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Main findings of EFAR FVG, a randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website

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Title:

Main findings of EFAR FVG, a randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website

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SUMMARY:

Background: Brief interventions delivered in primary care have been shown to be effective in reducing risky drinking, but implementation is limited. Facilitated access to a digital application offers a novel alternative to face-to-face intervention, but its relative effectiveness is unknown.

Methods: Primary care based, non-inferiority, randomised controlled trial comparing general practitioner facilitated access to an interactive alcohol reduction website with standard face-to-face brief intervention. Patients screening positive on AUDIT C were invited to participate in the trial. Assessment at baseline, 3 months and 12 months was carried out using AUDIT and EQ5D 5L questionnaires.

Findings: 58 participating GPs approached 9080 patients (>18yrs/old) of whom 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. 347 (45.5 %) were allocated to facilitated access and 416 (54.5%) to BI. 698 (91·5%) were followed up at 3 months and 620 (81·2%) at 12 months. Analysis of the primary outcome provided clear evidence of non inferiority of facilitated access compared with standard brief intervention, and pre-specified subgroup analysis and indicated benefits for older patients and those with higher levels of computer literacy and lower baseline severity. Post hoc analyses undertaken to address possible response bias in the brief intervention group did not provide support for the conclusion of non inferiority within the pre-specified 10% boundary.

Interpretation: Our main findings provide clear evidence of non-inferiority for facilitated access versus face-to-face brief intervention, and support the case for developing this approach for a broader set of digital applications. However the post hoc analyses raise important questions of interpretation and further research is needed to determine whether the findings of this trial can be replicated using different outcome measures.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The trial evaluated a potentially important development for primary care, namely the use by GPs of facilitated access to a digital application as an alternative to traditional face to face consultation, in this case for patients with risky drinking.
- It was developed and delivered by an international multidisciplinary team in the UK and Italy
- All components of the trial were delivered online with the exception of the face to face intervention, thus reducing the cost of the trial, allowing real-time tracking of the findings, ensuring consistency of conduct and avoiding errors of transcription.
- Follow up rates exceeded 90% at 3 months and 80 % at 12 months
- Probable response bias in the brief intervention group indicates that some caution should be exercised in interpreting the main findings

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INTRODUCTION:

Alcohol is the third leading cause of diseases and premature death globally[i] and accounts for 3·8% of deaths and 4·6% of disability-adjusted life years.[ii] Brief interventions delivered in primary health care settings have been demonstrated repeatedly to be effective in reducing hazardous and harmful drinking.[iii] However, barriers prevent their widespread implementation, including insufficient training, lack of resources and constraints in time.[4] Digital applications including websites and apps which are based on behaviour change techniques may be helpful in overcoming these barriers,[iv,v] and clinicians may actively encourage patients to use approved applications through a process known as facilitated access. Initially adopted primarily for the management of patients with mental health problems including depression and anxiety, facilitated access has been extended to digital applications for addictive behaviours including smoking cessation and alcohol screening, and health promotion and the management of some long term conditions.[vi vii]

Facilitated access offers a novel alternative to face-to-face brief intervention (BI) for risky drinking, but it is not known whether it is as effective. A review of trials of computer-based interventions offered to college drinkers found them to be more effective than no treatment and as effective as alternative treatment approaches.[viii] A systematic review of electronic interventions for risky drinkers concluded that there were significant reductions in weekly alcohol consumption between intervention and control conditions between 3 months and less than 12 months follow-up, indicating this may be an effective intervention.[ix]

A review of digital and computer-based alcohol intervention programs promoted in primary care settings identified fifteen small scale trials of which nine were associated with a reduction in alcohol use at follow-up.[x] The indications from these studies about the likely effectiveness and cost effectiveness of internet applications in primary care were generally positive, but firm conclusions could not be drawn because of limitations of sample size and study design. An adequately powered and appropriately designed trial was therefore required to provide more definitive evidence on the use of facilitated access as an alternative to face to face BI for the reduction of hazardous and harmful drinking, and to indicate the potential for this approach to be adopted more generally in the management of health conditions by general practitioners.

The aim of the study was to determine whether facilitated access to an interactive alcohol reduction website was as effective in reducing hazardous and harmful drinking as face to face BI.

METHODS:

Study design:

Primary care based, non-inferiority, randomised controlled trial of brief intervention of hazardous and harmful drinkers comparing general practitioner (GP) facilitated access to an interactive alcohol reduction website (facilitated access) with standard face-to-face BI. With the exception of face to face intervention, all components of the trial were delivered online to patients following receipt of a brochure describing the website and providing a unique trial log-on number. Access to the website

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was via the healthy lifestyle portal of the official website of the Region of Friuli-Venezia Giulia (www.itatvb.it). GPs were recruited via the official register of the Friuli-Venezia Giulia region of Northern Italy. All participating GPs attended a one-day training event including an overview of the trial and interactive sessions on the delivery of face-to-face BI using the principles of brief motivation interviewing. They were also encouraged to familiarise themselves with the trial website and to use the menu-driven online GP personalisation facility to create their own tailored patient messages at up to four key points of the programme (see Procedures and Screenshots 1&2).

The protocol was approved by the Isontina Independent Local Health Unit Ethics Committee on 14 June 2012.[xi]

Patients:

All patients aged 18 or over who attended the participating practices during the study period were eligible for the trial, but those known to suffer from severe psychiatric disorder, alcohol dependence, serious visual impairment or terminal illness were excluded, as were those judged to have inadequate command of the Italian language.

Randomisation and masking:

Randomisation was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.

Procedures

For the purposes of screening, eligible patients were given a trial brochure with a unique log in code and actively encouraged by their GP to access the specially designed healthy lifestyle website. Once online, they were asked to complete the three-question short Alcohol Use Disorders Identification Test (AUDIT-C)[xii xiii] and to provide consent for the result of the test to be sent to their practice. For the purposes of the trial, cut points of 4 for women and 5 for men were used to identify probable hazardous or harmful drinkers. Patients screening below the cut points received an online message advising that their responses indicated that their stated drinking patterns fell within the guidelines for sensible drinking. Those scoring at or above the cut points received a personalised online message from their GP advising that their stated drinking patterns indicated that they were at risk from their drinking and encouraging them to take part in the study. Screen positive subjects were asked to complete an online form confirming that they did not meet any of the exclusion criteria and were subsequently invited to review the online patient information leaflet and to complete the online consent module. Those providing consent were invited to complete online questionnaires including a demographic questionnaire seeking information on age, gender, level of education and occupation, the 10-question AUDIT validated Italian version,[xiv -xv] and the EQ-5D 5L quality-of-life questionnaire, validated Italian version.[xvi] Completion of baseline questionnaires was followed automatically by concealed online randomisation to either facilitated access to the alcohol reduction website or to face to face BI.

The alcohol reduction website was adapted from the Down Your Drink Website (www.downyourdrink.org.uk), details of which have been reported elsewhere.[xvii] Country-specific information for Italy such as the recommended guidelines for alcohol intake, definitions of standard drinks and alcohol-related laws were included in the website. The website was further adapted to

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include a menu-driven facility which the participating GPs to create personalised automated tailored online messages for their patients. These were available at 4 key points in the programme, and included options to customise written text, add photographs and insert audio/video recorded messages.[xviii]

(Screenshots 1 and 2 here)

Patients allocated to facilitated access were directed to the opening page of the alcohol reduction website containing a personalised online message from their GP with tailored feedback about their responses to the AUDIT questionnaire. Further online messages emphasised the importance of adopting healthy drinking choices, and provided encouragement to spend at least 15 minutes engaging with the alcohol reduction website in the first instance. An automated email was sent 1 week later encouraging further log on. Patients were also asked online to review their alcohol consumption and were invited to discuss their website experience when they next saw their GP.

Patients allocated to face-to-face BI were invited to check a box online which automatically generated an email to their GP requesting an appointment within the next 7–10 days. GPs were instructed to offer a BI lasting 5-15 minutes based on the brief motivational interview.[xix] Non-attenders were offered up to three additional appointments.

Follow-up assessment

Follow-up took place 3 and 12 months after randomisation and a series of approaches were adopted to optimise response rates. In the first instance, each patient in the trial received an automated email requesting them to log in to the website to complete their assessment questionnaires. Failure to do so resulted in further automated emails at one and two week intervals. Persistent failure was notified to the patient's GP, who was asked to ensure that they were contacted by letter, phone or in person in order to complete their assessment. Where necessary, assessment was completed over the phone.

Outcomes

The primary outcome measure was the proportion of hazardous or harmful drinkers as defined by a score ≥8 points on the AUDIT questionnaire.[xx] The secondary outcome measure was the EQ-5D quality of life questionnaire, validated Italian version for use in economic evaluations. Advice to seek additional medical advice was given online to all patients scoring >20 on the AUDIT. Regular checks of the quality of the data were carried out under the supervision of the research team. Data files generated by the patients' interactions with the alcohol reduction website were stored securely on servers in accordance with EU regulations. The only identifiers were the unique login number. The files generated by the practices linking the unique login numbers to the patient identifiers were stored securely along with other clinical data in the practice and were accessible only to practice staff.

Statistical analysis

Facilitated access was deemed not inferior to face-to-face treatment at a one-sided α of 2·5% if the difference between the proportions of hazardous or harmful drinkers in the facilitated access group and the face-to-face BI group is below a specified absolute margin of non-inferiority of 10%.

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Assuming a reduction of 30% in the proportion of hazardous or harmful drinkers in the face to face BI group and allowing for an overall attrition of 10% of patients in the trial, it was calculated that 500 patients would be required in each group to give the trial 90% power (1-β) to reject the null hypothesis that facilitated access is inferior to face-to face intervention. All analyses were described in a statistical analysis plan completed before database lock. To assess the non-inferiority of facilitated access compared with face-to-face BI, the proportions of hazardous or harmful drinkers in each group were computed and compared using generalised non-linear mixed models accounting for general practices as random effects. Additional, pre-specified, supportive analyses were conducted as follows: Supportive 1 = including baseline values for hazardous or harmful drinkers; Supportive 2 = including a random residual term in replacement for the generalised random intercept term and baseline values for hazardous / harmful drinkers; Supportive 3 = AUDIT score as a continuous outcome, including the baseline AUDIT score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

As less than 30% of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on AUDIT, post hoc analyses were performed for the 3 months principal outcome measure on the basis of subjects who were, and were not, classified as hazardous or harmful drinkers at baseline. Additional post-hoc analyses were performed removing the final question of the AUDIT because of potential bias introduced by the question in the face-to-face BI group. All calculations were performed on the basis of intention to treat. An independent trial steering committee oversaw the general conduct of the trial and undertook data monitoring. The national clinical trial registration number was 01638338

Health economic analysis was undertaken to evaluate the cost-effectiveness of facilitated access to a website for hazardous drinkers compared to face-to-face BI, and the findings are reported in a separate paper (Hunter et al in this issue).

Trial Registration: ClinicalTrials.org NCT: 01638338

Role of the funding source:

This study was jointly supported by the Italian Ministry of Health and by the regional school for the training in Primary Care of the Region Friuli-Venezia Giulia, Italy (grant number: D25E12002900003). The funders had no direct influence over the design or conduct of the study.

RESULTS:

The trial was conducted in two phases – a pilot phase involving 11 GPs who recruited 89 subjects between 14th January 2013 and 31st May 2013, and the main trial phase involving 58 GPs who recruited 674 subjects between 20th January 2014 and 31st August 2014. The trial design was identical in both phases. Brochures were distributed to a total of 9080 patients across the 58 practices, and resulted in 4529 (49·9 %) patients logging on to the healthy lifestyle website. Of these, 3841 (84·5%) undertook screening with the AUDIT-C, and 822 (21·4%) screened positive. Of the screen positives, 763 (92·8%) were recruited to the trial, following consent, completion of baseline

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measures and randomisation. The minimum number of subjects recruited per practice was 1, and the maximum 89. The median number of subjects recruited per practice was 10 and the interquartile range was 3 to 19.

Figure 1 describes the progress of the 763 subjects through the trial. Three hundred and forty seven (45·5%) were allocated to facilitated access to the alcohol reduction website and 416 (54·5%) to face to face BI. A total of 698 (91·5%) subjects completed the three month follow-up assessment, and 620 (81·2%) the 12 month follow-up assessment. One subject was excluded due to inadvertent randomisation to both the intervention and control groups.

Baseline characteristics

Table 1 describes the baseline characteristics of the subjects in each group. The median age of the subjects was 49 years (IQR 35-61), and 469 (61·9%) were male. The median score on the AUDIT was 5.5 (IQR 4-9). 218 (28·6%) of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on the AUDIT.

Table 1: Baseline characteristics

Item	Facilitated Access n=346	Face to Face n=415
Male (%)	214 (62.0%)	255 (61.9%)
Marital Status		
Single (%)	95 (27.9%)	116 (28.4%)
Married (%)	208 (61.0%)	247 (60.4%)
Separated (%)	28 (8.2%)	36 (8.8%)
Widowed (%)	10 (2.9%)	10 (2.4%)
Ethnicity		
Caucasian (%)	8 (2.4%)	6 (1.5%)
Bengalese (%)	1 (0.3%)	1 (0.25%)
Indian (%)	1 (0.3%)	2 (0.5%)
Italian (%)	320 (95.8%)	385 (96.3%)
North African (%)	0 (0%)	1 (0.25%)
Mixed race (%)	1 (0.3%)	1 (0.25%)
Black African (%)	3 (0.9%)	4 (1.0%)
Familiarity with IT		
Not	58 (16.9%)	62 (15.2%)
Fairly	84 (24.5%)	93 (22.8%)
Familiar	91 (26.5%)	119 (29.2%)
Very	110 (32.1%)	134 (32.8%)
Qualifications		
None	2 (0.6%)	2 (0.5%)
Elementary/junior school	112 (32.9%)	126 (30.9%)
High school	174 (51.2%)	184 (45.1%)
University	45 (13.2%)	78 (19.1%)
Higher degree	7 (2.1%)	18 (4.4%)
Age, median (IQR)	49 (37, 59)	50 (35, 61)
Number of Children, median (IQR)	1 (0, 2)	1 (0, 2)
AUDIT 10, median (IQR)	5 (4, 8)	6 (4, 9)
Hazardous/Harmful Drinker (Audit-10 ≥8) (%)	95 (27.5%)	123 (29.6%)

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Engagement with face to face BI and facilitated access:

Of the 416 patients allocated to face to face BI, 325 (78.1%) were offered an appointment and 304 (73.1%) received a BI from their GP. Of the BIs, 171 (56.3%) were recorded as lasting less than 5 minutes, 87 (28.6) from 5-10 minutes and 46 (15.1%) more than 10 minutes. Table 2 describes engagement with the alcohol reduction website by the 342 patients in the facilitated access group as assessed in terms by numbers of log-ins, numbers of pages downloaded and the numbers of occasions on which an entry was made to the Thinker Drinker Record (TDR) section of the website.

Table 2: Engagement with alcohol reduction website by patients in facilitated access group (n=346)

Engagement variable	Mean (SD)	Interquartile range
User logins/patient	1.2 (0.85)	1 – 1
User page views/patient	33.5 (75.17)	1 – 41
TDR* total submissions/patient	18.5 (22.54)	3 – 27
TDR* total records/patient	14.8 (16.53)	3 - 22
TDR* total pages/patient	6.9 (6.88)	2 - 10

*TDR - Thinker Drinker Record entries made by patients on website pages

AUDIT scores

Figure 2 shows the mean AUDIT-10 scores and 95% confidence intervals for the subjects in each group at baseline, 3 months and 12 months. At baseline, 95 (27.5%) of the patients allocated to facilitated access were classified as hazardous or harmful drinkers by a score ≥8 points on the AUDIT, compared with 123 (20.6%) of the patients allocated to face to face BI. In the patients assessed at 3m, the number in this category in the facilitated access group reduced to 85 (26·8%) while in the face to face BI group it rose unexpectedly to 141 (37%). The difference was largely accounted for by responses to AUDIT question 10: *Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?*

Pre-specified analyses

Table 3 describes the results for the pre-specified analysis of the main outcome and the additional supportive analyses.

Table 3: Primary analysis and supportive analyses

Analysis		Estimate	Lower 95% CI	Upper 95% CI	P
Primary	(OR)	0.63	0.45	0.89	0.008
Supportive 1*	(OR)	0.62	0.43	0.90	0.012
Supportive 2**	(OR)	0.61	0.42	0.88	0.009
Supportive 3***	(OR)	-0.17	-0.58	0.25	0.43

* including baseline values for risky drinkers

** including a random residual term in replacement for the generalised random intercept term and baseline values for risky drinkers

*** AUDIT 10 score as a continuous outcome, including the baseline score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

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Analysis of the primary outcome shows statistically significant benefit for facilitated access compared with face to face BI. This is replicated in the additional pre-specified analyses and in all cases non-inferiority for facilitated access was demonstrated. Figure 3 describes the effects and interactions for the pre-specified subgroups. There was a significant interaction for age, and some indication of an interaction effect for computer literacy and baseline severity. Table 4 describes the results of the analyses at 12 months on the proportion of hazardous or harmful drinkers per group, and the difference in mean AUDIT. The 12 months odds ratio for hazardous or harmful drinking demonstrated non-inferiority of facilitated access compared with face-to-face BI, but non-inferiority was not demonstrated for the mean AUDIT scores at this time point.

Table 4: 12 month results – difference in hazardous/harmful drinkers and mean AUDIT-10

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Hazardous/harmful drinkers (OR)	0.943	1.432	0.621	0.784
Mean AUDIT-10	-0.3126	-0.8159	0.1906	0.2229

Post hoc analyses

Table 5 shows the findings of post-hoc analysis in relation to the primary outcome in hazardous or harmful drinkers only.

Table 5: Hazardous/harmful drinking at 3 months by hazardous/harmful drinking at baseline

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Not hazardous/harmful drinkers at baseline (OR)	0.476	0.289	0.782	0.004
Hazardous/harmful drinkers at baseline (OR)	0.772	0.431	1.383	0.382

Test for interaction between the groups p=0.192

Table 6 shows the result of analysis excluding the final question of the AUDIT, undertaken in order to address possible response bias in the face to face BI group due to final question of the AUDIT questionnaire (see Discussion). The mean score for the facilitated access group was 0·22 points higher than for the face to face BI group, and in this analysis the non-inferiority boundary was not achieved (lower confidence interval 11·7% worse).

Table 6: Difference in mean AUDIT at 3 months when question 10 is excluded

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Difference in mean AUDIT 9 at 3 months (OR)	0.2161	-0.1028	0.535	0.2161

Table 7 shows the results of further continuous and categorical analyses based upon the AUDIT C questions, neither of which supported non-inferiority of facilitated access.

Table 7

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Risky Drinkers on AUDIT C (OR)	1.555	2.127	1.136	0.006
Difference in mean AUDIT C score	-0.185	-0.396	0.027	0.087

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DISCUSSION

As far as we are aware, this is the first trial comparing effectiveness of facilitated access by general practitioners to an alcohol reduction website with delivery of face to face BI. It has demonstrated that this approach can be successfully implemented in general practice, with 58 participating GPs each providing facilitated access to an average of more than 150 patients, and nearly half of the patients subsequently following their GP's advice to log on and undertake screening . Furthermore, the great majority of patients randomised to facilitated access to the website went on to engage actively, downloading several pages and making multiple entries. The ODHIN trial which tested the relative impact on GP screening and BI activity of providing access to an alcohol reduction website (eBI), financial incentives and education and training, found that eBI was not associated with increased rates of activity.[xxi] However, the training and familiarisation with the website offered to the GPs was almost certainly less rigorous than in the EFAR- FVG trial.[xxii] Furthermore, the organisation of general practice in the 5 countries where ODHIN trial was conducted may have been less favourable to GP facilitated access.

The trial has a number of limitations. Fewer participants were recruited than the figure defined by the power calculation, though the effects observed were nonetheless sufficient to establish non-inferiority according to the pre-specified analyses. Randomisation led to a chance imbalance between the numbers of subjects in the two groups, but checks at several points during the trial confirmed that the imbalance was not due to a programming error and we were able to confirm that the software was operating correctly. The AUDIT-C screening tool performed poorly as a predictor of hazardous or harmful drinking as defined by a score of ≥8 points on the AUDIT. As a result, a minority (29·6%) of screen positive patients satisfied these criteria and only modest reductions were seen in mean AUDIT scores in both groups, possibly due to a threshold effect. Furthermore the trial did not observe the scale of reduction in the proportions of hazardous or harmful drinkers in the patients following brief intervention by their GPs which had informed our sample size calculation. Instead there was a paradoxical increase in the proportion of patients in the face-to-face BI group categorised as hazardous or harmful drinkers at 3 months, probably largely due to bias introduced by the final AUDIT question. This asks about advice to reduce drinking from a health care professional and might therefore be expected to elicit a positive response following face-to-face brief intervention. This hypothesis is supported by failure to confirm non-inferiority when the final question was omitted in the post hoc analysis, and suggests that alternative outcome measures such as the timeline follow-back questionnaire[xxiii] should be considered in studies where a face to face intervention is delivered in only one arm of a trial.

The main strengths of the study include the size of the study population, numbers of GPs involved, high levels of facilitated access activity, and high follow up rates of at both 3 months (91·5%) and 12 months (81·2%). The use of the Internet to deliver all components of the trial with the exception of the face to face intervention for patients in the control group reduced the cost of the trial, ensured consistency of conduct of all phases, avoided errors of transcription and enabled real-time tracking of trial activity by the study team. Furthermore, there were no reported breaches of data security.

Analysis of all pre-specified outcome measures demonstrated clear evidence of non-inferiority for facilitated access versus face to face brief intervention. Although post hoc analyses on subsets of the

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questions on the AUDIT raise important questions about the interpretation of the results, the findings of this trial are consistent with much of the growing literature on the effectiveness of digital interventions indicating that users benefit from online alcohol interventions and that this approach may be particularly useful for groups less likely to access traditional alcohol-related services, such as women, young people, and at-risk users. [xxiv-xxv] The main findings from the pre-specified analyses imply that a simple message given by the GP to the patient during facilitated access combined with provision of the log on code for the alcohol reduction website was no less effective in prompting behavioural change than a 5-10 minute brief intervention delivered face to face. This is consistent with the findings of a number of studies, most notably the SIPS trial which found the outcomes in patients screening positive hazardous or harmful drinking provided with a patient information leaflet were no worse than for those given five minutes of structured brief advice or 20 minutes of brief lifestyle counselling.[xxvi]

Further research is needed to determine whether the findings of the trial can be replicated in general practice settings involving larger clinical teams and greater numbers of registered patients. At least one such trial is currently underway in Catalunya, Spain and others are under development in Australia and Sweden.[xxvii] Additional study is also needed to improve understanding of the mechanisms underlying the impact of facilitated access and the conditions required to optimise it, including the role played by online GP personalisation. There are substantial opportunities to develop and evaluate facilitated access for a broader set of digital health applications.

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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 PW, PS, FS, RDV, CT were responsible for the management of the study and follow up of patients. NF was responsible for statistical analyses and RH for the health economic analyses. PW, PS and NF wrote the first draft and RH, PW, PS and NF contributed to its revision. ES participated in the management of the study and contributed to the review of the manuscript and its final approval, together with all the other authors.

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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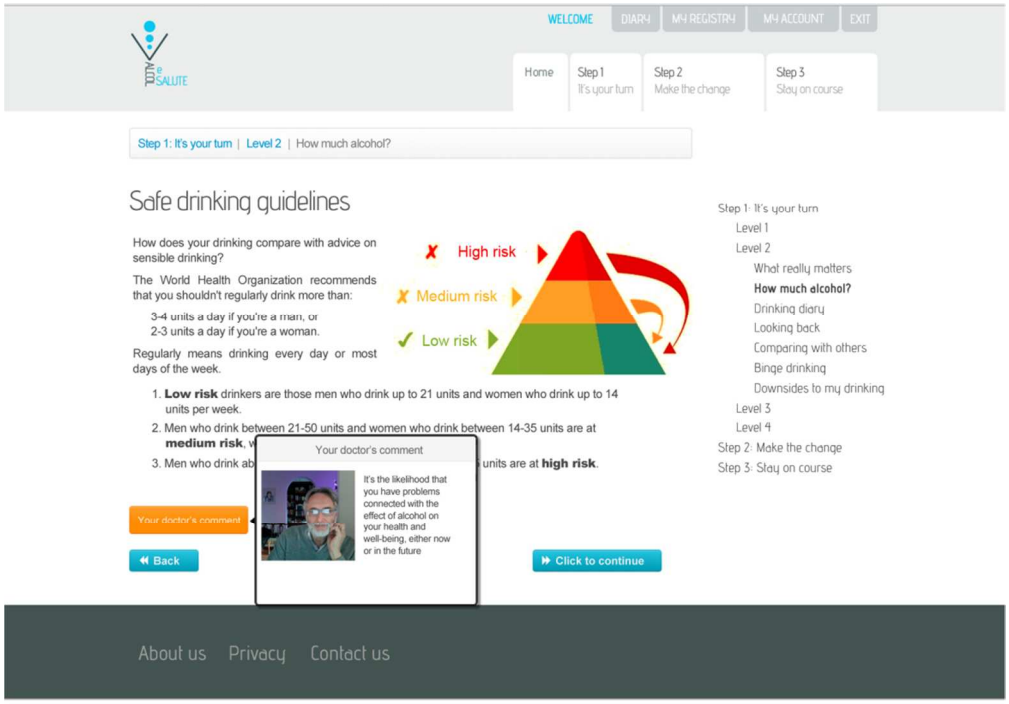
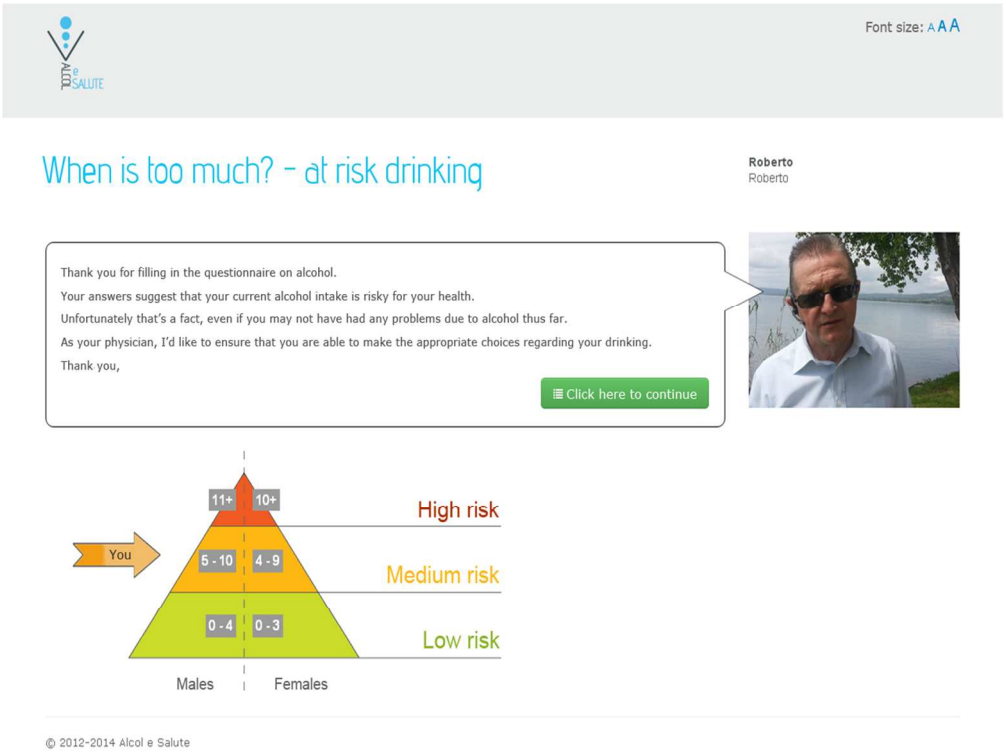


Screenshot 1: Welcome page: safe drinking guidelines with GP personalisation

view only



Screenshot 2: Tailored feedback on male subject's AUDIT C score of 7 with GP personalisation

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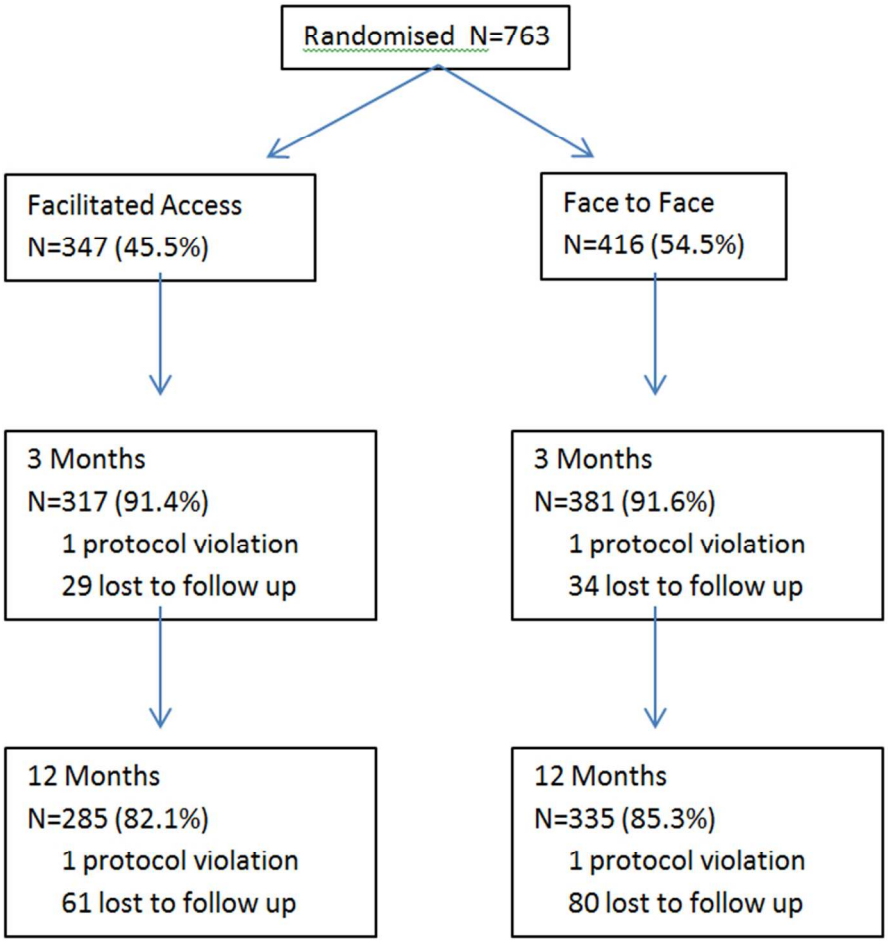

Figure 1 Patient progress through the trial

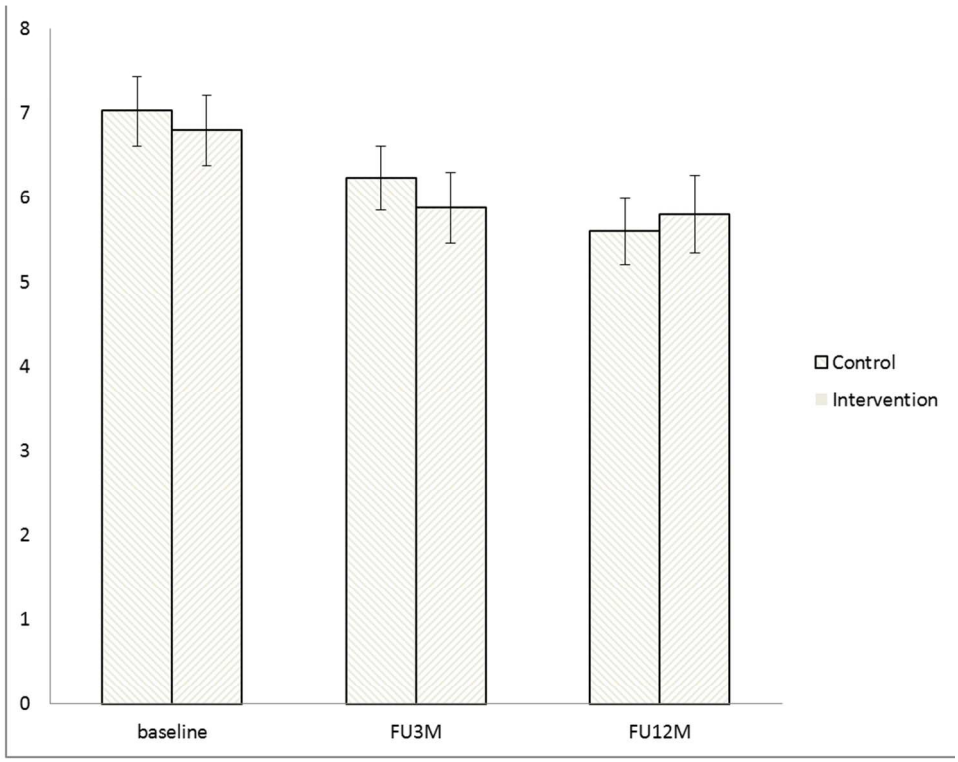

Figure 2: Mean AUDIT scores and 95% confidence intervals for subjects in each group at baseline, 3 months and 12 months.

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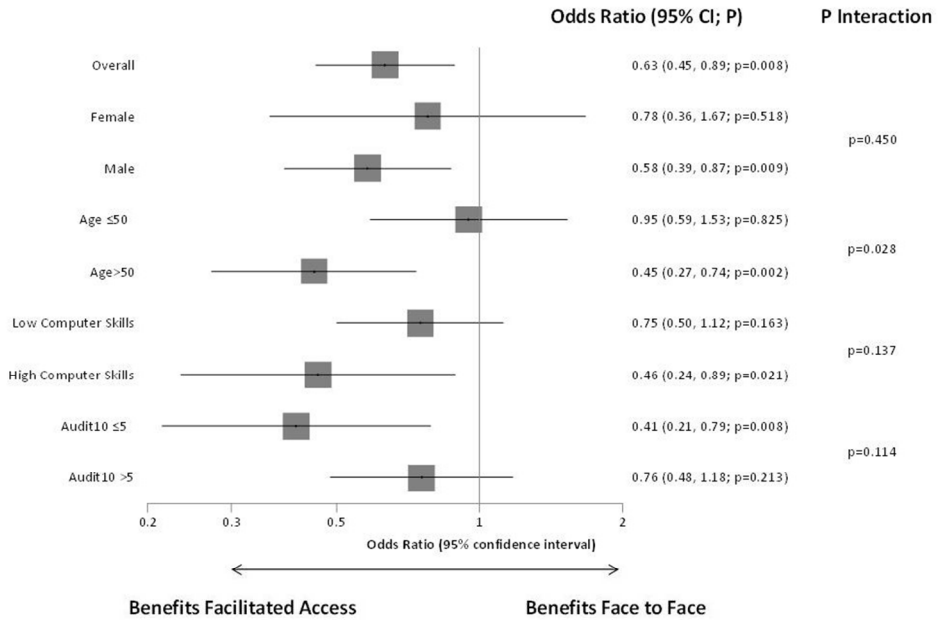

Figure 3: Pre-specified Subgroup Analyses

273x209mm (96 x 96 DPI)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **PAGE 1 (5-6)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **PAGE 6 (37)**
	2b	All items from the World Health Organization Trial Registration Data Set **N/A**
Protocol version	3	Date and version identifier **PAGE 20**
Funding	4	Sources and types of financial, material, and other support **PAGE 6 (41-44)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **TITLE PAGE**
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities PAGE 6 (41-44)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **N/A**
Introduction		

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Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **PAGE 3 (6-41)**
	6b	Explanation for choice of comparators **PAGE 3 (36-41)**
Objectives	7	Specific objectives or hypotheses **PAGE 3 (43-44)**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **PAGE 4 (52-58)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **PAGE 4 (2-6)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **PAGE 4 (18-22)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **PAGE 4 (54-58) / PAGE 5 (3-23)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **N/A**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **PAGE 5 (40-51)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **PAGE 6 (50-54)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **PAGE 6 (3-7)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Page 4 (6-11)**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **PAGE 4 (26-27)**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **PAGE 4 (26-27)**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **PAGE 4 (26-27)**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **PAGE 4 (26-27)**

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **N/A**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Page 5 (40-51)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Page 5 (28-35)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Page 5 (45-51**)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Page 5 (53-58) / page 6 (2-27)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **PAGE 6 (12-27)**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **DMC NOT REQUIRED**

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **N/A**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **N/A**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **N/A**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **PAGE 4 (12-14)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **N/A**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **PAGE 4 (42-46)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **N/A**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **PAGE 5 (44-51)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **PAGE 12-(13-18)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

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Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		**IN SUBMISSION TO BMJ OPEN**
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **N/A**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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

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Manuscripts

Title:

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

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SUMMARY:

Background: Brief interventions delivered in primary care have been shown to be effective in reducing risky drinking, but implementation is limited. Facilitated access to a digital application offers a novel alternative to face-to-face intervention, but its relative effectiveness is unknown.

Methods: Primary care based, non-inferiority, randomised controlled trial comparing general practitioner facilitated access to an interactive alcohol reduction website (FA) with face-to-face brief intervention (BI) for risky drinking. Patients screening positive on AUDIT C were invited to participate in the trial. Assessment at baseline, 3 months and 12 months was carried out using AUDIT and EQ5D 5L questionnaires.

Findings: 58 participating GPs approached 9080 patients of whom 3841 (84·8%) undertook online screening, 822 (21.4%) screened positive and 763 (19·9%) were recruited. 347 (45.5 %) were allocated to FA and 416 (54.5%) to BI. At 3 months, subjects in FA group with AUDIT score ≥8 reduced from 95 (27.5%) to 85 (26·8%) while those in BI group increased from 123 (20.6%) to 141 (37%) Differences between groups were principally due to responses to AUDIT question 10. Analysis of primary outcome indicated non inferiority of FA compared with BI, and pre-specified subgroup analysis indicated benefits for older patients and those with higher levels of computer literacy and lower baseline severity. Additional analyses undertaken to take account of bias in response to AUDIT question 10 failed to support non inferiority within the pre-specified 10% boundary.

Interpretation: Pre specified protocol driven analyses of the trial indicate that FA is non inferior to BI, however identified bias in the outcome measure and further supportive analyses question the robustness of this finding. It is therefore not possible to draw firm conclusions from this trial, and further research is needed to determine whether the findings can be replicated using more robust outcome measures.

Trial Registration: ClinicalTrials.gov NCT: 01638338

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The trial evaluated a potentially important development for primary care, namely the use by GPs of facilitated access to a digital application as an alternative to traditional face to face consultation, in this case for patients with risky drinking.
- It was developed and delivered by an international multidisciplinary team in the UK and Italy
- All components of the trial were delivered online with the exception of the face to face intervention, thus reducing the cost of the trial, allowing real-time tracking of the findings, ensuring consistency of conduct and avoiding errors of transcription.
- Follow up rates exceeded 90% at 3 months and 80 % at 12 months
- Levels of hazardous and harmful drinking in trial participants were lower than anticipated

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- Probable bias in the brief intervention group indicates that caution should be exercised in interpreting the main findings

INTRODUCTION:

Alcohol is the third leading cause of diseases and premature death globally[1] and accounts for 3·8% of deaths and 4·6% of disability-adjusted life years.[2] Brief interventions delivered in primary health care settings have been demonstrated repeatedly to be effective in reducing hazardous and harmful drinking.[3] However, barriers prevent their widespread implementation, including insufficient training, lack of resources and constraints in time.[4] Digital applications including websites and apps which are based on behaviour change techniques may be helpful in overcoming these barriers,[5 6] and clinicians may actively encourage patients to use approved applications through a process known as facilitated access. Initially adopted primarily for the management of patients with mental health problems including depression and anxiety, facilitated access has been extended to digital applications for addictive behaviours including smoking cessation and alcohol screening, and health promotion and the management of some long term conditions.[7 8]

Facilitated access offers a novel alternative to face-to-face brief intervention (BI) for risky drinking, but it is not known whether it is as effective. A review of trials of computer-based interventions offered to college drinkers found them to be more effective than no treatment and as effective as alternative treatment approaches.[9] A systematic review of electronic interventions for risky drinkers concluded that there were significant reductions in weekly alcohol consumption between intervention and control conditions between 3 months and less than 12 months follow-up, indicating this may be an effective intervention.[10]

A review of digital and computer-based alcohol intervention programs promoted in primary care settings identified fifteen small scale trials of which nine were associated with a reduction in alcohol use at follow-up.[11] The indications from these studies about the likely effectiveness and cost effectiveness of internet applications in primary care were generally positive, but firm conclusions could not be drawn because of limitations of sample size and study design. An adequately powered and appropriately designed trial was therefore required to provide more definitive evidence on the use of facilitated access as an alternative to face to face BI for the reduction of hazardous and harmful drinking, and to indicate the potential for this approach to be adopted more generally in the management of health conditions by general practitioners. The research question addressed by the trial was “Is facilitated access to an interactive alcohol reduction website as effective in reducing hazardous and harmful drinking as face to face BI?”

METHODS:

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Study design:

Primary care based, non-inferiority, randomised controlled trial of brief intervention for risky drinkers comparing general practitioner (GP) facilitated access to an interactive alcohol reduction website (facilitated access) with standard face-to-face BI. With the exception of face to face intervention, all components of the trial were delivered online to patients following receipt of a brochure describing the website and providing a unique trial log-on number. Access to the website was via the healthy lifestyle portal of the official website of the Region of Friuli-Venezia Giulia (www.itatvb.it). GPs were recruited via the official register of the Friuli-Venezia Giulia region of Northern Italy. All participating GPs attended a one-day training event including an overview of the trial and interactive sessions on the delivery of face-to-face BI using the principles of brief motivational interviewing. They were encouraged to familiarise themselves with the trial website and to use the menu-driven online GP personalisation facility to create their own tailored patient messages at up to four key points of the programme (see Procedures and Figure 1). They were also given brief guidance about how to actively encourage patients to access the website.

The protocol was approved by the Isontina Independent Local Health Unit Ethics Committee on 14 June 2012.[12]

Patients:

All patients aged 18 or over who attended the participating practices during the study period were eligible for the trial, but those known by the GPs to suffer from severe psychiatric disorder, alcohol dependence, serious visual impairment or terminal illness were excluded, as were those judged to have inadequate command of the Italian language.

Randomisation and masking:

Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.

Procedures

For the purposes of screening, GPs spoke briefly to eligible patients, gave them a trial brochure with a unique log in code and actively encouraged them to access the trial website. Those who logged on were asked to complete the three-question short Alcohol Use Disorders Identification Test (AUDIT-C)[13] and to provide consent for the result of the test to be sent to their practice. For the purposes of the trial, cut points of 4 for women and 5 for men were used to identify probable hazardous or harmful drinkers. Patients screening below the cut points received an online message advising that their responses indicated that their stated drinking patterns fell within the guidelines for sensible drinking. Those scoring at or above the cut points received a personalised online message from their GP advising that their stated drinking patterns indicated that they were likely to be at risk from their drinking and encouraging them to take part in the study. They were then invited to review the online patient information leaflet and to complete the consent module. Following consent, patients were invited to complete online questionnaires including a demographic questionnaire seeking information on age, gender, level of education and occupation, the 10-question AUDIT validated Italian version,[14 15] and the EQ-5D 5L quality-of-life questionnaire, validated

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Italian version.[16] Completion of baseline questionnaires was followed automatically by concealed online randomisation to either facilitated access to the alcohol reduction website or to face to face BI.

The alcohol reduction website was adapted from the Down Your Drink Website (www.downyourdrink.org.uk), details of which have been reported elsewhere.[17] Country-specific information for Italy such as the recommended guidelines for alcohol intake, definitions of standard drinks and alcohol-related laws were included in the website. The website was further adapted to include a menu-driven facility which the participating GPs to create personalised automated tailored online messages for their patients. These were available at 4 key points in the programme, and included options to customise written text, add photographs and insert audio/video recorded messages.[18] An example of a screenshot of tailored feedback with GP personalisation is shown. (Figure 1)

Patients allocated to facilitated access were directed to the opening page of the alcohol reduction website containing a personalised online message from their GP with tailored feedback about their responses to the AUDIT questionnaire. Further online messages emphasised the importance of adopting healthy drinking choices. They provided encouragement to spend at least 15 minutes engaging with the alcohol reduction website, including making entries in the personal Thinking Drinking Record (TDR) about their assessment of costs and benefits of their current levels of drinking. An automated email was sent 1 week later encouraging further log on. Patients were also asked online to review their alcohol consumption and were invited to discuss their website experience when they next saw their GP.

Patients allocated to face-to-face BI were invited to check a box online which automatically generated an email to their GP requesting an appointment within the next 7–10 days. GPs were instructed to offer a BI lasting 5-15 minutes based on the brief motivational interview.[19] Non-attenders were offered up to three additional appointments.

Follow-up assessment

Follow-up took place 3 and 12 months after randomisation and a series of approaches were adopted to optimise response rates. In the first instance, each patient in the trial received an automated email requesting them to log in to the website to complete their assessment questionnaires. Failure to do so resulted in further automated emails at one and two week intervals. Persistent failure was notified to the patient's GP, who was asked to ensure that they were contacted by letter, phone or in person in order to complete their assessment. Where necessary, assessment was completed over the phone.

Outcomes

The pre-specified primary outcome measure was the proportion of hazardous or harmful drinkers as defined by a score ≥8 points on the AUDIT questionnaire at 3 months follow up.[20] The secondary outcome measure was the EQ-5D quality of life questionnaire, validated Italian version for use in economic evaluations. Advice to seek additional medical advice was given online to all patients scoring >20 on the AUDIT. Regular checks of the quality of the data were carried out under the supervision of the research team. Data files generated by the patients' interactions with the alcohol

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reduction website were stored securely on servers in accordance with EU regulations. The only identifiers were the unique login number. The files generated by the practices linking the unique login numbers to the patient identifiers were stored securely along with other clinical data in the practice and were accessible only to practice staff.

Statistical analysis

Facilitated access was deemed not inferior to face-to-face treatment at a one-sided α of 2·5% if the difference between the proportions of hazardous or harmful drinkers in the facilitated access group and the face-to-face BI group is below a specified absolute margin of non-inferiority of 10%. Assuming a reduction of 30% in the proportion of hazardous or harmful drinkers in the face to face BI group and allowing for an overall attrition of 10% of patients in the trial, it was calculated that 500 patients would be required in each group to give the trial 90% power (1-β) to reject the null hypothesis that facilitated access is inferior to face-to face intervention. Analyses were described in a statistical analysis plan completed before database lock. To assess the non-inferiority of facilitated access compared with face-to-face BI, the proportions of hazardous or harmful drinkers in each group were computed and compared using generalised non-linear mixed models accounting for general practices as random effects in order to address possible therapist effects and other practice level clustering. Additional, pre-specified, supportive analyses designed to provide further information about the trial outcomes were conducted as follows: Supportive 1 = random intercept term for practices and baseline values for hazardous or harmful drinkers; Supportive 2 = included a random residual term in replacement for the generalised random intercept term and baseline values for hazardous / harmful drinkers; Supportive 3 = AUDIT score as a continuous outcome, including the baseline AUDIT score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

Post hoc analyses were designed to address the unexpected finding that less than 30% of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on AUDIT, and the unexpected rise at follow-up in the proportions of patients in the face-to-face BI group scoring ≥8 points on AUDIT. Analysis was therefore carried out for the 3 months principal outcome measure on the basis of subjects who were, and were not, classified as hazardous or harmful drinkers at baseline, and additionally by removing the final question of the AUDIT which may have introduced bias favouring the experimental condition. All calculations were performed on the basis of intention to treat. An independent trial steering committee oversaw the general conduct of the trial and undertook data monitoring.

Health economic analysis was undertaken to evaluate the cost-effectiveness of facilitated access to a website for hazardous drinkers compared to face-to-face BI, and the findings are reported in a separate paper (Hunter et al, Cost effectiveness analysis of EFAR FVG. Submitted to BMJ Open 4th October 2016 and currently under review: manuscript ID is bmjopen-2016-014577).

Trial Registration: ClinicalTrials.gov NCT: 01638338

Role of the funding source:

This study was jointly supported by the Italian Ministry of Health and by the regional school for the training in Primary Care of the Region Friuli-Venezia Giulia, Italy (grant number: D25E12002900003). The funders had no direct influence over the design or conduct of the study.

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RESULTS:

The trial was conducted in two phases – a pilot phase involving 11 GPs who recruited 89 subjects between 14th January 2013 and 31st May 2013, and the main trial phase involving 58 GPs who recruited 674 subjects between 20th January 2014 and 31st August 2014. The trial design was identical in both phases. Brochures were distributed to a total of 9080 patients across the 58 practices, and resulted in 4529 (49·9 %) patients logging on to the healthy lifestyle website. Of these, 3841 (84·5%) undertook screening with the AUDIT-C, and 822 (21·4%) screened positive. Of the screen positives, 763 (92·8%) were recruited to the trial, following consent, completion of baseline measures and randomisation. The minimum number of subjects recruited per practice was 1, and the maximum 89. The median number of subjects recruited per practice was 10 and the interquartile range was 3 to 19.

Figure 2 describes the progress of the 763 subjects through the trial. Three hundred and forty seven (45·5%) were allocated to facilitated access to the alcohol reduction website and 416 (54·5%) to face to face BI. A total of 698 (91·5%) subjects completed the three month follow-up assessment, and 620 (81·2%) the 12 month follow-up assessment. One subject was excluded due to inadvertent randomisation to both the intervention and control groups.

Baseline characteristics

Table 1 describes the baseline characteristics of the subjects in each group. The median age of the subjects was 49 years (IQR 35-61), and 469 (61·9%) were male. The median score on the AUDIT was 5.5 (IQR 4-9). 218 (28·6%) of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on the AUDIT.

Table 1: Baseline characteristics

Item	Facilitated Access n=346	Face to Face n=415
Male (%)	214 (62.0%)	255 (61.9%)
Marital Status		
Single (%)	95 (27.9%)	116 (28.4%)
Married (%)	208 (61.0%)	247 (60.4%)
Separated (%)	28 (8.2%)	36 (8.8%)
Widowed (%)	10 (2.9%)	10 (2.4%)
Ethnicity		
Bengalese (%)	1 (0.3%)	1 (0.25%)
Indian (%)	1 (0.3%)	2 (0.5%)
Italian (%)	328 (98.2%)	391 (97.8%)
North African (%)	0 (0%)	1 (0.25%)
Mixed race (%)	1 (0.3%)	1 (0.25%)
Black African (%)	3 (0.9%)	4 (1.0%)
Familiarity with IT		
Not	58 (16.9%)	62 (15.2%)
Fairly	84 (24.5%)	93 (22.8%)
Familiar	91 (26.5%)	119 (29.2%)
Very	110 (32.1%)	134 (32.8%)

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Qualifications		
None	2 (0.6%)	2 (0.5%)
Elementary/junior school	112 (32.9%)	126 (30.9%)
High school	174 (51.2%)	184 (45.1%)
University	45 (13.2%)	78 (19.1%)
Higher degree	7 (2.1%)	18 (4.4%)
Age, median (IQR)	49 (37, 59)	50 (35, 61)
Number of Children, median (IQR)	1 (0, 2)	1 (0, 2)
AUDIT 10, median (IQR)	5 (4, 8)	6 (4, 9)
Hazardous/Harmful Drinker (AUDIT ≥8) (%)	95 (27.5%)	123 (29.6%)

Engagement with face to face BI and facilitated access:

Of the 416 patients allocated to face to face BI, 325 (78.1%) were offered an appointment and 304 (73.1%) received a BI from their GP. Of the BIs, 171 (56.3%) were recorded as lasting less than 5 minutes, 87 (28.6) from 5-10 minutes and 46 (15.1%) more than 10 minutes.

Table 2 describes engagement with the alcohol reduction website by the 342 patients in the facilitated access group as assessed in terms by numbers of log-ins, numbers of pages downloaded and the numbers of occasions on which an entry was made to the Thinker Drinker Record (TDR) section of the website.

Table 2: Engagement with alcohol reduction website by patients in facilitated access group (n=346)

Engagement variable	Mean (SD)	Interquartile range
User logins/patient	1.2 (0.85)	1 – 1
User page views/patient	33.5 (75.17)	1 – 41
TDR* total submissions/patient	18.5 (22.54)	3 – 27
TDR* total records/patient	14.8 (16.53)	3 - 22
TDR* total pages/patient	6.9 (6.88)	2 - 10

*TDR - Thinker Drinker Record entries made by patients on website pages

AUDIT scores

At baseline, 95 (27.5%) of the patients allocated to facilitated access were classified as hazardous or harmful drinkers by a score ≥8 points on the AUDIT, compared with 123 (20.6%) of the patients allocated to face to face BI.

Table 3 Number of risky drinkers at baseline, 3 and 12 months by randomised condition

Time period n in follow up	Face to Face n (%)	Facilitated n (%)
Baseline n=761	123 (29.6%)	95 (27.5%)
3 months n=698	141 (37.1%)	85 (26.8%)

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12 months n=620	88 (26.3%)	71 (24.9%)

In the patients assessed at 3m, the number in this category in the facilitated access group reduced to 85 (26·8%) while in the face to face BI group it rose unexpectedly to 141 (37%), dropping at 12 m to 88 (26.3%). The difference at 3m was largely accounted for by responses to AUDIT question 10: *Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?*

Pre-specified analyses

Table 4 describes the results for the pre-specified analysis of the main outcome at 3 months and the additional supportive analyses.

Table 4: Primary analysis and supportive analyses

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Primary – proportion of hazardous or harmful drinkers (OR)	0.63	0.45	0.89	0.008
Supportive analysis 1* (OR)	0.62	0.43	0.90	0.012
Supportive analysis 2** (OR)	0.61	0.42	0.88	0.009
Supportive analysis 3 *** (OR)	-0.17	-0.58	0.25	0.43

* proportion of hazardous or harmful drinkers; including baseline values for risky drinkers and random intercept term for practice

** including a random residual term in replacement for the generalised random intercept term for practice and baseline values for risky drinkers

*** AUDIT 10 score as a continuous outcome, including the baseline score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

Analysis of the primary outcome, difference in the odds of hazardous and harmful drinkers, shows statistically significant benefit for facilitated access compared with face to face BI. This is replicated in the additional pre-specified analyses and in all cases non-inferiority for facilitated access was demonstrated. Figure 3 describes the effects and interactions for the pre-specified subgroups. There was a significant interaction for age, and some indication of an interaction effect for computer literacy and baseline severity.

Table 5 describes the results of the analyses at 12 months on the proportion of hazardous or harmful drinkers per group, and the difference in mean AUDIT scores. The 12 months odds ratio for hazardous or harmful drinking demonstrated non-inferiority of facilitated access compared with face-to-face BI, but non-inferiority was not demonstrated for the mean AUDIT scores at this time point.

Table 5: 12 month results – difference in hazardous/harmful drinkers and mean AUDIT-10

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Hazardous/harmful drinkers (OR)	0.943	1.432	0.621	0.784
Mean AUDIT-10	-0.3126	-0.8159	0.1906	0.2229

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Post hoc analyses

Table 6 shows the findings of post-hoc analysis on the subsets of participants who were and were not hazardous /harmful drinkers at baseline. The analysis did not support non-inferiority of facilitated access at 3 month follow-up for those with hazardous/harmful drinking at baseline.

Table 6: Hazardous/harmful drinking at 3 months by hazardous/harmful drinking at baseline.

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Not hazardous/harmful drinkers at baseline n= 545 (OR)	0.476	0.289	0.782	0.004
Hazardous/harmful drinkers at baseline n= 218 (OR)	0.772	0.431	1.383	0.382

Test for interaction between the groups p=0.192

Table 7 shows the proportions of participants classified as hazardous/harmful drinkers at 3m and 12m using a cut point of >7 points on the AUDIT questionnaire with question 10 removed.

Table 7 Proportions of hazardous/harmful drinking as defined by >7 points on AUDIT with question 10 removed

Time period n in follow up	Face to Face n (%)	Facilitated n (%)
Baseline n=761	93 (22.4%)	79 (22.8%)
3 months n=698	28 (7.4%)	32 (10.1%)
12 months n=620	27 (8.1%)	35 (12.3%)

Table 8 shows the results of further continuous and categorical analyses based upon the AUDIT C questions. Neither analysis supported non-inferiority of facilitated access.

Table 8 Continuous and categorical analyses based upon the AUDIT C questions.

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Risky Drinkers on AUDIT C (OR)	1.555	2.127	1.136	0.006
Difference in mean AUDIT C score	-0.185	-0.396	0.027	0.087

EQ5D

The results of the EQ5D are reported in a separate paper (Hunter et al, Cost effectiveness analysis of EFAR FVG. Submitted to BMJ Open 4th October 2016 and currently under review: manuscript ID: bmjopen-2016-014577).

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DISCUSSION

As far as we are aware, this is the first trial comparing effectiveness of facilitated access by general practitioners to an alcohol reduction website with delivery of face to face BI. It has demonstrated that this approach can be successfully implemented in general practice, with 58 participating GPs each providing facilitated access to an average of more than 150 patients, and nearly half of the patients subsequently following their GP's advice to log on and undertake screening . Furthermore, the great majority of patients randomised to facilitated access to the website went on to engage actively, downloading several pages and making multiple entries. The ODHIN trial which tested the relative impact on GP screening and BI activity of providing access to an alcohol reduction website (eBI), financial incentives and education and training, found that eBI was not associated with increased rates of activity.[21] However, the training and familiarisation with the website offered to the GPs was almost certainly less rigorous than in the EFAR- FVG trial.[22] Furthermore, the organisation of general practice in the 5 countries where ODHIN trial was conducted may have been less favourable to GP facilitated access.

The trial has a number of limitations. Fewer participants were recruited than the figure defined by the power calculation, and more importantly the AUDIT-C screening tool performed poorly as a predictor of hazardous or harmful drinking as defined by a score of ≥8 points on the AUDIT. This meant that the trial population included only a minority (29·6%) of hazardous/harmful drinkers as defined by an AUDIT score ≥8. The resultant threshold effect was almost certainly responsible at least in part for the only modest reductions seen in the proportions of hazardous/harmful drinkers in both groups. The use of AUDIT C cut points of 5 for men and 4 for women would have been expected to lead to the inclusion of substantially higher proportions of hazardous and harmful drinkers as defined by a score of 8 or more on the AUDIT.[23,24] The AUDIT C has also been validated in Italian populations and found to perform similarly.[10] However a recent paper has suggested that higher cut points should be used to reliably identify risky drinkers.[25]

The trial did not observe the scale of reduction in the proportions of hazardous or harmful drinkers in the patients following brief intervention by their GPs which had informed our sample size calculation. Instead there was a paradoxical increase in the proportion of patients in the face-to-face BI group categorised as hazardous or harmful drinkers at 3 months though this was not maintained at 12 months. We postulated that this was largely due to bias introduced by the final AUDIT question which asks about advice to reduce drinking from a health care professional, and might therefore be expected to elicit a positive response in the short term following face-to-face brief intervention. This hypothesis was supported by failure to confirm non-inferiority when the final question was omitted in the post hoc analysis.

The main strengths of the study include the size of the study population, numbers of GPs involved, high levels of facilitated access activity, and high follow up rates of at both 3 months (91·5%) and 12 months (81·2%). The use of the Internet to deliver all components of the trial with the exception of the face to face intervention for patients in the control group reduced the cost of the trial, ensured consistency of conduct of all phases, avoided errors of transcription and enabled real-time tracking of trial activity by the study team. Furthermore, there were no reported breaches of data security.

Analysis of all pre-specified outcome measures demonstrated evidence of non-inferiority for facilitated access versus face to face brief intervention. On the face of it, this implies that a simple

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message given by the GP to the patient during facilitated access combined with provision of the log on code for the alcohol reduction website was no less effective in prompting behavioural change than a 5-10 minute brief intervention delivered face to face. This is consistent with the findings of a number of studies, most notably the SIPS trial which found the outcomes in patients screening positive hazardous or harmful drinking provided with a patient information leaflet were no worse than for those given five minutes of structured brief advice or 20 minutes of brief lifestyle counselling.[26] These findings are also consistent with much of the growing literature on the effectiveness of digital interventions indicating that users benefit from online alcohol interventions and that this approach may be particularly useful for groups less likely to access traditional alcohol-related services, such as women, young people, and at-risk users.[27]

However, the reliability of the conclusions from the primary analyses is seriously called into question by the results of the post hoc analyses performed in order to deal with the presumptive evidence of response bias in the face to face group. When these were performed using both a subset of the questions on the AUDIT omitting question 10, and the three questions of the AUDIT C, the results no longer supported the conclusion of non-inferiority of facilitated access. This raises real questions about the reliability of the trial's main findings, and further research will be needed to determine whether these can be replicated. Alternative cut points on the screening AUDIT C could be used to ensure the inclusion of greater proportions of hazardous/harmful drinkers in future studies, and an alternative outcome measure such as the timeline follow-back questionnaire[28] could be used in order to avoid bias introduced by the AUDIT. It would also be helpful to replicate the trial in general practice settings involving larger clinical teams and greater numbers of registered patients. At least one such trial is currently underway in Catalunya, Spain and others are under development in Australia and Sweden.[29] Additional study is also needed to improve understanding of the mechanisms underlying the impact of facilitated access and the conditions required to optimise it, including the role played by online GP personalisation.

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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. NF was responsible for statistical analyses. PW, PS and NF wrote the first draft. RH, PW, PS and NF contributed to its revision and all authors contributed to 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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Data sharing:

Anonymised trial data is held on secure servers at University College London. For access to the data please contact the corresponding author, supplying study protocol and approval.

Figure legends:

Figure 1: Screenshot showing tailored feedback on AUDIT C with GP personalisation (translated from original Italian)

Figure 2: Subject progress through the trial

Figure 3: Primary outcome – pre-specified sub-group analyses

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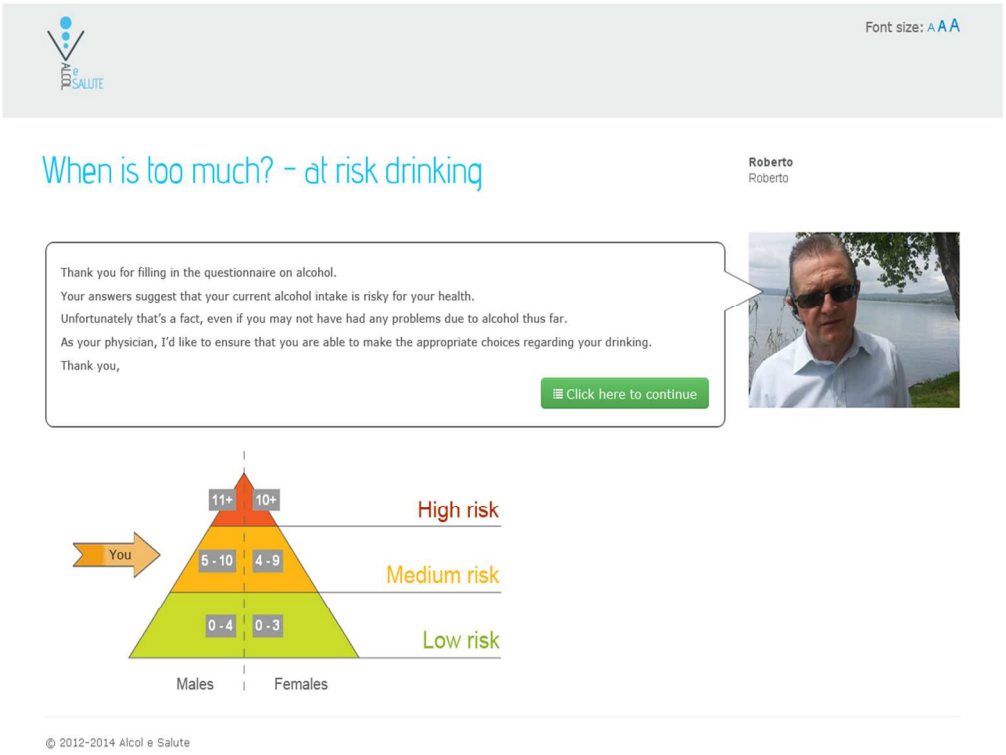

Figure 1: Screenshot showing tailored feedback on AUDIT C with GP personalisation (translated from original Italian)

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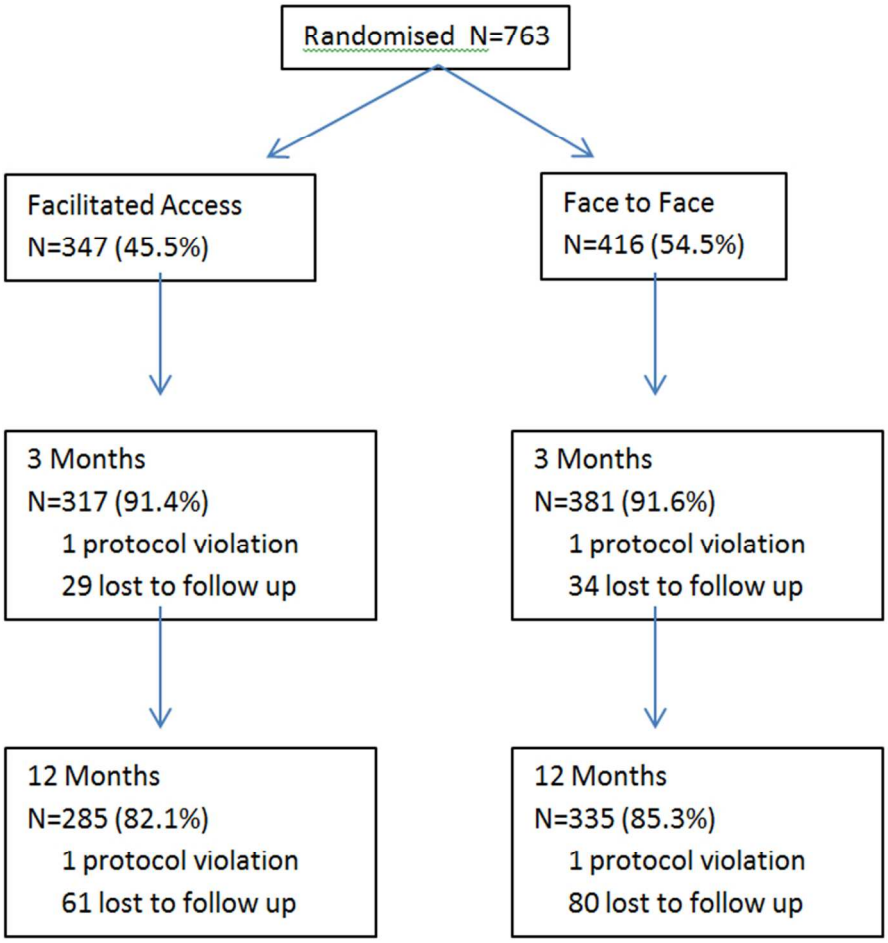

Figure 2: Subject progress through the trial

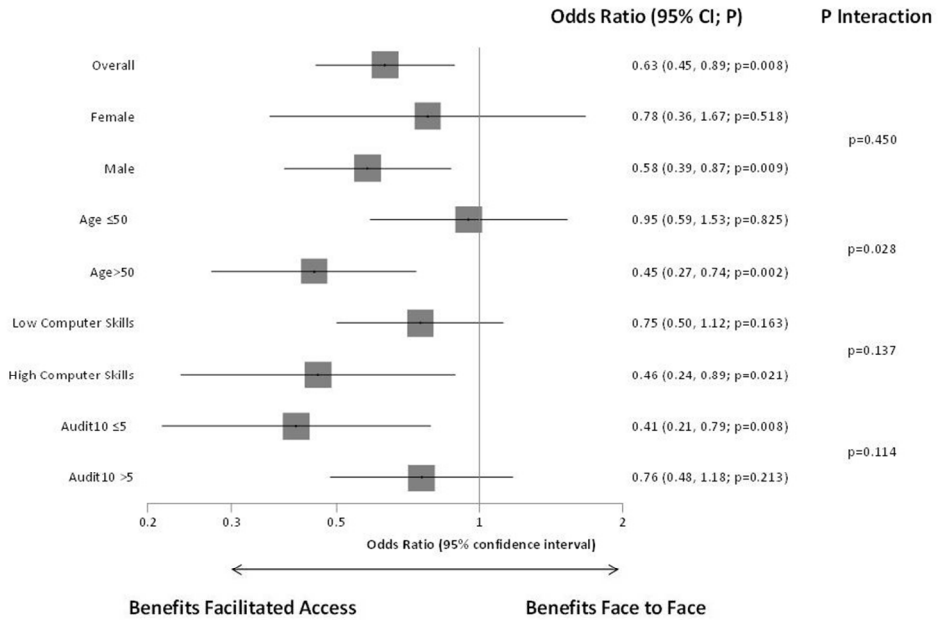

Figure 3: Primary outcome – pre-specified sub-group analyses

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CONSORT Statement 2006 - Checklist for Non-inferiority and Equivalence Trials

Items to include when reporting a non-inferiority or equivalence randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned"), *specifying that the trial is a non-inferiority or equivalence trial.* Title: Randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website Abstract: Primary care based, non-inferiority, randomised controlled trial comparing general practitioner facilitated access to an interactive alcohol reduction website (FA) with face-to-face brief intervention (BI) for risky drinking	1 2
INTRODUCTION Background	2	Scientific background and explanation of rationale, *including the rationale for using a non-inferiority or equivalence design.* Facilitated access offers a novel alternative to face-to-face brief intervention (BI) for risky drinking, but it is not known whether it is as effective. .. An adequately powered and appropriately designed trial was therefore required to provide more definitive evidence on the use of facilitated access as an alternative to face to face BI for the reduction of hazardous and harmful drinking, and to indicate the potential for this approach to be adopted more generally in the management of health conditions by general practitioners. The research question addressed by the trial was "Is facilitated access to an interactive alcohol reduction website as effective in reducing hazardous and harmful drinking as face to face BI?"	3 3
METHODS Participants	3	Eligibility criteria for participants *(detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment)* and the settings and locations where the data were collected. All patients aged 18 or over who attended the participating practices during the study period were eligible for the trial, but those known by the GPs to suffer from severe psychiatric disorder, alcohol dependence, serious visual impairment or terminal illness were excluded, as were those judged to have inadequate command of the Italian language…. Following consent, patients were invited to complete online questionnaires including a demographic questionnaire seeking information on age, gender, level of education and occupation, the 10-question AUDIT validated Italian version, and the EQ-5D 5L quality-of-life questionnaire, validated Italian version…. Follow-up took place 3 and 12 months after randomisation and a series of approaches were adopted to optimise response rates. In the first instance, each patient in the trial received an automated email requesting them to log in to the website to complete their assessment questionnaires. Failure to do so resulted in further automated emails at one and two week intervals. Persistent failure was notified to the patient's GP, who was asked to ensure that they were contacted by letter, phone or in person in order to complete their assessment. Where necessary, assessment was completed over the phone.	4 4 5
Interventions	4	Precise details of the interventions intended for each group *detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered	

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		Patients allocated to facilitated access were directed to the opening page of the alcohol reduction website containing a personalised online message from their GP with tailored feedback about their responses to the AUDIT questionnaire. Further online messages emphasised the importance of adopting healthy drinking choices. They provided encouragement to spend at least 15 minutes engaging with the alcohol reduction website, including making entries in the personal Thinking Drinking Record (TDR) about their assessment of costs and benefits of their current levels of drinking. An automated email was sent 1 week later encouraging further log on. Patients were also asked online to review their alcohol consumption and were invited to discuss their website experience when they next saw their GP. Patients allocated to face-to-face BI were invited to check a box online which automatically generated an email to their GP requesting an appointment within the next 7–10 days. GPs were instructed to offer a BI lasting 5-15 minutes based on the brief motivational interview. Non-attenders were offered up to three additional appointments.	5 5
Objectives	5	Specific objectives and hypotheses, *including the hypothesis concerning non-inferiority or equivalence.* The research question addressed by the trial was "Is facilitated access to an interactive alcohol reduction website as effective in reducing hazardous and harmful drinking as face to face BI?"	3
Outcomes	6	Clearly defined primary and secondary outcome measures *detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors). The pre-specified primary outcome measure was the proportion of hazardous or harmful drinkers as defined by a score ≥8 points on the AUDIT questionnaire at 3 months follow up. The secondary outcome measure was the EQ-5D quality of life questionnaire, validated Italian version for use in economic evaluations.	5
Sample size	7	How sample size was determined *detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules (*and whether related to a non-inferiority or equivalence hypothesis*). Facilitated access was deemed not inferior to face-to-face treatment at a one-sided α of 2·5% if the difference between the proportions of hazardous or harmful drinkers in the facilitated access group and the face-to-face BI group is below a specified absolute margin of non-inferiority of 10%. Assuming a reduction of 30% in the proportion of hazardous or harmful drinkers in the face to face BI group and allowing for an overall attrition of 10% of patients in the trial, it was calculated that 500 patients would be required in each group to give the trial 90% power (1-β) to reject the null hypothesis that facilitated access is inferior to face-to face intervention.	6
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification) Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification	4

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		or blinding.	
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.	4
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.	4
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), *specifying whether a one or two-sided confidence interval approach was used.* Methods for additional analyses, such as subgroup analyses and adjusted analyses. Analyses were described in a statistical analysis plan completed before database lock. To assess the non-inferiority of facilitated access compared with face-to-face BI, the proportions of hazardous or harmful drinkers in each group were computed and compared using generalised non-linear mixed models accounting for general practices as random effects in order to address possible therapist effects and other practice level clustering. Additional, pre-specified, supportive analyses designed to provide further information about the trial outcomes were conducted as follows: Supportive 1 = random intercept term for practices and baseline values for hazardous or harmful drinkers; Supportive 2 = included a random residual term in replacement for the generalised random intercept term and baseline values for hazardous / harmful drinkers; Supportive 3 = AUDIT score as a continuous outcome, including the baseline AUDIT score as a patient level explanatory variable, with generalised random intercept terms for GP practices. Post hoc analyses were designed to address the unexpected finding that less than 30% of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on AUDIT, and the unexpected rise at follow-up in the proportions of patients in the face-to-face BI group scoring ≥8 points on AUDIT. Analysis was therefore carried out for the 3 months principal outcome measure on the basis of subjects who were, and were not, classified as hazardous or harmful drinkers at baseline, and additionally by removing the final question of the AUDIT which may have introduced bias favouring the experimental condition. All calculations were performed on the basis of intention to treat. An independent trial steering committee oversaw the general conduct of the trial and undertook data monitoring.	6 6

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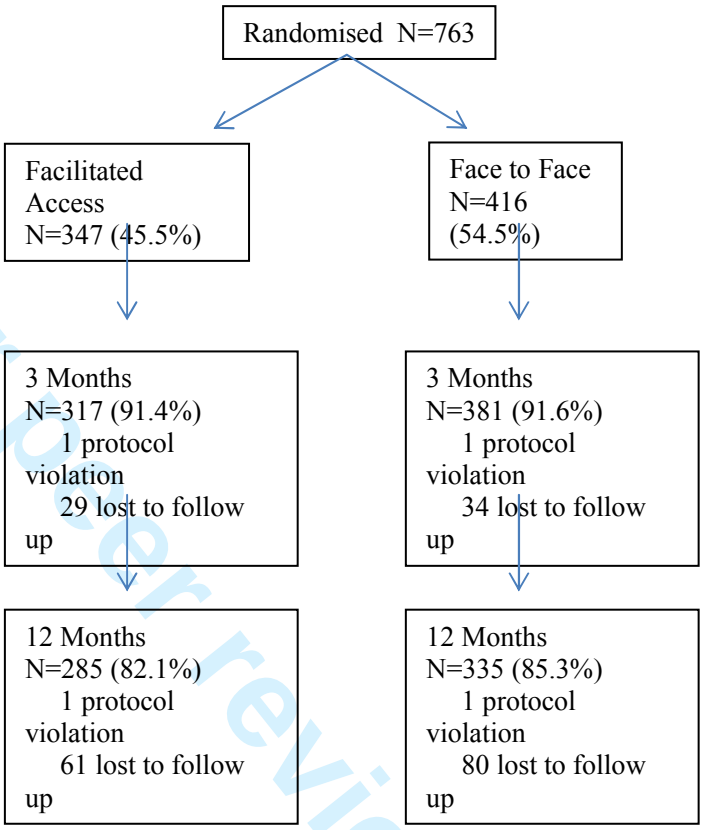
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. **Figure 1 Flow of patients through the study**  Figure 1 describes the progress of the 763 subjects through the trial. Three hundred and forty seven (45·5%) were allocated to facilitated access to the alcohol reduction website and 416 (54·5%) to face to face BI. A total of 698 (91·5%) subjects completed the three month follow-up assessment, and 620 (81·2%) the 12 month follow-up assessment. One subject was excluded due to inadvertent randomisation to both the intervention and control groups.	7
Recruitment	14	Dates defining the periods of recruitment and follow-up. The trial was conducted in two phases – a pilot phase involving 11 GPs who recruited 89 subjects between 14th January 2013 and 31st May 2013, and the main trial phase involving 58 GPs who recruited 674 subjects between 20th January 2014 and 31st August 2014. The trial design was identical in both phases.	7
Baseline data	15	Baseline demographic and clinical characteristics of each group. Item | Facilitated Access Male (%) | 214 (62.0%) Marital Status | Single (%) | 95 (27.9%) Married (%) | 208 (61.0%) Separated (%) | 28 (8.2%) Widowed (%) | 10 (2.9%) Ethnicity | Caucasian (%) | 8 (2.4%)	7

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		Bengalese (%)	1 (0.3%)		1 (0.25%)
		Indian (%)	1 (0.3%)		2 (0.5%)
		Italian (%)	320 (95.8%)		385 (96.3%)
		North African (%)	0 (0%)		1 (0.25%)
		Mixed race (%)	1 (0.3%)		1 (0.25%)
		Black African (%)	3 (0.9%)		4 (1.0%)
		Familiarity with IT			
		Not	58 (16.9%)		62 (15.2%)
		Fairly	84 (24.5%)		93 (22.8%)
		Familiar	91 (26.5%)		119 (29.2%)
		Very	110 (32.1%)		134 (32.8%)
		Qualifications			
		None	2 (0.6%)		2 (0.5%)
		Elementary/junior school	112 (32.9%)		126 (30.9%)
		High school	174 (51.2%)		184 (45.1%)
		University	45 (13.2%)		78 (19.1%)
		Higher degree	7 (2.1%)		18 (4.4%)
		Age, median (IQR)	49 (37, 59)		50 (35, 61)
		Number of Children, median (IQR)	1 (0, 2)		1 (0, 2)
		AUDIT 10, median (IQR)	5 (4, 8)		6 (4, 9)
		Hazardous/Harmful Drinker (Audit-10 ≥8) (%)	95 (27.5%)		123 (29.6%)

Numbers analyzed — 16

Number of participants (denominator) in each group included in each analysis and whether the analysis was *"intention-to-treat" and/or alternative analyses were conducted.* State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).

Table 3 Number of risky drinkers at baseline, 3 and 12 months by randomised condition

Time period n in follow up	Face to Face n (%)
Baseline n=761	123 (29.6%)
3 months n=698	141 (37.1%)
12 months n=620	88 (26.3%)

8/9

Outcomes and estimation — 17

For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval). *For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*

Table 4: Primary analysis and supportive analyses

Analysis		Estima
Primary – proportion of hazardous or harmful drinkers (OR)		0
Supportive analysis 1*	(OR)	0
Supportive analysis 2**	(OR)	0
Supportive analysis 3 ***	(OR)	-0

* proportion of hazardous or harmful drinkers; including baseline values for risky drinkers and random intercept term for practice

** including a random residual term in replacement for the generalised random intercept term for practice and baseline values for risky drinkers

*** AUDIT 10 score as a continuous outcome, including the baseline score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

9

Table 5: 12 month results – difference in hazardous/harmful drinkers and mean AUDIT-10

Analysis	Estimate	Lower 95% CI	Up
Hazardous/harmful drinkers (OR)	0.943	1.432	
Mean AUDIT-10	-0.3126	-0.8159	

9/10

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<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Ancillary analyses</td><td>18</td><td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.

Table 6: Hazardous/harmful drinking at 3 months by hazardous/harmful drinking at baseline.<table><tr><td>Analysis</td><td>Estimate</td></tr><tr><td>Not hazardous/harmful drinkers at baseline n= 545 (OR)</td><td>0.476</td></tr><tr><td>Hazardous/harmful drinkers at baseline n= 218 (OR)</td><td>0.772</td></tr></table>Test for interaction between the groups p=0.192

Table 7 Proportions of hazardous/harmful drinking as defined by >7 points on AUDIT with question 10 removed<table><tr><td>Time period n in follow up</td><td>Face to Face n (%)</td></tr><tr><td>Baseline n=761</td><td>93 (22.4%)</td></tr><tr><td>3 months n=698</td><td>28 (7.4%)</td></tr><tr><td>12 months n=620</td><td>27 (8.1%)</td></tr></table>
Table 8 Continuous and categorical analyses based upon the AUDIT C questions.<table><tr><td>Analysis</td><td>Estimate</td><td>Lower 95% CI</td><td>U</td></tr><tr><td>Risky Drinkers on AUDIT C (OR)</td><td>1.555</td><td>2.127</td><td></td></tr><tr><td>Difference in mean AUDIT C score</td><td>-0.185</td><td>-0.396</td><td></td></tr></table></td><td>10

10

10</td></tr>
<tr><td>Adverse events</td><td>19</td><td>All important adverse events or side effects in each intervention group.

N/A</td><td></td></tr>
<tr><td>DISCUSSION
Interpretation</td><td>20</td><td>Interpretation of the results, taking into account the non-inferiority or equivalence hypothesis and any other study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.

Analysis of all pre-specified outcome measures demonstrated evidence of non-inferiority for facilitated access versus face to face brief intervention. On the face of it, this implies that a simple message given by the GP to the patient during facilitated access combined with provision of the log on code for the alcohol reduction website was no less effective in prompting behavioural change than a 5-10 minute brief intervention delivered face to face……..

However, the reliability of the conclusions from the primary analyses is seriously called into question by the results of the post hoc analyses performed in order to deal with the presumptive evidence of response bias in the face to face group. When these were performed using both a subset of the questions on the AUDIT omitting question 10, and the three questions of the AUDIT C, the results no longer supported the conclusion of non-inferiority of facilitated access. This raises real questions about the reliability of the trial's main findings, and further research will be needed to determine whether these can be replicated.</td><td>11/12

12</td></tr>
<tr><td>Generalizability</td><td>21</td><td>Generalizability (external validity) of the trial findings.

It would … be helpful to replicate the trial general practice settings involving larger clinical teams and greater numbers of registered patients. At least one such trial is currently underway in Catalunya, Spain and others are underway in Australia and Sweden.</td><td>12</td></tr>
</table>

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Overall evidence	22	General interpretation of the results in the context of current evidence. Pre specified protocol driven analyses of the trial indicate that FA is non inferior to BI, however identified bias in the outcome measure and further supportive analyses question the robustness of this finding. It is therefore not possible to draw firm conclusions from this trial, and further research is needed to determine whether the findings can be replicated using more robust outcome measures.	2

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

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Title:

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

Authors:

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SUMMARY:

Background: Brief interventions delivered in primary care have been shown to be effective in reducing risky drinking, but implementation is limited. Facilitated access to a digital application offers a novel alternative to face-to-face intervention, but its relative effectiveness is unknown.

Methods: Primary care based, non-inferiority, randomised controlled trial comparing general practitioner facilitated access to an interactive alcohol reduction website (FA) with face-to-face brief intervention (BI) for risky drinking. Patients screening positive on AUDIT C were invited to participate in the trial. Assessment at baseline, 3 months and 12 months was carried out using AUDIT and EQ5D 5L questionnaires.

Findings: 58 participating GPs approached 9080 patients of whom 4529 (49·9 %) logged on, 3841 (84·8%) undertook screening, 822 (21.4%) screened positive and 763 (19·9%) were recruited. 347 (45.5 %) were allocated to FA and 416 (54.5%) to BI. At 3 months, subjects in FA group with AUDIT score ≥8 reduced from 95 (27.5%) to 85 (26·8%) while those in BI group increased from 123 (20.6%) to 141 (37%) Differences between groups were principally due to responses to AUDIT question 10. Analysis of primary outcome indicated non inferiority of FA compared with BI, and pre-specified subgroup analysis indicated benefits for older patients and those with higher levels of computer literacy and lower baseline severity. Additional analyses undertaken to take account of bias in response to AUDIT question 10 failed to support non inferiority within the pre-specified 10% boundary.

Interpretation: Pre specified protocol driven analyses of the trial indicate that FA is non inferior to BI, however identified bias in the outcome measure and further supportive analyses question the robustness of this finding. It is therefore not possible to draw firm conclusions from this trial, and further research is needed to determine whether the findings can be replicated using more robust outcome measures.

Trial Registration: ClinicalTrials.gov NCT: 01638338

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The trial evaluated a potentially important development for primary care, namely the use by GPs of facilitated access to a digital application as an alternative to traditional face to face consultation, in this case for patients with risky drinking.
- It was developed and delivered by an international multidisciplinary team in the UK and Italy
- All components of the trial were delivered online with the exception of the face to face intervention, thus reducing the cost of the trial, allowing real-time tracking of the findings, ensuring consistency of conduct and avoiding errors of transcription.
- Follow up rates exceeded 90% at 3 months and 80 % at 12 months

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- Levels of hazardous and harmful drinking in trial participants were lower than anticipated
- Probable bias in the brief intervention group indicates that caution should be exercised in interpreting the main findings

INTRODUCTION:

Alcohol is the third leading cause of diseases and premature death globally[1] and accounts for 3·8% of deaths and 4·6% of disability-adjusted life years.[2] Brief interventions delivered in primary health care settings have been demonstrated repeatedly to be effective in reducing hazardous and harmful drinking.[3] However, barriers prevent their widespread implementation, including insufficient training, lack of resources and constraints in time.[4] Digital applications including websites and apps which are based on behaviour change techniques may be helpful in overcoming these barriers,[5 6] and clinicians may actively encourage patients to use approved applications through a process known as facilitated access. Initially adopted primarily for the management of patients with mental health problems including depression and anxiety, facilitated access has been extended to digital applications for addictive behaviours including smoking cessation and alcohol screening, and health promotion and the management of some long term conditions.[7 8]

Facilitated access offers a novel alternative to face-to-face brief intervention (BI) for risky drinking, but it is not known whether it is as effective. A review of trials of computer-based interventions offered to college drinkers found them to be more effective than no treatment and as effective as alternative treatment approaches.[9] A systematic review of electronic interventions for risky drinkers concluded that there were significant reductions in weekly alcohol consumption between intervention and control conditions between 3 months and less than 12 months follow-up, indicating this may be an effective intervention.[10]

A review of digital and computer-based alcohol intervention programs promoted in primary care settings identified fifteen small scale trials of which nine were associated with a reduction in alcohol use at follow-up.[11] The indications from these studies about the likely effectiveness and cost effectiveness of internet applications in primary care were generally positive, but firm conclusions could not be drawn because of limitations of sample size and study design. An adequately powered and appropriately designed trial was therefore required to provide more definitive evidence on the use of facilitated access as an alternative to face to face BI for the reduction of hazardous and harmful drinking, and to indicate the potential for this approach to be adopted more generally in the management of health conditions by general practitioners. The research question addressed by the trial was “Is facilitated access to an interactive alcohol reduction website as effective in reducing hazardous and harmful drinking as face to face BI?”

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METHODS:

Study design:

Primary care based, non-inferiority, randomised controlled trial of brief intervention for risky drinkers comparing general practitioner (GP) facilitated access to an interactive alcohol reduction website (facilitated access) with standard face-to-face BI. With the exception of face to face intervention, all components of the trial were delivered online to patients following receipt of a brochure describing the website and providing a unique trial log-on number. Access to the website was via the healthy lifestyle portal of the official website of the Region of Friuli-Venezia Giulia (www.itatvb.it). GPs were recruited via the official register of the Friuli-Venezia Giulia region of Northern Italy. All participating GPs attended a one-day training event including an overview of the trial and interactive sessions on the delivery of face-to-face BI using the principles of brief motivational interviewing. They were encouraged to familiarise themselves with the trial website and to use the menu-driven online GP personalisation facility to create their own tailored patient messages at up to four key points of the programme (see Procedures and Screenshots 1&2). They were also given brief guidance about how to actively encourage patients to access the website.

The protocol was approved by the Isontina Independent Local Health Unit Ethics Committee on 14 June 2012.[12]

Patients:

All patients aged 18 or over who attended the participating practices during the study period were eligible for the trial, but those known by the GPs to suffer from severe psychiatric disorder, alcohol dependence, serious visual impairment or terminal illness were excluded, as were those judged to have inadequate command of the Italian language.

Randomisation and masking:

Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.

Procedures

For the purposes of screening, GPs spoke briefly to eligible patients, gave them a trial brochure with a unique log in code and actively encouraged them to access the trial website. Those who logged on were asked to complete the three-question short Alcohol Use Disorders Identification Test (AUDIT-C)[13] and to provide consent for the result of the test to be sent to their practice. For the purposes of the trial, cut points of 4 for women and 5 for men were used to identify probable hazardous or harmful drinkers. Patients screening below the cut points received an online message advising that their responses indicated that their stated drinking patterns fell within the guidelines for sensible drinking. Those scoring at or above the cut points received a personalised online message from their GP advising that their stated drinking patterns indicated that they were likely to be at risk from their drinking and encouraging them to take part in the study. They were then invited to review the online patient information leaflet and to complete the consent module. Following consent, patients were invited to complete online questionnaires including a demographic

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questionnaire seeking information on age, gender, level of education and occupation, the 10-question AUDIT validated Italian version,[14 15] and the EQ-5D 5L quality-of-life questionnaire, validated Italian version.[16] Completion of baseline questionnaires was followed automatically by concealed online randomisation to either facilitated access to the alcohol reduction website or to face to face BI.

The alcohol reduction website was adapted from the Down Your Drink Website (www.downyourdrink.org.uk), details of which have been reported elsewhere.[17] Country-specific information for Italy such as the recommended guidelines for alcohol intake, definitions of standard drinks and alcohol-related laws were included in the website. The website was further adapted to include a menu-driven facility which the participating GPs to create personalised automated tailored online messages for their patients. These were available at 4 key points in the programme, and included options to customise written text, add photographs and insert audio/video recorded messages.[18] An example of a screenshot of tailored feedback with GP personalisation is shown in Figure 1.

Patients allocated to facilitated access were directed to the opening page of the alcohol reduction website containing a personalised online message from their GP with tailored feedback about their responses to the AUDIT questionnaire. Further online messages emphasised the importance of adopting healthy drinking choices. They provided encouragement to spend at least 15 minutes engaging with the alcohol reduction website, including making entries in the personal Thinking Drinking Record (TDR) about their assessment of costs and benefits of their current levels of drinking. An automated email was sent 1 week later encouraging further log on. Patients were also asked online to review their alcohol consumption and were invited to discuss their website experience when they next saw their GP.

Patients allocated to face-to-face BI were invited to check a box online which automatically generated an email to their GP requesting an appointment within the next 7–10 days. GPs were instructed to offer a BI lasting 5-15 minutes based on the brief motivational interview.[19] Non-attenders were offered up to three additional appointments.

Follow-up assessment

Follow-up took place 3 and 12 months after randomisation and a series of approaches were adopted to optimise response rates. In the first instance, each patient in the trial received an automated email requesting them to log in to the website to complete their assessment questionnaires. Failure to do so resulted in further automated emails at one and two week intervals. Persistent failure was notified to the patient's GP, who was asked to ensure that they were contacted by letter, phone or in person in order to complete their assessment. Where necessary, assessment was completed over the phone.

Outcomes

The pre-specified primary outcome measure was the proportion of hazardous or harmful drinkers as defined by a score ≥8 points on the AUDIT questionnaire at 3 months follow up.[20] The secondary outcome measure was the EQ-5D quality of life questionnaire, validated Italian version for use in economic evaluations. Advice to seek additional medical advice was given online to all patients

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scoring >20 on the AUDIT. Regular checks of the quality of the data were carried out under the supervision of the research team. Data files generated by the patients' interactions with the alcohol reduction website were stored securely on servers in accordance with EU regulations. The only identifiers were the unique login number. The files generated by the practices linking the unique login numbers to the patient identifiers were stored securely along with other clinical data in the practice and were accessible only to practice staff.

Statistical analysis

Facilitated access was deemed not inferior to face-to-face treatment at a one-sided α of 2·5% if the difference between the proportions of hazardous or harmful drinkers in the facilitated access group and the face-to-face BI group is below a specified absolute margin of non-inferiority of 10%. Assuming a reduction of 30% in the proportion of hazardous or harmful drinkers in the face to face BI group and allowing for an overall attrition of 10% of patients in the trial, it was calculated that 500 patients would be required in each group to give the trial 90% power (1-β) to reject the null hypothesis that facilitated access is inferior to face-to face intervention. Analyses were described in a statistical analysis plan completed before database lock. To assess the non-inferiority of facilitated access compared with face-to-face BI, the proportions of hazardous or harmful drinkers in each group were computed and compared using generalised non-linear mixed models accounting for general practices as random effects in order to address possible therapist effects and other practice level clustering. Additional, pre-specified, supportive analyses designed to provide further information about the trial outcomes were conducted as follows: Supportive 1 = random intercept term for practices and baseline values for hazardous or harmful drinkers; Supportive 2 = included a random residual term in replacement for the generalised random intercept term and baseline values for hazardous / harmful drinkers; Supportive 3 = AUDIT score as a continuous outcome, including the baseline AUDIT score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

Post hoc analyses were designed to address the unexpected finding that less than 30% of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on AUDIT, and the unexpected rise at follow-up in the proportions of patients in the face-to-face BI group scoring ≥8 points on AUDIT. Analysis was therefore carried out for the 3 months principal outcome measure on the basis of subjects who were, and were not, classified as hazardous or harmful drinkers at baseline, and additionally by removing the final question of the AUDIT which may have introduced bias favouring the experimental condition. All calculations were performed on the basis of intention to treat. An independent trial steering committee oversaw the general conduct of the trial and undertook data monitoring.

Health economic analysis was undertaken to evaluate the cost-effectiveness of facilitated access to a website for hazardous drinkers compared to face-to-face BI, and the findings are reported in a separate paper (Hunter et al, Cost effectiveness analysis of EFAR FVG. Submitted to BMJ Open 4th October 2016 and currently under review: manuscript ID is bmjopen-2016-014577).

Trial Registration: ClinicalTrials.gov NCT: 01638338

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Role of the funding source:

This study was jointly supported by the Italian Ministry of Health and by the regional school for the training in Primary Care of the Region Friuli-Venezia Giulia, Italy (grant number: D25E12002900003). The funders had no direct influence over the design or conduct of the study.

RESULTS:

The trial was conducted in two phases – a pilot phase involving 11 GPs who recruited 89 subjects between 14th January 2013 and 31st May 2013, and the main trial phase involving 58 GPs who recruited 674 subjects between 20th January 2014 and 31st August 2014. The trial design was identical in both phases. Brochures were distributed to a total of 9080 patients across the 58 practices, and resulted in 4529 (49·9 %) patients logging on to the healthy lifestyle website. Of these, 3841 (84·5%) undertook screening with the AUDIT-C, and 822 (21·4%) screened positive. Of the screen positives, 763 (92·8%) were recruited to the trial, following consent, completion of baseline measures and randomisation. The minimum number of subjects recruited per practice was 1, and the maximum 89. The median number of subjects recruited per practice was 10 and the interquartile range was 3 to 19.

Figure 2 describes the progress of the 763 subjects through the trial. Three hundred and forty seven (45·5%) were allocated to facilitated access to the alcohol reduction website and 416 (54·5%) to face to face BI. A total of 698 (91·5%) subjects completed the three month follow-up assessment, and 620 (81·2%) the 12 month follow-up assessment. One subject was excluded due to inadvertent randomisation to both the intervention and control groups.

Baseline characteristics

Table 1 describes the baseline characteristics of the subjects in each group. The median age of the subjects was 49 years (IQR 35-61), and 469 (61·9%) were male. The median score on the AUDIT was 5.5 (IQR 4-9). 218 (28·6%) of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on the AUDIT.

Table 1: Baseline characteristics

Item	Facilitated Access n=346	Face to Face n=415
Male (%)	214 (62.0%)	255 (61.9%)
Marital Status		
Single (%)	95 (27.9%)	116 (28.4%)
Married (%)	208 (61.0%)	247 (60.4%)
Separated (%)	28 (8.2%)	36 (8.8%)
Widowed (%)	10 (2.9%)	10 (2.4%)
Ethnicity		
Bengalese (%)	1 (0.3%)	1 (0.25%)
Indian (%)	1 (0.3%)	2 (0.5%)
Italian (%)	328 (98.2%)	391 (97.8%)
North African (%)	0 (0%)	1 (0.25%)
Mixed race (%)	1 (0.3%)	1 (0.25%)

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Black African (%)	3 (0.9%)	4 (1.0%)
Familiarity with IT		
Not	58 (16.9%)	62 (15.2%)
Fairly	84 (24.5%)	93 (22.8%)
Familiar	91 (26.5%)	119 (29.2%)
Very	110 (32.1%)	134 (32.8%)
Qualifications		
None	2 (0.6%)	2 (0.5%)
Elementary/junior school	112 (32.9%)	126 (30.9%)
High school	174 (51.2%)	184 (45.1%)
University	45 (13.2%)	78 (19.1%)
Higher degree	7 (2.1%)	18 (4.4%)
Age, median (IQR)	49 (37, 59)	50 (35, 61)
Number of Children, median (IQR)	1 (0, 2)	1 (0, 2)
AUDIT 10, median (IQR)	5 (4, 8)	6 (4, 9)
Hazardous/Harmful Drinker (AUDIT ≥8) (%)	95 (27.5%)	123 (29.6%)

Engagement with face to face BI and facilitated access:

Of the 416 patients allocated to face to face BI, 325 (78.1%) were offered an appointment and 304 (73.1%) received a BI from their GP. Of the BIs, 171 (56.3%) were recorded as lasting less than 5 minutes, 87 (28.6) from 5-10 minutes and 46 (15.1%) more than 10 minutes.

Table 2 describes engagement with the alcohol reduction website by the 342 patients in the facilitated access group as assessed in terms by numbers of log-ins, numbers of pages downloaded and the numbers of occasions on which an entry was made to the Thinker Drinker Record (TDR) section of the website.

Table 2: Engagement with alcohol reduction website by patients in facilitated access group (n=346)

Engagement variable	Mean (SD)	Interquartile range
User logins/patient	1.2 (0.85)	1 – 1
User page views/patient	33.5 (75.17)	1 – 41
TDR* total submissions/patient	18.5 (22.54)	3 – 27
TDR* total records/patient	14.8 (16.53)	3 - 22
TDR* total pages/patient	6.9 (6.88)	2 - 10

*TDR - Thinker Drinker Record entries made by patients on website pages

AUDIT scores

At baseline, 95 (27.5%) of the patients allocated to facilitated access were classified as hazardous or harmful drinkers by a score ≥8 points on the AUDIT, compared with 123 (20.6%) of the patients allocated to face to face BI.

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The numbers (%) of risky drinkers at the three assessment points of the trial are shown in Table 3.

Table 3 Number of risky drinkers at baseline, 3 and 12 months by randomised condition

Time period n in follow up	Face to Face n (%)	Facilitated n (%)
Baseline n=761	123 (29.6%)	95 (27.5%)
3 months n=698	141 (37.1%)	85 (26.8%)
12 months n=620	88 (26.3%)	71 (24.9%)

In the patients assessed at 3m, the number in this category in the facilitated access group reduced to 85 (26·8%) while in the face to face BI group it rose unexpectedly to 141 (37%), dropping at 12 m to 88 (26.3%). The difference at 3m was largely accounted for by responses to AUDIT question 10: *Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?*

Pre-specified analyses

Table 4 describes the results for the pre-specified analysis of the main outcome at 3 months and the additional supportive analyses.

Table 4: Primary analysis and supportive analyses

Analysis		Estimate	Lower 95% CI	Upper 95% CI	P
Primary – proportion of hazardous or harmful drinkers (OR)		0.63	0.45	0.89	0.008
Supportive analysis 1*	(OR)	0.62	0.43	0.90	0.012
Supportive analysis 2**	(OR)	0.61	0.42	0.88	0.009
Supportive analysis 3 ***	(OR)	-0.17	-0.58	0.25	0.43

* proportion of hazardous or harmful drinkers; including baseline values for risky drinkers and random intercept term for practice

** including a random residual term in replacement for the generalised random intercept term for practice and baseline values for risky drinkers

*** AUDIT 10 score as a continuous outcome, including the baseline score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

Analysis of the primary outcome, difference in the odds of hazardous and harmful drinkers, shows statistically significant benefit for facilitated access compared with face to face BI. This is replicated in the additional pre-specified analyses and in all cases non-inferiority for facilitated access was demonstrated. Figure 3 describes the effects and interactions for the pre-specified subgroups. There was a significant interaction for age, and some indication of an interaction effect for computer literacy and baseline severity.

Table 5 describes the results of the analyses at 12 months on the proportion of hazardous or harmful drinkers per group, and the difference in mean AUDIT scores. The 12 months odds ratio for hazardous or harmful drinking demonstrated non-inferiority of facilitated access compared with face-to-face BI, but non-inferiority was not demonstrated for the mean AUDIT scores at this time point.

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Table 5: 12 month results – difference in hazardous/harmful drinkers and mean AUDIT-10

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Hazardous/harmful drinkers (OR)	0.943	1.432	0.621	0.784
Mean AUDIT-10	-0.3126	-0.8159	0.1906	0.2229

Post hoc analyses

Table 6 shows the findings of post-hoc analysis on the subsets of participants who were and were not hazardous /harmful drinkers at baseline. The analysis did not support non-inferiority of facilitated access at 3 month follow-up for those with hazardous/harmful drinking at baseline.

Table 6: Hazardous/harmful drinking at 3 months by hazardous/harmful drinking at baseline.

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Not hazardous/harmful drinkers at baseline n= 545 (OR)	0.476	0.289	0.782	0.004
Hazardous/harmful drinkers at baseline n= 218 (OR)	0.772	0.431	1.383	0.382

Test for interaction between the groups p=0.192

Table 7 shows the proportions of participants classified as hazardous/harmful drinkers at 3m and 12m using a cut point of >7 points on the AUDIT questionnaire with question 10 removed.

Table 7 Proportions of hazardous/harmful drinking as defined by >7 points on AUDIT with question 10 removed

Time period n in follow up	Face to Face n (%)	Facilitated n (%)
Baseline n=761	93 (22.4%)	79 (22.8%)
3 months n=698	28 (7.4%)	32 (10.1%)
12 months n=620	27 (8.1%)	35 (12.3%)

Table 8 shows the results of further continuous and categorical analyses based upon the AUDIT C questions. Neither analysis supported non-inferiority of facilitated access.

Table 8 Continuous and categorical analyses based upon the AUDIT C questions.

Analysis	Estimate	Lower 95% CI	Upper 95% CI	P
Risky Drinkers on AUDIT C (OR)	1.555	2.127	1.136	0.006
Difference in mean AUDIT C score	-0.185	-0.396	0.027	0.087

EQ5D

The results of the EQ5D are reported in a separate paper (Hunter et al, Cost effectiveness analysis of EFAR FVG. Submitted to BMJ Open 4th October 2016 and currently under review: manuscript ID: bmjopen-2016-014577).

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DISCUSSION

As far as we are aware, this is the first trial comparing effectiveness of facilitated access by general practitioners to an alcohol reduction website with delivery of face to face BI. It has demonstrated that this approach can be successfully implemented in general practice, with 58 participating GPs each providing facilitated access to an average of more than 150 patients, and nearly half of the patients subsequently following their GP's advice to log on and undertake screening . Furthermore, the great majority of patients randomised to facilitated access to the website went on to engage actively, downloading several pages and making multiple entries. The ODHIN trial which tested the relative impact on GP screening and BI activity of providing access to an alcohol reduction website (eBI), financial incentives and education and training, found that eBI was not associated with increased rates of activity.[21] However, the training and familiarisation with the website offered to the GPs was almost certainly less rigorous than in the EFAR- FVG trial.[22] Furthermore, the organisation of general practice in the 5 countries where ODHIN trial was conducted may have been less favourable to GP facilitated access.

The trial has a number of limitations. Fewer participants were recruited than the figure defined by the power calculation, and more importantly the AUDIT-C screening tool performed poorly as a predictor of hazardous or harmful drinking as defined by a score of ≥8 points on the AUDIT. This meant that the trial population included only a minority (29·6%) of hazardous/harmful drinkers as defined by an AUDIT score ≥8. The resultant threshold effect was almost certainly responsible at least in part for the only modest reductions seen in the proportions of hazardous/harmful drinkers in both groups. The use of AUDIT C cut points of 5 for men and 4 for women would have been expected to lead to the inclusion of substantially higher proportions of hazardous and harmful drinkers as defined by a score of 8 or more on the AUDIT.[23,24] The AUDIT C has also been validated in Italian populations and found to perform similarly.[10] However a recent paper has suggested that higher cut points should be used to reliably identify risky drinkers.[25] In addition, the statistical analyses assumed a similar clustering effect for both treatment conditions at the practice level, through fitting practice level random effects. It could be argued that differences in the intervention could lead to difference in the clustering within practices, however our assumption a priori, based upon substantial relevant experience, was that shared practice characteristics were likely to be the dominant factors in our analysis. Given the overall nature of the results and their interpretation we have not undertaken further supportive analyses on this question.

The trial did not observe the scale of reduction in the proportions of hazardous or harmful drinkers in the patients following brief intervention by their GPs which had informed our sample size calculation. Instead there was a paradoxical increase in the proportion of patients in the face-to-face BI group categorised as hazardous or harmful drinkers at 3 months though this was not maintained at 12 months. We postulated that this was largely due to bias introduced by the final AUDIT question which asks about advice to reduce drinking from a health care professional, and might therefore be expected to elicit a positive response in the short term following face-to-face brief intervention. This hypothesis was supported by failure to confirm non-inferiority when the final question was omitted in the post hoc analysis.

The main strengths of the study include the size of the study population, numbers of GPs involved, high levels of facilitated access activity, and high follow up rates of at both 3 months (91·5%) and 12

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months (81·2%). The use of the Internet to deliver all components of the trial with the exception of the face to face intervention for patients in the control group reduced the cost of the trial, ensured consistency of conduct of all phases, avoided errors of transcription and enabled real-time tracking of trial activity by the study team. Furthermore, there were no reported breaches of data security.

Analysis of all pre-specified outcome measures demonstrated evidence of non-inferiority for facilitated access versus face to face brief intervention. On the face of it, this implies that a simple message given by the GP to the patient during facilitated access combined with provision of the log on code for the alcohol reduction website was no less effective in prompting behavioural change than a 5-10 minute brief intervention delivered face to face. This is consistent with the findings of a number of studies, most notably the SIPS trial which found the outcomes in patients screening positive hazardous or harmful drinking provided with a patient information leaflet were no worse than for those given five minutes of structured brief advice or 20 minutes of brief lifestyle counselling.[26] These findings are also consistent with much of the growing literature on the effectiveness of digital interventions indicating that users benefit from online alcohol interventions and that this approach may be particularly useful for groups less likely to access traditional alcohol-related services, such as women, young people, and at-risk users.[27]

However, the reliability of the conclusions from the primary analyses is seriously called into question by the results of the post hoc analyses performed in order to deal with the presumptive evidence of response bias in the face to face group. When these were performed using both a subset of the questions on the AUDIT omitting question 10, and the three questions of the AUDIT C, the results no longer supported the conclusion of non-inferiority of facilitated access. This raises real questions about the reliability of the trial's main findings, and further research will be needed to determine whether these can be replicated. Alternative cut points on the screening AUDIT C could be used to ensure the inclusion of greater proportions of hazardous/harmful drinkers in future studies, and an alternative outcome measure such as the timeline follow-back questionnaire[28] could be used in order to avoid bias introduced by the AUDIT. It would also be helpful to replicate the trial general practice settings involving larger clinical teams and greater numbers of registered patients. At least one such trial is currently underway in Catalunya, Spain and others are under development in Australia and Sweden.[29] Additional study is also needed to improve understanding of the mechanisms underlying the impact of facilitated access and the conditions required to optimise it, including the role played by online GP personalisation.

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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. NF was responsible for statistical analyses. PW, PS and NF wrote the first draft. RH, PW, PS and NF contributed to its revision and all authors contributed to 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.

Acknowledgements:

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Data sharing:

Anonymised trial data is held on secure servers at University College London. For access to the data please contact the corresponding author, supplying study protocol and approval.

Figure legends:

Figure 1: Screenshot showing tailored feedback on AUDIT C with GP personalisation (translated from original Italian)

Figure 2: Subject progress through the trial

Figure 3: Primary outcome – pre-specified sub-group analyses

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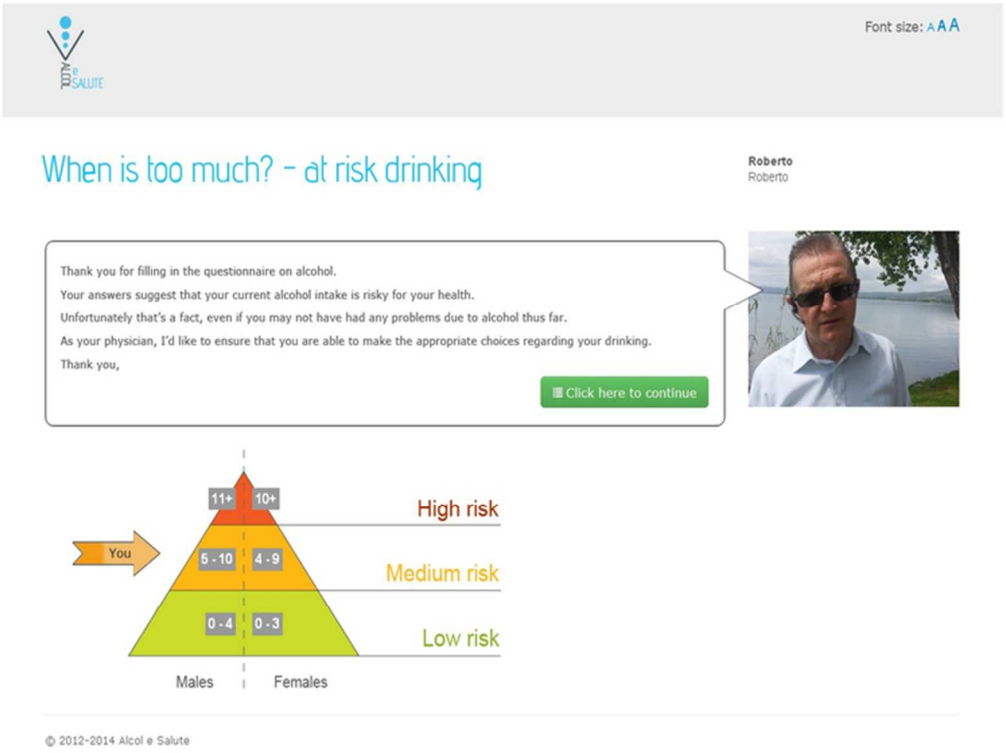

Figure 1: Screenshot showing tailored feedback on AUDIT C with GP personalisation (translated from original Italian)

62x50mm (300 x 300 DPI)

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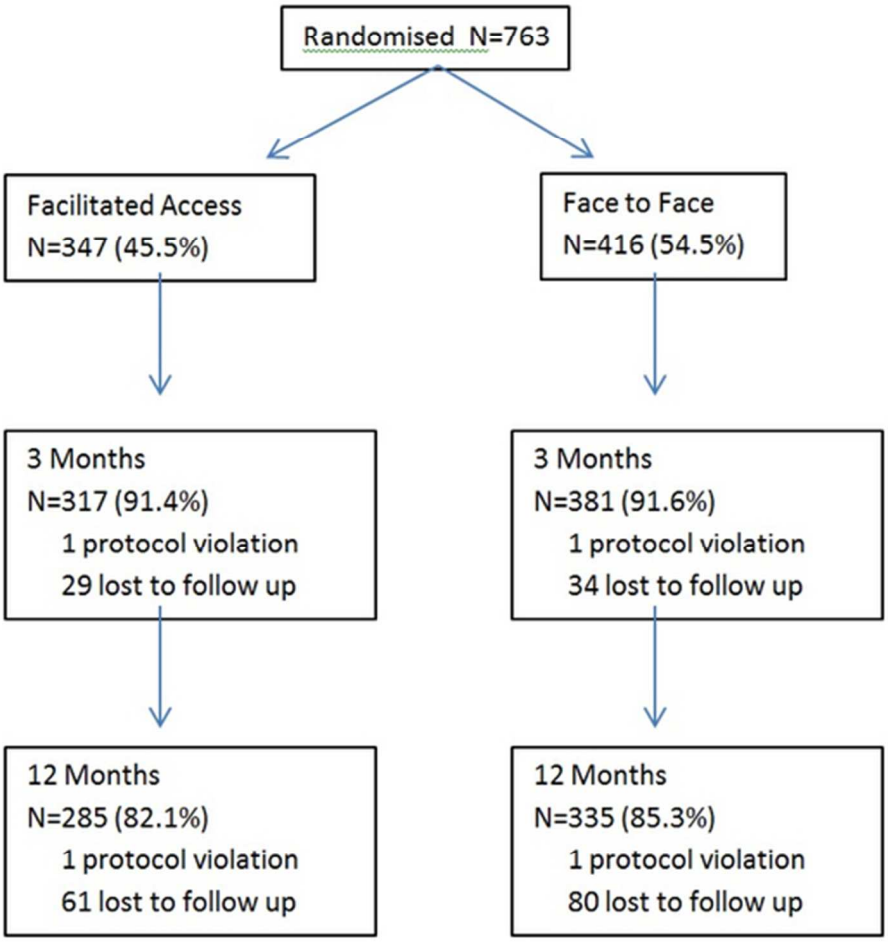

Figure 2: Subject progress through the trial

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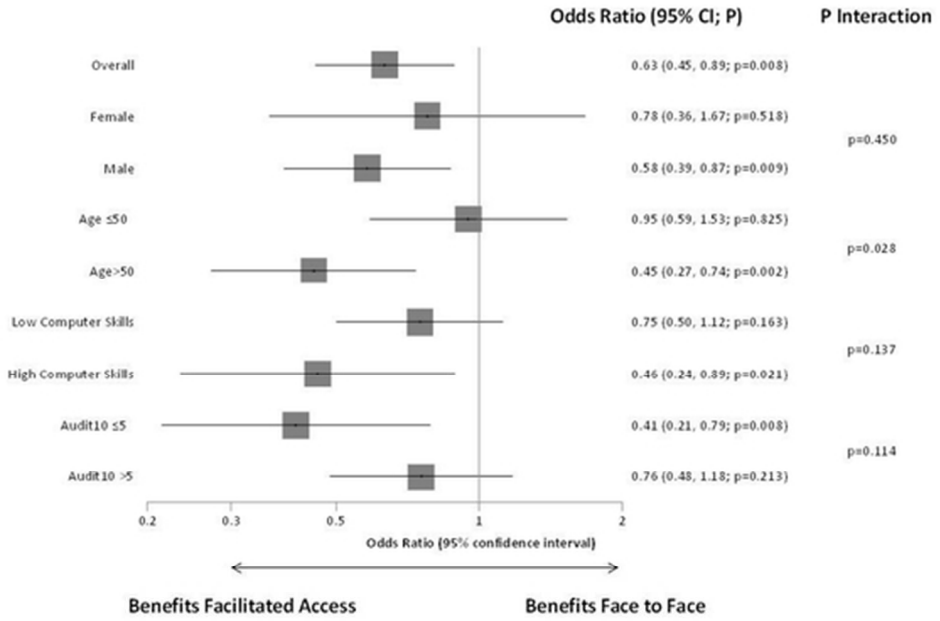

Figure 3: Primary outcome – pre-specified sub-group analyses

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CONSORT Statement 2006 - Checklist for Non-inferiority and Equivalence Trials

Items to include when reporting a non-inferiority or equivalence randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned"), *specifying that the trial is a non-inferiority or equivalence trial.* Title: Randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website Abstract: Primary care based, non-inferiority, randomised controlled trial comparing general practitioner facilitated access to an interactive alcohol reduction website (FA) with face-to-face brief intervention (BI) for risky drinking	1 2
INTRODUCTION Background	2	Scientific background and explanation of rationale, *including the rationale for using a non-inferiority or equivalence design.* Facilitated access offers a novel alternative to face-to-face brief intervention (BI) for risky drinking, but it is not known whether it is as effective. .. An adequately powered and appropriately designed trial was therefore required to provide more definitive evidence on the use of facilitated access as an alternative to face to face BI for the reduction of hazardous and harmful drinking, and to indicate the potential for this approach to be adopted more generally in the management of health conditions by general practitioners. The research question addressed by the trial was "Is facilitated access to an interactive alcohol reduction website as effective in reducing hazardous and harmful drinking as face to face BI?"	3 3
METHODS Participants	3	Eligibility criteria for participants *(detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment)* and the settings and locations where the data were collected. All patients aged 18 or over who attended the participating practices during the study period were eligible for the trial, but those known by the GPs to suffer from severe psychiatric disorder, alcohol dependence, serious visual impairment or terminal illness were excluded, as were those judged to have inadequate command of the Italian language…. Following consent, patients were invited to complete online questionnaires including a demographic questionnaire seeking information on age, gender, level of education and occupation, the 10-question AUDIT validated Italian version, and the EQ-5D 5L quality-of-life questionnaire, validated Italian version…. Follow-up took place 3 and 12 months after randomisation and a series of approaches were adopted to optimise response rates. In the first instance, each patient in the trial received an automated email requesting them to log in to the website to complete their assessment questionnaires. Failure to do so resulted in further automated emails at one and two week intervals. Persistent failure was notified to the patient's GP, who was asked to ensure that they were contacted by letter, phone or in person in order to complete their assessment. Where necessary, assessment was completed over the phone.	4 4 5
Interventions	4	Precise details of the interventions intended for each group *detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered	

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		Patients allocated to facilitated access were directed to the opening page of the alcohol reduction website containing a personalised online message from their GP with tailored feedback about their responses to the AUDIT questionnaire. Further online messages emphasised the importance of adopting healthy drinking choices. They provided encouragement to spend at least 15 minutes engaging with the alcohol reduction website, including making entries in the personal Thinking Drinking Record (TDR) about their assessment of costs and benefits of their current levels of drinking. An automated email was sent 1 week later encouraging further log on. Patients were also asked online to review their alcohol consumption and were invited to discuss their website experience when they next saw their GP. Patients allocated to face-to-face BI were invited to check a box online which automatically generated an email to their GP requesting an appointment within the next 7–10 days. GPs were instructed to offer a BI lasting 5-15 minutes based on the brief motivational interview. Non-attenders were offered up to three additional appointments.	5 5
Objectives	5	Specific objectives and hypotheses, *including the hypothesis concerning non-inferiority or equivalence.* The research question addressed by the trial was "Is facilitated access to an interactive alcohol reduction website as effective in reducing hazardous and harmful drinking as face to face BI?"	3
Outcomes	6	Clearly defined primary and secondary outcome measures *detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors). The pre-specified primary outcome measure was the proportion of hazardous or harmful drinkers as defined by a score ≥8 points on the AUDIT questionnaire at 3 months follow up. The secondary outcome measure was the EQ-5D quality of life questionnaire, validated Italian version for use in economic evaluations.	5
Sample size	7	How sample size was determined *detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules (*and whether related to a non-inferiority or equivalence hypothesis*). Facilitated access was deemed not inferior to face-to-face treatment at a one-sided α of 2·5% if the difference between the proportions of hazardous or harmful drinkers in the facilitated access group and the face-to-face BI group is below a specified absolute margin of non-inferiority of 10%. Assuming a reduction of 30% in the proportion of hazardous or harmful drinkers in the face to face BI group and allowing for an overall attrition of 10% of patients in the trial, it was calculated that 500 patients would be required in each group to give the trial 90% power (1-β) to reject the null hypothesis that facilitated access is inferior to face-to face intervention.	6
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification) Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification	4

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		or blinding.	
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.	4
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. Randomisation was at the individual level and was automated, concealed and undertaken online using software which generated randomisation with an allocation ratio 1:1. There was no stratification or blinding.	4
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), *specifying whether a one or two-sided confidence interval approach was used.* Methods for additional analyses, such as subgroup analyses and adjusted analyses. Analyses were described in a statistical analysis plan completed before database lock. To assess the non-inferiority of facilitated access compared with face-to-face BI, the proportions of hazardous or harmful drinkers in each group were computed and compared using generalised non-linear mixed models accounting for general practices as random effects in order to address possible therapist effects and other practice level clustering. Additional, pre-specified, supportive analyses designed to provide further information about the trial outcomes were conducted as follows: Supportive 1 = random intercept term for practices and baseline values for hazardous or harmful drinkers; Supportive 2 = included a random residual term in replacement for the generalised random intercept term and baseline values for hazardous / harmful drinkers; Supportive 3 = AUDIT score as a continuous outcome, including the baseline AUDIT score as a patient level explanatory variable, with generalised random intercept terms for GP practices. Post hoc analyses were designed to address the unexpected finding that less than 30% of the participants were classified at baseline as hazardous or harmful drinkers by a score ≥8 points on AUDIT, and the unexpected rise at follow-up in the proportions of patients in the face-to-face BI group scoring ≥8 points on AUDIT. Analysis was therefore carried out for the 3 months principal outcome measure on the basis of subjects who were, and were not, classified as hazardous or harmful drinkers at baseline, and additionally by removing the final question of the AUDIT which may have introduced bias favouring the experimental condition. All calculations were performed on the basis of intention to treat. An independent trial steering committee oversaw the general conduct of the trial and undertook data monitoring.	6 6

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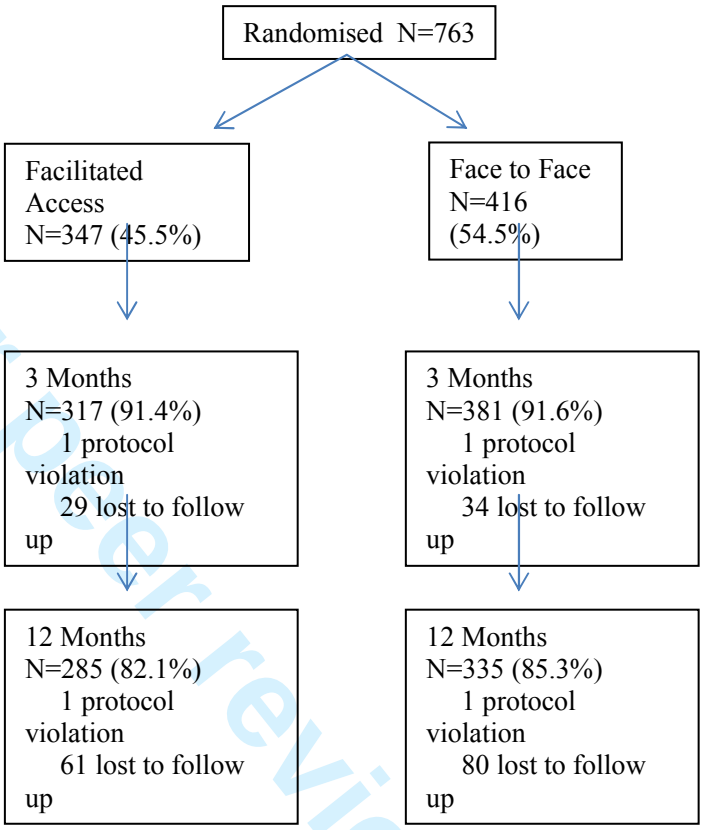
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. **Figure 1 Flow of patients through the study**  Figure 1 describes the progress of the 763 subjects through the trial. Three hundred and forty seven (45·5%) were allocated to facilitated access to the alcohol reduction website and 416 (54·5%) to face to face BI. A total of 698 (91·5%) subjects completed the three month follow-up assessment, and 620 (81·2%) the 12 month follow-up assessment. One subject was excluded due to inadvertent randomisation to both the intervention and control groups.	7
Recruitment	14	Dates defining the periods of recruitment and follow-up. The trial was conducted in two phases – a pilot phase involving 11 GPs who recruited 89 subjects between 14th January 2013 and 31st May 2013, and the main trial phase involving 58 GPs who recruited 674 subjects between 20th January 2014 and 31st August 2014. The trial design was identical in both phases.	7
Baseline data	15	Baseline demographic and clinical characteristics of each group. Item | Facilitated Access Male (%) | 214 (62.0%) Marital Status | Single (%) | 95 (27.9%) Married (%) | 208 (61.0%) Separated (%) | 28 (8.2%) Widowed (%) | 10 (2.9%) Ethnicity | Caucasian (%) | 8 (2.4%)	7

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		Bengalese (%)	1 (0.3%)		1 (0.25%)
		Indian (%)	1 (0.3%)		2 (0.5%)
		Italian (%)	320 (95.8%)		385 (96.3%)
		North African (%)	0 (0%)		1 (0.25%)
		Mixed race (%)	1 (0.3%)		1 (0.25%)
		Black African (%)	3 (0.9%)		4 (1.0%)
		Familiarity with IT			
		Not	58 (16.9%)		62 (15.2%)
		Fairly	84 (24.5%)		93 (22.8%)
		Familiar	91 (26.5%)		119 (29.2%)
		Very	110 (32.1%)		134 (32.8%)
		Qualifications			
		None	2 (0.6%)		2 (0.5%)
		Elementary/junior school	112 (32.9%)		126 (30.9%)
		High school	174 (51.2%)		184 (45.1%)
		University	45 (13.2%)		78 (19.1%)
		Higher degree	7 (2.1%)		18 (4.4%)
		Age, median (IQR)	49 (37, 59)		50 (35, 61)
		Number of Children, median (IQR)	1 (0, 2)		1 (0, 2)
		AUDIT 10, median (IQR)	5 (4, 8)		6 (4, 9)
		Hazardous/Harmful Drinker (Audit-10 ≥8) (%)	95 (27.5%)		123 (29.6%)

Numbers analyzed — 16

Number of participants (denominator) in each group included in each analysis and whether the analysis was *"intention-to-treat" and/or alternative analyses were conducted.* State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).

Table 3 Number of risky drinkers at baseline, 3 and 12 months by randomised condition

Time period n in follow up	Face to Face n (%)
Baseline n=761	123 (29.6%)
3 months n=698	141 (37.1%)
12 months n=620	88 (26.3%)

8/9

Outcomes and estimation — 17

For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval). *For the outcome(s) for which non-inferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*

Table 4: Primary analysis and supportive analyses

Analysis		Estima
Primary – proportion of hazardous or harmful drinkers (OR)		0
Supportive analysis 1*	(OR)	0
Supportive analysis 2**	(OR)	0
Supportive analysis 3 ***	(OR)	-0

* proportion of hazardous or harmful drinkers; including baseline values for risky drinkers and random intercept term for practice

** including a random residual term in replacement for the generalised random intercept term for practice and baseline values for risky drinkers

*** AUDIT 10 score as a continuous outcome, including the baseline score as a patient level explanatory variable, with generalised random intercept terms for GP practices.

9

Table 5: 12 month results – difference in hazardous/harmful drinkers and mean AUDIT-10

Analysis	Estimate	Lower 95% CI	Up
Hazardous/harmful drinkers (OR)	0.943	1.432	
Mean AUDIT-10	-0.3126	-0.8159	

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<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Ancillary analyses</td><td>18</td><td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.

Table 6: Hazardous/harmful drinking at 3 months by hazardous/harmful drinking at baseline.<table><tr><td>Analysis</td><td>Estimate</td></tr><tr><td>Not hazardous/harmful drinkers at baseline n= 545 (OR)</td><td>0.476</td></tr><tr><td>Hazardous/harmful drinkers at baseline n= 218 (OR)</td><td>0.772</td></tr></table>Test for interaction between the groups p=0.192

Table 7 Proportions of hazardous/harmful drinking as defined by >7 points on AUDIT with question 10 removed<table><tr><td>Time period n in follow up</td><td>Face to Face n (%)</td></tr><tr><td>Baseline n=761</td><td>93 (22.4%)</td></tr><tr><td>3 months n=698</td><td>28 (7.4%)</td></tr><tr><td>12 months n=620</td><td>27 (8.1%)</td></tr></table>
Table 8 Continuous and categorical analyses based upon the AUDIT C questions.<table><tr><td>Analysis</td><td>Estimate</td><td>Lower 95% CI</td><td>U</td></tr><tr><td>Risky Drinkers on AUDIT C (OR)</td><td>1.555</td><td>2.127</td><td></td></tr><tr><td>Difference in mean AUDIT C score</td><td>-0.185</td><td>-0.396</td><td></td></tr></table></td><td>10

10

10</td></tr>
<tr><td>Adverse events</td><td>19</td><td>All important adverse events or side effects in each intervention group.

N/A</td><td></td></tr>
<tr><td>DISCUSSION
Interpretation</td><td>20</td><td>Interpretation of the results, taking into account the non-inferiority or equivalence hypothesis and any other study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.

Analysis of all pre-specified outcome measures demonstrated evidence of non-inferiority for facilitated access versus face to face brief intervention. On the face of it, this implies that a simple message given by the GP to the patient during facilitated access combined with provision of the log on code for the alcohol reduction website was no less effective in prompting behavioural change than a 5-10 minute brief intervention delivered face to face……..

However, the reliability of the conclusions from the primary analyses is seriously called into question by the results of the post hoc analyses performed in order to deal with the presumptive evidence of response bias in the face to face group. When these were performed using both a subset of the questions on the AUDIT omitting question 10, and the three questions of the AUDIT C, the results no longer supported the conclusion of non-inferiority of facilitated access. This raises real questions about the reliability of the trial's main findings, and further research will be needed to determine whether these can be replicated.</td><td>11/12

12</td></tr>
<tr><td>Generalizability</td><td>21</td><td>Generalizability (external validity) of the trial findings.

It would … be helpful to replicate the trial general practice settings involving larger clinical teams and greater numbers of registered patients. At least one such trial is currently underway in Catalunya, Spain and others are underway in Australia and Sweden.</td><td>12</td></tr>
</table>

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Overall evidence	22	General interpretation of the results in the context of current evidence. Pre specified protocol driven analyses of the trial indicate that FA is non inferior to BI, however identified bias in the outcome measure and further supportive analyses question the robustness of this finding. It is therefore not possible to draw firm conclusions from this trial, and further research is needed to determine whether the findings can be replicated using more robust outcome measures.	2

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