PROTOCOL

Health4Her: Increasing knowledge of alcohol as a risk factor for breast cancer among women attending breast screening services

Clinicaltrials.gov Registration Number: NCT04715516
Protocol Version # and date: **Version 7, 8th August 2021**

Revision Chronology:

Date of change	Summary of changes
1st February 2019	Version 1: original document
16th July 2019	Version 2: update to section 5.3 *Recruitment and identification of potential participants,* addition of researcher script, conduct formative evaluation focus groups/surveys with Lifepool, clarification of subsample to complete alcohol consumption/intervention feasibility questions, increase number of participants to power the pilot trial (update power and sample size calculation), refine aims, update alcohol items, add protocol for providing contact details for additional support as required, add implied consent via use of a iPAD landing page, add VicHealth funder, update title, update timeline.
29th July 2019	Version 3: references to PICF in sections 8.1 and 8.2 changed to refer to Participant Information Sheet (PIS; consent provided via iPAD landing page)
27th August 2019	Version 4: Addition of donation to breast cancer research for pre-trial feasibility survey / focus group participation
19th January 2021	Version 5: refined study outcomes and measures. Updated power and sample size calculation, and data analysis plan. Minor changes to inclusion/exclusion criteria. Refined title and description of the intervention. Added verbal consent procedure to replace iPad landing consent page. Added Eastern Health COVID-19 safety procedures at Maroondah BreastScreen. Updated project timeline.
12th May 2020	Version 6: introduced potential for participants to provide written consent when recruitment is busy. Added process whereby Maroondah BreastScreen reception provide a reminder text message or phone call prior to recruitment days and flag the study occurring onsite.
8th August 2020	Version 7: Minor changes to protocol based on trial procedures in practice; updated description of data collection to more accurately reflect functionality of REDCap and use/security of identifiable and re-identifiable data.

Sponsor

Eastern Health

Funded By

2019 Easter Health Foundation Research and Innovation Grant
2019 VicHealth Impact Research Grant

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

CONTENTS

PROTOCOL SYNOPSIS

TITLE	Health4Her: Increasing knowledge of alcohol as a risk factor for breast cancer among women attending breast screening services
OBJECTIVES	Alcohol consumption is a major modifiable risk factor for breast cancer in women. Research demonstrates a strong link between alcohol and breast cancer risk, even at low drinking levels. This project aims to reduce alcohol consumption among women attending an Eastern Health BreastScreen service for routine mammography.
DESIGN	Pragmatic randomised controlled trial
OUTCOMES	Baseline, 4-week and 12-week measures will be administered. PRIMARY OUTCOME At 4-weeks post-randomisation, proportion of participants in the active condition (relative to control) accurately identifying alcohol as a clear risk factor for breast cancer. SECONDARY OUTCOMES At 4-weeks post-randomisation: - Change in participants' attitudes regarding alcohol and breast cancer risk (items adapted from previous literature, e.g. Fisher et al. 2017) - Proportion of participants accurately identifying i) the amount of alcohol in an Australian standard drink; ii) the number of standard drinks in an average restaurant serve of red wine; iii) the maximum number of standard drinks per week recommended by current Australian Alcohol Guidelines (items adapted from previous literature, e.g. Bowden et al. 2014) - Proportion of participants who have accessed health information on i) alcohol harms, ii) alcohol and breast cancer risk, and iii) alcohol harm-reduction At 4-weeks and 12-weeks post-randomisation: - Proportion of participants drinking less than or equal to 10 standard drinks per week (i.e. within current Australian Alcohol Guidelines) (14-day Timeline Followback; TLFB) - Among participants who drink more than 10 standard drinks per week at baseline: Proportion of participants drinking less than or equal to 10 standard drinks per week (14-day TLFB) - Change in alcohol consumption (14-day TLFB; AIHW alcohol frequency/quantity items) - Among participants who drink more than 10 standard drinks per week at baseline: Change in alcohol consumption (14-day TLFB; AIHW alcohol frequency/quantity items) - Change in general health (SF-12) and quality of life (EUROHIS-QOL single item)

	Feasibility of implementing alcohol brief intervention in a breast screening setting will be assessed through formative, process and impact evaluation, examining factors such as: - The proportion of patients who agree to receive alcohol health promotion - Acceptability of the intervention prototype and research procedures - Women's attitudes toward receiving alcohol health promotion intervention in the BreastScreen setting - Staff feedback on alcohol health promotion intervention implemented in the breast screen setting
STUDY DURATION	2.5 years
INTERVENTIONS	**Active:** The intervention arm will receive 4 minutes of alcohol brief intervention, and 3 minutes of lifestyle health promotion (physical activity; maintaining a healthy weight), to increase knowledge of how to improve women's health and reduce breast cancer risk. Alcohol and lifestyle information will be delivered by way of an animation on an iPad. Participant responses to questions about current alcohol use will branch to personalised feedback consistent with level of alcohol consumption (i.e. drinking within or above current Australian Alcohol Guidelines). Take-home pamphlets - a pamphlet summarising the alcohol information presented during the animation, and a pamphlet on nutrition to maintain a healthy weight, will be provided. **Control:** The control arm will receive 3 minutes of lifestyle health promotion (physical activity; maintaining a healthy weight) to increase knowledge of how to improve women's health and reduce breast cancer risk, not inclusive of alcohol information. Lifestyle information will be delivered by way of an animation on an iPad. Take-home pamphlet - a pamphlet on nutrition to maintain a healthy weight will be provided.
# PARTICIPANTS	548 participants
POPULATION	Inclusion criteria: • Female, attending the BreastScreen setting for routine mammography • 40+ years of age • English as a first language or fluent • Regular access to a telephone • Able to provide informed consent to participate • Any level of alcohol consumption (including non-drinkers) Exclusion criteria: • Hearing impairment sufficient to prohibit a telephone interview • Pregnancy • Not able to read or comprehend English to provide informed consent or receive the brief intervention

1 ADMINISTRATIVE INFORMATION

1.1. Trial registration

Trial to be registered with Clinicaltrials.gov, registration number: NCT04715516

1.2. Expected duration of study

This study is expected to take 24 months to complete.

Project Timeline – Health4Her

Jun 2019 – Feb 2021

Study set-up: (< Jun 2019: full protocol developed, ethics application submitted) finalise ethics approval, iOS software development, pamphlet development, full statistical analyses plan, randomisation schedule, REDCap database, RA recruitment and training, Maroondah BreastScreen site briefing

(Sep 2019) Set-up program evaluation, including formative evaluation with Lifepool

Dec 2019 - Sep 2020

Implement formative evaluation with Lifepool: online survey (N = 391) and focus groups (N = 31) with women from the Lifepool community, to determine acceptability of alcohol and lifestyle health promotion offered within the breast screening setting, and to collaboratively design the health promotion content and research procedures planned for the Phase II trial. Adapt intervention accordingly.

Feb 2021 – Nov 2021

Implement intervention: recruit 248 participants over 7 months, consent, baseline assessment, deliver alcohol brief intervention (or control), 4-week and 12-week follow-up telephone assessments, data entry.

(Aug 2021) Last participant recruited

(Nov 2021) Last 12-week follow-up assessment completed

(Feb - Nov 2021) Process and impact program evaluation

Sep 2021 - Feb 2022

Data cleaning, statistical and qualitative analyses, preparation of publications, finalise VicHealth reporting requirements (i.e. full research final report, research summary), acquittal report to EH Foundation, final report to HRECs, study archiving

(Aug – Dec 2021) Implementation maintenance evaluation

1.3. Contributorship

Name	Summary of contribution
Professor Dan Lubman Turning Point, Eastern Health; Eastern Health Clinical School, Monash University	Principal Investigator. Develop protocol. Oversee project management and the research team.
Dr Jasmin Grigg Turning Point, Eastern Health; Eastern Health Clinical School, Monash University	Co-Investigator. Develop protocol. Project management.
Associate Professor Victoria Manning Turning Point, Eastern Health; Eastern Health Clinical School, Monash University	Co-Investigator. Inform the development of protocol. Oversee project management.
Professor Robin Bell Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University	Co-Investigator (on the pilot component of this project only). Inform the development of protocol. Oversee project management.
Dr Darren Lockie Maroondah BreastScreen, Eastern Health	Co-Investigator. Inform the development of protocol. Oversee project implementation at Maroondah BreastScreen
Associate Professor Liam Smith BehaviourWorks Australia, Monash Sustainable Development Institute, Monash University	Co-Investigator. Inform the alcohol health promotion content. Inform the development of protocol.
Associate Professor Peter Bragge BehaviourWorks Australia, Monash Sustainable Development Institute, Monash University	Co-Investigator. Inform the alcohol health promotion content. Inform the development of protocol.
Ms Michelle Clemson Maroondah BreastScreen, Eastern Health	Co-Investigator. Oversee project implementation at Maroondah BreastScreen.

2 INTRODUCTION AND BACKGROUND

Alcohol use is a major modifiable risk factor for breast cancer in women, even in low amounts, with evidence of a clear dose-response relationship. Indeed, meta-analyses reveal that the relative risk of breast cancer increases by 4%, 23% and 61% for light, moderate and heavy alcohol consumption, respectively (Bagnardi, 2015).

Women who are eligible for mammography are typically aged 50-74 years and, due to their age, are at increased risk for breast cancer (McPherson, 2000; White, 2014). This is a population who are particularly vulnerable to the harmful effects of alcohol. While breast cancer mortality has reduced by 28-30% due to earlier detection (Roder, 2008) and improved treatment protocols (Burton, 2012), a key health promotion and disease prevention strategy is to reduce women's drinking (WHO, 2017).

In Australia, awareness of the link between alcohol and breast cancer is surprisingly low (Bowden, 2014). While recommended upper limits of alcohol use are emerging as too generous, and associated with increased breast cancer risk, this is not widely understood even by health practitioners or policy makers, let alone the general population (Simapivapan, 2017). Low health

literacy regarding alcohol is a significant barrier to making informed decisions about reducing one's alcohol use (Rundle-Thiele, 2013).

Risky alcohol use – including daily drinking – is most common and stable among this cohort (AIHW, 2016; Daly, 2009), yet remains largely under-detected (O'Connell 2003). As such, a large proportion of women do not receive information, advice or effective intervention. Delivering a targeted health promotion strategy aimed at reducing alcohol consumption, within the context of an already institutionalised breast screening program, represents a unique opportunity to prevent alcohol-attributable harm in a large population for which there is great potential for health gain.

Internationally, computerised alcohol brief interventions (i.e. feedback on personal drinking levels compared with age/gender norms, alongside information about alcohol risks/harms) have received strong empirical support as a simple, cost-effective method of reducing drinking and related harm (Donoghue, 2014), and one which overcomes the logistical issues of providing intervention within busy healthcare environments.

No evidence currently exists regarding the utility of brief intervention delivered within breast screening services, a setting uniquely positioned to provide timely, strategic public health messages to prevent alcohol-attributable harm. With 240,970 Victorian women undergoing mammography in 2015 (BreastScreen Victoria, 2016), this setting has the potential for extensive reach. The breast screening setting provides a significant opportunity to engage this population in alcohol health promotion, and complements and adds value to this established healthcare service.

Therefore, we seek to conduct the first randomised controlled trial examining the efficacy of a computerised brief intervention in reducing risky drinking identified within a breast screening setting.

3 STUDY OBJECTIVES

3.1 Primary aim and hypothesis

At 4-weeks post-randomisation, proportion of participants in the active condition (relative to control) accurately identifying alcohol as a clear risk factor for breast cancer.

We hypothesise that at 4-weeks post-randomisation, compared to the control group, a greater proportion of participants receiving alcohol brief intervention will be able to accurately identify alcohol as a clear risk factor for breast cancer.

3.2 Secondary aims and hypotheses

*At **4-weeks** post-randomisation:*

- *Change in participants' attitudes regarding alcohol and breast cancer risk (items adapted from previous literature, e.g. Fisher et al. 2017)*

- *Proportion of participants accurately identifying i) the amount of alcohol in an Australian standard drink; ii) the number of standard drinks in an average restaurant serve of red wine; iii) the maximum number of standard drinks per week recommended by current Australian Alcohol Guidelines (multiple choice and open-ended questions, adapted from previous literature, e.g. Bowden et al. 2014)*
  Proportion of participants who have accessed health information on i) alcohol harms, ii) alcohol and breast cancer risk, and iii) alcohol harm-reduction

We hypothesise that at 4 weeks post-randomisation, compared to the control group:

(i) (Among women who drink >10 standard drinks per week at baseline) Participants receiving alcohol brief intervention will be significantly more likely to endorse an attitude of harm reduction toward alcohol and breast cancer risk
(ii) A significantly greater proportion of participants receiving alcohol brief intervention will be able to accurately identify i) the amount of alcohol in an Australian standard drink; ii) the number of standard drinks in an average restaurant serve of red wine; iii) the maximum number of standard drinks per week recommended by current Australian Alcohol Guidelines
(iii) (Among women who drink >10 standard drinks per week at baseline) A significantly greater proportion of participants receiving alcohol brief intervention will have accessed health information on i) alcohol harms, ii) alcohol and breast cancer risk, and iii) alcohol harm-reduction

*At **4-weeks** and **12-weeks** post-randomisation:*

- *Proportion of participants drinking less than or equal to 10 standard drinks per week (i.e. within current Australian Alcohol Guidelines) (14-day Timeline Followback; TLFB)*
- *Among participants who drink more than 10 standard drinks per week at baseline: Proportion of participants drinking less than or equal to 10 standard drinks per week (14-day TLFB)*
- *Change in alcohol consumption (14-day TLFB; AIHW alcohol frequency/quantity items)*
- *Among participants who drink more than 10 standard drinks per week at baseline: Change in alcohol consumption (14-day TLFB; AIHW alcohol frequency/quantity items)*
- *Change in general health (SF-12)*
- *Change in quality of life (EUROHIS-QOL single item)*

We hypothesise that compared to those in the control group, at 4-weeks and 12-weeks post-randomisation:

(iv) A significantly greater proportion of participants receiving alcohol brief intervention will be drinking less than or equal to 10 standard drinks per week (i.e. within current Australian Alcohol Guidelines)

(v) Of participants who drink more than 10 standard drinks per week, a significantly greater proportion of those receiving alcohol brief intervention will be drinking less than 10 standard drinks per week
(vi) Participants receiving alcohol brief intervention will report significantly greater reductions in alcohol consumption
(vii) Of participants who drink more than 10 standard drinks per week, those receiving the alcohol brief intervention will report significantly greater reductions in alcohol consumption
(viii) Participants receiving alcohol brief intervention will report significantly greater improvements in general health and quality of life

3.3 Feasibility assessment

Feasibility of implementing the alcohol brief intervention in a breast screening setting will be assessed through formative, process and impact evaluation, by examining factors such as:

(i) The proportion of patients who agree to receive alcohol health promotion
(ii) Acceptability of the intervention prototype and research procedures
(iii) Women's attitudes toward receiving alcohol health promotion intervention
(iv) Staff feedback on alcohol health promotion intervention implemented in the breast screen setting

4 STUDY DESIGN

4.1 Type of Study

This study is a single site, parallel group, two arm, pragmatic randomised controlled trial (RCT), with participants randomly allocated to receive either:

Active: Alcohol brief intervention + lifestyle health promotion

The intervention arm will receive 4 minutes of alcohol brief intervention, and 3 minutes of lifestyle health promotion (physical activity; maintaining a healthy weight), to increase knowledge of how to improve women's health and reduce breast cancer risk. Alcohol and lifestyle information will be delivered by way of an animation on an iPad. Participant responses to questions about current alcohol use will branch to personalised feedback consistent with level of alcohol consumption (i.e. drinking within or above current Australian Alcohol Guidelines).

Take-home pamphlets - a pamphlet summarising the alcohol information presented during the animation, and a pamphlet on nutrition to maintain a healthy weight, will be provided.

Control: lifestyle health promotion, not inclusive of alcohol information

The control arm will receive 3 minutes of lifestyle health promotion (physical activity; maintaining a healthy weight) to increase knowledge of how to improve women's health and reduce breast cancer

risk, not inclusive of alcohol information. Lifestyle information will be delivered by way of an animation on an iPad.
Take-home pamphlet - a pamphlet on nutrition to maintain a healthy weight will be provided.

4.2 Study Setting

The proposed pilot study will be conducted at Eastern Health's Maroondah BreastScreen. This service has an annual throughput of 29,824 women (~570 per week), making it an ideal setting to test the alcohol brief intervention.

The study will be conducted in line with Eastern Health's COVIDSafe Plan to ensure the safety of Maroondah BreastScreen's clients and staff as well as Researcher 1, who will be recruiting participants and conducting the baseline assessment. COVID-19 safety procedures will include, for example, wearing of masks by the Researcher and participants, using alcohol wipes to clean iPad devices prior to and after each use, the provision of single-use earphones to watch the health promotion video (which women can take home with them), the maintenance of physical distancing and limiting researcher-participant interactions to a maximum of 15 minutes.

5 PARTICIPANTS AND RECRUITMENT

5.1 Number of Participants

The study aims to recruit 548 participants (274 participants per trial arm).

5.2 Eligibility Criteria

Individuals will be randomly assigned to one of the study treatments only if they meet eligibility criteria.

5.2.1 Inclusion criteria

Individuals must meet all of the following criteria to be enrolled in this study:

- Female, attending the BreastScreen setting for routine mammography
- Aged 40+ years
- English as a first language or fluent
- Regular access to a telephone
- Able to provide informed consent to participate

Women at any level of alcohol risk, including non-drinkers, will be eligible to participate to determine any change in non-drinking status and other outcomes over time. This approach also serves to negate the stigma that may occur if only women drinking at risky levels are included in the study.

5.2.2 Exclusion criteria

Individuals meeting any of the following criteria will be excluded from the study:

- Hearing impairment sufficient to prohibit a telephone interview
- Pregnancy

- Not able to read or comprehend English to provide informed consent or receive the brief intervention

5.3 Recruitment and identification of potential participants

Recruitment will occur at the Maroondah BreastScreen site 2-days per week over 7 months from Feb 2021. Women will be sent a study flyer with their breast screening appointment reminder email 3 days prior to their appointment. Maroondah BreastScreen reception staff will provide a reminder text message or phone call one day prior to recruitment days to flag the study occurring onsite (as well as confirming women's attendance). Upon arrival at Maroondah BreastScreen, the receptionist will query whether women are aware of the study and provide them with a study flyer to read while waiting for their appointment. Study posters will also be visible on the waiting room notice board and in the screening rooms. At the end of the screening appointment, the radiographer will ask whether the client would like to hear more about the study from the onsite researcher / be involved, and if the client agrees or has further questions, the radiographer will introduce the client to Researcher 1. Participation in the study will occur only after the screening appointment is complete. A script has been developed to assist Researcher 1 with discussing the project with potential participants.

5.4 Consent

Researcher 1 will either i) provide a verbal explanation of the trial (aims, procedures, risks and benefits), in lay terms, to women who are interested in participating, guided by the participant information sheet; or ii) (if the Researcher is finishing up with another participant) provide a written summary of the trial (aims, procedures, risks and benefits), guided by the participant information sheet. Potential participants will have the opportunity to discuss the trial and ask questions. Participants will be advised that they can withdraw from the study at any time without prejudice and that their decision whether to take part or not to take part, or to take part and then withdraw, will not affect their routine care or their relationship with Maroondah BreastScreen or Eastern Health.

Women who are willing to take part will be asked to provide either i) verbal informed consent to participate in the study, recorded by Researcher 1 in the trial's REDCap electronic data form; or ii) written consent to participate in the study, recorded in paper form. Participants will be asked to provide consent to the following items: 1. I consent to participate in the computer survey and health promotion. 2. I consent to receive two follow-up calls from a study researcher, in 4 and 12 weeks' time. 3. I consent to the information I provide for this project to be used in possible future related projects, as described in the Participant Information Sheet. I understand that future, related projects will only ever use my information in such a way that I cannot be identified.

A copy of the participant information sheet will be provided to the participant. The consent process and participation in study procedures will occur after the participant's breast screen appointment, so as to not interfere with routine service delivery.

5.4.1 Consent to future use of data

As part of informed consent, and outlined in the participant information sheet, participants will be asked to provide their consent for their re-identifiable data (i.e. their name will not be attached to the data, but only by the unique participant code assigned to both personal information and data, making the data technically re-identifiable), to be used in any future, related research projects conducted by the research team or for student projects. Separate ethics approval will be sought for any subsequent, related project requesting to use these data. Security of participant data will be

upheld at all times, and persons working with the research team on subsequent, related studies will not ever have access to participants' personal information/identifiable data, nor the spreadsheet containing re-identifiable information.

6 RANDOMISATION AND BLINDING

Women who consent to participate will complete a quick demographic questionnaire and a series of brief measures (evaluating alcohol use, alcohol literacy, quality of life and general health) administered by Researcher 1 or partially self-completed if the Researcher is helping another participant, before being provided with an iPad and randomised at a 1:1 ratio (using computer sequenced block randomisation) to receive the computerised active or control condition.

Randomisation will use a standard computer generated "permuted blocks of variable size" scheme for each stratum. Randomisation lists for each stratum will be generated at the start of the study by the data scientist assisting with the development of the iPad intervention and linked to a unique identification code. The data scientist will play no other role in the randomisation. Randomisation will be linked to a unique identification code, which will be in a re-identifiable format.

Participants will be informed that the study is concerned with promoting health across a range of lifestyle factors (e.g. alcohol use, diet/exercise), which accurately corresponds to the planned outcome measures and intervention conditions and therefore will blind participants to group allocation. Intervention and control computer tasks will be visually identical and will be self-paced. The study researcher performing outcome assessments (Researcher 2) is expected to remain blind to trial allocation.

7 INTERVENTION

7.1 Intervention arms

There will be two trial arms (alcohol brief intervention, control group).

7.2 Intervention Period

The intervention period runs for 4-7 minutes.

7.3 Intervention Conditions

7.3.1 Group 1: Alcohol Brief Intervention

Nested within the lifestyle health promotion provided in both conditions, participants randomised to the experimental condition will receive an alcohol brief intervention (7 minutes total). The strong evidence-base for alcohol brief intervention, amplified by Co-Investigators' Smith and Bragge's (BehaviourWorks) approaches to applied behaviour change, has provided the framework for the development of the alcohol brief intervention used in this study. This intervention comprises personalised feedback on alcohol consumption levels, comparison to gender/age drinking norms, and information and behaviour-change content regarding alcohol consumption (i.e. negative-framed messaging around alcohol risks and harms, positive-framed messaging on the health benefits of reducing alcohol intake, alcohol harm reduction strategies).

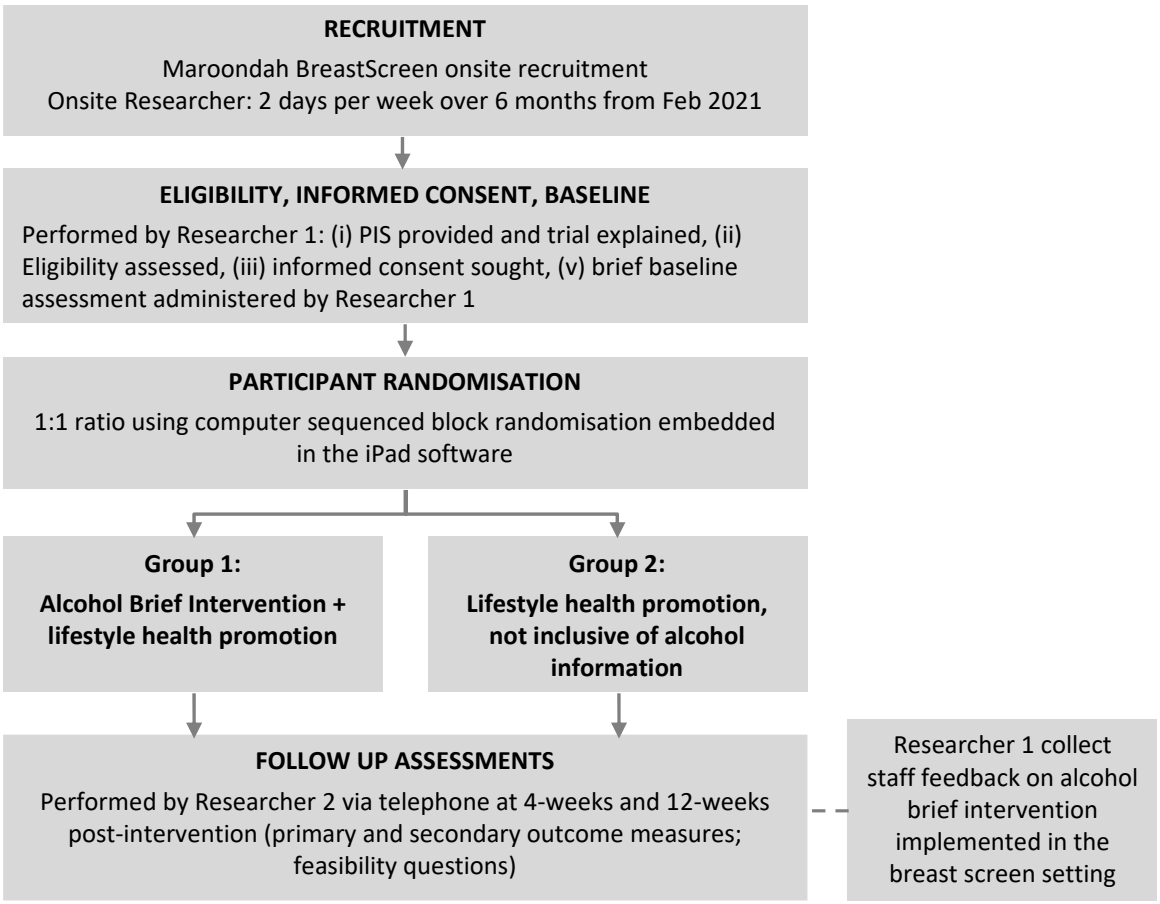
7.3.2 Group 2: Control Group

Lifestyle health promotion specific to physical activity and maintaining a healthy weight, developed to be relevant to women attending breast screening services, will be provided to Group 2 (4 minutes

total). Data from several studies suggest that mere exposure to baseline questions about alcohol use can impact positively on alcohol consumption levels (McQueen, 2011). Baseline questioning effects may operate through similar mechanisms, prompting reflection and the self-regulation of behaviour (McCambridge, 2011). Still, pooling effect sizes over large numbers of alcohol BI studies has been able to provide a powerful estimate of how this form of health promotion performs (Kaner, 2007; McQueen, 2011; O'Donnell, 2013). Therefore, while participants in the control condition may experience some benefit from participation, we expect this will be less than that obtained for the active condition.

8 STUDY PROCEDURES

8.1 Study flow chart



8.2 Schedule of assessments

Week:	Pre-trial	BreastScreen setting 0	Telephone 4	Telephone 12
Trial explanation		x		
Eligibility		x		
PIS provided		x		
Informed consent		x		
RANDOMISATION		x		
INTERVENTION		x		
MEASURES				
Alcohol Use (14-day Timeline Followback; AIHW alcohol frequency/quantity items))		x	x	x
Alcohol literacy (attitudes, **knowledge** - primary outcome, access to further information)		x	x	
Quality of life (EUROHIS-QOL single item)		x	x	x
General health (SF-12)		x	x	x
Feasibility questions (trial participants)				x
Feasibility questions (focus groups and survey with Lifepool women)	x			

9 ASSESSMENT

Researcher 1 will perform the eligibility assessment. Follow-up assessments (4-week, 12-week) will be conducted over the telephone by Researcher 2. Baseline and follow-up assessments will take 5-10 minutes to complete.

9.1 SCREENING MEASURES

Standard *demographic characteristics* (e.g., age, gender, education level) will be recorded during the initial eligibility assessment, as well as information pertaining to the study's inclusion/exclusion criteria.

9.2 OUTCOME MEASURES

9.2.1 Primary outcome measure – Knowledge of alcohol as a breast cancer risk factor

An item adapted from previous research in this area (e.g. Fisher, Wilkinson et al. (2017)) will be used to measure participants' knowledge of alcohol as a breast cancer risk factor. Participants will be asked to rate 6 factors (family history of breast cancer, physical inactivity, antiperspirant deodorant use, alcohol, processed meats and being overweight) as either a clear risk factor for breast cancer ("*there is strong, consistent evidence that this factor increases the risk of breast cancer*"), possible risk factor ("*there is some evidence that this factor increases the risk of breast cancer, but not enough to be certain*"), not a proven risk factor ("*the evidence is too limited to determine whether this factor increases the risk of breast cancer*"), or unsure. The correct responses were taken from Cancer Australia's 2018 review of the evidence on breast cancer risk factors (Cancer Australia 2018). The primary outcome will be the proportion of participants in the active condition (relative to

control) who accurately identify alcohol as a clear risk factor for breast cancer at 4-weeks post-intervention.

9.2.2 Alcohol Measures

9.2.2.1 14-day Timeline Followback

The *14-day Timeline Followback* (TLFB) (Sobell and Sobell 1992) is a calendar-based assessment tool created to assist participant recall of drug and alcohol consumption over the previous month, with well-established psychometric properties (Agrawal, Sobell et al. 2008, Robinson, Sobell et al. 2014). The TLFB will be used to measure amount of alcohol consumed over the past 14 days and to inform normative feedback provided in the brief intervention.

9.2.2.2 AIHW alcohol frequency/quantity items

The Australian Institute of Health and Welfare (AIHW) alcohol frequency/quantity items will be used to measure frequency / volume of alcohol consumption, and to inform normative feedback provided in the brief intervention. It consists of two items which ask about past-month frequency alcohol consumption, and the number of drinks consumed on a typical drinking day.

9.2.3 Alcohol health literacy

Alcohol health literacy will be measured using a brief questionnaire to ascertain the following: i) attitudes regarding alcohol and breast cancer risk using a series of 5-point Likert scales from strongly agree to strongly disagree (adapted from previous literature, e.g. Fisher, Wilkinson et al. (2017)); ii) alcohol knowledge (additional to the primary outcome) using a series of multiple choice and open-ended questions (i.e. amount of alcohol in an Australian standard drink, standard drinks in an average restaurant serve of wine, knowledge of Australian Alcohol Guidelines) adapted from previous literature (e.g. Bowden, Delfabbro et al. (2014)); and iii) access to health information on alcohol harms, alcohol-breast cancer risk, and alcohol harm reduction. Alcohol items will be nested among general health questions to conceal the focus on alcohol.

9.2.4 Wellbeing and Health Measures

9.2.4.1 EUROHIS-QOL single item

The *EUROHIS-QOL 8-item index* (Nosikov and Gudex 2003) is a reliable and valid instrument for assessing quality of life (QOL). It demonstrates cross-cultural performance and is recommended for use in public health research (Schmidt, Mühlan et al. 2006). We will be using the global question ("*On a scale of 1 to 5, with 1 being "very poor" and 5 being "very good", how would you rate your quality of life?*") from the EUROHIS-QOL 8-item index, which has been validated for use as a single-item approach to assessing QOL (Nosikov and Gudex 2003).

9.2.4.2 SF-12

The widely used 12-Item Short-Form Health Survey (SF-12) (Ware, 1998) will be used in this study as a brief measure of general health.

9.2.5 Alcohol Brief Intervention Feasibility Questions

Feasibility of the alcohol brief intervention in a breast screening setting will be assessed by examining women's attitudes toward receiving alcohol health promotion intervention in the context of the breast screening setting.

Before the trial commences, focus groups (V1 27 08 19) recruited from Lifepool (a participant resource of Victorian women who are eligible for/have had a screening mammogram) will be used to test the acceptability of the intervention prototype and research procedures. A survey (V1 27 08 19) will also be sent to Lifepool participants to determine women's views on receiving alcohol advice in the context of the BreastScreen setting. We will also access existing Lifepool data to examine alcohol consumption levels (i.e. need for alcohol brief intervention) in this cohort of women who are eligible/have had a screening mammogram. Relevant approvals will be sought from Lifepool.

Brief telephone semi-structured interviews with trial participants at follow-up will elicit feedback on the intervention (e.g. "*which parts, if any, of the computerised health promotion were most helpful to you? How were these most helpful?"*; "*What did you think about the delivery, format and duration of the computerised health promotion?"*). A subsample of the active arm (~30 participants who are not abstainers) will be selected, using random start systematic sampling, to provide this feedback. Verbal consent will be sought to voice record feedback sessions. Confidentiality and privacy of recordings will be upheld at all times, and will be stored securely, in line with ethical and regulatory requirements.

Staff feedback on alcohol health promotion intervention implemented in the breast screen setting will also be sought by way of a brief survey.

10 PARTICIPANT WITHDRAWAL

10.1 Withdrawing consent to participate and/or future use of data

All participants have the right to withdraw their consent to take part in the trial. The right to withdraw without consequence (i.e. without affecting their care received by Maroondah BreastScreen or Eastern Health) will be outlined during the consenting process and in the participant information sheet. If a participant wishes to withdraw consent, verbal revocation of consent can be provided by the participant. No further contact with the participant will be initiated by the research team upon verbal revocation of informed consent. Participants will have the option to remove all of their previously collected data or just remove consent for further data collection.

10.2 Discontinuation criteria and Investigator withdrawal

In instances where it has been identified that a participant meets exclusion criteria during the study, this will be explained sensitively to the individual, with referral to appropriate support as required.

Where it has been identified that it is not in the best interests of the participant to remain in the study (i.e. during follow-up), Researcher 2 will alert the Principal Investigator who, in deliberation with Co-Chief Investigators when necessary, will make the decision whether to withdraw the participant from the trial. In the event that it is determined appropriate to withdraw a participant from the trial, the reasoning for this will be explained sensitively to the participant. The participant will be withdrawn and offered information on how to access other support.

Following withdrawal from the trial no further data collection will occur, with the exception of the details regarding adverse events, as described in section 11 of this protocol.

10.3 Losses to follow-up

Participants who cannot be contacted after 5 phone calls will be deemed to be missing at that data collection time point. The research team will attempt to contact them again at the next data collection time point, following the same procedure.

11 ADVERSE EVENTS AND RISKS

11.1 Risks

The risks of harm and discomfort to participants are anticipated to be relatively minor. Some participants who do experience alcohol problems may find that discussing their alcohol use (including at follow-up assessments) triggers cravings for alcohol or psychological distress. However, our experience from previous studies suggests that this is uncommon and any distress is usually minor and transient.

11.2 Adverse Events

The research team will look out for possible adverse effects throughout the conduct of this trial. Any adverse events (AEs) or serious adverse events (SAEs) occurring during the course of this study, whether or not they are deemed to be related to participation in this study, will be followed rigorously, and in conjunction with the participant's treating primary care practitioner (PCP) when required (PCP details will be requested from the participant when this is deemed appropriate). Participants will be withdrawn from the study if any events compromise their treatment or well-being.

11.3 Additional support and resources

During baseline and telephone follow-up assessments, all participants will be advised to contact their primary care provider if they are concerned about any aspect of their health raised during the course of this research (i.e. alcohol use, general health and lifestyle factors). Take home pamphlets for women receiving the alcohol information (active arm) will contain the contact details for additional sources of support (e.g. DirectLine, CounsellingOnline). The researcher performing follow-up assessments will also provide participants with specific contact details for additional support whenever a need for this is identified.

12 DATA MANAGEMENT

12.1 Data Collection

There are several components of data collection and storage for this trial.

An electronic Case Report Form (eCRF) will be completed for each participant using REDCap (Research Electronic Data Capture), which contains all demographic, screening and study data. REDCap is a secure, web-based application designed to support data capture and storage for research studies collecting highly sensitive information (including case report forms, real time data entry validation and audit trails). REDCap is hosted on a secure server and managed by Eastern Health IT Services, and researchers access it via a secure login. Only approved members of the research team will have access to the eCRF. While a unique identifying code is generated by REDCap in order to retain data integrity, REDCap is used to collect *all* data for participants, which means that it stores identifiable data (i.e. name, contact information) as well as study data (i.e. participant responses to trial measures). However, identifiers will be flagged in REDCap, which then provides additional protection for these data elements (e.g. identifiers can then be automatically removed from all data exports where the user does not have permission to export identifiers). Data access and identifiers will be accessible only to the Co-Primary investigator (Jasmin Grigg) and the research assistants conducting baseline and follow-up assessments. On completion of the data collection,

non-identifiable trial data will be transferred from the eCRF to a statistical software package for analysis.

The Qualtrics Insight Platform, a secure platform and Monash University's preferred online survey tool which uses Transport Layer Security (TLS) encryption (also known as HTTPS) for all transmitted data, will be used for some data collection in this study – i.e. the baseline data on alcohol consumption that precedes the alcohol/control brief intervention provided to participants on the iPad. Data includes identifiable (i.e. first name only) and re-identifiable information (i.e. screening number, randomisation number). Participants' first name (i.e. identifiable information) is required in order to generate the *personalised* alcohol/control brief intervention. Identifiers will be removed from all exported data generated by Qualtrics before being transferred to a statistical software packaging for analysis. Access to Qualtrics data is via a secure login and will be limited to the research assistant directly involved in baseline data collection and Dr Jasmin Grigg.

Spread sheets containing identifiable information (i.e. name, contact number) and re-identifiable information (i.e. screening number, randomisation number) as well as administrative information will be used for the purpose of a) recruitment, and b) conducting follow-ups. These spreadsheets will only be accessed by the research assistants performing these roles, and will be password-protected and held on secure drives.

Electronic calendar-calculator spreadsheets containing TLFB substance use data contain only re-identifiable information (i.e. screening number, randomisation number) will only be accessed by the research assistants performing these roles, and will be password-protected and held on secure drives.

As paper records need to be used because of the fast pace of this trial (i.e. baseline assessments are partially completed by the participant in paper form) and will be PDF replicas of the trial's REDCap forms, it is not always feasible to remove identifiable information from the study data recorded on these paper records. All information in paper form will be stored securely in a locked filing cabinet on a secure level at Turning Point, and will be accessible only to the researchers conducting data collection and the trial manager, Dr Jasmin Grigg.

12.2 Data Retention

All data collected during this study will be retained by the Investigator for a period of 5 years as outlined in the Australian Code for the Responsible Conduct of Research.

13 STUDY OVERSIGHT

13.1 Study Monitoring

The Chief Investigators of this study have expertise relevant to the trial and capacity to monitor the research team, monitor compliance with the protocol, monitor compliance with ethical and clinical governance, provide standardised training and other means of quality control and assurance as appropriate, oversee trial arm fidelity, monitor adverse events reported, and provide necessary support to the research team (e.g. debriefing). Regular liaison between the research staff and Principal Investigator will occur to permit discussion of day-to-day trial progress and any potential

concerns. The broader research team will meet intermittently to review overall progress of the project.

14 STATISTICAL METHODS

14.1 Sample Size Estimation

Since the aims of this pilot RCT include preliminary hypothesis testing for effectiveness, a power and sample size calculation has been performed (Moore, Carter et al. 2011). Power and sample size estimates were carried out using PS: Power and Sample Size Calculation V3.1.2 (Dupont and Plummer 1990), assuming a type 1 error probability of $\alpha < 0.05$, 2-tailed, and equal-sized groups. Power calculations are based on the primary endpoint, proportion of participants who accurately identify alcohol as a clear risk factor for breast cancer.

Our sample size estimation is based on our previousonline survey study with 391 women who have attended/are eligible to attend breast screening services (Health4Her Phase I). If the proportion of control participants who accurately identify alcohol as a clear risk factor for breast cancer is 0.22 and the true response rate for participants receiving the alcohol brief intervention is 12% greater at 0.34, and compensating for 20% attrition at follow-up, then 548 participants (274 per arm) will provide power of 80% to be able to reject the null hypothesis.

Given the lack of definitive evidence regarding alcohol BI effects in women, and particularly women of middle- and older-age in a breast screening setting, this powered pilot RCT will inform the development of a subsequent, comprehensive multicentre trial. This pilot RCT will generate preliminary data on intervention response using exploratory surrogate/proximal markers of effectiveness (e.g. proportion of participants accurately identifying alcohol as a breast cancer risk factor, proportion of participants drinking within guidelines, alcohol consumption and well-being), and will provide concrete estimates of risky alcohol consumption prevalence, and expected rates of missing data and participant attrition specific to the population under study (Moore, Carter et al. 2011).

14.2 Statistical Analysis Plan

A detailed statistical analysis plan will describe the statistical methods for each outcome as well as how missing data will be dealt with. Data will be collated, cleaned and validated, using programmed edit checks, in a database that will be locked prior to analyses. All statistical tests will be two-tailed, with alpha level set to 0.05. Statistical analyses will be adjusted for multiple comparisons when indicated. 95% confidence intervals will be reported throughout. All randomised participants will be included in the analysis (i.e. intention-to-treat) for primary and secondary outcomes. Demographic characteristics (e.g. age) and baseline measurements (e.g. knowledge of alcohol as a clear risk factor for breast cancer, alcohol consumption) will be summarised and reported by intervention arm. The analyses will examine change in outcomes over time (4-weeks and/or 12-weeks) relative to baseline. The complete details of the analyses will be specified in a Statistical Analysis Plan that will be reviewed and approved by a study team prior to database lock. Analyses will be conducted using the most appropriate procedures in R and STATA.

15 ETHICS AND DISSEMINATION

This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (1999) and the Notes for Guidance on

Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines.

15.1 Research Ethics Approval

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Eastern Health Human Research Ethics Committee (HREC). A letter of protocol approval by the HREC will be obtained prior to the commencement of the study, as well as approval for other study documents subject to HREC review. It is the responsibility of the Principal Investigator to report annual study progress to the Eastern Health HREC.

15.2 Modifications to the protocol

Protocol amendments will be submitted to the Eastern Health HREC. No changes to the protocol will be implemented without prior approval.

15.3 Protocol Deviations

All protocol deviations must be recorded on the CRF and must be reported to the Principal Investigator. Protocol deviations will be assessed for significance by the Principal Investigator, and reported to the Eastern Health HREC if deemed to have a potential impact on the integrity of the study results, patient safety or ethical acceptability of the trial.

15.4 Confidentiality

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants must be treated in strict confidence. Data, which identify any trial participant, must not be revealed to anyone not directly involved in the trial or the clinical care of that participant.

15.5 Participant Reimbursement

Trial participants will go into a draw to win one of ten $100 supermarket vouchers. For the pre-trial component of this project being undertaken with the Lifepool cohort, an incentive of a pledge of $1 to breast cancer research for every survey completed will be used to optimise survey participation. Additionally, an incentive of a pledge of $10 to breast cancer research for focus group participation will be used to optimise participation.

15.6 Financial Disclosure and Conflicts of Interest

The trial is funded via a 2019 Eastern Health Foundation Research and Innovation Grant and a VicHealth Impact Research Grant.

15.7 Dissemination and translation plan

Dissemination of findings to the research community will be via peer-reviewed publications and conference presentations. Participants will be informed they can access the Eastern Health website for a summary report of trial findings in 2022. The summary report will also be made available at Maroondah BreastScreen.

REFERENCES

Agrawal, S., M. B. Sobell and L. C. Sobell (2008). "The Timeline Followback: A scientifically and clinically useful tool for assessing substance use." Calendar and time diary methods in life course research **57**: 68.

Bowden, J. A., P. Delfabbro, R. Room, C. L. Miller and C. Wilson (2014). "Alcohol consumption and NHMRC guidelines: has the message got out, are people conforming and are they aware that alcohol causes cancer?" Australian and New Zealand journal of public health **38**(1): 66-72.

Bush, K., D. R. Kivlahan, M. B. McDonell, S. D. Fihn and K. A. Bradley (1998). "The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking." Archives of internal medicine **158**(16): 1789-1795.

Cancer Australia (2018). Risk factors for breast cancer: A review of the evidence, Cancer Australia.

Daly, M. D., M. E. Passey and A. J. Harvey (2009). "Another opportunity for prevention: assessing alcohol use by women attending breast screening services in Lismore, NSW." New South Wales Public Health Bulletin **20**(6): 90-92.

Donoghue, K., R. Patton, T. Phillips, P. Deluca and C. Drummond (2014). "The effectiveness of electronic screening and brief intervention for reducing levels of alcohol consumption: a systematic review and meta-analysis." Journal of Medical Internet Research **16**(6).

Dupont, W. D. and W. D. Plummer (1990). "Power and sample size calculations: a review and computer program." Controlled Clinical Trials **11**(2): 116-128.

Fisher, B. A., L. Wilkinson and A. Valencia (2017). "Women's interest in a personal breast cancer risk assessment and lifestyle advice at NHS mammography screening." Journal of Public Health **39**(1): 113-121.

Kaner, E. F., H. O. Dickinson, F. Beyer, E. Pienaar, C. Schlesinger, F. Campbell, J. B. Saunders, B. Burnand and N. Heather (2009). "The effectiveness of brief alcohol interventions in primary care settings: a systematic review." Drug and Alcohol Review **28**(3): 301-323.

Moore, C. G., R. E. Carter, P. J. Nietert and P. W. Stewart (2011). "Recommendations for planning pilot studies in clinical and translational research." Clinical and translational science **4**(5): 332-337.

Napper, L. E., D. G. Fisher, M. E. Johnson and M. M. Wood (2010). "The reliability and validity of drug users' self reports of amphetamine use among primarily heroin and cocaine users." Addictive behaviors **35**(4): 350-354.

Nosikov, A. and C. Gudex (2003). "Development of a common instrument for quality of life." EUROHIS: Developing common instruments for health surveys **57**: 145.

Robinson, S. M., L. C. Sobell, M. B. Sobell and G. I. Leo (2014). "Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use." Psychology of addictive behaviors **28**(1): 154.

Schmidt, S., H. Mühlan and M. Power (2006). "The EUROHIS-QOL 8-item index: psychometric results of a cross-cultural field study." The European Journal of Public Health **16**(4): 420-428.

Sobell, L. C. and M. B. Sobell (1992). Timeline follow-back. Measuring alcohol consumption, Springer**:** 41-72.

Verplanken, B. and S. Orbell (2003). "Reflections on past behavior: A self-report index of habit strength." Journal of Applied Social Psychology **33**(6): 1313-1330.

Whitlock, E. P., M. R. Polen, C. A. Green, T. Orleans and J. Klein (2004). "Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use by adults: a summary of the evidence for the US Preventive Services Task Force." Annals of Internal Medicine **140**(7): 557-568.