmful drinkers compared to a standard face-to-face brief intervention (BI) over 12 months. Hazardous drinkers are defined as people with an alcohol consumption level that is potentially detrimental to their health and is measured using the Alcohol Use Disorders Identification Test (AUDIT)[7]. These will be reported alongside potential benefits. Face-to-face BI for hazardous drinking has been recommended for widespread implementation in the English National Health System (NHS), but that evidence suggests this has not happened[6]. We have therefore included a secondary analysis of the potential cost savings to the English NHS of facilitated access to a website to provide additional information to NHS policy makers.

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Methods

EFAR Trial

EFAR-FVG is a randomised 1:1 trial, with the primary aim of testing for non-inferiority of a face-to-face brief intervention for hazardous and harmful drinkers delivered by a GP (face-to-face BI) compared to facilitated access to an interactive website for reducing hazardous and harmful drinking (facilitated access). GPs from the region of Northern Italy, Friuli-Venezia, were recruited via the official register for the region. Patients aged 18 years and over and who did not meet any of the exclusion criteria for the trial were recruited to the trial by being given a trial brochure and encouraged by their GP to access a healthy lifestyle website. Patients that accessed the website were asked to complete the short Alcohol Use Disorders Identification test (AUDIT-C)[8 9]. The AUDIT-C is comprised of three questions to identify probable hazardous or harmful drinking, with a lower threshold score of 5 for men and 4 for women. Patients scoring at the threshold and above on the AUDIT-C were advised of their risk via a personalised message from their GP and advised to enter the study. Following consent to the study patients completed baseline questionnaires and were randomised to face-to-face brief intervention or facilitated access (the GP gives the patient a leaflet that directs them to the website) to a version of the Down Your Drink Website (www.downyourdrink.org.uk) adapted for an Italian audience. Further details of the EFAR FVG trial[10] [11] and Down Your Drink website[12] can be found elsewhere.

Costs

The aim of this analysis is to assess the short term resource impact of facilitated access to a website. There is unlikely to be a significant immediate health benefit to patients as a result of reductions in alcohol consumption given the long term impact and health risk of hazardous and harmful drinking. As a result the only resource use collected as part of the trial was time spent by GPs delivering the standard face-to-face brief intervention as this is likely to be the main source of cost-savings. GPs indicated if the face-to-face brief intervention took less than 5 minutes, 5 to 10 minutes or greater than 10 minutes. The cost per minute of a GP appointment was then multiplied by 5, 10 or 15 minutes for each patient to obtain the cost per patient of the face-to-face intervention. The time and cost of screening was not included given that it was assumed to be the same in both groups. GPs were also asked to report how long it took them to refer patients to the website.

The cost of a GP appointment was taken from the Italian study published by Gerzeli et al (2014)[13] and was estimated at €11 an appointment for 2010 costs. No health care cost inflation index for Italy could be located so instead the English health care cost inflation index was applied to bring the cost

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to 2015/2016 values[14] at €12 an appointment. Assuming an average appointment length of 9 minutes[15], this equates to a cost per minute of €1.27.The primary analysis for costs is from the Italian health care perspective. A secondary analysis evaluating the potential cost-savings for the English NHS costs has also been conducted to provide hypothetical information on the probability the intervention is cost-effective in England. As reported in Hobbs[15] study of 101.8 million GP consultations carried out in English GPs, the average duration of a GP appointment in England is 9.2 minutes at a cost of £31[14]. The significantly higher cost of GP time in the English NHS compared to INHS is likely to be a result of higher salaries and overhead costs in the English NHS.

All GPs attended a 1 day training session for the delivery of a face-to-face brief intervention for hazardous and harmful drinking using motivational interviewing, with an average cost per GP participant of €51 for the cost of trainers, resources and room hire. The cost of an honorarium and travel costs for experts leading the training (€10 971), and cost of the GP's time attending the training (at €533 per GP per day) was also included in the cost of training.

The cost of adapting the website was collected as part of the trial at a total cost of €35 000. GPs were asked to familiarise themselves with use of the website prior to start of the trial at a cost per GP of €76.

Quality Adjusted Life Years (QALYs)

QALYs represent a measure of mortality and morbidity over time, anchored at 1 for perfect health and 0 for death, with 1 year spent in perfect health equal to 1 QALY. They are used to assist health care policy makers with decisions about the implementation of new interventions in health care in an equitable and standardised way. The cost of the new intervention minus current practice is divided by the additional QALYs generated by the new intervention to calculate the cost per QALY gained, with a lower mean cost per QALY being preferable. The new intervention might also dominate current practice by resulting in more QALYs for a lower average cost per patient. The EuroQol EQ-5D[16] and its associated preference based tariff[17] is the most common way to calculate QALYs in most developed countries.

Euroqol EQ-5D 5 level (EQ-5D-5L)[18] was administered to all patients in the trial to complete at baseline, 3 months and 12 months. Patients were asked to complete questionnaires online in the first instance, but for some patients questionnaires were completed over the phone following multiple attempts to contact the patient to complete the questionnaire online. The 5-level version of the EQ-5D was chosen given recent evidence of a reduced ceiling effect compared to the 3-level[19]. Time-trade off values for the EQ-5D-5L were used to calculate patient level utility tariffs. As no

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Italian weights are currently available in the cross-walk or time-trade off value sets for the EQ-5D-5L, the time-trade off algorithm for the UK was applied[20].

Patient level QALYs were calculated from baseline, 3 month and 12 month patient level utility scores, adjusting for timing of follow-ups to calculate the area under the curve. Adjustments though were not patient specific, and were counted specifically as 3 months and 12 months regardless of when the patient actually completed the questionnaire so as not to introduce bias from delayed responses. As responses at all three time points are required to calculate QALYs, values reported are for complete case analysis (patients that have complete EQ-5D-5L responses for all 3 time points). The mean QALYs per patient reported have been adjusted for baseline EQ-5D-5L utility values using linear regression analysis and including a co-efficient for randomisation[21]. Confidence intervals (CIs) are from 1000 bootstrap replications.

Cases of hazardous or harmful drinking prevented

As hazardous drinkers also include a generally healthy population, with potential QALY losses occurring in the far future as a result of future chronic alcohol related health problems, the EQ-5D has been found to be insensitive to changes in hazardous drinking at the point of behaviour change for risk reduction[22]. As a result additional analyses of costs versus cases of hazardous or harmful drinking prevented have been included. Patients completed the 10 question version of the AUDIT (AUDIT-10) at baseline, 3 months and 12 months, with hazardous or harmful drinking defined as a score ≥8. Cases of hazardous or harmful drinking prevented at 12 months have been calculated using the data from the main paper for the trial using AUDIT-10 data at 12 months [23]. This was converted to cases prevented per 1000 patients by calculating the percentage of patients that are hazardous or harmful drinkers at 12 months in the face-to-face intervention, changing this to a rate per 1000 patient years and applying the odds ratio reported in the main clinical paper[23] for 12 months.

Sensitivity analysis: missing data

It was assumed that data at follow-up time points was missing at random. Additional analyses have been conducted using alternative ways to account for missing data in QALYs. This includes an incomplete case analysis using all data collected, not just complete cases, to calculate QALYs and calculating QALYs imputing missing data using chained equations as recommended in Hunter et al (2015)[24].

Cost effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

Results from the bootstrapped, complete case, QALYs were used to generate the CEP and CEAC.

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To represent the uncertainty in costs the average duration of the appointment was calculated using the proportion of patients that had appointments of different lengths and the Dirichlet process[25]. The cost was varied using a random number generated in Excel and the gamma distribution assuming that the standard error is equal to the mean cost of an appointment (€12 for IHNS and £31 in the UK). An average cost per appointment was then generated for each of the 1000 simulated iterations and for Italian and UK costs.

The CEAC is calculated using the formula $(\beta_1)WTP-(C_1-C_2)$, where β_1 is the beta co-efficient for the treatment effect from one of the iterations of the bootstrapped linear regressions adjusting for baseline EQ-5D-5L utility scores, WTP is the willingness to pay for a QALY gained, $C_1$is the average cost per patient of facilitated access and C_2 is cost of the average cost per patient of the face-to-face BI. The probability that facilitated access is cost-effective compared to the face-to-face BI for a given WTP for a QALY is based on the proportion of times the formula is positive from the 1000 bootstrap iterations combined with the 1000 simulated iterations.

No discount rate was applied to the analysis given the 12 month time horizon.

Hypothesis testing

Given the hypothesis of non-inferiority between the two groups as the primary analysis for the trial, it was assumed that there would be no difference in QALYs or cases of hazardous or harmful drinking between the two groups. Instead the analysis focuses on the potential benefit per 1000 patients with facilitated access to the alcohol reduction website compared to a brief face-to-face intervention. As no information of the average GP appointment duration in Italy is available it has been assumed that the average appointment duration in Italy is similar to that of the English NHS of 9 minutes.

Results

Patient numbers and loss to follow-up for the trial are reported in Figure 1. Further patient demographics can be found in the main trial findings paper[23].

Costs

Of the 416 patients allocated to the face to face BI group, 304 (73%) received the intervention from their GP. Information on the duration of each BI was recorded by the GPs using a questionnaire. For 171 patients (56.3%) the BI took less than 5 minutes, 5 to 10 minutes for 87 patients (28.6%) and

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more than 10 minutes for 46 patients (15.1%). The average time required for the face-to-face BI is 8 minutes (95% confidence interval (CI) 7.5 minutes to 8.6 minutes). The amount of time spent facilitating access to the website was less than 5 minutes. Based on this we made the conservative estimate that facilitated access required 5 minutes of a GP's time. The difference of 3 minutes between the two groups is equivalent to having time for another appointment for every three patients referred to the website.

The average cost per patient of a face-to-face BI, including patients randomised to face-to-face BI but who did not receive the face-to-face appointment was €10,16 per patient (95% CI €9,53 to €10,92). If patients who did not receive the face-to-face BI are excluded from the analysis the average cost is €11,10 per patient (95% CI €10,52 to €11,69).

The average cost per GP of training to deliver the face-to-face BI was €774. The cost per patient of training for face-to-face BI is dependent on how many patients the GP delivers a face-to-face BI to. Assuming that GPs could have provided a face-to-face BI to patients in either group, the total number of interventions they could have provided was 763, or 13 patients per GP, resulting in an average cost per patient of €60 for training for face-to-face BI.

The total cost of website development and piloting was €47 408, including the cost of GPs familiarising themselves with the website. Assuming 763 patients received facilitated access, the cost per patient of the website is €62,13. Each patient was also given a leaflet from the GP directing them to the website at a total cost per patient of €0,51. In the most conservative scenario (lowest possible cost difference between the two groups) of €70 per patient for face-to-face BI (€60 for training and €10,16 for the GP time to deliver the BI) and facilitated access costs €68 per patient (5 minutes for facilitated access, the cost of the leaflet and an additional cost per patient of updating the website of €62), facilitated access costs €2 less per patient compared to face-to-face BI.

In the least conservative estimate (highest possible cost difference between the two groups) we assume that the cost of the website approaches zero given that there is no upper limit to the number of patients that could feasibly access the website. Instead the only costs for facilitated access are the cost of the leaflet (€0,51 per patient), GP time referring patients to the website (5 minutes at a cost of €6,35 per patient) and time spent familiarising themselves with the website (€5,86). In the least conservative estimate we assume that the cost per patient for face-to-face BI is €71 (€60 for training and €11,10 for the GP time to deliver the BI) and facilitated access costs €13 per patient (5 minutes for facilitated access and an additional cost of the leaflet and GPs time

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familiarise themselves with the website of €6,37) facilitated access results in a cost saving of €58 per patient compared to face-to-face BI.

Utility scores and QALYs

The results for mean complete case analysis for utility scores and QALYs are reported in Table 1.

There was no significant difference in QALYs between facilitated access to the website and the face-to-face BI. Complete case analysis and adjusting for baseline the difference in QALYs for facilitated access minus face-to-face BI was 0.002 per patient (95% CI -0.007 to 0.011). At a willingness to pay (WTP) of €25 000 per QALY gained, as recommended by the INHS[26], facilitated access could cost an additional €50 per patient on average compared to face-to-face BI and be considered cost-effective. At the lower end of the CI where facilitated access results in a QALY decrement of -0.007 QALYs over 1 year facilitated access would need to save €175 per patient to be cost-effective. The difference in utility scores and QALYs is described in table 2. Based on the results of the multiple imputation analysis, facilitated access can cost an additional €15 compared to face-to-face BI and be considered cost effective (95% CI -€225 to €250).

Table 1. Mean utility scores and QALYs for face-to-face and facilitated access

	Face-to-face				Facilitated Access			
	Baseline	3 months	12 months	QALYs	Baseline	3 months	12 months	QALYs
N	415	381	335	331	346	317	285	275
Mean	0.914	0.942	0.938	0.937	0.913	0.942	0.938	0.937
SE	0.004	0.004	0.004	0.004	0.005	0.004	0.005	0.004
95% CI - lower	0.905	0.934	0.93	0.929	0.903	0.934	0.929	0.929
95% CI - Upper	0.923	0.949	0.948	0.944	0.923	0.95	0.948	0.945

STD = standard deviation SE= standard error

Table 2. Difference in health utility of facilitated access compared to face-to-face BI at 3 months and 12 months and adjusted difference in QALYs

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Complete Case				

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3 month EQ-5D-5L	0.003	-0.010	0.013	0.658
12 month EQ5D 5L	-0.0003	-0.013	0.012	0.960
QALYS (adjusted)	0.002	-0.007	0.01	0.622
Incomplete-Case				
3 month EQ-5D-5L	0.0006	-0.011	0.012	0.914
12 month EQ-5D-5L	0.0004	-0.013	0.013	0.955
QALYS (from means)	0.0003			
Multiple Imputation				
3 month EQ-5D-5L	0.0006	-0.010	0.012	0.913
12 month EQ-5D-5L	0.0005	-0.012	0.013	0.935
QALYS (adjusted)	0.0006	-0.009	0.01	0.901

Cost effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC)

Results of the CEP and CEAC are reported in Figure 2. There is a 70% probability that the intervention is cost-effective from an INHS cost perspective when all relevant costs are included (intervention delivery, training and website development) at a willingness to pay for a QALY of €25 000, and an 84% probability if only the cost of training (excluding website development costs) are included. There is a 75% probability that the website is cost-effective compared to face-to-face BI if English NHS costs are used and intervention costs only are included, at a willingness to pay for a QALY of £25 000.

Benefits per 1000 patients referred

The results from the AUDIT analysis are reported in the clinical paper[23]. At 12 months there was no significant difference between two groups in the number of hazardous or harmful drinkers with an odds ratio of 0.94 (95% CI 1.432 to 0.621). At 12 months, of the patients randomised to face-to-face BI 26.3% were hazardous or harmful drinkers (AUDIT-10 ≥ 8) or 263 patients per 1000. Change this to a rate of 263 patients per 1000 patient years and applying an odds ratio of 0.94, 18 patients per 1000 patient years are prevented from hazardous or harmful drinking if they were given facilitated access instead of a face-to-face BI. Facilitated access compared to the face-to-face BI also results in time for an additional 333 appointments.

Question 10 in the AUDIT-10 asks patients if a health care professional has recommended that they reduce their drinking. Potentially as a result of the nature of the intervention (a GP discussing their drinking with them) this was the question most frequently with a score above 0 compared to other

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questions on the AUDIT. In the face-to-face group 40% of patients answered greater than 0 to question 10 and 31% in the intervention group at 12 months. If this is taken into account and a lower threshold of 7 for hazardous drinking applied, 16% of patients fall above the threshold for risky drinking in the face-to-face group and 18% in the facilitated access group with an odds ratio of 1.9 (95% CI 1 to 3.7). This equates to 158 additional hazardous or harmful drinkers per 1000 patient years for facilitated access compared to face-to-face BI.

Discussion

Our findings indicate that in the INHS system, the chance that facilitated access to a website to reduce hazardous drinking is cost-effective compared to a face-to-face BI delivered by a GP is between 70% and 84%. However these numbers are dependent on assumptions made about the number of patients given facilitated access versus those given a face-to-face BI given the high up-front costs of website modification or training, respectively. The costs per patient decrease as more patients access each treatment.

Although no data on the long term benefits was included as part of this trial other modelling studies in Italy have looked at the potential long term benefits of BIs. Angus et al (2014)[5] modelled screening of the adult Italian population and providing a standard brief intervention for those identified as hazardous drinkers over 10 years. They estimated that 32% of population receive the intervention at a cost of €411 million, with a potential cost saving of €370 million and a QALY gain of 75,200. This translates to an incremental cost-effectiveness ratio (ICER) of 550 per QALY gained. Given that facilitated access to a website costs significantly less than the standard brief intervention across a whole population it is likely that population level screening for hazardous drinking and a facilitated access to a website is potentially cost-saving. The lower cost in terms of time required of facilitated access compared to face-to-face may also increase the probability that brief interventions are implemented in the INHS.

Given the low level of implementation in the English NHS and the higher cost per hour of English GPs, if the findings from the Italian study were equivalent in England, there would be an even greater probability that facilitated access is cost-effective compared to a face-to-face BI. This result though should be interpreted with caution and points to the need for additional research in this area in England.

Strengths and weaknesses

Limited resource use data was collected as part of the trial. In particular there was no data on what impact access to the website had on follow-up GP appointments. If patients had concerns about the

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information they accessed on the website it is the possible that they went to see their GP for additional advice, representing an additional cost that was not included in this analysis. Conversely, any cost savings as a result of prevention of alcohol related admissions were not captured as part of this study. If the wider costs to society beyond health care are considered the cost to the economy of productivity losses as a result of alcohol related days off work and loss of productivity were also not included. A trial of an online brief intervention implemented in the work place found that the intervention group were less likely to have sick leave and for less days in total, although not significantly so[27]. This though represents an important consideration for inclusion for trials in this area and population group.

Obtaining high quality information on the cost of GP time in Italy was challenging, with availability only of limited information on GP time and costs and no published national costs[5]. As a result there is limited information to use for costing. However, the two sources used to cost GP time resulted in a similar value per minute of GP time suggesting consistency in the way GP time is costed in Italy. The lack of availability of an Italian tariff for the EQ-5D-5L is also a limitation of this study. An Italian tariff developed for the 3 level version of the EQ-5D found that Italian valuations were higher, particularly for more severe health states[28]. Further research would be required to evaluate the implications for studies similar to these.

We have used data from the English NHS to estimate the potential cost-effectiveness of the intervention in an English Primary Care population. Previous trials of online interventions for reducing hazardous drinking in the United Kingdom (UK) have found it challenging to achieve high enough rates of follow-up to enable reliable measurement of effectiveness and cost-effectiveness.[22] It is not possible to be sure that there would be a similar level of effectiveness of facilitated access compared to face-to-face BI in England, but the cost savings are likely to be similar to those projected here if GPs take a similar amount of time to conduct a brief intervention.

The use of the AUDIT-10 as an outcome measure to measure the effectiveness of treatments for hazardous or harmful drinking is questionable. This is due to the problem with question 10 in the AUDIT which asks whether a health care professional has suggested reducing drinking. This is more likely to receive a positive response for patients screened for hazardous drinking and provided with any form of intervention – face-to-face BI or facilitated access. Advice is potentially more memorable at face-to-face BI and hence the reversal of results when this question was removed. This is discussed further in the main clinical paper[23].

Conclusions

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There is a high probability that facilitated access to a website to reduce alcohol consumption could deliver more benefits for fewer resources given that it costs less than the standard face-to-face BI. Additional benefits may also include an increase in the rates of delivery of brief intervention via facilitated access given the lower time requirement for GPs compared to face-to-face BI.

Word Count: 4,347

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Contributors:

PW, PS and RDV conceived the study and together with NF developed the design. PS, PW, RDV, CT, CL and RMcG were responsible for the development of the website, and PS, FS, RDV, CT were responsible for follow up of patients. RH was responsible for the analysis with the oversight of NF. RH wrote the first draft, and authors PW, PS, PDV, FS, CT, CL RMcG, ES and NF contributed to its revision and final approval.

Declaration of interests:

PW has intellectual property rights for www.downyourdrink.org.uk, is Chief Medical Advisor to the UK charity Drinkaware and has provided private consultancy on the topic of screening and brief interventions to several agencies. CL is the cofounder and Chief Executive Officer at Lumos Medica Srl, which provides software solutions for clinical trials. The other authors declare no competing interests.

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Ethics Approval:
Ethical Committee of the Azienda Sanitaria 4 Medio Friuli,Udine, IT. The protocol was approved on 14 June 2012 by the Independent Local Ethics Committee for Clinical Research of the Health Services Agency No 2 Isontina, Italy.

Data Sharing Agreement:
Anonymised trial data is held on secure servers at University College London. For access to the data please contact the corresponding author. Access will be granted subject to approval by the steering committee.

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Figure Legend

Figure 1: Consort diagram

Figure 2: Blue - INHS GP time only; Orange - English NHS; Grey - INHS Training and Website; Yellow - INHS Training only.

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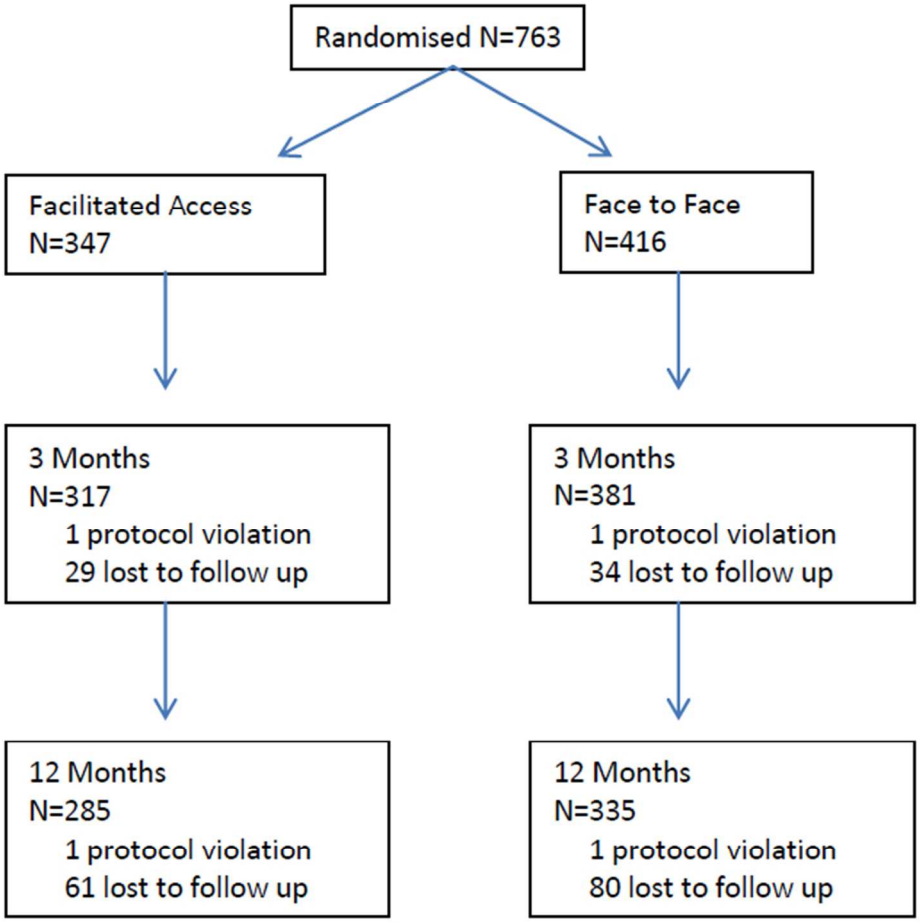

Figure 1: Patient progress through trial for the primary outcome

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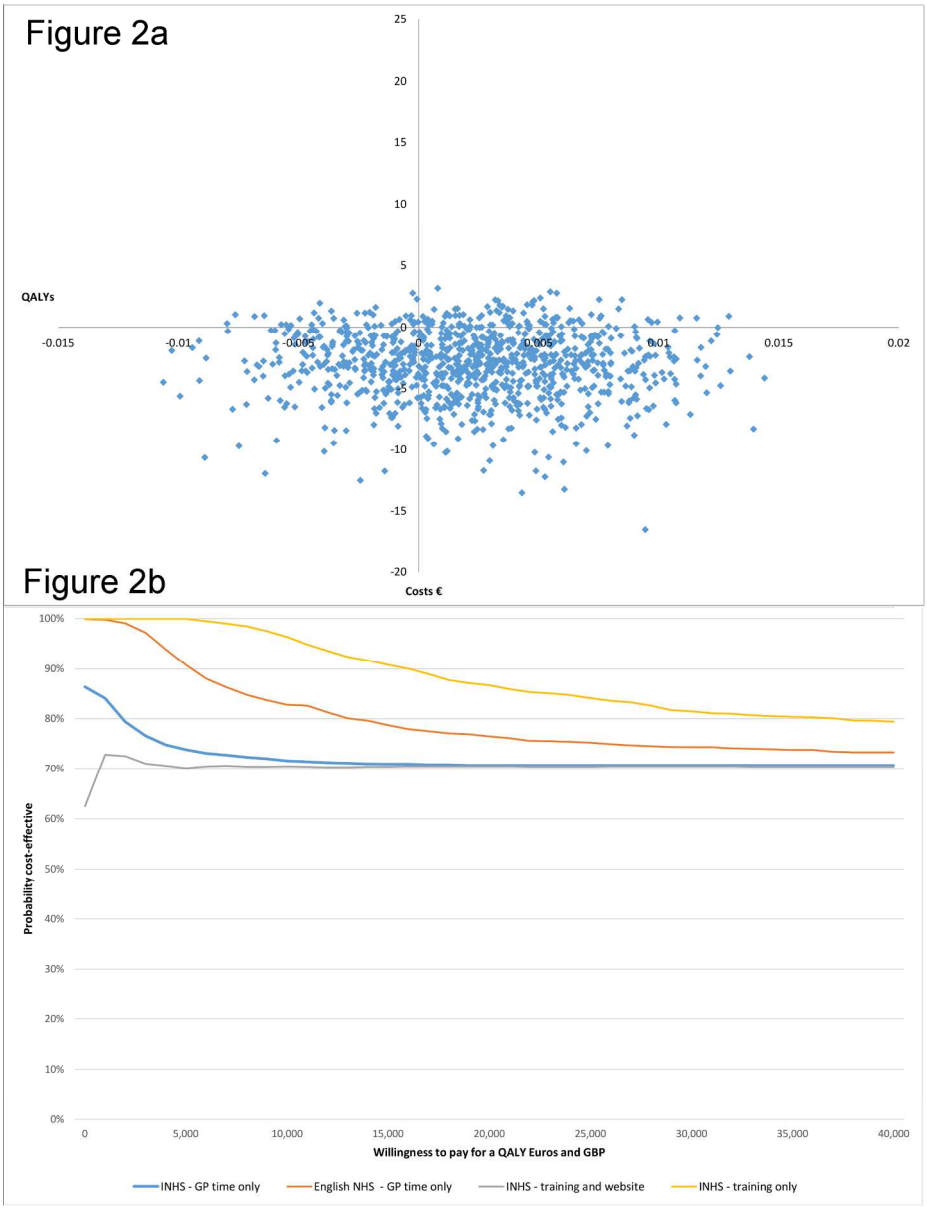

Cost-effectiveness plane of INHS GP costs only (2a) and cost-effectiveness acceptability curves (2b).

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The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

BJOG: An International Journal of Obstetrics and Gynaecology
BMC Medicine 2013; 11:80
BMJ 2013;346:f1049
Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)
Cost Effectiveness and Resource Allocation 2013 11:6.
The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
International Journal of Technology Assessment in Health Care
Journal of Medical Economics 2013 Mar 25. [Epub ahead of print]
Pharmacoeconomics 2013 Mar 26. [Epub ahead of print]
Value in Health 2013 March - April;16(2):e1-e5

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and	

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		outcomes and say why appropriate.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.

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Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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