

The assertive cardiac care trial: A randomised controlled trial of a coproduced assertive cardiac care intervention to reduce absolute cardiovascular disease risk in people with severe mental illness in the primary care setting

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ABSTRACT

Background: Cardiovascular disease (CVD) accounts for 40% of the excess mortality identified in people with severe mental illness (SMI). Modifiable CVD risk factors are higher and can be exacerbated by the cardiometabolic impact of psychotropic medications. People with SMI frequently attend primary care presenting a valuable opportunity for early identification, prevention and management of cardiovascular health. The ACCT Healthy Hearts Study will test a coproduced, nurse-led intervention delivered with general practitioners to reduce absolute CVD risk (ACVDR) at 12 months compared with an active control group.

Methods/design: ACCT is a two group (intervention/active control) individually randomised (1:1) controlled trial (RCT). Assessments will be completed baseline (pre-randomisation), 6 months, and 12 months. The primary outcome is 5-year ACVDR measured at 12 months. Secondary outcomes include 6-month ACVDR; and blood pressure, lipids, HbA1c, BMI, quality of life, physical activity, motivation to change health behaviour, medication adherence, alcohol use and hospitalisation at 6 and 12 months. Linear mixed-effects regression will

Abbreviations: ACCT, Assertive Cardiac Care Trial; ACT, Assertive Community Treatment; ACVDR, Absolute Cardiovascular Disease Risk; ACTRN, Australian Clinical Trials Registration Number; AE, Adverse Event; ANZCTR, Australia and New Zealand Clinical Trials Registry; AQOL-4D, Assessment of Quality of Life Scale; AUDIT-C, Alcohol Use Disorders Identification Test; BMI, Body Mass Index; CACE, Complier Average Causal Effect; CVD, Cardiovascular Disease; EDMC, Expert Data Monitoring Committee; GP, General Practitioner; HbA1c, Glycated Haemoglobin; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; HRUQ, Health Resource Use Questionnaire; ICH-GCP, International Council for Harmonisation-Good Clinical Practice; IPAQ-SF, International Physical Activity Questionnaire Short Form; MATCH, Motivation and Attitudes to Changing Health; MBS, Medical Benefits Scheme; MI, Motivational Interviewing; NHMRC, National Health and Medical Research Council; NPT, Normalisation Process Theory; NVDPA, National Vascular Disease Prevention Alliance; PBS, Pharmaceutical Benefits Scheme; POC, Point of Care; QALYs, Quality of Life Years; RACGP, Royal Australia College of General Practitioners; RAMS, Reported Adherence to Medication Scale; RCT, Randomised Controlled Trial; SAE, Serious Adverse Event; SAP, Statistical Analysis Plan; SMART Goals, Specific Measurable Agreed upon, Realistic Time-Based Goals; SMI, Severe Mental Illness; SMS, Short Messaging Service; Tot-c, Total Cholesterol

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estimate mean difference between groups for primary and secondary continuous outcomes. Economic cost-consequences analysis will be conducted using quality of life and health resource use information and routinely collected government health service use and medication data. A parallel process evaluation will investigate implementation of the intervention, uptake and outcomes.

Discussion: ACCT will deliver a coproduced and person-centred, guideline level cardiovascular primary care intervention to a high need population with SMI. If successful, the intervention could lead to the reduction of the mortality gap and increase opportunities for meaningful social and economic participation.

Trial registration

ANZCTR Trial number: ACTRN12619001112156.

1. Introduction

1.1. Background and rationale

People with severe mental illnesses (SMI) such as psychosis, schizophreniaiform disorders, bipolar disorder and major depression are at increased risk of cardiovascular disease (CVD) and metabolic syndrome than those without SMI. [1,2] Antipsychotic use can dramatically increase CVD risk in people with SMI [3,4], but modifiable risk factors contribute substantially and include abdominal obesity, insulin resistance/glucose intolerance, high blood pressure, high cholesterol, physical inactivity, diet, smoking, and alcohol or other drug use. [5–8] This is further complicated by systemic issues of poor care integration across health and social care sectors and stigma.

Although CVD-related mortality rates have declined in the general population, [9,10] CVD continues to contribute 40–50% [11] of the 10–25 year mortality gap for people with SMI. [12] The Australian Survey of High Impact Psychosis (SHIP) reported cardiometabolic illness rates that were substantially higher in people with SMI compared with the general population for diabetes (21% vs 4.9%); heart or circulatory conditions (27% vs 4.8%) and high cholesterol (31% vs 6.1%). [13,14] Medication was being taken by 52% diagnosed with hypertension; 40% diagnosed with diabetes/hyperglycaemia; and 40% diagnosed with high cholesterol. [5] High 5-year absolute cardiovascular disease risk (ACVDR) was identified in 24% of SMI respondents, and 7% had moderate risk [5] compared against the general population where 11.9% had high and 8.8% had moderate risk. [15] ACVDR is determined through the use of algorithms that determine a person's risk of developing CVD or having a cardiac event based on key risk factors. Internationally, the Framingham Risk Equation [16] is most widely used, and the Australian version is based on this tool [17]. Importantly, general population ACVDR algorithms may underestimate risk for people living with SMI by up to two thirds. [18]

The increased CVD risk for people with SMI compared with people without SMI indicates that people with SMI should be viewed as a high-risk population for CVD. Currently, Australian medical guidelines do not address this elevated risk, outside advice for smoking cessation. (e.g. [19]) It is recognised that the integration of evidence-based lifestyle interventions for physical health in mental healthcare is an essential first step to addressing the life expectancy gap. [20]

Reduction of ACVDR is difficult to achieve in all populations, and successful interventions in people with SMI have often achieved only small to medium effects. [21] Larger effects have been reported when interventions were multifactorial, tailored, enduring, targeted at people with elevated risk, and combined pharmacological and non-pharmacological approaches. [21–25] Clinical impacts were maximised when people with SMI were engaged for sufficient duration and contact. [25] Increasingly this success is linked with people with lived-experience coproducing interventions that incorporate their expertise and views. [26,27] Given that people with SMI have been documented to attend general practice twice as frequently than the general population (9 vs 5 times annually), [13] primary care presents an important setting for the delivery of interventions to reduce ACVDR for people with SMI. This builds on the central role primary care has in the prevention, detection,

monitoring and treatment of ACVDR. [28]

We outline the protocol for a stratified, individually randomised controlled trial (RCT) of a 12-month coproduced assertive cardiac care intervention for individuals with SMI attending general practice; ACCT. The protocol follows the SPIRIT guidelines for RCTs. [29]

2. Materials and methods

2.1. Objectives

2.1.1. Primary objective

To determine whether the ACCT intervention, a nurse-led collaboration with GPs to deliver multifactorial CVD risk reduction incorporating tailored pharmacological and non-pharmacological approaches, reduces the 5-year absolute cardiovascular disease risk (ACVDR) in people with SMI at 12 months relative to an active control group.

2.1.2. Secondary objectives

To determine whether the ACCT intervention will differ from an active control in improving 6-month ACVDR; and systolic and diastolic blood pressure, total cholesterol, HDL and LDL cholesterol, triglycerides, HbA1c (12 months only), BMI; quality of life, physical activity, motivation to change health behaviour, medication adherence, alcohol use and hospitalisation compared to active controls at 6 months and 12 months. An economic cost-consequences analysis of health economic factors and a parallel process evaluation will be conducted. Outcome measures are further described below.

2.2. Trial design

The ACCT study is a 2 group (intervention/active control) individually randomised RCT with assessments at baseline, 6 months and 12 months post-randomisation.

2.3. Methods: participants, interventions, and outcomes

2.3.1. Study setting

This study will be conducted in primary care which includes general practices and community health centres across Victoria, Australia. There are over 1600 accredited general practices across Victoria [30] and 86 Community Health Services made up of 31 independently managed community health centres and 55 services that are a part of larger rural or metropolitan health services. Urban, rural and regional sites will be recruited that are responsible for the delivery of clinical and/or psychosocial recovery services. As patient diagnostic, clinical and contact data is held in clinic-specific electronic medical record software, individual sites will be recruited followed by an invitation to individuals [31].

2.3.2. Eligibility criteria

Primary care sites (general practices and community health centres) will be eligible to be enrolled in the study if they:

- provide care for people who meet study inclusion criteria (Table 1);
- can assist to identify and contact eligible patients;
- have general practitioners (GPs) willing to be involved and retain clinical responsibility for their patients;
- can provide, subject to individuals granting consent, access to each participant's practice medical records; and
- have a space (where required) available for the researchers to meet with study participants.

Patients will be eligible if they meet the inclusion and exclusion criteria listed in Table 1.

The age limits ensure that the sample will meet the age restrictions for the ACVDR calculation. The ACVDR age range is 45–74 years but guidelines allow for the inclusion of some populations with elevated risk aged from 35 years (such as Aboriginal and Torres Strait Islanders). This age criterion has been extended to the SMI population in this study. [17] Women who are pregnant or breastfeeding will be excluded due to potential for impact on the cardiometabolic endpoints and distortion of outcome data. People who are experiencing an acute manic or psychotic episode will be ineligible at that time but can be approached again after two weeks to one month to provide a flexible participation option. This accords with clinical advice that acute symptoms could resolve within two weeks following active treatment.

Eligible participants will be invited to complete a Healthy Heart Check with a research nurse using point of care (POC) testing at their usual practice to determine ACVDR. [17] Everyone who attends a Healthy Heart Check will be provided with a coproduced ACCT Healthy Hearts Information booklet that contains general information on ways to maintain or improve cardiovascular health based on established guidelines.

People who have an ACVDR $\geq 3\%$ will be eligible to be randomised to intervention or active control. Participants who score $< 3\%$ ACVDR will not meet study eligibility criteria and will be informed of a lower risk result. They will be offered the opportunity to join the Co-Design Living Labs—a research registry of people with lived experience who take part in co-design, intervention development, piloting and prototype development and research translation. The 3% ACVDR minimum has been adopted to ensure that participants have some level of risk that can be addressed in the study, and to minimise the chance that floor effects could be observed in the primary outcome variable.

2.3.3. Interventions

Participants that meet the eligibility criteria will be randomised to the Assertive Cardiac Care Intervention Group or Active Control group.

2.3.3.1. Assertive cardiac care intervention group

2.3.3.1.1. Intervention overview. The Assertive Cardiac Care intervention has been coproduced by people who have lived experience of SMI, a multidisciplinary team of clinicians and mental health researchers. Box 1 describes the coproduction process undertaken to develop the intervention (see Box 1). In brief, the

Assertive Cardiac Care intervention integrates guideline level CVD preventive care with key principles of Assertive Community Treatment (ACT: [32]) and Motivational Interviewing (MI). [33] An integrated, person-centred approach has been employed based on Assertive Community Treatment principles including assertive outreach, a coordinated team approach, frequent contact in the community, a focus on self-determination and active medication management. [32,34] This is supplemented by a MI-informed approach where the motivation to change is elicited from a person through engagement and understanding of the person's readiness to change. MI is a collaborative process that is ongoing and supportive to elicit and maintain the motivation for change, as well as supporting the development of confidence, strategies and the resilience to overcome potential barriers to change [35,36]. The intervention will be delivered over 12 months.

A training program for research nurses has been developed by investigators in the team with input from GPs, nurses, psychiatrists (trained in ACT) and a clinical psychologist (trained in MI). Training will be delivered by those team members with support from the trial manager and refresher training is planned during the intervention course. Research nurses will be trained in completion of ACVDR assessments (Healthy Heart Checks) using POC testing (explained below) and the use of the purposefully built digital platform that has a dual function of being the study database and houses the intervention components (conversation aid, goals form and actions, healthy heart action plan, phone and SMS tailored message and short form risk reduction guidance for nurses). This is followed by comprehensive training in the intervention which includes dedicated skills development for MI and ACT and coproduced intervention components. Training will be conducted over two, three-hour sessions. Research nurses will receive ongoing support from study investigators. Fig. 1 describes the conceptual theoretical model and the active ingredients of the assertive cardiac care intervention.

An additional program has been developed for study research assistants for data collection using the digital study platform. Research assistants will not be involved in intervention delivery.

Following completion of ACVDR, the intervention has two key components:

- The Healthy Hearts Action Plan Appointment
- Provision of Assertive Support

2.3.4. The healthy hearts action plan appointment

At the completion of the Healthy Heart Check participants who are randomised to the Intervention Group will be booked to attend a Healthy Hearts Action Plan appointment. This appointment may take up to 60 min and the participants and the research nurse will:

- discuss the ACVDR results and risk factors that contribute to CVD risk;
- discuss CVD risks that the participant may experience using the co-

Table 1
Participant Inclusion and Exclusion Criteria for ACCT.

Participants	
Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> - age 35–74 years reflecting the parameters of the ACVDR calculation algorithm - ability to understand instructions of the study in English and complete questionnaires without an interpreter - existing diagnosis of schizophrenia, bipolar disorder, major depression, or recording of psychosis, or other SMI identified - OR currently prescribed anti-psychotic medication 	<ul style="list-style-type: none"> - severe acute manic or psychotic episode (unresolved) - acute physical illness or existing cardiac condition - previous CVD event - unable to provide informed consent at time of enrolment - pregnancy or breastfeeding
+	
<ul style="list-style-type: none"> - ACVDR $\geq 3\%$ (determined at the Baseline Healthy Heart Check) 	<ul style="list-style-type: none"> - ACVDR $< 3\%$ (determined at the Baseline Healthy Heart Check)

Box 1**Coproduction cycles for the assertive cardiac care intervention**

Six iterative coproduction cycles were held with people with lived-experience of SMI to determine how to (a) present heart health information, (b) develop tools to support risk conversations and decision-making, (c) encourage uptake of interventions to reduce CVD risk, and (d) co-design an intervention fit for purpose.

The first coproduction cycle involved ten people with lived-experience of SMI. In this group people discussed the content, format and wording of publicly available heart health information or cardiovascular risk information from the internet which represented guidance from the UK, US and Australia. Participants identified what worked and what did not work in the guidance provided, including selection of preferred images to communicate information.

The first coproduction cycle identified three key intervention components: 1) the need for a conversation aid to support CVD risk discussion and the identification of areas for change, 2) the need for a take home option for actions that was simple, easy to read and store at home but visually engaging, and 3) a healthy heart information booklet.

Prototypes of possible conversation aids were formulated and tested out in three more coproduction cycles conducted with a new group of participants who also had experience of living with SMI. A graphic designer was engaged to develop graphics to represent nine CVD risk factors and a final conversation aid prototype was produced based on lived experience participant preferences. A healthy hearts information booklet and a take home action form were also developed to support the intervention delivery. The information booklet used the same graphics as the conversation aid to ensure consistency in approach and messaging, and combined evidence from existing CVD guidelines about risk reduction in a format that was understandable and straightforward.

The final materials were shared with participants in a fifth coproduction cycle. These were deemed to be acceptable and feasible to that group. As part of the coproduction cycle we also consulted with five multidisciplinary professionals to gather feedback on the conversation aid and information booklet. There were minimal changes that followed these sessions. The sixth coproduction cycle included a pilot of the intervention with people with lived-experience to ensure fit for purpose.

produced conversation aid;

- develop goals and actions to reduce ACVDR; and
- complete a management plan for ACVDR in conjunction with the participant's GP.

The digital study platform calculates the ACVDR based on data collected in the Healthy Heart Check and generates a “risk arrow” outlining the person's ACVDR. The “risk arrow” is based on the format used by the National Vascular Disease Prevention Alliance in ACVDR management guidelines [37] to indicate the broad level of identified risk (see Fig. 2). Feedback from the coproduction cycles indicated the arrow format was easy to interpret and was user-friendly for people with lived-experience of SMI. The research nurse and the participant will use the “risk arrow” to enter into the discussion about ACVDR and the factors that contribute to this risk.

In presenting the risk results, research nurses will adopt a MI approach which attempts to identify the person's existing knowledge and motivation they might already have about their CVD risk and to build on this to facilitate change. Responses will guide the discussion between the participant and research nurse about how the relevant CVD risks could be addressed with pharmacological (where indicated) and non-pharmacological treatments. Nine areas for improvement for heart health are outlined using the coproduced conversation aid. These improvement areas are documented in current guidelines as ways to improve heart health and include making changes to salt consumption, drinking alcohol, eating healthy food, smoking, exercise, strength building, alcohol use, take away foods, inactivity and loneliness/stress where indicated and possible. The conversation aid has been designed with guiding questions and responses modelled on MI to foster participants' own reasons for making changes and to address key CVD risk



Fig. 1. The conceptual theoretical model and active ingredients of the assertive cardiac care intervention.

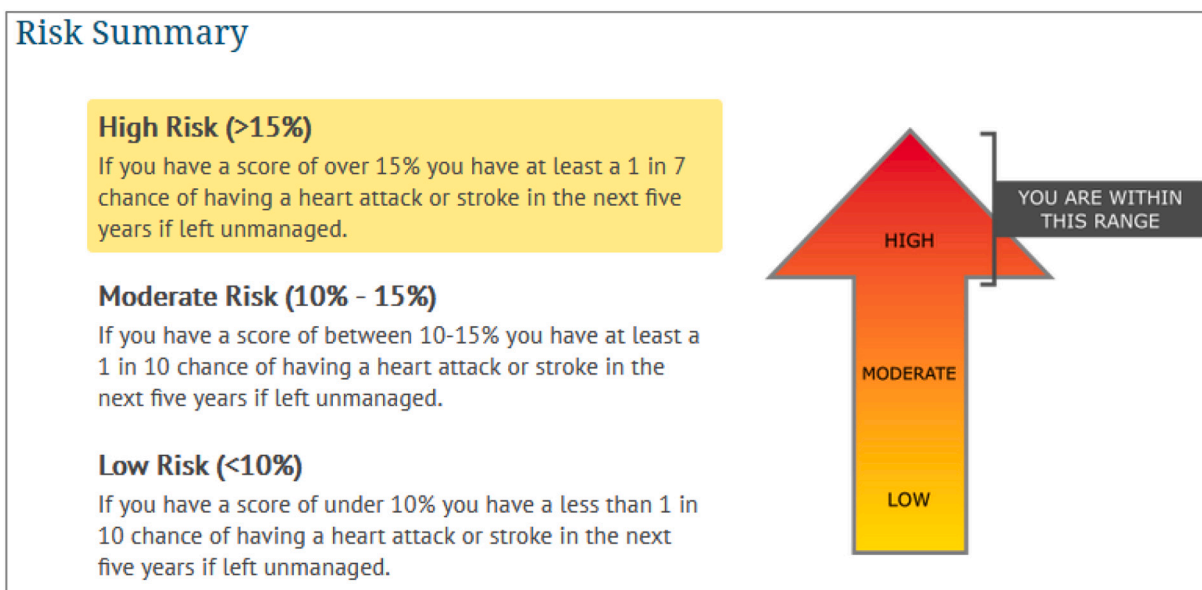


Fig. 2. Mock example of Absolute Cardiovascular Disease Risk Communication Arrow [37].

factors. The responses to the conversation aid will indicate which areas an individual seeks to improve. These responses will be used to inform goals for change and can be re-visited in future intervention contacts. The conversation aid is completed collaboratively via a digital platform or as a paper-based tool depending on participant preference. If the paper-based aid is used, the answers will be entered into the digital platform to maintain the study record.

Up to two behavioural/lifestyle targets for change to reduce ACVDR will be collaboratively decided on by the participant and nurse, including identification of risk factors that warrant pharmacological treatments. Participants will then use the targets to work with the research nurse to develop actions to support goals that are meaningful and reflect the participant's confidence, motivation and circumstances. A SMART (Specific; Measurable; Achievable; Relevant; Time-Bound) format will guide goal and action formulation. [38] The selected goals will be recorded alongside the actions in the digital platform, and participants will be provided a hard copy version of these goals and actions to take home.

The final step in the Healthy Hearts Action Plan appointment will be to document the goals and actions with input from the participant's GP. The GP will collaborate in a review of the Healthy Heart Check results and discuss the plan developed to reduce ACVDR for the participant. The GP will initiate medication as indicated based on ACVDR level and their clinical judgement. Treatment recommendations will be based on national guidelines [19,39] and have been developed into short form guidance accessible within the digital platform for the GP and research nurse. The GP and research nurse will document the Healthy Hearts Action Plan with the participant using a template within the digital platform. Key components of the Healthy Hearts Action Plan will be prefilled within the digital platform drawn from the baseline questionnaires and Healthy Heart Check. The Healthy Hearts Action Plan incorporates the main components of a GP management plan and/or chronic disease management plan and conforms with routine structures and payment systems for Australian general practice.

2.3.5. Assertive support

Following the Healthy Hearts Action Plan, intervention participants will receive assertive support from the research nurse additional to usual care provided by the GP. All ongoing contacts will be scheduled and structured within the digital platform with data entered as it is being collected. The research nurse delivering the intervention will

provide:

- Weekly phone contact that alternates each week between phone calls and positive messages via SMS. The contacts will be conducted using MI techniques and use a semi-structured approach allowing the participant to guide the discussion, update progress and troubleshoot barriers. At each fortnightly phone call the research nurse will be able to access and refer to the person's goals in the digital platform. Research nurses will work with the person to understand progress toward the goals and what has been working well, and any impediments to progress. The goals can be modified using the SMART Goal format if they have been attained; if they are judged too difficult; if they are demotivating the person; or as the person's health or life circumstances change. Any updates to established goals will be tracked and the reasons for the changes recorded in the digital platform.
- The SMS messaging in alternate weeks will be tailored to the individual to foster activation to achieve the set goals through supportive feedback, encouragement and motivation. The messages aim to reflect the participant's actions and goals, and will be guided by example messages that will be provided in the nurse manual. Messages will be collated within the participant record in the digital platform.
- In-person appointments with a research nurse: Intervention participants will meet with the research nurse at week 6, 12, 26, 38 and 52. These will coincide with Healthy Heart Checks and assessments at 26 weeks and 52 weeks. Some participants may not need to attend 6, 12 and 38 week appointments if they have not had medication initiated by the GP in the study.
- The GPs of intervention participants will be provided a summary of the Healthy Heart Check from the baseline, 6-month and 12-month assessments. GPs will collaborate in the in-person appointments to discuss the Healthy Hearts Action Plan, review medications, initiate and monitor referrals and monitor progress. Ongoing usual care will be maintained between times. GP study involvement will be recorded in the digital platform.
- At 52 weeks the research nurse will complete a handover process with the GP and participant. Goal progression over the year will be reviewed alongside all Healthy Heart Check results. Efforts to engage and motivate the participant will be made and strategies to maintain motivation and momentum to achieve the goals will be co-

developed. A printed study summary will be presented to the GP and participant.

2.3.5.1. ACCT active control group. Participants allocated to active control group will receive the coproduced Healthy Hearts Information booklet, and a recommendation to book an appointment with a GP to follow up their cardiovascular health. Active Control participants will complete a Healthy Heart Check at baseline, 6 and 12 months but no results will be fed back to active control participants or their GP during the study. At 52 weeks the research nurse will complete a handover process where the GP and participant both receive a printed summary of all Healthy Heart Check results.

Active controls will receive monthly calls from trained research assistants following a generic, scripted template designed to monitor any changes in health or treatment such as medication changes and any hospitalisation/s. These contacts will allow for other health issues to be brought to the attention of the research team. Information collected at these contacts will be recorded in the digital platform. Participants will be advised to direct any enquiries about their health to their GP.

2.3.6. Outcomes

Outcome assessments will be conducted prior to randomisation at baseline, and at 6 months and 12 months post-randomisation. Questionnaires will be administered by a research assistant via telephone and Healthy Heart Checks conducted by a research nurse usually at the participants' primary care practice (or another setting where appropriate) to collect anthropomorphic measures. Study outcomes are listed in Table 2.

2.3.6.1. Primary outcome. The primary outcome is change from baseline to 12 months post randomisation in 5-year ACVDR calculated using the algorithm developed by the National Vascular Disease Prevention Alliance (NVDPA). [17] ACVDR will be calculated at Healthy Heart Check appointments. These appointments will involve measures of blood pressure using an Omron HEM-907 (Omron Corporation; Vernon Hills, Illinois, USA) and Total Cholesterol and

Table 3
CardioChek PA analyser range of measurement for Total Cholesterol and HDL Cholesterol.

	US units	Australian units
Total Cholesterol	100–400 mg/dl	2.59–10.36 mmol/l
HDL cholesterol	15–100 mg/dl	0.39–2.59 mmol/l

HDL cholesterol measured using the CardioChek PA (PTS Diagnostics; Whitestown, Indiana) POC blood pathology assessment device. POC cholesterol results will be used to determine the ACVDR at each Healthy Heart Check and will allow the ACVDR to be calculated within the Healthy Heart Check appointment.

The CardioChek PA cholesterol results are subject to range restriction (see Table 3). Contingencies have been developed to address this possibility. Results below the ranges shown in Table 3 will present a “LOW” reading on the POC device and results above the upper limits will show as “HIGH” on the POC device. If one of these results occurs, or an unexpected result occurs, a second test will be conducted with a new test strip. If on the second assessment the results remain outside the upper or lower limits, the following will occur:

- if the POC reading value is **LOW**: The lower limit value should be included in the ACVDR calculation and updated with laboratory-based pathology results once they are available in the digital platform.

- if the POC reading value is **HIGH**: The upper limit value of the POC device should be included in the ACVDR calculation and updated with laboratory-based pathology results once they are available in the digital platform.

It is anticipated that these out of range values will be infrequent. In cases where this approach is required, the digital platform will include variables that indicate that the calculation is based on the laboratory-based pathology results and all subsequent ACVDR calculations will be based on the laboratory-based pathology results.

2.3.6.2. Secondary outcome measures. Secondary outcome measures are outlined in Table 1 and are presented in more detail here.

Table 2
ACCT Study Outcome Measures and Assessment Timepoints.

	Timepoint		
Anthropomorphic measures (collected at Healthy Heart Check)	Baseline	6 months	12 months
5-year ACVDR risk score [17]	X	X	X
Systolic and diastolic blood pressure	X	X	X
Lipids (HDL cholesterol, LDL cholesterol, Triglycerides)	X	X	X
Glycated haemoglobin (HbA1c)	X		X
Body Mass Index (BMI)	X	X	X
Survey measures (collected via telephone interview)	Baseline	6 months	12 months
Assessment of Quality of Life 4D (AQOL-4D: [40]).	X	X	X
Motivation and Attitudes Toward Changing Health (MATCH: [41])	X	X	X
International Physical Activity Questionnaire – Short Form (IPAQ: [42])	X	X	X
Reported Adherence to Medication Scale (RAMS: [43])	X	X	X
Alcohol Use Disorders Identification Test (AUDIT-C: [44])	X	X	X
Hospitalisation data	Baseline	6 months	12 months
Emergency department presentations (Victorian Emergency Minimum Dataset)	X	X	X
Hospital admissions (Victorian Admitted Episodes Dataset)	X	X	X
Economic cost consequences analysis	Baseline	6 months	12 months
Health Resource Utilisation Questionnaire (HRUQ)	X	X	X
Medical Benefits Schedule Data	X	X	X
Pharmaceutical Benefit Schedule Data	X	X	X

2.3.6.2.1. 6 month ACVDR. The change in 5 year ACVDR [17] from baseline will be calculated at the 6 month Healthy Heart Check.

2.3.6.2.2. Systolic and diastolic blood pressure. Measured in mm/hg. Blood pressure will be measured at baseline, 6 months and 12 months. Participants will be seated in a comfortable position and rested prior to the measurement of blood pressure. Three separate measurements will

be recorded at least one to 2 min apart, and the second and third measures will be recorded in the database.

2.3.6.2.3. Total cholesterol, High Density Lipoprotein (HDL) Cholesterol, Low-Density Lipoprotein (LDL) Cholesterol and triglycerides. Non-fasting blood samples will be taken at baseline, 6 months and 12 months. Total cholesterol and HDL cholesterol will

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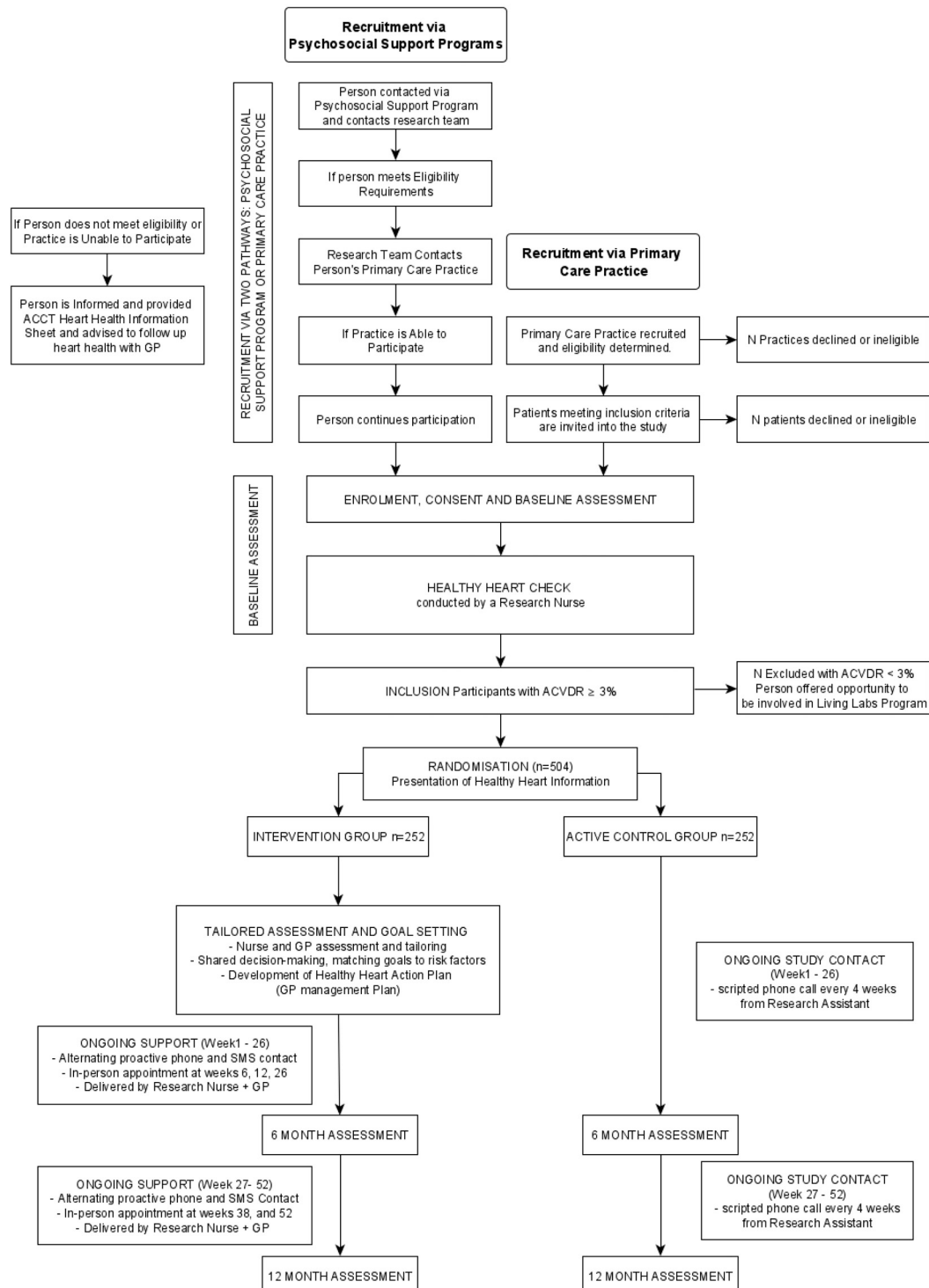


Fig. 3. Participant timeline from initial contact, recruitment and flow through study.

be analysed using POC analysis solely for use in the ACVDR calculation. Additional blood samples taken at the Healthy Heart Checks will be analysed using standard pathology services available to each site and will be used as secondary outcome variables. LDL will be manually calculated. Results will be expressed as mmol/l. Existing pathology results in the primary care records for Tot-c, HDL-c, LDL-c and triglycerides within 6 months of the baseline assessment will be accepted as baseline measures to reduce the burden on participants. Clinicians within the investigator team determined that lipids collected within 6-months of baseline would be considered current.

2.3.6.2.4. Glycated haemoglobin (HbA1c). Non-fasting blood samples will be taken at baseline and 12 months. HbA1c will be determined using standard pathology services available to each site. Results will be expressed as mmol/l. Existing pathology results in the primary care records for HbA1c within 6 months of the baseline assessment will be accepted as baseline measures to reduce the burden on participants.

All GPs will have access to any laboratory pathology data that has been requested (Total, HDL & LDL cholesterol; Triglycerides; HbA1c) for all intervention and active control participants.

2.3.6.2.5. Body mass index (BMI). Will be calculated in the digital portal at baseline, 6 months and 12 months. Height will be measured at the baseline assessment for all participants and weight will be measured at baseline, 6 months and 12 months. BMI is calculated using the formula: $BMI = \text{Weight (kg)} / \text{Height (m)}^2$. Results will be expressed as kg/m^2 .

2.3.6.2.6. Quality of life (QOL). The Assessment of Quality of Life 4D (AQOL-4D: [40]) will be completed by participants at baseline, 6 months and 12 months. It will be used both as a stand-alone measure of QOL and will be used in the health economic evaluation. Scoring will be conducted using standard approaches. The psychometric measure approach will be used to determine the stand-alone QOL score. The utility weight scoring system will be used in the health economic evaluation to estimate quality-adjusted life years (QALYs).

2.3.6.2.7. Motivation and attitudes to change. The Motivation and Attitudes Toward Changing Health (MATCH: [41]) is an internally consistent and validated 9-item scale that provides a profile of factors influencing motivation that can be used in clinical and research settings. It assesses the domains of willingness, worthwhileness, and ability. Standard scoring will be used. Assessments will be conducted at baseline, 6 months and 12 months and data collected from MATCH will be utilised in the process evaluation to examine engagement and activation.

2.3.6.2.8. Physical activity. The International Physical Activity Questionnaire – Short Form (IPAQ: [42]) measures the amount and type of physical activity conducted in the previous week. Standard scoring will be used. Assessments will be conducted at baseline, 6 months and 12 months.

2.3.6.2.9. Medication adherence. The Reported Adherence to Medication Scale (RAMS: [43]) is a 4-item scale to assess adherence to medication with specific focus on remembering to take medication, adjusting doses. RAMS has been used across a wide number of populations. RAMS will be completed at baseline, 6 months and 12 months. Standard scoring will be used.

2.3.6.2.10. Alcohol use. The Alcohol Use Disorders Identification Test (AUDIT-C: [44]) is a three item brief alcohol screen that identifies problematic levels of alcohol use and alcohol use disorders. Standard scoring will be used.

2.3.6.2.11. Hospitalisation information (optional). Participants will be asked to provide consent for the researchers to request state held information on emergency department presentations via the Victorian Emergency Minimum Dataset (VEMD) and hospital admission data held in the Victorian Admitted Episodes Dataset (VAED).

2.3.6.3. Economic outcomes. A comprehensive economic evaluation that draws data from several listed and supplementary outcome

measures is embedded in the study. A cost-consequences analysis will compare the incremental costs of the intervention to the full spectrum of outcomes included in the study. Inclusion of the AQoL-4D enables a cost-utility analysis to be undertaken. The evaluation will measure: (1) any value change to the use of health care resources over the study period between the trial groups (including the costs of delivering the intervention to the intervention group) and (2) then compare any additional costs to the additional outcomes achieved using standardised “within trial” economic evaluation techniques.

A study specific Health Resource Use Questionnaire (HRUQ) was modified from a resource use questionnaire frequently used in Australian mental health-related economic evaluations (e.g. [45]). The HRUQ covers service use and medication use, hospital use, accommodation, diagnostic tests, employment, National Disability Insurance Support (NDIS), and other services used. This will inform the economic evaluation along with the AQOL-4D [40]. The HRUQ covers a 6-month period and will be completed at baseline, 6 months and 12 months.

Participants can provide optional informed consent for the research team to request federal government held Medicare Benefits Schedule (MBS) and Pharmaceutical Benefit Scheme (PBS) data that outline government reimbursed medical services and filled pharmacy prescriptions. State government held data on hospital admissions and emergency department presentations will supplement the economic evaluation for the sample.

2.3.7. Participant timeline

Fig. 3 outlines the participant flow through the study for both the intervention and active control groups. Assessments at 6 and 12 months include a Healthy Heart Check conducted by a research nurse and questionnaires will be conducted over the telephone and administered by a research assistant.

2.3.8. Sample size

Randomisation of 504 individuals (252 per trial group) will provide 80% power for a two-sided alpha level at 5% to detect a two-percentage point absolute difference in the mean 5-year risk for cardiovascular disease between the intervention and active control groups calculated using the Australian ACVDR Calculator at 12 months. [17] This between-group difference in means is consistent with previous studies using a similar care planning and coordination intervention and would constitute a clinically meaningful outcome. [7] Sample size estimation assumes a standard deviation of 6.7 [7] and allows for 30% loss to follow-up at 12 months based on the CORE study trial (which recruited participants with SMI from the community health setting) and other related studies conducted in this population. [46]

2.3.9. Recruitment

Recruitment will occur via two pathways. The first will be conducted via General Practice clinics and Community Health Centres that have GPs within the service. The second recruitment pathway will be via psychosocial support services that do not have embedded GPs.

2.3.9.1. General practice clinics and community health centres. General practices and Community Health Centres that meet the study inclusion criteria will be recruited into the study and sign an ACCT site agreement. Once a practice has enrolled into the study, practice administrative staff will work with a research team member to identify eligible patients. A list of patients that meet eligibility criteria (the patient list) will be developed for each practice.

Eligible patients will be mailed an introductory letter to the study from the practice and university with a study brochure; study postcard and a reply-paid envelope. All patients on the “patient list” will be followed up by practice staff to ensure that the information was received and to advise them about how to contact the research team to obtain further information or enrol in the trial. Additionally, the study brochure and study postcard will be left at participating sites allowing

for opportunistic recruitment. Ethics requirements do not allow the research team to directly access identifiable information about the person until they contact the research team.

People interested in taking part will contact the research team via a free-call number, study email address, or post their details. A researcher will address any queries that the potential participant has and will send a full plain language statement to the person via SMS, email or mail. A time will be made to contact the person and discuss the study further. People interested in participating in the trial will then commence enrolment and consent.

2.3.9.2. Psychosocial support services. Community Health Centres that provide psychosocial support services to people with SMI will be approached as an avenue to invite eligible people. Staff working in these organisations will identify clients that meet the broad age and diagnostic criteria and present the information on the study. This will include a study postcard that people can complete and return to the research team, and a study email address and free-call number that can be used to contact the research team and express interest in participating.

Once a person makes contact, the person will inform the research team of their GP and clinic. Contact will be made with the GP and clinic and the broad aims of the study will be discussed, and interest in the study gauged. If the GP and clinic agree to participate in the study, they will sign an ACCT Site Agreement, and can involve other patients in the practice if they are happy to do so. At this point the person will be informed and will complete the enrolment and consent process outlined below.

If the GP and clinic are unable to participate in the study, the participant will be informed that we will not be able to involve them in the study. The person will be offered the opportunity to be involved in other coproduced research through the department.

2.3.9.3. Strategies for achieving adequate participant enrolment to reach target sample size. Both targeted and opportunistic recruitment strategies will be employed in the study. The avenues of recruitment include inviting potential participants via primary care clinics as well as via psychosocial support services delivered through community health centres. Site recruitment will continue until the target sample size has been reached.

The recruitment approach will be actively monitored and assessed within the research team, the study Investigators and the Expert Data Monitoring Committee. Modifications to study recruitment will be submitted to ethics and updated on the trial registry. There is provision to extend the study into other states if required, and a decision to do this will be based on recruitment rates, resource availability and feedback from the Investigator group and the Expert Data Monitoring Committee. Participants will be provided with bi-annual study reports and primer materials sent for questionnaires and appointment reminders will utilise established engagement methods to encourage retention.

2.4. METHODS: assignment of interventions

2.4.1. Allocation

2.4.1.1. Sequence generation. Participants will be randomised in a 1:1 ratio to the intervention or active control groups using a random allocation sequence generated using a biased-coin algorithm [47] and stratified by each primary care site. The imbalance tolerance of the randomisation algorithm is adaptive to ensure balance between trial group within the sites and overall.

2.4.1.2. Allocation concealment mechanism and implementation. The randomisation algorithm is inbuilt into the digital study platform and will be activated after the Baseline questionnaire and Baseline Healthy Heart Check have been completed, and the participant meets all study

inclusion criteria. Randomisation will use a biased-coin algorithm which allows group allocations to be concealed while maintaining equal allocation to both trial groups [48]. Research staff will have no knowledge or ability to influence group allocation.

2.4.2. Blinding (masking)

Consent and baseline assessment of participants will occur prior to randomisation to minimise selection and assessment bias. Due to the nature of the intervention we will use a single blind design where participants are blinded to their group allocation and are not informed whether they are allocated to the intervention or active control group. As the frequency and type of contact differs markedly between the intervention and active control groups, research staff and GPs working directly with participants in the trial will be able to determine the group allocation of a participant by the tasks being completed.

There is some risk of contamination between the trial groups, but it is anticipated that this will be small. GP clinics will be involved in the identification of potential participants, but the clinic and individual GPs will not be involved in the enrolment or consent of participants making it difficult for practice staff to know who is enrolled in the study and randomisation outcomes. The numbers of people with SMI are likely to be small per site given their low prevalence rate. As most of the intervention and support delivery are conducted by the research nurse the opportunities for contamination are reduced considerably, but GPs will know if someone is in the intervention by nature of collaboration with the research nurse. While other patients may inform their GP that they are participating in ACCT, GPs will not be informed of group allocation and as the research nurse is responsible for the majority of intervention delivery this limits the likelihood that GPs will deliver additional care to the active control.

Study investigators and the statistician who will be conducting the study analysis will be blind to the group allocation until after the statistical analyses have been completed.

2.5. METHODS: data collection, management and analysis

2.5.1. Data collection methods

Questionnaires will be administered by computer-assisted telephone interviewers (CATI) who are trained in the study protocol and follow scripts presented in the digital study platform. These will be administered prior to the face to face Healthy Heart Checks at each assessment point. Where participants' consent, study contacts via phone will be audio-recorded to ensure data has been collected appropriately and for quality checking. All research assistants involved in the study will undergo protocol training alongside specific training in using the digital database, participant engagement, dealing with participant distress, and study research processes. A comprehensive manual covering all CATI processes for the study, and a three-hour training program for research assistants, has been developed.

Healthy Heart Checks and intervention appointments will be conducted by a trained research nurse with current professional registration and delivered according to protocol. The research nurses will be unblinded to group allocation.

2.6. Data management

Participant study data will be collected in the digital study platform, a web accessible, purpose-built SQL database that allows data to be entered offsite. Data integrity is enforced using forced or multiple-choice items wherever possible. Valid value and range checks are also built into the platform for free text fields where appropriate. The data manager will check all the data to identify and resolve possible errors prior to analysis. Variables will be coded, labelled and scales scored according to each instrument's guidelines. Datasets will be merged as required for analysis with the unique record identifier. The data will be retained by investigators for 15 years as per the requirements of the

National Health and Medical Research Council Statement on Ethical Conduct of Research with humans. [49]

2.7. Statistical methods

Descriptive statistics will be used to compare baseline participant factors between trial groups. Linear mixed-effects regression will be used to estimate the difference in outcome means between groups for primary and secondary outcomes at 6 and 12 months where individuals will be treated as random effects to account for the repeated outcome measures; time (baseline, 6, 12 months), and trial group (intervention and control) will be treated as fixed effects, with two-way interactions between group and time, except at baseline where group means will be constrained to be equal. Sensitivity analyses will be conducted using the same regression analysis as described above with a further adjustment for primary care practice treated as random effects. Marginal logistic regression using Generalised Estimating Equations with robust standard errors to adjust for repeated outcome measures on individuals will be used to compare binary outcomes between the two trial groups. Pre-specified baseline variables strongly associated with the outcome will also be considered for adjustment in the regression analysis. Estimated intervention effects will be reported as the difference in the means between trial groups (intervention-control) for continuous outcomes and odd ratios for binary outcomes, with 95% confidence intervals and *p* values, respectively. Pre-specified baseline variables strongly associated with the primary outcome will also be considered for adjustment in the regression analysis. In a secondary analysis, complier average casual effect (CACE) analysis will be used to examine the intervention effect on individuals who engage in their assigned intervention. [50] Analysis will use an intention to treat strategy, where participants will be analysed in their assigned trial group, whether they received all, parts or none of the intervention components. [51] Strategies will be implemented to minimise missing outcome data. Reasons for attrition will be documented. Sensitivity analyses will be used to assess the robustness of the assumption about the missing data patterns.

A full structured [52] statistical analysis plan (SAP) will be developed that will provide further details on all secondary and planned subgroup analysis. The SAP will be uploaded to the trial registry prior to the commencement of any statistical analysis of the primary or secondary outcomes. Analysis will be conducted in Stata 15 (StataCorp).

2.8. Economic evaluation

A cost-consequences analysis will compare the incremental costs of the intervention to the full spectrum of outcomes included in the study. Inclusion of the AQL-4D [40] enables a cost-utility analysis to be undertaken, thereby allowing practical judgments regarding value for money credentials of the interventions to be made. The evaluation will measure:

1. any value change to the use of health care resources over the study period between the trial groups (including the costs of delivering the intervention to the intervention group);
2. compare any additional costs to the additional outcomes achieved using standardised 'within trial' economic evaluation techniques. However, since the main benefits of the intervention will occur beyond the study time frame (i.e. reduction of CVD events) the lifetime and population cost-effectiveness of the intervention will be determined using modelling techniques.

Information from government held administrative data sets such as Medicare and Pharmaceutical Benefits Schedule (MBS/PBS) will be used in this analysis for participants who have provided optional consent to this. Study records and financial systems will be used to determine the costs of implementing and delivering the intervention. Standardised economic statistical methods, including generalised linear

modelling for cost data will be used to analyse economic outcomes.

2.8.1. Process evaluation

A parallel process evaluation will be conducted during the trial to examine:

1. the contextual factors that support or impede implementation of the intervention,
2. the experiences of GPs and patients who participated in the trial,
3. the mechanisms of action for the intervention participants.

Qualitative and quantitative data will be collected to inform the process evaluation. Descriptive data will be collected about sites by recruiters and research nurses will complete notes outlining implementation challenges and enablers. All GPs in participating practices will be invited to complete a brief questionnaire pre and post intervention implementation. The questionnaire will include demographic information alongside completion of the clinician support for patient activation (CS-PAM®) survey. [53] This will provide data to further analyse potential mechanisms of action related to the intervention.

Up to 50 (20%) intervention participants will be invited to participate in telephone interviews alongside a sub-sample of participating GPs. Interviews will elicit participant experiences and provide data on implementation challenges and enablers. The interview data will also be used to examine mechanisms of action for the intervention in conjunction with data collected from fortnightly phone contacts with intervention participants and structured reviews, and using secondary outcomes from the MATCH questionnaires.

2.9. Methods: monitoring

2.9.1. Data monitoring

An Expert Data Monitoring Committee (EDMC) has been convened and a charter has been established following the guidance from the Data Monitoring and Outcomes Study Group (DAMOCLES) (See Supplementary File 1). The EDMC is comprised of an independent biostatistician, GPs, an endocrinologist, mental health nurse practitioner and a consumer representative. Members of the EDMC will meet biannually and will review adverse events and monitor the trial to safeguard the interests of participants and the safety of the intervention.

2.9.2. Harms

Harms will be monitored at each participant contact and will be formally assessed at each of the key face to face data collection points (baseline, 6 months, 12 months) by the research nurse.

At each patient encounter, research staff will be alert to Adverse Events (AEs) and Serious Adverse Events (SAEs). AEs and SAEs will be reported using standard reporting forms using definitions based on International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) guidance [54].

AEs will be monitored from the time of consent through to the final visit and handover at week 52. At all times responsibility for the clinical management of the participant will remain with the GP and AE will be reviewed by a Medical Monitor. Ethics reporting will follow institutional guidelines. Causality will be determined by the Medical Monitor and all AEs and SAEs will be reviewed at 6 monthly intervals by the EDMC.

A separate protocol has been developed for indications of self-harm or suicidal ideation that outlines responses by researchers and the reporting requirements to be implemented by research staff.

2.9.3. Auditing

Ongoing monitoring and auditing will be the responsibility of the steering committee and trial EDMC.

Adherence to intervention delivery and fidelity will be assessed by

checking 15% of the available audio recordings of the Healthy Hearts Action Plan Completion appointments. Adherence to all steps within the discussion, goal setting, and MI principles will be evaluated. Notes of follow-up appointments and research nurse phone contacts with the same group of intervention participants will also be reviewed to check for fidelity to MI and ACT principles. Progress to goals and medication adherence will be continuously monitored and evaluated through the in-person and phone contacts through a semi-structured monitoring approach.

3. Ethics and dissemination

3.1. Research ethics approval and trial registration

The University of Melbourne Medicine and Dentistry Human Ethics Sub-Committee approved the study (Ethics ID: 1853050) and collaborating universities have also provided consent. The study has been prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN1261900112156). An application has been made to the Centre for Victorian Data Linkage to access the emergency department presentation data and hospital admission data for participants that provide signed consent to this process. The Department of Human Services has been approached to allow access to the MBS and PBS data for participants that provide signed consent to this process.

3.2. Protocol amendments

All modifications to the protocol that may affect: the conduct of the study; participant recruitment, enrolment, and procedures; sample size considerations; or information provided to participants and sites will be submitted to the University of Melbourne Human Ethics Sub-Committee as an amendment. Any substantive amendments to procedures will require active participants to re-consent to the new information. All participating services will be informed of any protocol amendment that will impact on their involvement or the involvement of their patients. The ANZCTR listing will be updated with all protocol amendments following approval from the Human Ethics Sub-Committee.

3.3. Consent or assent

Individuals will contact the research team to express interest in taking part in ACCT. A research assistant trained in the study protocol and procedures will conduct the enrolment and consent process via telephone. The enrolment and consent process is scripted within the digital study platform. The research assistant will review the Plain Language Statement with the participant and will answer any questions that the person may have about the study. The research assistant will confirm that the person meets eligibility criteria, outline what being involved in the study requires, and that the person can demonstrate they understand participation requirements.

Consent will be determined in two steps. First, the research assistant will read eleven statements of participation for the trial that the person will need to consent to. The consent process is to be audio recorded with responses entered into the digital study platform. This information will be stored on secure password protected University servers. Second, participants will be asked three “true” or “false” questions about study participation to demonstrate they understand study requirements. These questions are purpose designed to ensure that individuals understand the nature of the study they are signing up to and that they can withdraw any time. If a person does not answer all three questions correctly, the process allows two additional attempts to obtain consent. One attempt can be made by repeating the information during the current contact. The second attempt involves repeating the consent process a fortnight after the initial attempt. If the person remains unable to demonstrate an understanding of study requirements following the second attempt, they will be considered ineligible to participate and

will be thanked for their time and study involvement will end.

At the baseline Healthy Heart Check, all participants will be asked to sign an additional hard copy consent that will permit the research team to access their clinic held medical record for the duration of their involvement in the study. A copy of this participant signed consent will be stored with the clinic medical record.

In addition to general study consent, participants will be asked to provide additional consent to allow access to two sources of government held health information. The first process is to request participants consent to access their records in the Medicare Benefits Schedule (MBS) and the Pharmaceutical Benefits Scheme (PBS) held by the Commonwealth Department of Human Services. MBS data includes information on medical service use and the associated costs, while the PBS collects information on the prescription medications that have filled at pharmacies. The second consent process will be to the Centre for Victorian Data Linkages requesting state held information on emergency department presentations via the Victorian Emergency Minimum Dataset (VEMD) and hospital admission data held in the Victorian Admitted Episodes Dataset (VAED). Both consent processes are optional and do not impact on general study eligibility.

3.4. Confidentiality

On entry into the study all participants and sites will be allocated a unique identification number (UID) which will be the primary identifier in the study. All data will be identifiable/re-identifiable for the duration of the study and will be re-identifiable once the data is archived. All research data will be only available to the research team. All electronic research data will be stored in a password protected database and drive on departmental servers that are regularly backed up. The data will only be accessible with a username and password provided by the database manager. All audio records will be identified with the unique identifier and will be used by the research team to monitor treatment fidelity and quality and will be used to identify ongoing training needs in the research team. All audio recordings will be stored on department servers with access limited to members of the research team.

Some clinically relevant information collected in the study will be shared with the participant's treating GP and will be stored in their medical records and will follow clinical best practice. This will be provided to the GP clinic in hard copy form or as a PDF depending on the preference of the clinic, and local copies will be stored electronically within the password protected digital study platform.

3.5. Declaration of interests

Investigators and staff have reported that they currently have no conflicts of interest to declare in this study.

If any competing interests or conflicts of interest emerge during the study, they will be listed and submitted via a protocol amendment to the HREC and updated on the ANZCTR trial listing.

3.6. Access to data

All data remains with the investigators. De-identified data may be shared with named investigators or made available following publication of results as a condition of the journal. In this case all identifiers will be removed prior to the provision of the dataset. Participants will be informed of this possibility through the Plain Language Statement.

3.7. Ancillary and post-trial care

At the end of the trial the research nurse will conduct a handover and review to participants' treating GPs who have remained responsible for participant care through the study. Participants will be able to contact the research team with any queries, but any ongoing care will be managed by their GP.

3.8. Dissemination policy

Data will be collated and prepared for analysis at study completion. The investigators are responsible for all reporting and dissemination of results. No limits have been placed on the publication of results by the study funders. Research outputs will be developed by investigators and members of the research team and approved by the Principal Investigator. A statistical analysis plan will be developed and published by the research team in 2020. The primary outcome papers will be prepared and submitted following the statistical analysis plan and under guidance of the study investigators. A final report will be prepared and reviewed by all investigators for the funder and reports for the participating sites and participants who requested updates will be provided at the end of the study.

4. Discussion

The ACCT Healthy Hearts Study will systematically identify five-year absolute cardiovascular disease risk (ACVDR) and the contributing risk factors in people with SMI in the primary care setting. If the existing life expectancy gaps are to be addressed in people living with SMI we urgently need multifactorial CVD risk reduction interventions that adopt the best available pharmacological and non-pharmacological evidence. Interventions that employ coproduction methods are also required to ensure better fit for purpose, increased engagement and responsiveness. These need to be tailored, implemented and tested in the primary care setting where preventive approaches to CVD risk can be delivered.

In ACCT, participants will be supported to determine areas for improvement that may lead to better cardiovascular health and overall well-being. The intervention is designed to foster the development of a trustful relationship between the participant and research nurse with GP involvement through a supportive and person-centred discussion of identified CVD risk factors, their importance to ACVDR and ways to improve outcomes. The intervention aims to elicit and strengthen participants' motivation to improve their heart health using MI techniques that will lead participants to establish achievable and realistic goals, that with guided support and coaching, may reduce ACVDR. Ongoing support will be provided by a research nurse and GPs. Both pharmacological and non-pharmacological approaches will be considered in the risk response. The intervention is based on principles drawn from ACT and MI to provide assertive, frequent contact in the community working with participants to determine and facilitate their motivation to change to build capabilities and self-determination. [31,33] The ACCT intervention incorporates tailored CVD risk-reduction and goal setting based on identified risk factors and draws on the person's existing knowledge and motivation to address these.

Guided by previous work [25] the intervention targets people with SMI who have elevated ACVDR and allows sufficient time for people to engage with change. It must be acknowledged, however, that current algorithms to determine ACVDR can underestimate the risk of cardiovascular disease in people with a diagnosis of SMI. [18] This difference can be substantial with CVD risk being underestimated by about one-third in men and two-thirds in women. As this risk is equally present in both the intervention and control groups for the trial it should not impact on the between-group study outcomes. Beyond this study there is a need to develop a more appropriate risk calculation that better estimates true CVD risk for people with SMI and allows for identification of risk earlier in people's lives.

ACCT will assess a comprehensive, evidence-based, coproduced intervention with ongoing engagement to reduce ACVDR in a high-risk population of people experiencing SMI. A comprehensive economic evaluation will determine the economic impact of the intervention and the lifetime and population cost-effectiveness of the intervention will be determined using modelling techniques. The process evaluation data will be examined to identify implementation challenges and enablers to

inform future scalability of the intervention. To date, evidence indicates that combined pharmacological and non-pharmacological approaches that address multifactorial risk show promise. The development of models of care and approaches that are tested and ready for implementation in primary care still lag. This trial has important potential to improve the cardiovascular health of people with SMI in primary care to reduce the mortality gap attributable to CVD.

Authors' contributions

VP wrote the funding proposal and conceived the study with the named investigator team. All authors contributed to drafts and edited this protocol. ML led the development of the manuscript and coordinated input from the authors. KM contributed to MI informed approaches for the intervention. PC led the statistical analysis and study design sections with KD responsible for data management procedures. MP developed recruitment procedures. CM and YYL led the economic analysis. VP is the lead and is responsible for the conduct of the study.

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Declaration of Competing Interest

The funders have no role in the conduct of this study. The funders will not influence data collection, data management, data analysis or dissemination. The funders will have no role in the development of research outputs arising from this study.

All authors have completed a conflict of interest declaration and no conflicts have been identified.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cct.2020.106143>.

References

- [1] C.H. Hennekens, A.R. Hennekens, D. Hollar, D.E. Casey, Schizophrenia and increased risks of cardiovascular disease, *Am. Heart J.* 150 (6) (2005) 1115–1121.
- [2] C.U. Correll, M. Solmi, N. Veronese, B. Bortolato, S. Rosson, P. Santonastaso, N. Thapa-Chhetri, M. Fornaro, D. Gallicchio, E. Collantoni, G. Pigato, A. Favaro, F. Monaco, C. Kohler, D. Vancampfort, P.B. Ward, F. Gaughran, A.F. Carvalho, B. Stubbs, Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls, *World Psychiatry* 16 (2) (2017) 163–180.
- [3] C. Rummel-Kluge, K. Komossa, S. Schwarz, H. Hunger, F. Schmid, C.A. Lobos, W. Kissling, J.M. Davis, S. Leucht, Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a

- systematic review and meta-analysis, *Schizophr. Res.* 123 (2) (2010) 225–233.
- [4] T. Pillinger, R.A. McCutcheon, L. Vano, Y. Mizuno, A. Arumuham, G. Hindley, K. Beck, S. Natesan, O. Efthimiou, A. Cipriani, O.D. Howes, Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis, *Lancet Psychiatry* 7 (1) (2020) 64–77.
 - [5] C.A. Galletly, D.L. Foley, A. Waterreus, G.F. Watts, D.J. Castle, J.J. McGrath, A. Mackinnon, V.A. Morgan, Cardiometabolic risk factors in people with psychotic disorders: the second Australian national survey of psychosis, *Austral. N. Z. J. Psychiatry* 46 (8) (2012) 753–761.
 - [6] V.A. Morgan, J.J. McGrath, A. Jablensky, J.C. Badcock, A. Waterreus, R. Bush, V. Carr, D. Castle, M. Cohen, C. Galletly, C. Harvey, B. Hocking, P. McGorry, A.L. Neil, S. Saw, S. Shah, H.J. Stain, A. Mackinnon, Psychosis prevalence and physical, metabolic and cognitive co-morbidity: data from the second Australian national survey of psychosis, *Psychol. Med.* 44 (10) (2014) 2163–2176.
 - [7] B.G. Druss, S.A. von Esenwein, M.T. Compton, K.J. Rask, L. Zhao, R.M. Parker, The primary care access referral, and evaluation (PCARE) study: a randomized trial of medical care management for community mental health settings, *Am. J. Psychiatry* 167 (2) (2010) 151–159.
 - [8] S. Yusuf, S. Reddy, S. Ôunpuu, S. Anand, Global burden of cardiovascular diseases, *Circulation* 104 (22) (2001) 2746–2753.
 - [9] GBD 2015 Mortality and Causes of Death Collaborators, Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2013: a systematic analysis for the Global Burden of Disease Study 2015, *Lancet* 388 (10053) (2016) 1459–1544.
 - [10] Australian Institute of Health and Welfare, Trends in Cardiovascular Deaths. Bulletin 141 September 2017, Australian Institute of Health and Welfare, Canberra, 2017.
 - [11] P.A. Ringen, J.A. Engh, A.B. Birkenaes, I. Dieset, O.A. Andreassen, Increased mortality in schizophrenia due to cardiovascular disease – a non-systematic review of epidemiology, possible causes, and interventions, *Front. Psychiatry* 5 (2014).
 - [12] C.U. Correll, J. Detraux, J. De Lepeleire, M. De Hert, Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder, *World Psychiatry* 14 (2) (2015) 119–136.
 - [13] V.A. Morgan, A. Waterreus, A. Jablensky, A. Mackinnon, J.J. McGrath, V. Carr, R. Bush, D. Castle, M. Cohen, C. Harvey, C. Galletly, H.J. Stain, A.L. Neil, P. McGorry, B. Hocking, S. Shah, S. Saw, People Living With Psychotic Illness 2010: Report on the Second Australian National Survey, Australian Government, Canberra, 2011.
 - [14] Australian Bureau of Statistics, National Health Survey: First Results, 2017–18, <https://www.abs.gov.au/ausstats/abs@.nsf/mf/4364.0.55.001>, (2019).
 - [15] J. Welsh, R.J. Korda, G. Joshy, E. Banks, Primary absolute cardiovascular disease risk and prevention in relation to psychological distress in the Australian population: a nationally representative cross-sectional study, *Front. Public Health* 7 (126) (2019).
 - [16] R.B. D'Agostino, R.S. Vasan, M.J. Pencina, P.A. Wolf, M. Cobain, J.M. Massaro, W.B. Kannel, General cardiovascular risk profile for use in primary care: the Framingham heart study, *Circulation* 117 (6) (2008) 743–753.
 - [17] National Prescribing Service Limited, Australian Absolute Cardiovascular Disease Risk Calculator Functional Specifications, National Prescribing Service Limited, Surry Hills, 2009.
 - [18] R. Cunningham, K. Poppe, D. Peterson, S. Every-Palmer, I. Soosay, R. Jackson, Prediction of cardiovascular disease risk among people with severe mental illness: a cohort study, *PLoS One* 14 (9) (2019) e0221521.
 - [19] Royal Australian College of General Practitioners, Guidelines for Preventive Activities in General Practice, 9th edition, The Royal Australian College of General Practitioners, East Melbourne, 2016.
 - [20] J. Firth, N. Siddiqi, A. Koyanagi, D. Siskind, S. Rosenbaum, C. Galletly, S. Allan, C. Cane, R. Carney, A.F. Carvalho, M.L. Chatterton, C.U. Correll, J. Curtis, F. Gaughran, A. Heald, E. Hoare, S.E. Jackson, S. Kisely, K. Lovell, M. Maj, P.D. McGorry, C. Mihalopoulos, H. Myles, B. O'Donoghue, T. Pillinger, J. Sarris, F.B. Schuch, D. Shiers, L. Smith, M. Solmi, S. Suetani, J. Taylor, S.B. Teasdale, G. Thornicroft, J. Torous, T. Usherwood, D. Vancampfort, N. Veronesi, P.B. Ward, A.R. Yung, E. Killackey, B. Stubbs, The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness, *Lancet Psychiatry* 6 (8) (2019) 675–712.
 - [21] D. Vancampfort, J. Firth, C.U. Correll, M. Solmi, D. Siskind, M. De Hert, R. Carney, A. Koyanagi, A.F. Carvalho, F. Gaughran, B. Stubbs, The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials, *World Psychiatry* 18 (1) (2019) 53–66.
 - [22] P. Fleming, M. Godwin, Lifestyle interventions in primary care: systematic review of randomized controlled trials, *Can. Fam. Physician* 54 (12) (2008) 1706–1713.
 - [23] V.J. Palmer, M. Lewis, V. Stylianopoulos, J. Furler, Primary care prevention of the cardiovascular health crisis for people with severe mental illnesses, *Australian J. Gen. Pract.* 47 (12) (2018) 846–850.
 - [24] S. Seidu, N.S. Walker, D.H. Bodicoat, M.J. Davies, K. Khunti, A systematic review of interventions targeting primary care or community based professionals on cardiometabolic risk factor control in people with diabetes, *Diabetes Res. Clin. Pract.* 113 (2016) 1–13.
 - [25] E.E. McGinty, J. Baller, S.T. Azrin, D. Juliano-Bult, G.L. Daumit, Interventions to address medical conditions and health-risk behaviors among persons with serious mental illness: a comprehensive review, *Schizophr. Bull.* (2015) sbv101.
 - [26] T. Delbanco, D.M. Berwick, J.I. Boufford, G. Ollenschläger Edgman-Levitan, D. Plamping, R.G. Rockefeller, Healthcare in a land called PeoplePower: nothing about me without me, *Health Expect.* 4 (3) (2001) 144–150.
 - [27] L.B. Dixon, Y. Holoshitz, I. Nossel, Treatment engagement of individuals experiencing mental illness: review and update, *World Psychiatry* 15 (1) (2016) 13–20.
 - [28] A.A. Rothman, E.H. Wagner, Chronic illness management: what is the role of primary care? *Ann. Intern. Med.* 138 (3) (2003) 256–261.
 - [29] A. Chan, J.M. Tetzlaff, D.G. Altman, et al., SPIRIT 2013 statement: defining standard protocol items for clinical trials, *Ann. Intern. Med.* 158 (3) (2013) 200–207.
 - [30] Productivity Commission, Report on Government Services 2019. Part E, Chapter 10: Primary and Community Health, Productivity Commission, Canberra, 2019.
 - [31] J.E. Lockery, T.A. Collyer, W.P. Abhayaratna, S.M. Fitzgerald, J.J. McNeil, M.R. Nelson, S.G. Orchard, C. Reid, N.P. Stocks, R.E. Treva, R. Woods, Recruiting General Practice Patients for Large Clinical Trials: Lessons From the Aspirin in Reducing Events in the Elderly (ASPREE) Study, 0(0) (2020).
 - [32] G.R. Bond, R.E. Drake, The critical ingredients of assertive community treatment, *World Psychiatry* 14 (2) (2015) 240–242.
 - [33] W.R. Miller, S. Rollnick, Motivational Interviewing. Preparing People for Change, 2nd edition, The Guildford Press, New York, 2002.
 - [34] D.B. Herman, Transitional support for adults with severe mental illness: critical time intervention and its roots in assertive community treatment, *Res. Soc. Work. Pract.* 24 (5) (2014) 556–563.
 - [35] K.J. McKenzie, D. Pierce, J.M. Gunn, Guiding Patients Through Complexity, 47(1) (2018), p. 6.
 - [36] W.R. Miller, S. Rollnick, Motivational Interviewing: Preparing People for Change, 3rd ed., Guildford Press, New York, 2013.
 - [37] National Vascular Disease Prevention Alliance, Manage your heart and stroke risk: A 3-step guide to better health, National Vascular Disease Prevention Alliance, Australia, 2018.
 - [38] R.S. Rubin, Will the real SMART goals please stand up? *Industr. Organizational Psychol.* 39 (4) (2002) 26–27.
 - [39] National Vascular Disease Prevention Alliance, Guidelines for the Management of Absolute Cardiovascular Disease Risk, National Heart Foundation of Australia, Melbourne, 2009.
 - [40] G. Hawthorne, J. Richardson, R. Osborne, The assessment of quality of life (AQoL) instrument: a psychometric measure of health-related quality of life, *Qual. Life Res.* 8 (3) (1999) 209–224.
 - [41] D.M. Hessler, L. Fisher, W.H. Polonsky, V. Bowyer, M. Potter, Motivation and attitudes toward changing health (MATCH): a new patient-reported measure to inform clinical conversations, *J. Diabetes Complicat.* 32 (7) (2018) 665–669.
 - [42] C.L. Craig, A.L. Marshall, M. Sjostrom, A.E. Bauman, M.L. Booth, B.E. Ainsworth, M. Pratt, U. Ekelund, A. Yngve, J.F. Sallis, P. Oja, International physical activity questionnaire: 12-country reliability and validity, *Med. Sci. Sports Exerc.* 35 (8) (2003) 1381–1395.
 - [43] R. Horne, J. Weinman, M. Hankins, The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication, *Psychol. Health* 14 (1) (1999) 1–24.
 - [44] K. Bush, D.R. Kivlahan, M.B. McDonnell, S.D. Fihn, K.A. Bradley, f.t.A.C.Q.I. Project, The AUDIT Alcohol Consumption Questions (AUDIT-C): an effective brief screening test for problem drinking, *Arch. Intern. Med.* 158 (16) (1998) 1789–1795.
 - [45] N. Thomas, J. Farhall, F. Foley, S.L. Rossell, D. Castle, E. Ladd, D. Meyer, C. Mihalopoulos, N. Leitan, C. Nunan, R. Frankish, T. Smark, S. Farnan, B. McLeod, L. Sterling, G. Murray, E. Fossey, L. Brophy, M. Kyrios, Randomised controlled trial of a digitally assisted low intensity intervention to promote personal recovery in persisting psychosis: SMART-Therapy study protocol, *BMC Psychiatry* 16 (1) (2016) 312.
 - [46] V.J. Palmer, P. Chondros, D. Piper, R. Callander, W. Weavell, K. Godbee, M. Potiradis, L. Richard, K. Densely, H. Herrman, J. Furler, D. Pierce, T. Schuster, R. Iedema, J. Gunn, The CORE study protocol: a stepped wedge cluster randomised controlled trial to test a co-design technique to optimise psychosocial recovery outcomes for people affected by mental illness in the community mental health setting, *BMJ Open* 5 (3) (2015) e006688.
 - [47] J.F. Soares, C.F. Jeff Wu, Some restricted randomization rules in sequential designs, *Commun. Stat.* 12 (17) (1983) 2017–2034.
 - [48] A.C. Atkinson, Selecting a biased-coin design, *Stat. Sci.* 29 (1) (2014) 144–163.
 - [49] National Health and Medical Research Council, National Statement on Ethical Conduct in Human Research, National Health and Medical Research Council, Canberra, Australia, 2018.
 - [50] G. Dunn, M. Maracy, B. Tomenson, Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods, *Stat. Methods Med. Res.* 14 (4) (2005) 369–395.
 - [51] I.R. White, J. Carpenter, N.J. Horton, Including all individuals is not enough: lessons for intention-to-treat analysis, *Clin. Trials* 9 (4) (2012) 396–407.
 - [52] C. Gamble, A. Krishan, D. Stocken, S. Lewis, E. Juszcak, C. Doré, P.R. Williamson, D.G. Altman, A. Montgomery, P. Lim, J. Berlin, S. Senn, S. Day, Y. Barbachano, E. Loder, Guidelines for the content of statistical analysis plans in clinical trials, *JAMA* 318 (23) (2017) 2337–2343.
 - [53] J.H. Hibbard, P.A. Collins, E. Mahoney, L.H. Baker, The development and testing of a measure assessing clinician beliefs about patient self-management, *Health Expect.* 13 (1) (2010) 65–72.
 - [54] International Council for Harmonisation, ICH Harmonised Guideline Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), (2016).