

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Randomised controlled trial of screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the SAFER trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082047
Article Type:	Protocol
Date Submitted by the Author:	13-Nov-2023
Complete List of Authors:	<p>Mant, Jonathan; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Modi, Rakesh; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Dymond, Andrew; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Armstrong, Natalie; University of Leicester Department of Population Health Sciences, Department of Population Health Sciences</p> <p>Burt, Jenni; THIS labs</p> <p>Calvert, Peter; Liverpool Heart and Chest Hospital NHS Foundation Trust</p> <p>Cowie, Martin; King's College London School of Cardiovascular and Metabolic Medicine & Sciences</p> <p>Ding, Wern; Liverpool Heart and Chest Hospital NHS Foundation Trust</p> <p>Edwards, Duncan; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Freedman, Ben; The University of Sydney Charles Perkins Centre</p> <p>Griffin, Simon; University of Cambridge Primary Care Unit, Institute of Public Health; MRC Epidemiology Unit</p> <p>Hoare, Sarah ; University of Cambridge Primary Care Unit, Department of Public Health and Primary Care</p> <p>Hobbs, Richard; University of Oxford Nuffield Department of Primary Care Health Sciences</p> <p>Johnson, Rachel; University of Bristol</p> <p>Kaptoge, Stephen; Cambridge Biomedical Campus</p> <p>Lip, Gregory; Liverpool Heart and Chest Hospital NHS Foundation Trust; Aalborg University Department of Clinical Medicine, Danish Centre for Health Services Research</p> <p>Lobban, Trudie; AF Association, Arrhythmia Alliance and AF association</p> <p>Lown, Mark; University of Southampton School of Primary Care</p> <p>Population Sciences and Medical Education, Primary Care and Population Sciences</p> <p>Lund, Jenny; Strangeways Research Laboratory, Primary Care Unit, Department of Public Health & Primary Care</p> <p>McManus, Richard; University of Oxford Nuffield Department of Primary Care Health Sciences</p> <p>Mills, Mark; Liverpool Heart and Chest Hospital NHS Foundation Trust</p> <p>Morris, Stephen; University of Cambridge Primary Care Unit, Department of Public Health and Primary Care</p> <p>Powell, Alison; THIS Institute, University of Cambridge</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Proietti, Riccardo; Liverpool Heart and Chest Hospital NHS Foundation Trust Sutton, Stephen; University of Cambridge Primary Care Unit, Department of Public Health and Primary Care Sweeting, Mike; Cambridge Biomedical Campus Thom, Howard; University of Bristol Williams, Kate; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge SAFER Authorship Group, The; University of Cambridge Primary Care Unit
Keywords:	Primary Care < Primary Health Care, Mass Screening, Stroke < NEUROLOGY, Randomized Controlled Trial, CARDIOLOGY



Randomised controlled trial of screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the SAFER trial.

Corresponding author

Dr Rakesh N Modi

Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, 2 Worts' Causeway, Cambridge, UK, CB1 8RN

rnm30@medschl.cam.ac.uk

Authors

1. Professor Jonathan Mant, jm677@medschl.cam.ac.uk¹
2. Dr Rakesh N Modi, rnm30@medschl.cam.ac.uk¹
3. Andrew Dymond, ad486@medschl.cam.ac.uk¹
4. Professor Natalie Armstrong, natalie.armstrong@le.ac.uk²
5. Dr Jenni Burt, jenni.burt@thislabs.org³
6. Dr Peter Calvert, Peter.Calvert@lhch.nhs.uk⁴
7. Professor Martin Cowie, martin.cowie@astrazeneca.com⁵
8. Dr Wern Ding, dwyew@hotmail.com⁴
9. Dr Duncan Edwards, dae31@medschl.cam.ac.uk¹
10. Professor Ben Freedman, ben.freedman@sydney.edu.au⁶
11. Professor Simon J Griffin, profgp@medschl.cam.ac.uk^{1, 7}
12. Dr Sarah Hoare, seh91@medschl.cam.ac.uk¹
13. Professor F.D. Richard Hobbs, richard.hobbs@phc.ox.ac.uk⁸
14. Dr Rachel Johnson, rachel.johnson@bristol.ac.uk⁹
15. Dr Stephen Kaptoge, skk22@medschl.cam.ac.uk¹⁰
16. Professor Gregory Y.H. Lip, gregory.lip@liverpool.ac.uk⁴

17. Ms Trudie Lobban, MBE trudie@heartrhythmalliance.org¹¹
18. Dr Mark Lown, M.Lown@soton.ac.uk¹²
19. Dr Jenny Lund, jl897@medschl.cam.ac.uk¹
20. Professor Richard J McManus, richard.mcmanus@phc.ox.ac.uk⁸
21. Dr Mark T. Mills, Mark.Mills@LHCH.nhs.uk⁴
22. Professor Stephen Morris, sm2428@medschl.cam.ac.uk¹
23. Dr Alison Powell, alison.powell@thisinstitute.cam.ac.uk¹³
24. Dr Riccardo Proietti, Riccardo.Proietti@liverpool.ac.uk⁴
25. Professor Stephen Sutton, srs34@medschl.cam.ac.uk¹
26. Dr Mike Sweeting, michael.sweeting@astrazeneca.com¹⁴
27. Dr Howard Thom, howard.thom@bristol.ac.uk⁹
28. Dr Kate Williams, kmw36@medschl.cam.ac.uk¹
29. On behalf of the SAFER author group

1. Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, 2 Worts' Causeway, Cambridge, UK, CB1 8RN
2. Department of Population Health Sciences, University of Leicester, George Davies Centre, University Road, Leicester, UK, LE1 7RH
3. THIS Labs, 40B Trumpington Mews, High Street, Trumpington, Cambridge, CB2 9LS
4. Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Denmark
5. School of Cardiovascular Medicine & Sciences, Faculty of Lifesciences & Medicine, King's College London, London, UK
6. Heart Research Institute, University of Sydney, Room 3114, Level 3 East, D17 - Charles Perkins Centre, NSW, Australia, 2006
7. MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK, CB2 0SL
8. Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, UK, OX2 6GG
9. Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, UK, BS8 2PS
10. Cardiovascular Epidemiology Unit, University of Cambridge, Victor Phillip Dahdaleh Heart & Lung Research Institute, Papworth Road, Cambridge Biomedical Campus, Cambridge, CB2 0BB

- 1
- 2
- 3 11. Arrhythmia Alliance (A-A) and AF Association, Celixir House, Stratford Business
- 4 &Technology Park Innovation Way, Stratford upon Avon CV37 7GZ
- 5
- 6 12. Primary Care and Population Sciences, Faculty of Medicine, University of Southampton,
- 7 Aldermoor Health Centre, Aldermoor Close, Southampton, UK, SO16 5ST
- 8
- 9 13. THIS Institute (The Healthcare Improvement Studies Institute), University of Cambridge,
- 10 Strangeways Research Laboratory, 2 Worts Causeway, Cambridge UK CB1 8RN
- 11
- 12 14. AstraZeneca, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2
- 13 0AA
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

For peer review only

ABSTRACT

Introduction

There is a lack of evidence that the benefits of screening for atrial fibrillation (AF) outweigh the harms. Following the completion of the Screening for Atrial Fibrillation with electrocardiogram (ECG) to Reduce stroke (SAFER) pilot trial, the aim of the main SAFER trial is to establish whether screening for AF reduces incidence of stroke risk.

Methods and analysis

Approximately 82,000 people aged 70 years and over and not on oral anticoagulation are being recruited from general practices in England. Patients on the palliative care register or resident in a nursing home are excluded. Eligible people are identified using electronic patient records from general practices and sent an invitation and consent form to participate by post. Consenting participants are randomised at a ratio of 2:1 (control : intervention) with clustering by household. Those randomised to the intervention arm are sent an information leaflet inviting them to participate in screening, which involves use of a handheld single lead ECG four times a day for three weeks. ECG traces identified by an algorithm as possible AF are reviewed by cardiologists. Participants with AF are seen by a general practitioner for consideration of anticoagulation. The primary outcome is stroke. Major secondary outcomes are: death; major bleeding; and cardiovascular events. Follow up will be via electronic health records for an average of four years. The primary analysis will be by intention-to-treat using time-to-event modelling. Results from this trial will be combined with follow up data from the cluster-randomised pilot trial by fixed effect meta-analysis.

Ethics and dissemination

The London—Central Research Ethics Committee (19/LO/1597) provided ethical approval. Dissemination will include public-friendly summaries, reports and engagement with the UK National Screening Committee.

Trial registration number: ISRCTN72104369.

KEYWORDS

Atrial fibrillation; screening; randomised controlled trial; primary care; stroke prevention

ARTICLE SUMMARY

Strengths and limitations of this study

- This trial is more than twice the size of previous trials of atrial fibrillation (AF) screening and has adequate power to determine whether screening reduces risk of stroke.
- The power calculation has been refined based upon pilot data and the results of an earlier trial which used the same AF screening device.
- The screening intervention has been demonstrated by our feasibility and pilot studies to be feasible for national roll out if shown to be effective.
- There is a risk of contamination in the control group due to increasing availability of personal devices that enable self-screening of AF.
- Outcome data relies on electronic capture of routine data which risks incomplete ascertainment.

INTRODUCTION

The rationale for the Screening for Atrial Fibrillation with ECG to Reduce stroke (SAFER) trial has been described previously.¹ In brief, there is insufficient evidence that the potential benefits from screening for AF outweigh the potential harms.² Recent trials have failed to demonstrate that single time-point screening identifies more AF than usual care.³⁻⁵ This is likely to be due to better AF identification within usual care than was prevalent when the Screening for Atrial Fibrillation in the Elderly (SAFE) trial demonstrated the value of single time point screening in identifying additional cases of AF in the early 2000s.⁶ Therefore, interest has focussed on newer technologies that enable continuous or intermittent heart rhythm monitoring, such as hand-held ECGs, patches and implantable loop recorders.⁷⁻⁹ These approaches do identify more AF than usual care, but have not been shown to reduce incidence of stroke.⁷⁻⁹ Since these devices predominantly identify paroxysmal AF, it is important to determine whether such screening translates into reduced incidence of stroke, as paroxysmal AF may be associated with a lower risk of stroke than permanent AF.¹⁰

While the evidence base for stroke risk reduction with anticoagulation in AF is based on trials that included participants with paroxysmal AF, the new technologies diagnose people with lower AF burden than will have been typical of those with (usually symptomatic) paroxysmal AF in these trials.¹¹ Stroke risk in paroxysmal AF is related to AF burden,¹² so it is conceivable that people with low burden paroxysmal AF may not benefit from anticoagulation. Indeed, this was the tentative conclusion drawn by the LOOP study investigators who diagnosed AF in over 30% of the intervention arm of a screening trial using an implantable loop recorder.⁸

The emergence of consumer-led screening over recent years has provided further impetus to the SAFER trial.¹³ Several commercially available devices are directly marketed to consumers for detection of AF.¹³ The results of SAFER will also guide clinicians on the appropriate course of action in AF identified through consumer-led screening.¹³

In addition to stroke prevention, there are other benefits to treating AF with anticoagulation, including improved survival and reduced risk of myocardial infarction.¹¹ Indeed, the STROKESTOP screening trial reported a marginally significant reduction in a revised composite primary end-point of stroke, systemic embolism, bleeding leading to hospitalisation and all cause death.⁹ Another potential benefit of screening for AF is to reduce risk of cognitive decline and vascular dementia.¹⁴⁻¹⁷

1
2
3 In terms of harm, the major concern is risk of bleeding as a result of anticoagulation of people
4 identified as being in AF. There is clear evidence in the trials of treatment of AF with anticoagulation
5 that benefit outweighs harm,¹¹ but the ratio of benefit to harm of treatment might be different for
6 people with AF identified through screening. For example, in the LOOP trial, the 20% relative risk
7 reduction in stroke was largely offset by the 26% relative increase in risk of major bleeding.⁸
8
9

10
11
12
13 The aim of the SAFER trial is to determine if screening for AF using a hand-held single-lead ECG
14 device intermittently over a period of three weeks is effective and cost-effective at reducing stroke
15 compared to usual care and to quantify other potential benefits and harms of screening. The design
16 of the SAFER pilot trial (now successfully completed) has already been reported.¹ This protocol
17 paper therefore focuses on changes in methods between the pilot and the main trial. The SPIRIT
18 checklist when writing this paper.¹⁸
19
20
21
22

23 24 25 **METHODS AND ANALYSIS**

26 27 28 **Design**

29
30
31
32 SAFER is a multi-centre randomised controlled trial. Randomisation is at the individual level with
33 clustering by household (i.e., if there is more than one participant from the same address, they will
34 be allocated to the same arm). This is a change from the original intention to randomise at the level
35 of the general practice.¹ This decision was made during the internal pilot trial, when it became clear
36 that remote delivery of the screening intervention greatly reduced the risk of contamination, so
37 negating the value of cluster randomisation by practice. However, it was recognised that there
38 would be a residual risk of contamination if members of the same household were in different arms
39 of the trial. The first patient was randomised in March 2022. It is currently estimated that
40 randomisation will finish in January 2024 and follow-up will finish in March 2027. The trial design is
41 summarised in Figure 1.
42
43
44
45
46
47
48

49
50
51 <<Figure 1. SAFER trial schema>>
52
53

54 55 **Participants**

56
57
58 Participant eligibility is unchanged from the pilot study, being people aged 70 years or older who are
59 registered with participating general practices.¹ Those who are on the practice palliative care
60

1
2
3 register or in a nursing or residential home are excluded, as are those already on anticoagulation
4 therapy. People with a prior record of AF but not currently on anticoagulation are eligible.¹ General
5 practices are being recruited from throughout England. It is anticipated that about 195 practices will
6 be involved.
7
8
9

10 11 **Recruitment**

12
13
14
15 Unlike in the pilot cluster randomised trial, where there was little gain in power from increasing
16 sample size in each cluster, all eligible patients (as opposed to a random sample) are sent an
17 invitation pack by their practice. This includes a consent form to be returned to the study team
18 either by post or online.
19
20
21
22

23 24 **Randomisation**

25
26
27 Randomisation is performed on-line at the Oxford Primary Care Clinical Trials Unit following return
28 of consent forms, stratified by practice. Random permuted blocks ensure allocations are balanced at
29 a ratio of 2:1 (control : intervention) in batches per practice. If there is more than one participant in
30 the same household, they are randomised as a cluster to the same arm.
31
32
33
34

35 36 **Baseline data**

37
38
39 This is unchanged from the pilot trial, includes demographics and comorbidities, and is collected
40 from the GP electronic medical records.¹
41
42
43
44

45 46 **Screening Intervention**

47
48 This is unchanged from the pilot trial.¹ In brief, participants randomised to screening will receive a
49 postal invitation to participate. Those who accept this invitation receive a call from the trial team to
50 arrange delivery of the single-lead ECG device (Zenicor) and instructions (written with online video
51 available) and an offer of subsequent support by telephone on how to use it. They are asked to carry
52 out screening four times a day for three weeks, and take additional traces if symptomatic (e.g.
53 palpitations, dizziness). Each trace runs for 30 seconds. Participants transmit their recordings to a
54 remote database using the mobile capability within the device.
55
56
57
58
59
60

1
2
3 A proprietary algorithm (Cardiolund) analyses the ECG traces,¹⁹ and those that show possible AF are
4 reviewed by a cardiologist or cardiac technician. Review by a second cardiologist is performed if
5 there is uncertainty. AF is diagnosed if the rhythm is present continuously for 30 seconds. The results
6 are returned to the practice, which notifies participants of the results, and actively follows up
7 patients with AF or other significant diagnoses (e.g. ventricular tachycardia, high-degree
8 atrioventricular block). Participating GPs receive on line training on the National Institute for Health
9 and Care Excellence (NICE) AF guidelines.²⁰

16 Follow up

20 The target follow up duration has been reduced from an average of five years (as per the pilot
21 protocol)¹ to four years per participant. This is to compensate for the delays imposed on the trial by
22 COVID-19, and to lower the risk of control group contamination by AF detection device marketing
23 directly to the public.¹³ The revised sample size calculation (see below) takes this reduced length of
24 follow up into account. The programme steering committee will review stroke rate in the whole
25 study population (i.e., not by treatment arm), and may recommend modifying follow up duration if
26 stroke rates differ from what is expected. Follow up will be by electronic health records (including
27 GP records), Hospital Episode Statistics, Office for National Statistics mortality data and national
28 disease registries accessed via NHS Digital and ORCHID.²¹

37 Outcomes

41 The primary outcome is stroke. This includes stroke of any severity, but excludes events only labelled
42 as transient ischaemic attack. For the primary endpoint, ischaemic and haemorrhagic stroke events
43 will be combined.

47 Secondary outcomes include: all-cause death; cardiovascular death; major adverse cardiovascular
48 event (composite of myocardial infarction, stroke and other hospital admissions for cardiovascular
49 disease, including heart failure); myocardial infarction; major bleeding episode (defined as requiring
50 hospital admission); new diagnosis of dementia; new diagnosis of depression. AF detection rates and
51 anticoagulation uptake will be reported (principal outcomes of the internal pilot trial).

57 Sample size

1
2
3 The sample size calculation has been updated to reflect the changes in trial design, the result of a
4 recent trial of screening for AF using the Zenicor device,⁹ the interim results of the internal pilot trial,
5 and initial baseline findings from the main trial. In the STROKESTOP trial, an 8% reduction in risk of
6 stroke was observed.⁹ Due to higher uptake of screening in the intervention arm of SAFER, and the
7 greater observed differences in AF detection rates between intervention and control as compared to
8 STROKESTOP, a 12% relative risk reduction in stroke is now anticipated in SAFER. Assuming a
9 household cluster size of 1.21 (from observed cluster size to date), a household intraclass correlation
10 coefficient of 0.2,²² and a 1% annual risk of stroke in the control arm,⁹ this equates to needing
11 82,000 participants to detect a 12% relative reduction in risk of stroke after four years with 90%
12 power.
13
14
15
16
17
18
19
20

21 **Analysis**

22
23
24
25 The intention-to-treat principle will guide data analysis (outcome in all randomised participants will
26 be compared between intervention and control). All randomised participants will be included in the
27 analysis, regardless of participation in screening.
28
29
30

31
32 The primary analysis will be conducted separately for the cluster randomised pilot trial and the main
33 trial, with results then combined by fixed effect meta-analysis. Time-to-event modelling (i.e. a Cox
34 proportional hazards model) will be used to obtain an estimate (hazard ratio) of the effect of
35 screening on stroke risk (fatal and non-fatal), censoring other causes of death. Analysis time will be
36 from date of randomisation.
37
38
39
40

41
42 Clustering (by practice for pilot trial participants and by household for main trial participants) will be
43 accounted for using a robust sandwich estimator of the covariance matrix. The estimate of
44 intervention effect will be adjusted for pre-specified baseline co-variables such as age and sex.
45
46 Secondary outcomes will be analysed in a similar way.
47
48
49

50 For all analyses, we will test model assumptions. Should these be violated, flexible parametric
51 survival models will be considered to model the change in hazard ratio over time.
52
53
54

55 **Economic analysis**

1
2
3 To determine whether screening is cost-effective from the perspective of the NHS, we will adapt an
4 existing economic model.²³ This will incorporate data from the SAFER trial, including outcomes such
5 as mortality and cardiovascular endpoints, to determine incremental cost per QALY gained
6
7 comparing screening versus no screening over a 4 year time horizon. The model parameters that do
8
9 not come from the trial will be derived from updated literature reviews. We will extend the model to
10
11 a life-time horizon, and consider the impact on cost-effectiveness of repeated screening at different
12
13 time intervals and in different age groups.
14

15 16 **Management and oversight**

17
18
19 Management and oversight is delivered through the same structure as in the pilot trial.¹ The
20
21 University of Cambridge and NHS Cambridgeshire & Peterborough Integrated Care Board (ICB) are
22
23 co-sponsors. The trial management group meets monthly to review operational issues. The
24
25 programme steering committee (PSC), which has an independent chair and four independent
26
27 members, provides independent over-sight of the programme and acts as the Trial Steering
28
29 Committee. An active risk register has been compiled in consultation with the funder and sponsors
30
31 and will be monitored and updated throughout.
32
33

34 **Patient and public involvement (PPI)**

35
36
37 The same approach is being used as in the pilot trial.¹ In brief, we have engagement by PPI members
38
39 as an investigator (Trudie Lobban, chief executive of the Atrial Fibrillation Association, (AFA)), and as
40
41 contributors independent of the AFA.
42
43

44 **ETHICS AND DISSEMINATION**

45
46
47 Ethical approval has been provided by the London-Central NHS Research Ethics Committee
48
49 (19/LO/1597).
50

51
52
53 Public-friendly trial summary documents will be made available to participants at the end of the trial.
54
55 Accessible reports will be generated for the UK National Screening Committee, commissioners and
56
57 other decision makers. The pilot study protocol provides further details.¹
58
59
60

1
2
3 Requests for pseudonymised data will be directed to the study co-ordinator (Andrew Dymond using
4 SAFER@medschl.cam.ac.uk) and will be considered by the investigators, in accordance with
5 participant consent.
6
7
8
9

10 **AUTHOR CONTRIBUTIONS**

11
12
13 JM is the guarantor and drafted the manuscript with help from RNM. KW and AD are coordinating,
14 planning, gaining ethical approval, conducting, and helping design the study. JM, JB, NA, DE, JL, TL,
15 ML, GL, BF, SG, SS, FRH and RJM undertook design, planning and are overseeing conduct of the trial.
16 TL is a PPI representative who has informed the design, outcomes and dissemination plan. SM and
17 HT designed the economic evaluation and will oversee its conduct. SK designed the statistical
18 analysis and will oversee its conduct. GL, PC and RP conducted and refined the cardiology review
19 process of the intervention. The SAFER author group contributed to planning and design of study,
20 applying for funding, writing of the protocol for the ethical approval and have oversight of the
21 conduct of the trial. All authors reviewed and had the option to edit the final manuscript.
22
23
24
25
26
27
28
29

30 **FUNDING STATEMENT**

31
32
33 This SAFER trial is funded by the National Institute for Health and Care Research (NIHR) [Programme
34 Grants for Applied Research Programme (Reference Number [RP-PG-0217-20007](#))]. The views
35 expressed are those of the author(s) and not necessarily those of the NIHR or the Department of
36 Health and Social Care. SAFER is a contributor to / partner of AFFECT-EU receiving funding from the
37 European Union's Horizon 2020 research and innovation Programme under grant agreement NO.
38 847770. RM and JL are supported by the Wellcome Trust as part of the Wellcome Trust PhD
39 Programme for Primary Care Clinicians [grant number 203921/Z/16/Z]. AP is based in The Healthcare
40 Improvement Studies Institute (THIS Institute), University of Cambridge. THIS Institute is supported
41 by the Health Foundation, an independent charity committed to bringing about better health and
42 healthcare for people in the UK. FDRH acknowledges support from NIHR ARC OTV and Oxford BRC
43 (OUT). RJM is an NIHR Senior Investigator and acknowledges support from NIHR ARC OTV. NA is
44 supported by a Health Foundation Improvement Science Fellowship and also by the NIHR Applied
45 Research Collaboration East Midlands (ARC EM). RJ is an NIHR-funded Academic Clinical Lecturer.
46 The University of Cambridge has received salary support in respect of SJG from the NHS in the East
47 of England through the Clinical Academic Reserve. BF received funding from the Medical Research
48 Future Fund International Clinical Trial Collaboration Grant to perform SAFER-AUS as part of SAFER,
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 and a NSW Health Senior Researcher Cardiovascular Grant for work in AF. GYHL is a National
4 Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the
5 AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's
6 Horizon 2020 research and innovation programme under grant agreement No 899871. All the
7 funders and sponsors had no involvement in the development of this protocol and will have no
8 involvement in any aspect of the study itself. The views expressed are those of the author(s) and not
9 necessarily those of the NHS, the Wellcome Trust, the NIHR or the UK Department of Health and
10 Social Care.
11
12
13
14
15
16
17

18 **COMPETING INTEREST STATEMENT**

19
20
21
22 JM has performed consultancy work for BMS/Pfizer and Omron. FDRH reports occasional
23 consultancy for BMS/Pfizer, Bayer and BI over the past 5 years. NA is a member of the UK National
24 Screening Committee. MRC and MS are employed by AstraZeneca PLC. RJM's employer the
25 University of Oxford receives consultancy and licencing payments from Omron and Sensyne for BP
26 telemonitoring interventions. GYHL is a consultant and speaker for BMS/Pfizer, Boehringer
27 Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. SJG has received honoraria from
28 Astra Zeneca for lectures at postgraduate educational meetings for primary care teams about type 2
29 diabetes. BF has received speaker fees, honoraria, and non-financial support from the BMS and
30 Pfizer Alliance; grants to the Institution for investigator-initiated studies from the BMS and Pfizer
31 Alliance; and loan devices for investigator-initiated studies from Alivacor: all were unrelated to the
32 present study but related to screening for AF.
33
34
35
36
37
38
39
40
41

42 **ACKNOWLEDGEMENTS**

43
44
45 We would like to acknowledge the support of:

46
47 **Independent Programme Steering Committee:** Professor Christian Mallen, University of Keele
48 (chair); Professor Anthony Rudd, Kings College London (independent member); Professor Ann Marie
49 Swart, University of East Anglia (independent member); Professor Andy Vail, University of
50 Manchester (independent member); Dr Bob Ward (independent lay member)

51
52 **Patient and public involvement representatives:** Margaret Corbett; Jennifer Crockford; Trudie
53 Lobban MBE (Founder & CEO of Atrial Fibrillation Association); Sheilah Rengert; Dr Bob Ward
54
55
56
57
58
59
60

REFERENCES

1. Williams K, Modi RN, Dymond A, et al. Cluster randomised controlled trial of screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the pilot study for the SAFER trial. *BMJ Open* 2022;12(9):e065066. doi: 10.1136/bmjopen-2022-065066
2. Curry SJ, Krist AH, Owens DK, et al. Screening for Atrial Fibrillation With Electrocardiography: US Preventive Services Task Force Recommendation Statement. *Jama* 2018;320(5):478-84. doi: 10.1001/jama.2018.10321 [published Online First: 2018/08/09]
3. Kaasenbrood F, Hollander M, de Bruijn SH, et al. Opportunistic screening versus usual care for diagnosing atrial fibrillation in general practice: a cluster randomised controlled trial. *Br J Gen Pract* 2020;70(695):e427-e33. doi: 10.3399/bjgp20X708161 [published Online First: 2020/01/29]
4. Uittenbogaart SB, Verbiest-van Gurp N, Lucassen WAM, et al. Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial. *BMJ* 2020;370:m3208. doi: 10.1136/bmj.m3208
5. Lubitz SA, Atlas SJ, Ashburner JM, et al. Screening for Atrial Fibrillation in Older Adults at Primary Care Visits: VITAL-AF Randomized Controlled Trial. *Circulation* 2022;145(13):946-54. doi: doi:10.1161/CIRCULATIONAHA.121.057014
6. Fitzmaurice DA, Hobbs FD, Jowett S, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *Bmj* 2007;335(7616):383. doi: 10.1136/bmj.39280.660567.55 [published Online First: 2007/08/04]
7. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, et al. Screening for Atrial Fibrillation in the Older Population: A Randomized Clinical Trial. *JAMA Cardiology* 2021 doi: 10.1001/jamacardio.2021.0038
8. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *The Lancet* 2021 doi: [https://doi.org/10.1016/S0140-6736\(21\)01698-6](https://doi.org/10.1016/S0140-6736(21)01698-6)
9. Svennberg E, Friberg L, Frykman V, et al. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *The Lancet* 2021 doi: [https://doi.org/10.1016/S0140-6736\(21\)01637-8](https://doi.org/10.1016/S0140-6736(21)01637-8)
10. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;37(20):1591-602. doi: 10.1093/eurheartj/ehw007 [published Online First: 2016/02/19]
11. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005(3) doi: 10.1002/14651858.CD001927.pub2
12. Go AS, Reynolds K, Yang J, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study. *JAMA Cardiology* 2018;3(7):601-08. doi: 10.1001/jamacardio.2018.1176
13. Brandes A, Stavrakis S, Freedman B, et al. Consumer-Led Screening for Atrial Fibrillation: Frontier Review of the AF-SCREEN International Collaboration. *Circulation* 2022;146(19):1461-74. doi: 10.1161/circulationaha.121.058911 [published Online First: 2022/11/08]
14. Singh-Manoux A, Fayosse A, Sabia S, et al. Atrial fibrillation as a risk factor for cognitive decline and dementia. *European Heart Journal* 2017;38(34):2612-18.
15. Bezabhe WM, Bereznicki LR, Radford J, et al. Oral Anticoagulant Treatment and the Risk of Dementia in Patients With Atrial Fibrillation: A Population-Based Cohort Study. *Journal of the American Heart Association* 2022;11(7):e023098. doi: doi:10.1161/JAHA.121.023098

16. Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *European Heart Journal* 2019;40(28):2327-35. doi: 10.1093/eurheartj/ehz304
17. Mavaddat N, Roalfe A, Fletcher K, et al. Warfarin versus aspirin for prevention of cognitive decline in atrial fibrillation: randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged Study). *Stroke* 2014;45(5):1381-86.
18. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Bmj* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
19. Cardiolund. Cardiac Analysis 2023 [Available from: <https://www.cardiolund.com/> accessed 31/07/2023.
20. National Institute for Health and Care Excellence. Atrial fibrillation: diagnosis and management (ng196): National Institute of Health and Care Excellence, 2021.
21. Nuffield Department of Primary Care Health Sciences. ORCHID: University of Oxford; 2023 [Available from: <https://orchid.phc.ox.ac.uk/> accessed 13/11/2023.
22. Ukoumunne OC, Gulliford MC, Chinn S, et al. Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review. *Health technology assessment (Winchester, England)* 1999;3(5):iii-92. [published Online First: 2000/09/12]
23. Welton NJ, McAleenan A, Thom HH, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technology Assessment* 2017;21(29)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

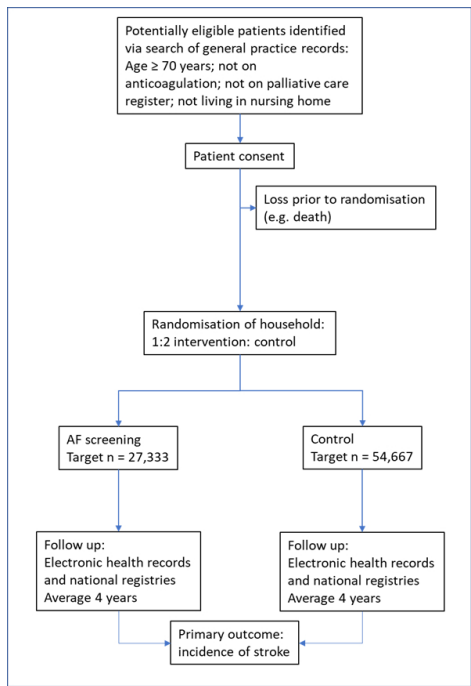


Figure 1. SAFER trial schema
225x180mm (144 x 144 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Administrative information	Reporting Item	Page Number
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	Date and version identifier	n/a
Funding	Sources and types of financial, material, and other support	12-13
Roles and responsibilities: contributorship	Names, affiliations, and roles of protocol contributors	1-3, 12
Roles and responsibilities: sponsor contact information	Name and contact information for the trial sponsor	11

1	Roles and	Role of study sponsor and funders, if any, in study design;	11-12
2			
3	responsibilities: sponsor	collection, management, analysis, and interpretation of	
4			
5	and funder	data; writing of the report; and the decision to submit the	
6			
7		report for publication, including whether they will have	
8			
9		ultimate authority over any of these activities	
10			
11			
12			
13	Roles and	Composition, roles, and responsibilities of the coordinating	11, 13
14			
15	responsibilities:	centre, steering committee, endpoint adjudication	
16			
17	committees	committee, data management team, and other individuals	
18			
19		or groups overseeing the trial, if applicable (see Item 21a	
20			
21		for data monitoring committee)	
22			
23			
24			
25	Introduction		
26			
27			
28	Background and	Description of research question and justification for	6-7
29			
30	rationale	undertaking the trial, including summary of relevant	
31			
32		studies (published and unpublished) examining benefits	
33			
34		and harms for each intervention	
35			
36			
37			
38	Background and	Explanation for choice of comparators	6-9
39			
40	rationale: choice of		
41			
42	comparators		
43			
44			
45			
46	Objectives	Specific objectives or hypotheses	7
47			
48			
49	Trial design	Description of trial design including type of trial (eg,	7
50			
51		parallel group, crossover, factorial, single group),	
52			
53		allocation ratio, and framework (eg, superiority,	
54			
55		equivalence, non-inferiority, exploratory)	
56			
57			
58			
59			
60			

1 **Methods: Participants,**
 2
 3 **interventions, and**
 4
 5 **outcomes**
 6
 7

8			
9	Study setting	Description of study settings (eg, community clinic,	7-8, 12
10		academic hospital) and list of countries where data will be	
11		collected. Reference to where list of study sites can be	
12		obtained	
13			
14			
15			
16			
17			
18			
19	Eligibility criteria	Inclusion and exclusion criteria for participants. If	7-8
20		applicable, eligibility criteria for study centres and	
21		individuals who will perform the interventions (eg,	
22		surgeons, psychotherapists)	
23			
24			
25			
26			
27			
28			
29	Interventions:	Interventions for each group with sufficient detail to allow	8-9
30	description	replication, including how and when they will be	
31		administered	
32			
33			
34			
35			
36	Interventions:	Criteria for discontinuing or modifying allocated	8-9
37	modifications	interventions for a given trial participant (eg, drug dose	
38		change in response to harms, participant request, or	
39		improving / worsening disease)	
40			
41			
42			
43			
44			
45			
46	Interventions: adherence	Strategies to improve adherence to intervention protocols,	9
47		and any procedures for monitoring adherence (eg, drug	
48		tablet return; laboratory tests)	
49			
50			
51			
52			
53			
54	Interventions:	Relevant concomitant care and interventions that are	8-9
55	concomitant care	permitted or prohibited during the trial	
56			
57			
58			
59			
60			

1	Outcomes	Primary, secondary, and other outcomes, including the	9
2			
3		specific measurement variable (eg, systolic blood	
4		pressure), analysis metric (eg, change from baseline, final	
5		value, time to event), method of aggregation (eg, median,	
6		proportion), and time point for each outcome. Explanation	
7		of the clinical relevance of chosen efficacy and harm	
8		outcomes is strongly recommended	
9			
10			
11			
12			
13			
14			
15			
16			
17			
18	Participant timeline	Time schedule of enrolment, interventions (including any	8-9
19		run-ins and washouts), assessments, and visits for	
20		participants. A schematic diagram is highly recommended	
21		(see Figure)	
22			
23			
24			
25			
26			
27			
28	Sample size	Estimated number of participants needed to achieve study	9-10
29		objectives and how it was determined, including clinical	
30		and statistical assumptions supporting any sample size	
31		calculations	
32			
33			
34			
35			
36			
37			
38	Recruitment	Strategies for achieving adequate participant enrolment to	7-8
39		reach target sample size	
40			
41			
42			
43	Methods: Assignment of		
44	interventions (for		
45	controlled trials)		
46			
47			
48			
49			
50			
51	Allocation: sequence	Method of generating the allocation sequence (eg,	8
52		computer-generated random numbers), and list of any	
53	generation	factors for stratification. To reduce predictability of a	
54		random sequence, details of any planned restriction (eg,	
55			
56			
57			
58			
59			
60			

1		blocking) should be provided in a separate document that	
2			
3		is unavailable to those who enrol participants or assign	
4			
5		interventions	
6			
7			
8	Allocation concealment	Mechanism of implementing the allocation sequence (eg,	n/a
9			
10	mechanism	central telephone; sequentially numbered, opaque, sealed	
11			
12		envelopes), describing any steps to conceal the sequence	
13			
14		until interventions are assigned	
15			
16			
17			
18	Allocation:	Who will generate the allocation sequence, who will enrol	8
19			
20	implementation	participants, and who will assign participants to	
21			
22		interventions	
23			
24			
25	Blinding (masking)	Who will be blinded after assignment to interventions (eg,	n/a
26			
27		trial participants, care providers, outcome assessors, data	
28			
29		analysts), and how	
30			
31			
32			
33	Blinding (masking):	If blinded, circumstances under which unblinding is	n/a
34			
35	emergency unblinding	permissible, and procedure for revealing a participant's	
36			
37		allocated intervention during the trial	
38			
39			
40			
41	Methods: Data		
42			
43	collection, management,		
44			
45	and analysis		
46			
47			
48	Data collection plan	Plans for assessment and collection of outcome, baseline,	8-9
49			
50		and other trial data, including any related processes to	
51			
52		promote data quality (eg, duplicate measurements,	
53			
54		training of assessors) and a description of study	
55			
56		instruments (eg, questionnaires, laboratory tests) along	
57			
58			
59			
60			

1		with their reliability and validity, if known. Reference to	
2			
3		where data collection forms can be found, if not in the	
4			
5		protocol	
6			
7			
8	Data collection plan:	Plans to promote participant retention and complete	9
9			
10	retention	follow-up, including list of any outcome data to be	
11			
12		collected for participants who discontinue or deviate from	
13			
14		intervention protocols	
15			
16			
17			
18	Data management	Plans for data entry, coding, security, and storage,	8, 11
19			
20		including any related processes to promote data quality	
21			
22		(eg, double data entry; range checks for data values).	
23			
24		Reference to where details of data management	
25			
26		procedures can be found, if not in the protocol	
27			
28			
29			
30	Statistics: outcomes	Statistical methods for analysing primary and secondary	10-11
31			
32		outcomes. Reference to where other details of the	
33			
34		statistical analysis plan can be found, if not in the protocol	
35			
36			
37			
38	Statistics: additional	Methods for any additional analyses (eg, subgroup and	10-11
39			
40	analyses	adjusted analyses)	
41			
42			
43	Statistics: analysis	Definition of analysis population relating to protocol non-	10
44			
45	population and missing	adherence (eg, as randomised analysis), and any	
46			
47	data	statistical methods to handle missing data (eg, multiple	
48			
49		imputation)	
50			
51			
52			
53	Methods: Monitoring		
54			
55			
56	Data monitoring: formal	Composition of data monitoring committee (DMC);	11, 13
57			
58			
59			
60			

1	committee	summary of its role and reporting structure; statement of	
2		whether it is independent from the sponsor and competing	
3		interests; and reference to where further details about its	
4		charter can be found, if not in the protocol. Alternatively,	
5		an explanation of why a DMC is not needed	
6			
7			
8			
9			
10			
11			
12	Data monitoring: interim	Description of any interim analyses and stopping	11, 13
13	analysis	guidelines, including who will have access to these interim	
14		results and make the final decision to terminate the trial	
15			
16			
17			
18			
19			
20	Harms	Plans for collecting, assessing, reporting, and managing	11
21		solicited and spontaneously reported adverse events and	
22		other unintended effects of trial interventions or trial	
23		conduct	
24			
25			
26			
27			
28			
29			
30	Auditing	Frequency and procedures for auditing trial conduct, if	11
31		any, and whether the process will be independent from	
32		investigators and the sponsor	
33			
34			
35			
36			
37			
38	Ethics and dissemination		
39			
40			
41	Research ethics	Plans for seeking research ethics committee / institutional	11-12
42	approval	review board (REC / IRB) approval	
43			
44			
45			
46	Protocol amendments	Plans for communicating important protocol modifications	11
47		(eg, changes to eligibility criteria, outcomes, analyses) to	
48		relevant parties (eg, investigators, REC / IRBs, trial	
49		participants, trial registries, journals, regulators)	
50			
51			
52			
53			
54			
55			
56	Consent or assent	Who will obtain informed consent or assent from potential	8
57			
58			
59			
60			

1		trial participants or authorised surrogates, and how (see	
2			
3		Item 32)	
4			
5			
6	Consent or assent:	Additional consent provisions for collection and use of	n/a
7			
8	ancillary studies	participant data and biological specimens in ancillary	
9			
10		studies, if applicable	
11			
12			
13	Confidentiality	How personal information about potential and enrolled	11-12
14			
15		participants will be collected, shared, and maintained in	
16			
17		order to protect confidentiality before, during, and after the	
18			
19		trial	
20			
21			
22			
23	Declaration of interests	Financial and other competing interests for principal	12-13
24			
25		investigators for the overall trial and each study site	
26			
27			
28			
29	Data access	Statement of who will have access to the final trial dataset,	12
30			
31		and disclosure of contractual agreements that limit such	
32			
33		access for investigators	
34			
35			
36	Ancillary and post trial	Provisions, if any, for ancillary and post-trial care, and for	n/a
37			
38	care	compensation to those who suffer harm from trial	
39			
40		participation	
41			
42			
43			
44	Dissemination policy:	Plans for investigators and sponsor to communicate trial	11
45			
46	trial results	results to participants, healthcare professionals, the public,	
47			
48		and other relevant groups (eg, via publication, reporting in	
49			
50		results databases, or other data sharing arrangements),	
51			
52		including any publication restrictions	
53			
54			
55			
56	Dissemination policy:	Authorship eligibility guidelines and any intended use of	12
57			
58			
59			
60			

1	authorship	professional writers	
2			
3	Dissemination policy:	Plans, if any, for granting public access to the full protocol,	12
4			
5	reproducible research	participant-level dataset, and statistical code	
6			
7			
8			
9	Appendices		
10			
11			
12	Informed consent	Model consent form and other related documentation	n/a
13			
14	materials	given to participants and authorised surrogates	
15			
16			
17	Biological specimens	Plans for collection, laboratory evaluation, and storage of	n/a
18			
19		biological specimens for genetic or molecular analysis in	
20			
21		the current trial and for future use in ancillary studies, if	
22			
23		applicable	
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

BMJ Open

Randomised controlled trial of population screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the SAFER trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082047.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Jan-2024
Complete List of Authors:	<p>Mant, Jonathan; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Modi, Rakesh; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Dymond, Andrew; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Armstrong, Natalie; University of Leicester Department of Population Health Sciences, Department of Population Health Sciences</p> <p>Burt, Jenni; THIS labs</p> <p>Calvert, Peter; Liverpool Heart and Chest Hospital NHS Foundation Trust</p> <p>Cowie, Martin; King's College London School of Cardiovascular and Metabolic Medicine & Sciences</p> <p>Ding, Wern; Liverpool Heart and Chest Hospital NHS Foundation Trust</p> <p>Edwards, Duncan; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge</p> <p>Freedman, Ben; The University of Sydney Charles Perkins Centre</p> <p>Griffin, Simon; University of Cambridge Primary Care Unit, Institute of Public Health; MRC Epidemiology Unit</p> <p>Hoare, Sarah ; University of Cambridge Primary Care Unit, Department of Public Health and Primary Care</p> <p>Hobbs, Richard; University of Oxford Nuffield Department of Primary Care Health Sciences</p> <p>Johnson, Rachel; University of Bristol</p> <p>Kaptoge, Stephen; Cambridge Biomedical Campus</p> <p>Lip, Gregory; Liverpool Heart and Chest Hospital NHS Foundation Trust; Aalborg University Department of Clinical Medicine, Danish Centre for Health Services Research</p> <p>Lobban, Trudie; AF Association, Arrhythmia Alliance and AF association</p> <p>Lown, Mark; University of Southampton School of Primary Care</p> <p>Population Sciences and Medical Education, Primary Care and Population Sciences</p> <p>Lund, Jenny; Strangeways Research Laboratory, Primary Care Unit, Department of Public Health & Primary Care</p> <p>McManus, Richard; University of Oxford Nuffield Department of Primary Care Health Sciences</p> <p>Mills, Mark; Liverpool Heart and Chest Hospital NHS Foundation Trust</p> <p>Morris, Stephen; University of Cambridge Primary Care Unit, Department of Public Health and Primary Care</p> <p>Powell, Alison; THIS Institute, University of Cambridge</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Proietti, Riccardo; Liverpool Heart and Chest Hospital NHS Foundation Trust Sutton, Stephen; University of Cambridge Primary Care Unit, Department of Public Health and Primary Care Sweeting, Mike; Cambridge Biomedical Campus Thom, Howard; University of Bristol Williams, Kate; Strangeways Research Laboratory, Primary Care Unit, University of Cambridge SAFER Authorship Group, The; University of Cambridge Primary Care Unit
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Public health
Keywords:	Primary Care < Primary Health Care, Mass Screening, Stroke < NEUROLOGY, Randomized Controlled Trial, CARDIOLOGY



Randomised controlled trial of population screening for atrial fibrillation in people aged 70 years and over to reduce stroke: protocol for the SAFER trial.

Corresponding author

Dr Rakesh N Modi

Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, 2 Worts' Causeway, Cambridge, UK, CB1 8RN

rnm30@medschl.cam.ac.uk

Authors

1. Professor Jonathan Mant, jm677@medschl.cam.ac.uk¹
2. Dr Rakesh N Modi, rnm30@medschl.cam.ac.uk¹
3. Andrew Dymond, ad486@medschl.cam.ac.uk¹
4. Professor Natalie Armstrong, natalie.armstrong@le.ac.uk²
5. Dr Jenni Burt, jenni.burt@thislabs.org³
6. Dr Peter Calvert, Peter.Calvert@lhch.nhs.uk⁴
7. Professor Martin Cowie, martin.cowie@astrazeneca.com⁵
8. Dr Wern Yew Ding, dwyew@hotmail.com⁴
9. Dr Duncan Edwards, dae31@medschl.cam.ac.uk¹
10. Professor Ben Freedman, ben.freedman@sydney.edu.au⁶
11. Professor Simon J Griffin, profgp@medschl.cam.ac.uk^{1, 7}
12. Dr Sarah Hoare, seh91@medschl.cam.ac.uk¹
13. Professor F.D. Richard Hobbs, richard.hobbs@phc.ox.ac.uk⁸
14. Dr Rachel Johnson, rachel.johnson@bristol.ac.uk⁹
15. Dr Stephen Kaptoge, skk22@medschl.cam.ac.uk¹⁰
16. Professor Gregory Y.H. Lip, gregory.lip@liverpool.ac.uk⁴

- 1
- 2
- 3
- 4 17. Ms Trudie Lobban, MBE trudie@heartrhythmalliance.org¹¹
- 5 18. Dr Mark Lown, M.Lown@soton.ac.uk¹²
- 6 19. Dr Jenny Lund, jl897@medschl.cam.ac.uk¹
- 7
- 8 20. Professor Richard J McManus, richard.mcmanus@phc.ox.ac.uk⁸
- 9 21. Dr Mark T. Mills, Mark.Mills@LHCH.nhs.uk⁴
- 10 22. Professor Stephen Morris, sm2428@medschl.cam.ac.uk¹
- 11 23. Dr Alison Powell, alison.powell@thisinstitute.cam.ac.uk¹³
- 12 24. Dr Riccardo Proietti, Riccardo.Proietti@liverpool.ac.uk⁴
- 13 25. Professor Stephen Sutton, srs34@medschl.cam.ac.uk¹
- 14 26. Dr Mike Sweeting, michael.sweeting@astrazeneca.com²
- 15 27. Dr Howard Thom, howard.thom@bristol.ac.uk⁹
- 16 28. Dr Kate Williams, kmw36@medschl.cam.ac.uk¹
- 17 29. On behalf of the SAFER author group
- 18
- 19
- 20
- 21
- 22
- 23
- 24

- 25 1. Primary Care Unit, Department of Public Health and Primary Care, University of
- 26 Cambridge, Strangeways Research Laboratory, 2 Worts' Causeway, Cambridge, UK,
- 27 CB1 8RN
- 28
- 29 2. Department of Population Health Sciences, University of Leicester, George Davies
- 30 Centre, University Road, Leicester, UK, LE1 7RH
- 31
- 32 3. THIS Labs, 40B Trumpington Mews, High Street, Trumpington, Cambridge, CB2 9LS
- 33
- 34 4. Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John
- 35 Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; Danish Center
- 36 for Health Services Research, Department of Clinical Medicine, Aalborg University,
- 37 Denmark
- 38
- 39 5. School of Cardiovascular Medicine & Sciences, Faculty of Lifesciences & Medicine,
- 40 King's College London, London, UK
- 41
- 42 6. Heart Research Institute, University of Sydney, Room 3114, Level 3 East, D17 - Charles
- 43 Perkins Centre, NSW, Australia, 2006
- 44
- 45 7. MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge,
- 46 Cambridge Biomedical Campus, Cambridge, UK, CB2 0SL
- 47
- 48 8. Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe
- 49 Observatory Quarter, Woodstock Road, Oxford, UK, OX2 6GG
- 50
- 51 9. Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, UK,
- 52 BS8 2PS
- 53
- 54 10. Cardiovascular Epidemiology Unit, University of Cambridge, Victor Phillip Dahdaleh
- 55 Heart & Lung Research Institute, Papworth Road, Cambridge Biomedical Campus,
- 56 Cambridge, CB2 0BB
- 57
- 58
- 59
- 60

- 1
- 2
- 3 11. Arrhythmia Alliance (A-A) and AF Association, Celixir House, Stratford Business
- 4 &Technology Park Innovation Way, Stratford upon Avon CV37 7GZ
- 5
- 6 12. Primary Care and Population Sciences, Faculty of Medicine, University of Southampton,
- 7 Aldermoor Health Centre, Aldermoor Close, Southampton, UK, SO16 5ST
- 8
- 9 13. THIS Institute (The Healthcare Improvement Studies Institute), University of Cambridge,
- 10 Strangeways Research Laboratory, 2 Worts Causeway, Cambridge UK CB1 8RN
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

For peer review only

ABSTRACT

Introduction

There is a lack of evidence that the benefits of screening for atrial fibrillation (AF) outweigh the harms. Following the completion of the Screening for Atrial Fibrillation with electrocardiogram (ECG) to Reduce stroke (SAFER) pilot trial, the aim of the main SAFER trial is to establish whether population screening for AF reduces incidence of stroke risk.

Methods and analysis

Approximately 82,000 people aged 70 years and over and not on oral anticoagulation are being recruited from general practices in England. Patients on the palliative care register or resident in a nursing home are excluded. Eligible people are identified using electronic patient records from general practices and sent an invitation and consent form to participate by post. Consenting participants are randomised at a ratio of 2:1 (control : intervention) with clustering by household. Those randomised to the intervention arm are sent an information leaflet inviting them to participate in screening, which involves use of a handheld single lead ECG four times a day for three weeks. ECG traces identified by an algorithm as possible AF are reviewed by cardiologists. Participants with AF are seen by a general practitioner for consideration of anticoagulation. The primary outcome is stroke. Major secondary outcomes are: death; major bleeding; and cardiovascular events. Follow up will be via electronic health records for an average of four years. The primary analysis will be by intention-to-treat using time-to-event modelling. Results from this trial will be combined with follow up data from the cluster-randomised pilot trial by fixed effect meta-analysis.

Ethics and dissemination

The London—Central NHS Research Ethics Committee (19/LO/1597) provided ethical approval. Dissemination will include public-friendly summaries, reports and engagement with the UK National Screening Committee.

Trial registration number: ISRCTN72104369.

KEYWORDS

Atrial fibrillation; screening; randomised controlled trial; primary care; stroke prevention

ARTICLE SUMMARY

Strengths and limitations of this study

- This trial is more than twice the size of previous trials of atrial fibrillation (AF) screening and has adequate power to determine whether screening reduces risk of stroke.
- The power calculation has been refined based upon pilot data and the results of an earlier trial which used the same AF screening device.
- The screening intervention has been demonstrated by our feasibility and pilot studies to be feasible for national roll out if shown to be effective.
- There is a risk of contamination in the control group due to increasing availability of personal devices that enable self-screening for AF.
- Outcome data relies on electronic capture of routine data which risks incomplete ascertainment.

INTRODUCTION

The rationale for the Screening for Atrial Fibrillation with ECG to Reduce stroke (SAFER) trial has been described previously.[1] In brief, there is insufficient evidence that the potential benefits from screening for AF outweigh the potential harms.[2] Recent trials have failed to demonstrate that single time-point screening identifies more AF than usual care.[3-5] This is likely to be due to better AF identification within usual care than was prevalent when the Screening for Atrial Fibrillation in the Elderly (SAFE) trial demonstrated the value of single time point screening in identifying additional cases of AF in the early 2000s.[6] Therefore, interest has focussed on newer technologies that enable continuous or intermittent heart rhythm monitoring, such as hand-held ECGs, patches and implantable loop recorders.[7-9] These approaches do identify more AF than usual care, but have not been shown to reduce incidence of stroke.[7-9] Since these devices predominantly identify paroxysmal AF, it is important to determine whether such screening translates into reduced incidence of stroke, as paroxysmal AF may be associated with a lower risk of stroke than permanent AF.[10]

While the evidence base for stroke risk reduction with anticoagulation in AF is based on trials that included participants with paroxysmal AF, the new technologies diagnose people with lower AF burden than will have been typical of those with (usually symptomatic) paroxysmal AF in these trials.[11] Stroke risk in paroxysmal AF is related to AF burden,[12] so it is conceivable that people with low burden paroxysmal AF may not benefit from anticoagulation. Indeed, this was the tentative conclusion drawn by the LOOP study investigators who diagnosed AF in over 30% of the intervention arm of a screening trial using an implantable loop recorder.[8]

The emergence of consumer-led screening over recent years has provided further impetus to the SAFER trial.[13] Several commercially available devices are directly marketed to consumers for detection of AF.[13] The results of SAFER will also guide clinicians on the appropriate course of action in AF identified through consumer-led screening.[13]

In addition to stroke prevention, there are other benefits to treating AF with anticoagulation, including improved survival and reduced risk of myocardial infarction.[11] Indeed, the STROKESTOP screening trial reported a marginally significant reduction in a revised composite primary end-point of stroke, systemic embolism, bleeding leading to hospitalisation and all cause death.[9] Another potential benefit of screening for AF is to reduce risk of cognitive decline and vascular dementia.[14-17]

1
2
3
4
5 In terms of harm, the major concern is risk of bleeding as a result of anticoagulation of people
6 identified as being in AF. There is clear evidence in the trials of treatment of AF with anticoagulation
7 that benefit outweighs harm,[11] but the ratio of benefit to harm of treatment might be different for
8 people with AF identified through screening. For example, in the LOOP trial, the 20% relative risk
9 reduction in stroke was largely offset by the 26% relative increase in risk of major bleeding.[8] This
10 concern is reinforced by the results of recent trials of anticoagulation in sub-clinical atrial fibrillation
11 and atrial high rate episodes (AHRES) detected as a result of implanted devices such as pacemakers,
12 defibrillators and loop recorders (i.e not identified as a result of screening).[18 19] In the NOAH-
13 AFNET6 trial, a non-significant 19% reduction in the primary efficacy outcome (composite of
14 cardiovascular death, stroke and systemic embolism) was offset by a significant 31% increase in the
15 risk of a safety outcome occurring (death from any cause or major bleeding).[18] In the ARTESIA
16 trial, a significant 37% reduction in risk of stroke or systemic embolism was offset by a significant
17 36% increase in the risk of major bleeding.[19]

18
19
20
21
22
23
24
25
26
27
28 The aim of the SAFER trial is to determine if population screening for AF using a hand-held single-
29 lead ECG device intermittently over a period of three weeks is effective and cost-effective at
30 reducing stroke compared to usual care and to quantify other potential benefits and harms of
31 screening. The design of the SAFER pilot trial (now successfully completed) has already been
32 reported.[1] This protocol paper therefore focuses on changes in methods between the pilot and
33 the main trial. The SPIRIT checklist provides the structure for this paper.[20]

34 35 36 37 38 39 40 **METHODS AND ANALYSIS**

41 42 43 44 **Design**

45
46
47 SAFER is a multi-centre randomised controlled trial. Randomisation is at the individual level with
48 clustering by household (i.e., if there is more than one participant from the same address, they will
49 be allocated to the same arm). This is a change from the original intention to randomise at the level
50 of the general practice.[1] This decision was made during the internal pilot trial, when it became
51 clear that remote delivery of the screening intervention greatly reduced the risk of contamination,
52 so negating the value of cluster randomisation by practice. However, it was recognised that there
53 would be a residual risk of contamination if members of the same household were in different arms
54 of the trial. The first participant was randomised in March 2022. It is currently estimated that
55
56
57
58
59
60

1
2
3 randomisation will finish in April 2024 and follow-up will finish in March 2027. The trial design is
4 summarised in Figure 1.
5
6
7

8 <<Figure 1. SAFER trial schema>>
9

10 11 **Participants** 12 13

14
15 Participant eligibility is unchanged from the pilot study, being people aged 70 years or older who are
16 registered with participating general practices.[1] Those who are on the practice palliative care
17 register or in a nursing or residential home are excluded, as are those already on anticoagulation
18 therapy. Non-UK residents are excluded, as are people who have already consented to another trial
19 that may affect participation in SAFER. People with a prior record of AF but not currently on
20 anticoagulation are eligible as this may encourage anticoagulation use in these participants as was
21 observed in STROKESTOP.[1] General practices are being recruited from throughout England. It is
22 anticipated that about 195 practices will be involved.
23
24
25
26
27
28
29

30 31 **Recruitment** 32 33

34 Unlike in the pilot cluster randomised trial, where there was little gain in power from increasing
35 sample size in each cluster, all eligible patients (as opposed to a random sample) are sent an
36 invitation pack by their practice. This includes a consent form (see supplementary file 1) to be
37 returned to the trial team either by post or online.
38
39
40
41

42 43 **Randomisation** 44 45

46 Randomisation is performed on-line at the Oxford Primary Care Clinical Trials Unit following return
47 of consent forms, stratified by practice. Random permuted blocks ensure allocations are balanced at
48 a ratio of 2:1 (control : intervention) in batches per practice. If there is more than one participant in
49 the same household, they are randomised as a cluster to the same arm. In recognition that trial
50 capacity would be limited primarily by how many participants could be screened, a 2:1
51 randomisation ratio was used to increase trial power for a given number of participants randomised
52 to screening.
53
54
55
56
57
58
59
60

Baseline data

This is unchanged from the pilot trial, includes demographics and comorbidities, and is collected from the GP electronic medical records.[1]

Screening Intervention

This is unchanged from the pilot trial.[1] In brief, participants randomised to screening will receive a further postal invitation to participate in screening. Those who accept this invitation receive a call from the trial team to arrange delivery of the single-lead ECG device (Zenicor One, Zenicor medical systems AB) and instructions (written with online video available) and an offer of subsequent support by telephone on how to use it. They are asked to carry out screening four times a day for three weeks, and take additional traces if symptomatic (e.g. palpitations, dizziness). Each trace runs for 30 seconds. Participants transmit their recordings to a remote database using the mobile capability within the device. Each ECG is tagged with a unique participant ID number.

A proprietary algorithm (Cardiolund) analyses the ECG traces,[21] and those that show possible AF are reviewed by a cardiologist or cardiac technician. A second cardiologist performs additional review if there is uncertainty. AF is diagnosed if the rhythm is present continuously for 30 seconds. The screening results are returned to the practice, which notifies all participants of their results, and actively follows up those with AF or other significant diagnoses (e.g. ventricular tachycardia, high-degree atrioventricular block). Participating GPs receive initial training when the practice is set up for the trial. This includes a reminder that confirmation of the diagnosis of AF with a 12 lead ECG is not required for diagnosis of paroxysmal AF.[22] -They are offered further on line training on the National Institute for Health and Care Excellence (NICE) AF guidelines.[22] GPs are asked to provide a reason if they do not initiate anticoagulation for a participant diagnosed through screening.

Usual care

Participants assigned to the control arm will receive usual care, which might involve single time point opportunistic screening.

Follow up

1
2
3 The target follow up duration has been reduced from an average of five years (as per the pilot
4 protocol)[1] to an average of four years per participant. This is to compensate for the delays
5 imposed on the trial by COVID-19, and to lower the risk of control group contamination with risking
6 direct marketing of AF detection devices directly to the public.[13] The revised sample size
7 calculation (see below) takes this reduced length of follow up into account. The programme steering
8 committee will review stroke rate in the whole trial population (i.e., not by treatment arm), and may
9 recommend modifying follow up duration if stroke rates differ from what is expected (approximately
10 1% per annum).[9] Follow up will be by electronic health records (including GP records), Hospital
11 Episode Statistics (HES), Office for National Statistics (ONS) mortality data and national disease
12 registries accessed via NHS England and ORCHID database.[23] Participants are linked to these
13 databases via a unique number (their NHS number). HES provides principal and secondary diagnosis
14 codes for all hospital admissions in England. ONS mortality data includes date of death, and
15 underlying and contributory causes of death for all deaths. National disease registries provide an
16 alternative source for stroke and myocardial infarction to HES. A comparison of these sources
17 suggests that data capture is more complete with combination of sources .[24]

18
19
20
21
22
23
24
25
26
27
28
29
30 Funding for longer term follow up will be sought. In particular, if AF screening is associated with
31 reduction in dementia, the screening benefit will manifest over a longer time period.

32 33 34 35 **Outcomes**

36
37
38 The primary outcome is stroke. This includes stroke of any severity, but excludes events only labelled
39 as transient ischaemic attack. For the primary endpoint, ischaemic and haemorrhagic stroke events
40 will be combined.

41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Secondary outcomes include: all-cause death; cardiovascular death; major adverse cardiovascular
event (composite of myocardial infarction, stroke and other hospital admissions for cardiovascular
disease, including heart failure); myocardial infarction; ischaemic stroke; haemorrhagic stroke;
major bleeding episode (defined as requiring hospital admission); new diagnosis of dementia; new
diagnosis of depression. AF detection rates and anticoagulation uptake will be reported (principal
outcomes of the internal pilot trial).

Outcome ascertainment will be restricted to data available from electronic health records without
event adjudication. A comparison of routine versus adjudicated follow up in a vascular events

1
2
3 outcome trial found that specificity of routine data was high (over 99%), and that sensitivity was
4 over 80% if transient ischaemic attack was excluded.[25] Furthermore, there was no difference in
5 effect size between the two sources of data.[25] The sample size calculation below takes into
6 account the 80% sensitivity, in that it is based on observed stroke rates in a trial where the follow up
7 also relied on routinely available data.[9]
8
9
10
11
12

13 **Sample size**

14
15
16
17 The sample size calculation has been updated to reflect the changes in trial design, the result of a
18 recent trial of screening for AF using the Zenicor One device,[9] the interim results of the internal
19 pilot trial, and initial baseline findings from the main trial. In the STROKESTOP trial, an 8% reduction
20 in risk of stroke was observed.[9] Due to higher uptake of screening in the intervention arm of
21 SAFER, and the greater observed differences in AF detection rates between intervention and control
22 as compared to STROKESTOP, a 12% relative risk reduction in stroke is now anticipated in SAFER.
23 Assuming a household cluster size of 1.21 (from observed cluster size to date), a household
24 intraclass correlation coefficient of 0.2,[26] and a 1% annual risk of stroke in the control arm,[9] this
25 equates to needing 82,000 participants to detect a 12% relative reduction in risk of stroke after four
26 years with 90% power. Overall, the target number of participants was reduced from 126,000 to
27 82,000, primarily as a result of the change from being a cluster randomised trial at the level of the
28 practice to randomisation by household. Our experience in our feasibility and pilot studies (which
29 will be reported separately) suggest that this number will be achievable.
30
31
32
33
34
35
36
37
38
39
40

41 **Analysis**

42
43
44 The intention-to-treat principle will guide data analysis (outcome in all eligible randomised
45 participants will be compared between intervention and control). All eligible randomised
46 participants will be included in the analysis, regardless of participation in screening.
47
48
49
50

51 The primary analysis will be conducted separately for the cluster randomised pilot trial and the main
52 trial, with results then combined by fixed effect meta-analysis. Time-to-event modelling (i.e. a Cox
53 proportional hazards model) will be used to obtain an estimate (hazard ratio) of the effect of
54 screening on stroke risk (fatal and non-fatal), censoring other causes of death. Analysis time will be
55 from date of randomisation.
56
57
58
59
60

1
2
3 Clustering (by practice for pilot trial participants and by household for main trial participants) will be
4 accounted for using a robust sandwich estimator of the covariance matrix. The estimate of
5 intervention effect will be adjusted for pre-specified baseline co-variates such as age and sex.
6
7
8 Secondary outcomes will be analysed in a similar way.
9

10
11 For all analyses, we will test model assumptions. Should these be violated, flexible parametric
12 survival models will be considered to model the change in hazard ratio over time.
13
14

15
16 A full statistical analysis plan will be lodged with the ISRCTN registration prior to data lock.
17
18

19 20 **Economic analysis**

21
22
23 To determine whether screening is cost-effective from the perspective of the NHS, we will adapt an
24 existing economic model.[27] This will incorporate data from the SAFER trial, including outcomes
25 such as mortality and cardiovascular endpoints, to determine incremental cost per QALY gained
26 comparing screening versus no screening over a 4 year time horizon. The model parameters that do
27 not come from the trial will be derived from updated literature reviews. We will extend the model to
28 a life-time horizon, and consider the impact on cost-effectiveness of repeated screening at different
29 time intervals and in different age groups.
30
31
32
33
34
35
36

37 38 **Management and oversight**

39
40
41 Management and oversight is delivered through the same structure as in the pilot trial.[1] The
42 University of Cambridge and NHS Cambridgeshire & Peterborough Integrated Care Board (ICB) are
43 co-sponsors. The trial management group meets monthly to review operational issues. The
44 programme steering committee (PSC), which has an independent chair and four independent
45 members, provides independent over-sight of the programme and acts as the Trial Steering
46 Committee. An active risk register has been compiled in consultation with the funder and sponsors
47 and will be monitored and updated throughout.
48
49
50
51
52
53

54 55 **Patient and public involvement (PPI)**

1
2
3 The same approach is being used as in the pilot trial.[1] In brief, we have engagement by PPI
4 members as an investigator (Trudie Lobban, chief executive of the Atrial Fibrillation Association,
5 (AFA)), and as contributors independent of the AFA.
6
7
8
9

10 **ETHICS AND DISSEMINATION**

11
12

13 Ethical approval has been provided by the London-Central NHS Research Ethics Committee
14 (19/LO/1597).
15
16

17
18 In addition to peer-reviewed publications and presentation at conferences, public-friendly trial
19 summary documents will be made available to participants at the end of the trial. Accessible reports
20 will be generated for the UK National Screening Committee, commissioners and other decision
21 makers. The pilot study protocol provides further details.[1]
22
23
24
25

26
27 Requests for pseudonymised data will be directed to the trial co-ordinator (Andrew Dymond using
28 SAFER@medschl.cam.ac.uk) and will be considered by the investigators, in accordance with
29 participant consent.
30
31
32

33 **AUTHOR CONTRIBUTIONS**

34
35
36

37 JM is the guarantor and drafted the manuscript with help from RNM. KW and AD are coordinating,
38 planning, gaining ethical approval, conducting, and helping design the trial. JM, JB, NA, DE, RJ, JL, TL,
39 ML, GL, BF, SG, SS, FRH and RJM undertook design, planning and are overseeing conduct of the trial.
40 SH and AP as qualitative researchers contributed to the design of the intervention. MC helped
41 design the trial. TL is a PPI representative who has informed the design, outcomes and dissemination
42 plan. SM and HT designed the economic evaluation and will oversee its conduct. SK designed the
43 statistical analysis and will oversee its conduct. MS contributed to the initial work on the trial design
44 and led statistical methods. SK contributed to revision of the trial design and will lead on
45 development of the statistical analysis plan and oversee progress. GL, PC, MM, WD and RP
46 conducted and refined the cardiology review process of the intervention. The SAFER author group
47 contributed to planning and design of the trial, applying for funding, writing of the protocol for the
48 ethical approval and have oversight of the conduct of the trial. All authors reviewed and had the
49 option to edit the final manuscript.
50
51
52
53
54
55
56
57
58
59
60

FUNDING STATEMENT

This SAFER trial is funded by the National Institute for Health and Care Research (NIHR) [Programme Grants for Applied Research Programme (Reference Number [RP-PG-0217-20007](#))]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. SAFER is a contributor to / partner of AFFECT-EU receiving funding from the European Union's Horizon 2020 research and innovation Programme under grant agreement NO. 847770. RM and JL are supported by the Wellcome Trust as part of the Wellcome Trust PhD Programme for Primary Care Clinicians [grant number 203921/Z/16/Z]. AP is based in The Healthcare Improvement Studies Institute (THIS Institute), University of Cambridge. THIS Institute is supported by the Health Foundation, an independent charity committed to bringing about better health and healthcare for people in the UK. FDRH acknowledges support from NIHR ARC OTV and Oxford BRC (OUT). RJM is an NIHR Senior Investigator and acknowledges support from NIHR ARC OTV. NA is supported by the National Institute for Health and Care Research (NIHR) Greater Manchester Patient Safety Research Collaboration (GM PSRC) by the NIHR Applied Research Collaboration East Midlands (ARC EM). RJ is an NIHR-funded Academic Clinical Lecturer. The University of Cambridge has received salary support in respect of SJG from the NHS in the East of England through the Clinical Academic Reserve. BF received funding from the Medical Research Future Fund International Clinical Trial Collaboration Grant to perform SAFER-AUS as part of SAFER, and a NSW Health Senior Researcher Cardiovascular Grant for work in AF. GYHL is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. All the funders and sponsors had no involvement in the development of this protocol and will have no involvement in any aspect of the trial itself. The views expressed are those of the author(s) and not necessarily those of the NHS, the Wellcome Trust, the NIHR or the UK Department of Health and Social Care.

COMPETING INTEREST STATEMENT

JM has performed consultancy work for BMS/Pfizer and Omron. FDRH reports occasional consultancy for BMS/Pfizer, Bayer and BI over the past 5 years. NA is a member of the UK National Screening Committee. MRC and MS are employed by AstraZeneca PLC, but at the time of involvement with the trial were employed by Universities (Kings College London and University of Leicester respectively), for which they still hold honorary contracts. RJM's employer the University

1
2
3 of Oxford receives consultancy and licencing payments from Omron and Sensyne for BP
4 telemonitoring interventions. GYHL is a consultant and speaker for BMS/Pfizer, Boehringer
5 Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. SJG has received honoraria from
6 Astra Zeneca for lectures at postgraduate educational meetings for primary care teams about type 2
7 diabetes. BF has received speaker fees, honoraria, and non-financial support from the BMS and
8 Pfizer Alliance; grants to the Institution for investigator-initiated studies from the BMS and Pfizer
9 Alliance; and loan devices for investigator-initiated studies from Alivacor: all were unrelated to the
10 present trial but related to screening for AF.
11
12
13
14
15
16
17

18 **ACKNOWLEDGEMENTS**

19
20
21 We would like to acknowledge the support of:

22
23 **Independent Programme Steering Committee:** Professor Christian Mallen, University of Keele
24 (chair); Professor Anthony Rudd, Kings College London (independent member); Professor Ann Marie
25 Swart, University of East Anglia (independent member); Professor Andy Vail, University of
26 Manchester (independent member); Dr Bob Ward (independent lay member)

27
28 **Patient and public involvement representatives:** Margaret Corbett; Jennifer Crockford; Trudie
29 Lobban MBE (Founder & CEO of Atrial Fibrillation Association); Sheilah Rengert; Dr Bob Ward
30
31
32
33
34

35 **REFERENCES**

- 36
37
38
39 1. Williams K, Modi RN, Dymond A, et al. Cluster randomised controlled trial of screening for atrial
40 fibrillation in people aged 70 years and over to reduce stroke: protocol for the pilot study for
41 the SAFER trial. *BMJ Open* 2022;12(9):e065066. doi: 10.1136/bmjopen-2022-065066
42
43 2. Curry SJ, Krist AH, Owens DK, et al. Screening for Atrial Fibrillation With Electrocardiography: US
44 Preventive Services Task Force Recommendation Statement. *Jama* 2018;320(5):478-84. doi:
45 10.1001/jama.2018.10321 [published Online First: 2018/08/09]
46
47 3. Kaasenbrood F, Hollander M, de Bruijn SH, et al. Opportunistic screening versus usual care for
48 diagnosing atrial fibrillation in general practice: a cluster randomised controlled trial. *Br J*
49 *Gen Pract* 2020;70(695):e427-e33. doi: 10.3399/bjgp20X708161 [published Online First:
50 2020/01/29]
51
52 4. Uittenbogaart SB, Verbiest-van Gorp N, Lucassen WAM, et al. Opportunistic screening versus usual
53 care for detection of atrial fibrillation in primary care: cluster randomised controlled trial.
54 *BMJ* 2020;370:m3208. doi: 10.1136/bmj.m3208
55
56
57
58
59
60

- 1
2
3 5. Lubitz SA, Atlas SJ, Ashburner JM, et al. Screening for Atrial Fibrillation in Older Adults at Primary
4 Care Visits: VITAL-AF Randomized Controlled Trial. *Circulation* 2022;145(13):946-54. doi:
5 doi:10.1161/CIRCULATIONAHA.121.057014
6
7
- 8 6. Fitzmaurice DA, Hobbs FD, Jowett S, et al. Screening versus routine practice in detection of atrial
9 fibrillation in patients aged 65 or over: cluster randomised controlled trial. *Bmj*
10 2007;335(7616):383. doi: 10.1136/bmj.39280.660567.55 [published Online First:
11 2007/08/04]
12
13
- 14 7. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, et al. Screening for Atrial Fibrillation in the Older
15 Population: A Randomized Clinical Trial. *JAMA Cardiology* 2021 doi:
16 10.1001/jamacardio.2021.0038
17
18
- 19 8. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial
20 fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *The Lancet*
21 2021 doi: [https://doi.org/10.1016/S0140-6736\(21\)01698-6](https://doi.org/10.1016/S0140-6736(21)01698-6)
22
23
- 24 9. Svennberg E, Friberg L, Frykman V, et al. Clinical outcomes in systematic screening for atrial
25 fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled
26 trial. *The Lancet* 2021 doi: [https://doi.org/10.1016/S0140-6736\(21\)01637-8](https://doi.org/10.1016/S0140-6736(21)01637-8)
27
28
- 29 10. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of
30 thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur*
31 *Heart J* 2016;37(20):1591-602. doi: 10.1093/eurheartj/ehw007 [published Online First:
32 2016/02/19]
33
34
- 35 11. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial
36 fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane*
37 *Database of Systematic Reviews* 2005(3) doi: 10.1002/14651858.CD001927.pub2
38
39
- 40 12. Go AS, Reynolds K, Yang J, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic
41 Stroke in Adults With Paroxysmal Atrial Fibrillation: The KP-RHYTHM Study. *JAMA Cardiology*
42 2018;3(7):601-08. doi: 10.1001/jamacardio.2018.1176
43
44
- 45 13. Brandes A, Stavrakis S, Freedman B, et al. Consumer-Led Screening for Atrial Fibrillation: Frontier
46 Review of the AF-SCREEN International Collaboration. *Circulation* 2022;146(19):1461-74. doi:
47 10.1161/circulationaha.121.058911 [published Online First: 2022/11/08]
48
49
- 50 14. Singh-Manoux A, Fayosse A, Sabia S, et al. Atrial fibrillation as a risk factor for cognitive decline
51 and dementia. *European Heart Journal* 2017;38(34):2612-18.
52
53
- 54 15. Bezabhe WM, Bereznicki LR, Radford J, et al. Oral Anticoagulant Treatment and the Risk of
55 Dementia in Patients With Atrial Fibrillation: A Population-Based Cohort Study. *Journal of the*
56 *American Heart Association* 2022;11(7):e023098. doi: doi:10.1161/JAHA.121.023098
57
58
59
60

16. Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *European Heart Journal* 2019;40(28):2327-35. doi: 10.1093/eurheartj/ehz304
17. Mavaddat N, Roalfe A, Fletcher K, et al. Warfarin versus aspirin for prevention of cognitive decline in atrial fibrillation: randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged Study). *Stroke* 2014;45(5):1381-86.
18. Kirchhof P, Toennis T, Goette A, et al. Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes. *New England Journal of Medicine* 2023;389(13):1167-79. doi: 10.1056/NEJMoa2303062
19. Healey JS, Lopes RD, Granger CB, et al. Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation. *New England Journal of Medicine* 2023;390(2):107-17. doi: 10.1056/NEJMoa2310234
20. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Bmj* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
21. Cardiolund. Cardiac Analysis 2023 [Available from: <https://www.cardiolund.com/> accessed 31/07/2023].
22. National Institute for Health and Care Excellence. Atrial fibrillation: diagnosis and management (ng196): National Institute of Health and Care Excellence, 2021.
23. Nuffield Department of Primary Care Health Sciences. ORCHID: University of Oxford; 2023 [Available from: <https://orchid.phc.ox.ac.uk/> accessed 13/11/2023].
24. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ : British Medical Journal* 2013;346:f2350. doi: 10.1136/bmj.f2350
25. Harper C, Mafham M, Herrington W, et al. Comparison of the Accuracy and Completeness of Records of Serious Vascular Events in Routinely Collected Data vs Clinical Trial–Adjudicated Direct Follow-up Data in the UK: Secondary Analysis of the ASCEND Randomized Clinical Trial. *JAMA Network Open* 2021;4(12):e2139748-e48. doi: 10.1001/jamanetworkopen.2021.39748
26. Ukoumunne OC, Gulliford MC, Chinn S, et al. Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review. *Health technology assessment (Winchester, England)* 1999;3(5):iii-92. [published Online First: 2000/09/12]

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

27. Welton NJ, McAleenan A, Thom HH, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technology Assessment* 2017;21(29)

For peer review only

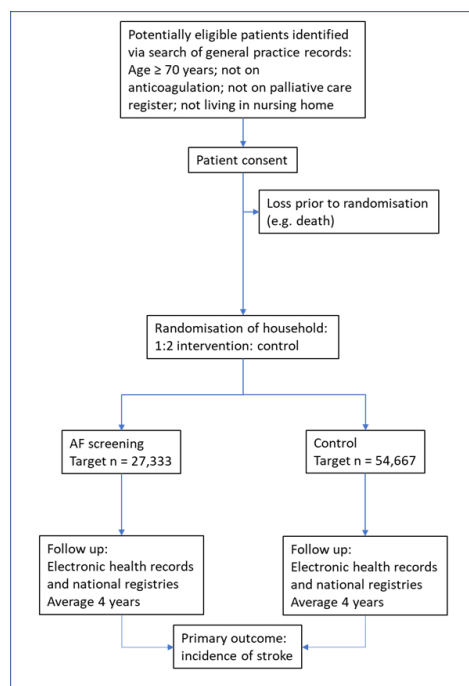


Figure 1. SAFER trial schema

225x180mm (144 x 144 DPI)

SAFER Trial Consent Form

Version 2.0 16-12-2021

Please complete and return this form only if you wish to join the SAFER Trial

Title: The SAFER Trial – Screening for Atrial Fibrillation with ECG to Reduce stroke

Chief Investigator: Professor Jonathan Mant, University of Cambridge

Ethics Reference number: 19/LO/1597

IRAS project ID: 272184

If you are willing to take part in the SAFER Trial, please read the following statements and if you agree, sign and date overleaf.

1	I have read and understood the Participant Information Sheet version 2.0, dated 16/12/2021 (remote) for the above trial. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.
2	I understand that my participation in this trial is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.
3	I understand that information from my medical records will be available to the research team as part of the trial.
4	I consent to my trial data being linked to Hospital Episodes Statistics (HES), civil registration mortality data, Sentinel Stroke National Audit Programme (SSNAP) and Myocardial Ischaemia National Audit Project (MINAP). This may involve sharing my personal data with these bodies. I understand that information held and managed by NHS Digital and the registries may be used in order to provide information about my health status (including after my death), my GP practice and my address (should I move). I understand that these details will be used for research purposes only. It is possible that in the future the research team may need to link to another health record or registry not listed that they consider to be relevant to the purposes of the research and I agree to this.
5	I understand that sections of my medical notes or information related directly to my participation in this trial may be looked at by responsible individuals from the sponsors, regulatory authorities and research personnel where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
6	I understand that my GP will be informed of my participation in this trial.
7	I understand that my unidentifiable trial data will be shared with other researchers, both internal and external to this trial, and with commercial partners. These parties may be outside the European Economic Area.
8	I understand that I may be contacted about future, related research studies, and that I am under no obligation to take part.
9	I agree to participate in this trial.

By signing this form you are consenting that you agree with all of the statements listed, and that the details listed below are correct.

Name of participant	Signature	Date

Please check the details below and amend/complete accordingly, then return this form to the trial team using the Freepost envelope enclosed. Alternatively you can complete this consent form online – please see the covering letter enclosed for instructions.

As the trial will be conducted remotely, it will be helpful if you could please supply phone number(s) and an email address. By providing these details you are agreeing to be contacted by the trial team via these methods (email, phone call, SMS text message) for the purposes of the trial.

Title:	
First name:	
Surname:	
Date of birth (dd/mm/yyyy):	
Gender (M/F/Mx):	
Address:	
Postcode:	
Home Tel.:	
Mobile no.:	
Email:	
NHS no:	
GP Practice name: Please note: if this is not your current practice and you have recently moved practice, you will not be able to take part at this point. It is possible that your new practice may take part in the future.	

The trial team will return a copy of this consent form to your GP practice for their records. If you would like a copy of your completed consent form please contact the trial team.

The trial team will only use these details in order to contact you for the purposes stated.

1x copy to be retained by the research team; 1x copy to be sent to the participant's GP practice.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Administrative

information	Reporting Item	Page Number
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	Date and version identifier	n/a
Funding	Sources and types of financial, material, and other support	12-13
Roles and responsibilities: contributorship	Names, affiliations, and roles of protocol contributors	1-3, 12

1	Roles and	Name and contact information for the trial sponsor	11
2			
3	responsibilities: sponsor		
4			
5	contact information		
6			
7			
8			
9	Roles and	Role of study sponsor and funders, if any, in study	11-12
10			
11	responsibilities: sponsor	design; collection, management, analysis, and	
12			
13	and funder	interpretation of data; writing of the report; and the	
14			
15			
16		decision to submit the report for publication,	
17			
18		including whether they will have ultimate authority	
19			
20		over any of these activities	
21			
22			
23	Roles and	Composition, roles, and responsibilities of the	11, 13
24			
25	responsibilities:	coordinating centre, steering committee, endpoint	
26			
27	committees	adjudication committee, data management team,	
28			
29		and other individuals or groups overseeing the trial,	
30			
31		if applicable (see Item 21a for data monitoring	
32			
33		committee)	
34			
35			
36			
37			
38	Introduction		
39			
40			
41	Background and	Description of research question and justification	6-7
42			
43	rationale	for undertaking the trial, including summary of	
44			
45		relevant studies (published and unpublished)	
46			
47		examining benefits and harms for each intervention	
48			
49			
50			
51	Background and	Explanation for choice of comparators	6-9
52			
53	rationale: choice of		
54			
55	comparators		
56			
57			
58			
59			
60			

1	Objectives	Specific objectives or hypotheses	7
2			
3			
4	Trial design	Description of trial design including type of trial (eg,	7
5		parallel group, crossover, factorial, single group),	
6		allocation ratio, and framework (eg, superiority,	
7		equivalence, non-inferiority, exploratory)	
8			
9			
10			
11			
12			
13			
14	Methods: Participants,		
15	interventions, and		
16	outcomes		
17			
18			
19			
20			
21			
22	Study setting	Description of study settings (eg, community clinic,	7-8, 12
23		academic hospital) and list of countries where data	
24		will be collected. Reference to where list of study	
25		sites can be obtained	
26			
27			
28			
29			
30			
31			
32	Eligibility criteria	Inclusion and exclusion criteria for participants. If	7-8
33		applicable, eligibility criteria for study centres and	
34		individuals who will perform the interventions (eg,	
35		surgeons, psychotherapists)	
36			
37			
38			
39			
40			
41			
42	Interventions:	Interventions for each group with sufficient detail to	8-9
43	description	allow replication, including how and when they will	
44		be administered	
45			
46			
47			
48			
49	Interventions:	Criteria for discontinuing or modifying allocated	8-9
50	modifications	interventions for a given trial participant (eg, drug	
51		dose change in response to harms, participant	
52		request, or improving / worsening disease)	
53			
54			
55			
56			
57			
58			
59			
60			

1 2 3 4 5 6 7 8	Interventions: adherence	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
9 10 11 12 13	Interventions: concomitant care	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-9
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Outcomes	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
33 34 35 36 37 38 39 40 41 42 43 44	Participant timeline	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Sample size	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10

1	Recruitment	Strategies for achieving adequate participant	7-8
2			
3			
4		enrolment to reach target sample size	
5			
6	Methods: Assignment of		
7	interventions (for		
8	controlled trials)		
9			
10			
11			
12			
13			
14	Allocation: sequence	Method of generating the allocation sequence (eg,	8
15		computer-generated random numbers), and list of	
16	generation	any factors for stratification. To reduce	
17		predictability of a random sequence, details of any	
18		planned restriction (eg, blocking) should be	
19		provided in a separate document that is	
20		unavailable to those who enrol participants or	
21		assign interventions	
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33	Allocation concealment	Mechanism of implementing the allocation	n/a
34		sequence (eg, central telephone; sequentially	
35	mechanism	numbered, opaque, sealed envelopes), describing	
36		any steps to conceal the sequence until	
37		interventions are assigned	
38			
39			
40			
41			
42			
43			
44			
45	Allocation:	Who will generate the allocation sequence, who	8
46			
47	implementation	will enrol participants, and who will assign	
48		participants to interventions	
49			
50			
51			
52			
53	Blinding (masking)	Who will be blinded after assignment to	n/a
54		interventions (eg, trial participants, care providers,	
55		outcome assessors, data analysts), and how	
56			
57			
58			
59			
60			

1 Blinding (masking): If blinded, circumstances under which unblinding is n/a
 2
 3 emergency unblinding permissible, and procedure for revealing a
 4
 5 participant's allocated intervention during the trial
 6
 7

8
 9 **Methods: Data**

10
 11 **collection, management,**
 12
 13 **and analysis**
 14

15
 16 Data collection plan Plans for assessment and collection of outcome, 8-9
 17
 18 baseline, and other trial data, including any related
 19
 20 processes to promote data quality (eg, duplicate
 21
 22 measurements, training of assessors) and a
 23
 24 description of study instruments (eg,
 25
 26 questionnaires, laboratory tests) along with their
 27
 28 reliability and validity, if known. Reference to where
 29
 30 data collection forms can be found, if not in the
 31
 32 protocol
 33
 34
 35
 36
 37

38 Data collection plan: Plans to promote participant retention and 9
 39
 40 retention complete follow-up, including list of any outcome
 41
 42 data to be collected for participants who
 43
 44 discontinue or deviate from intervention protocols
 45
 46

47
 48 Data management Plans for data entry, coding, security, and storage, 8, 11
 49
 50 including any related processes to promote data
 51
 52 quality (eg, double data entry; range checks for
 53
 54 data values). Reference to where details of data
 55
 56
 57
 58
 59
 60

1		management procedures can be found, if not in the	
2			
3		protocol	
4			
5			
6	Statistics: outcomes	Statistical methods for analysing primary and	10-11
7			
8		secondary outcomes. Reference to where other	
9			
10		details of the statistical analysis plan can be found,	
11			
12		if not in the protocol	
13			
14			
15			
16	Statistics: additional	Methods for any additional analyses (eg, subgroup	10-11
17			
18	analyses	and adjusted analyses)	
19			
20			
21	Statistics: analysis	Definition of analysis population relating to protocol	10
22			
23	population and missing	non-adherence (eg, as randomised analysis), and	
24			
25	data	any statistical methods to handle missing data (eg,	
26			
27		multiple imputation)	
28			
29			
30			
31	Methods: Monitoring		
32			
33			
34	Data monitoring: formal	Composition of data monitoring committee (DMC);	11, 13
35			
36	committee	summary of its role and reporting structure;	
37			
38		statement of whether it is independent from the	
39			
40		sponsor and competing interests; and reference to	
41			
42		where further details about its charter can be	
43			
44		found, if not in the protocol. Alternatively, an	
45			
46		explanation of why a DMC is not needed	
47			
48			
49			
50			
51	Data monitoring: interim	Description of any interim analyses and stopping	11, 13
52			
53	analysis	guidelines, including who will have access to these	
54			
55		interim results and make the final decision to	
56			
57		terminate the trial	
58			
59			
60			

1	Harms	Plans for collecting, assessing, reporting, and	11
2			
3		managing solicited and spontaneously reported	
4			
5		adverse events and other unintended effects of trial	
6			
7		interventions or trial conduct	
8			
9			
10			
11	Auditing	Frequency and procedures for auditing trial	11
12			
13		conduct, if any, and whether the process will be	
14			
15		independent from investigators and the sponsor	
16			
17			
18			
19	Ethics and		
20			
21	dissemination		
22			
23			
24	Research ethics	Plans for seeking research ethics committee /	11-12
25			
26	approval	institutional review board (REC / IRB) approval	
27			
28			
29	Protocol amendments	Plans for communicating important protocol	11
30			
31		modifications (eg, changes to eligibility criteria,	
32			
33		outcomes, analyses) to relevant parties (eg,	
34			
35		investigators, REC / IRBs, trial participants, trial	
36			
37		registries, journals, regulators)	
38			
39			
40			
41	Consent or assent	Who will obtain informed consent or assent from	8
42			
43		potential trial participants or authorised surrogates,	
44			
45		and how (see Item 32)	
46			
47			
48			
49	Consent or assent:	Additional consent provisions for collection and use	n/a
50			
51	ancillary studies	of participant data and biological specimens in	
52			
53		ancillary studies, if applicable	
54			
55			
56			
57			
58			
59			
60			

1	Confidentiality	How personal information about potential and	11-12
2			
3		enrolled participants will be collected, shared, and	
4			
5		maintained in order to protect confidentiality before,	
6			
7		during, and after the trial	
8			
9			
10			
11	Declaration of interests	Financial and other competing interests for	12-13
12			
13		principal investigators for the overall trial and each	
14			
15		study site	
16			
17			
18			
19	Data access	Statement of who will have access to the final trial	12
20			
21		dataset, and disclosure of contractual agreements	
22			
23		that limit such access for investigators	
24			
25			
26	Ancillary and post trial	Provisions, if any, for ancillary and post-trial care,	n/a
27			
28	care	and for compensation to those who suffer harm	
29			
30		from trial participation	
31			
32			
33			
34	Dissemination policy:	Plans for investigators and sponsor to	11
35			
36	trial results	communicate trial results to participants,	
37			
38		healthcare professionals, the public, and other	
39			
40		relevant groups (eg, via publication, reporting in	
41			
42		results databases, or other data sharing	
43			
44		arrangements), including any publication	
45			
46		restrictions	
47			
48			
49			
50			
51	Dissemination policy:	Authorship eligibility guidelines and any intended	12
52			
53	authorship	use of professional writers	
54			
55			
56			
57			
58			
59			
60			

1 Dissemination policy: Plans, if any, for granting public access to the full 12
2
3 reproducible research protocol, participant-level dataset, and statistical
4
5 code
6
7

8 Appendices

9
10
11 Informed consent Model consent form and other related Supplemental
12
13 materials documentation given to participants and authorised material
14
15 surrogates
16
17

18
19 Biological specimens Plans for collection, laboratory evaluation, and n/a
20
21 storage of biological specimens for genetic or
22
23 molecular analysis in the current trial and for future
24
25 use in ancillary studies, if applicable
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60