Title:	**In-silico trials of targeted screening for abdominal aortic aneurysm using linked healthcare data: Can the efficiency of the NHS Abdominal Aortic Aneurysm Screening Programme be improved whilst maintaining publicly acceptable levels of disease detection in an ethically acceptable manner.**
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Sponsor:	**University of Leicester**
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Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and / or Sponsor.

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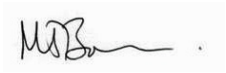
Principal Investigator signature: 

Date: **25/02/2025**

Contents

Section 1

1.1: Amendment History

Substantial Amendment 1: December 2018

Change of CI from Mr D Sidloff to Professor M Bown

Change of primary care datasets for data linkage

Revised data linkage methods

Substantial Amendment 2: July 2022

Change of study title

Addition of plain English and scientific summaries

Change of investigators

Addition of funder details

PPI section updated

Change of primary care datasets: reversion to Clinical Practice Research Datalink

Revised methods section

Additional of qualitative study (medical ethics)

Substantial Amendment 3: March 2023

Change of qualitative evidence synthesis method and the searched databases in the systematic literature review in the Qualitative Study

Addition of second wave of focus groups/ interviews and a fourth category of focus groups with members of the public in the Qualitative Study

Change in the inclusion criteria for the Qualitative Study to include members of the the public

Addition of communication/invite route details for the Qualitative Study

Substantial Amendment 4 May 2023

Inclusion of study documents: Four set of topic guides for the focus groups in the Qualitative study, one for each category of focus group, depending on participant type: 1) Men who attended AAA screening; 2) men who did not attend AAA; 3) men who will be invited for screening in the next five years, and 4) members of the public.

Changes to the protocol wording:

1) Modification of the protocol wording to reflect that the topic guides for the focus group have been submitted to HRA for review.

3) Modification of the protocol wording to specify the process of recording consent when this has been provided by email in concordance with the process reflected in approved PIS for Patients (22/02/2023, v.2.0) and PIS for Members of the Public (22/02/2023, v.1.0)

Substantial Amendment 5 September 2024

1) Data flow:

Changes resulting from Public Health England (PHE) being disbanded in 2021 and the NHS AAA Screening Programme management moving from PHE to NHS England require the data linkage process and data flows to be updated.

2) Change to the date range and therefore the number of results to be analysed from the NHS AAA Screening Programme
3) Focus Group recruitment – addition of Be Part of Research NIHR platform
4) Focus group and interview data – clarification of analysis
5) Inclusion criteria – removal of the age of 65 years at time if invitation as screening invite can be received at the age of 64
6) Literature review – New change of qualitative evidence synthesis method from meta-ethnography to thematic synthesis.

Non - Substantial Amendment 3 February 2025

Change in Figure 1 flow diagram in the protocol. Wording changed in boxes 7 c and 9 from pseudonymised to effectively anonymised as requested by CPRD. Change of wording in the protocol from pseudonymised to match this.

1.2 Abbreviations

AAA – Abdominal Aortic Aneurysm
CAG – Confidentiality Advisory Group
CI – Chief Investigator
CPRD – Clinical Practice Research Datalink
DSCRO – Data Services for Commissioners Regional Offices
EMIS – Egton Medical Information Systems (a primary care clinical informatics system supplier)
GP – General Practitioner
GPES – General Practice Extraction Service
HRA – Health Research Authority
HTA – Health Technology Assessment
ICH - International Conference on Harmonisation
IG – Information Governance
INPS – In Practice Systems (a primary care clinical informatics system supplier)
IRAS – Integrated Research Application System
ISP – Information Security Policy
ISAC – Independent Scientific Advisory Committee
NAAASP – NHS AAA Screening Programme
NECSWS – NEC Software Solutions (clinical informatics system provider for the NAAASP)
NHS – National Health Service
NHSE – NHS England
NIHR – National Institute for Health Research
PPI – Patient and Public Involvement
QOL – Quality of Life
RFS – Research File Store
SCWDSCRO – South Central and West DSCRO
TPP – The Phoenix Partnership (a primary care clinical informatics system supplier)
TRIPOD - Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
UK – United Kingdom

1.3 PLAIN ENGLISH SUMMARY:

Background: An abdominal aortic aneurysm (AAA) is a swelling of the main blood vessel in the body, the aorta. If an AAA gets too large it can burst (rupture) and cause internal bleeding. This is usually fatal. If they are found before they burst, AAAs can be repaired by having an operation. To reduce the number of people dying from ruptured AAA the NHS offers AAA screening to men at the age of 65, about 280,000 men each year. 1 in 100 men are found to have an AAA. This screening programme costs the NHS about £7.75 million per year. Much of this cost is spent on screening the 99% of men who do not have AAAs however.

Smoking is the main risk factor for AAA. As the number of people who smoke has decreased over time, AAAs are also becoming less common. In 2010, 1.50% of men screened by the NHS had an AAA and this fell to 0.97% in 2019. As AAAs become less common, AAA screening costs more per person found to have an AAA. Eventually the NHS will not be able to justify spending money on AAA screening.

An alternative, more cost-effective approach is to only invite men for AAA screening if they are at high risk of having an AAA. This is done in the United States where only men who are current or ex-smokers are invited for AAA screening. This reduces the number of men who are screened. It is not known if this approach misses many men with AAAs in the group who are not offered screening.

Research plan: In this research we will analyse results from the NHS AAA Screening Programme from 2013-2024. General practice records will be obtained for around one fifth of the men invited for screening using a process that ensures all men remain anonymous to the research team. By combining the results of AAA screening with general practice records we will work out what would have happened if only men with known risk factors for AAA had been invited for AAA screening. This work will be extended to see if there are other details in general practice records that can be used to identify men at high, or low risk of AAA. This information will be used to see if AAA screening can be targeted at groups of men who are at a high risk of having an AAA and, if so, whether such a targeted screening programme will still identify the majority of men with AAAs. The ethics and acceptability of targeted screening will be explored with members of the public.

Public involvement: This research has been planned with the public to find out what is important for those who might be affected by changes to the AAA screening programme. This identified that the main consideration in this research is to make sure that any targeted screening programme still diagnoses the majority of people with AAAs. During this research we will continue to consult with the public to ensure our work is relevant to those who will be affected by any recommendations resulting from this research.

Sharing our findings: The results of this research will be made available to the public and to researchers. We have good links with UK public health bodies that will ensure the results of this research are acted upon.

Impact: This research will find out whether a new, more economic, way of delivering AAA screening programme can be designed that is acceptable to the public.

1.4 SCIENTIFIC SUMMARY:

Research question: Can the effectiveness of abdominal aortic aneurysm (AAA) screening be improved by targeting screening at individuals most likely to have an AAA, whilst ensuring that AAA detection rates remain acceptable to patients and the public?

Background: Screening for AAA is both clinically and economically effective. The main determinant of this effectiveness is disease prevalence. AAA prevalence is decreasing over time, steadily reducing the efficiency of the current NHS AAA Screening Programme (NAAASP) screening policy. One alternative to whole population screening is targeted screening of high-risk groups such as smokers. Whether this would detect a clinically and publicly acceptable proportion of disease, and whether it would improve cost-effectiveness is unknown.

Aim: To determine the clinical outcomes and cost-effectiveness of targeted AAA screening.

Objectives: 1) Explore the ethical implications and public acceptability of targeted AAA screening; 2) Link individual mens' NAAASP screening records to primary care records and prepare the linked dataset for analysis; 3) Use the linked dataset to undertake in-silico trials of targeted AAA screening including long-term clinical and economic effectiveness modelling.

Methods: Rather than conduct an expensive and time consuming randomized trial to directly test targeted screening, we will undertake in-silico trials of targeted AAA screening. To determine success criteria for the in-silico trials, and as a specific research output, the ethics and issues around acceptability of targeted screening will first be explored using qualitative measures. To perform the in-silico trials individual mens' outcomes from the NAAASP (2013 to 2024, ≈3,100,000 men, 1% with AAA) will be linked to primary care data from the Clinical Practice Research Datalink (CPRD) (20% overlap of records). Risk factors for AAA will be used as targeted screening criteria in in-silico trials, with diagnostic accuracy as the primary outcome. Trial results will be used to re-parameterise a discrete event simulation model of AAA screening to estimate the long-term (30 year) clinical and economic effectiveness of the targeted screening.

Anticipated impact and dissemination: We expect this project to have a direct and significant impact on NHS, UK and worldwide AAA screening policies. Our dissemination strategy will be to target those involved in screening policy decisions. The results of the research will be disseminated via our contact networks directly to Public Health England and the other UK AAA screening stakeholders, including an evidence review submission to the National Screening Committee. We will use conventional media as the main route for public dissemination as this is the most effective way to reach those affected by this research. Academic audiences will be reached through peer-reviewed publications, conference presentations and online electronic dissemination.

Section 2 - Background and Rationale

AAA is a significant cause of mortality and morbidity. In England and Wales each year AAA rupture causes over 4,000 deaths and over 8,000 patients undergo surgical AAA repair to prevent rupture. The MASS trial of AAA screening demonstrated a 52% reduction in AAA-related mortality in men screened for AAA(1) and this led to the introduction of screening for men aged 65 across the UK(2) and elsewhere. Further trials performed since the MASS trial have confirmed the long-term effectiveness of screening in reducing the risk of dying from ruptured AAA and an additional benefit in terms of all-cause mortality in men who attend for screening(3). Screening men for AAA is cost-effective at current disease prevalence(4), however re-organization of the programme may both improve and maintain effectiveness, protecting this service that is valued highly by patients and the public.

Whole population AAA Screening is inefficient because of low disease prevalence: The NHS AAA Screening Programme (NAAASP), which is the biggest provider of AAA screening in the UK and most relevant to this application, invites all men in the year of their 65th birthday for a one-off ultrasound scan to screen for AAA. Around 280,000 men are invited each year at a cost of approximately £7,755,000(5). In the 2018/19 screening year, 292,629 men were invited for screening and 237,416 men attended (81%). In those who attended 1% (2309) were found to have an AAA(6). The majority of men screened for AAA do not have an aneurysm and therefore a significant proportion of the cost of screening is spent on screening these men who do not have disease. Unnecessary screening of healthy individuals has both considerable financial implications and negative psychological effects(7).

Reducing AAA prevalence threatens de-commissioning of AAA screening: AAA prevalence is the key determinant of screening cost-effectiveness. NAAASP strategy is cost-effective at current prevalence(4), but AAA prevalence in NAAASP is lower than that in the MASS trial, the key study on which current AAA screening practices are based, and is reducing over time(8) (**Table 1**). As disease prevalence falls over time screening will become less and less cost-effective. Ultimately this may result in de-commissioning of the programme and places those men with occult AAA at risk of death from AAA rupture.

Screening year:	**2013/14**	**2014/15**	**2015/16**	**2016/17**	**2017/18**	**2018/19**
Men invited for screening:	300,889	293,779	284,583	281,575	282,583	292,629
Men attending for screening:	235,409	233,426	227,543	223,371	222,887	237,416
Attendance:	78.24%	79.46%	79.96%	79.33%	78.87%	81.13%
Men with AAA (>3.0cm):	2,941	2,773	2,549	2,387	2,232	2309
AAA prevalence:	**1.25%**	**1.19%**	**1.12%**	**1.07%**	**1.00%**	**0.97%**

Table 1: Reducing prevalence of AAA over time in the NHS AAA Screening Programme. Numbers of men invited for and attending for AAA screening, and prevalence of AAA between 2013 and 2019.

A recent analysis by Glover et al. estimated that the critical threshold for cost-effectiveness of AAA screening is a disease prevalence of 0.35% amongst those screened[3]. A newer discrete event simulation model of AAA screening has shown that the threshold prevalence for AAA screening cost-effectiveness could be as high as 0.55%(9). Whilst current prevalence is higher than both of these estimates at just under 1%, the falling AAA prevalence in NAAASP suggests that AAA screening may become unviable for the NHS within the next 10 to 15 years. Recent negative analyses of AAA screening(10, 11), also contribute to the clinical argument against AAA screening. Therefore it is even more important to investigate alternative screening strategies now, well before prevalence falls to a level where screening is ineffective on economic grounds alone.

Targeted AAA screening has the potential to improve cost-effectiveness and ensure the longevity of the AAA screening programme but needs to be tested. Any targeted screening strategy is likely to be based, at least in part, on AAA risk factors such as smoking. Targeted screening is unlikely to detect the same proportion of disease as a whole population screening strategy. In the case of AAA screening this means some men who would have been offered screening in a whole population screening programme will not be offered screening and will be at risk of fatal AAA rupture. There is therefore the potential for stigmatisation, inequity and loss of justice with targeted screening. The public acceptability of, and ethical issues raised by, targeted screening therefore require exploration.

In this research we will first seek to understand the ethical aspects and public acceptability of targeted screening through a qualitative literature review and focus group discussions. The outputs from our focus group work will be used to set the success criteria for the later quantitative analyses and frame our overall project results. To determine the clinical and cost-effectiveness of targeted AAA screening, rather than conduct an expensive and long randomized trial, we propose to use a statistical modelling approach using real-world screening data to investigate targeted AAA screening. We will link individual-level patient data from the NAAASP and English primary care practices for the 3.1 million men invited for AAA screening in the 11 screening years from 2013 to 2024. We expect to have primary care data for at least 20% of these men. Screening outcomes will be compared between those men with established and proposed risk factors for AAA, such as smoking, hypertension, hyperlipidaemia, diabetes (protective factor), high cardiovascular risk scores, and those men without risk factors. These data will be used to re-parameterise an established discrete event simulation statistical model of AAA screening to determine the clinical and cost-effectiveness of targeted AAA screening.

Why is this research needed now?

Our previous Patient and Public Involvement (PPI) work in AAA screening has identified that the public strongly value AAA screening. Ensuring that AAA screening continues in the future is a priority for patients. We have specifically explored the concept of targeted AAA screening as part of the PPI programme for our previous NIHR funded AAA screening research projects (HTA 14/179/01 and RfPB PB-PG-0614-34024). This work has shown that there is public support for a targeted approach to AAA screening, particularly if this is required to maintain NHS funding for AAA screening. The limitation of this previous work is that it is based on established PPI groups who all have an interest in AAA screening. It may be that the opinions expressed are not generalizable to the general public.

In 2017 the Vascular Society of Great Britain and Ireland conducted a research priority setting process using James Lind Alliance methodology. Optimisation of AAA screening was identified as the highest ranked research priority in the area of screening. This top priority ranking was consistent across Vascular Surgeons, Vascular Nurses and Vascular Technologists. This research directly addresses this identified research priority.

Targeted screening for AAA will have significant financial benefits for the NHS. Our previous financial modelling has shown that the screening examination is the main contributor to the costs of screening programmes, with the costs of emergency surgery in those in whom AAAs are missed at screening making only a very small contribution to the overall cost of screening. This has to be balanced with the main drivers of clinical effectiveness, the prevention of death due to AAA rupture and the reduced need for emergency surgery.(4, 5) If screening cohort sizes were halved by targeting screening at current and ex-smokers, this would save the NHS around £3.5m per annum in screening costs.(5)

The methods to be used in this research are transferable and relevant to other clinical areas, both within and outside of screening. The concepts, pathways and processes of using available NHS-wide data to model refinements to a national clinical programme is novel and this research is likely to be a model for a broad range of data-driven monitoring, quality improvement, and service refinement projects in the future.

Review of existing evidence:

Targeted AAA screening:

Smoking is the most important risk-factor linked to AAA development. One option to improve cost-effectiveness is to target screening at high-risk groups such as smokers,(12) a strategy used in the US Veterans' Administration AAA screening programme, and one that would reduce the number of men being invited for screening in NAAASP by around 45%.(13) This approach is reinforced in the recent United States Preventative Services Taskforce (USPTF) recommendation to only offer AAA screening to men with a history of smoking.(14) The USPTF also state that offering AAA screening to men who have not smoked is only of marginal net benefit and should not be routinely offered.(14) Targeting AAA screening towards men with a primary care record indicating a history of smoking may improve cost-effectiveness(12) but it is not known if this strategy might miss a clinically important number of men with AAAs at screening or what the downstream effects on AAA-related mortality would be.

Strategies for targeted AAA screening have previously been investigated in the Australian(15) and Danish(16) screening study datasets. Whilst these studies both concluded that disease detection rates for targeted screening were too low to be acceptable, these studies were based on a different age range of men than that invited in NAAASP, were performed at a time when disease prevalence was higher, and did not examine the use of primary care data as a method for cohort identification. Furthermore, no cost-effectiveness analyses were performed in either study and no other economic assessment of targeted AAA screening has ever been performed. There have been no prospective randomized controlled trials of targeted screening for AAA.

Is targeted AAA screening feasible within the current NHS digital infrastructure?

In the NHS, primary care data is used as the main method to identify cohorts for screening in targeted screening programmes. The Diabetic Eye Screening programme provides the best example of this process and one that is relevant to AAA. In the Diabetic Eye Screening programme primary care records are interrogated on a national scale using the NHS Digital General Practice Extraction Service (GPES) to identify the appropriate cohort for screening. The same process and legal pathway could therefore be applied to identify high risk cohorts for AAA screening.

What demographic or clinical factors might be used to target AAA screening in the NHS?

AAA shares many risk factors with other cardiovascular diseases. Established risk factors for AAA are age, male sex, smoking and a family history of disease.(17-19) Hyperlipidaemia and hypertension are also associated with risk of AAA.(20-22) More recently, observations from screening programmes have identified associations between obesity/body mass index, systolic blood pressure, lipid levels and lifestyle factors such as reduced physical activity with AAA.(23, 24) In some cases, these associations are disputed however.(25) In stark contrast to other cardiovascular diseases, there is an inverse relationship between diabetes and AAA,(26, 27) and diabetes is also associated with slower disease progression.(28) Empirical screening and clinical studies have demonstrated high prevalence of AAA in those with prevalent cardiovascular disease.(29-33) AAA is strongly linked to ethnicity with non-white ethnic groups having a much reduced prevalence of disease.(25, 34, 35) All of the above are routinely recorded in primary care and could be used to define risk groups for targeted AAA screening. Family history of AAA is not routinely recorded in any NHS records and is the only significant risk factor(36) for AAA that is currently unavailable for targeted AAA screening strategies in the NHS.

2.1 Patient and Public Involvement supporting this research

In order to determine the acceptability of this research proposal to patients and the public the details of this project were presented to the NIHR Leicester Biomedical Research Centre's PPI committee in November 2012. The PPI group felt that this was an appropriate use of pseudonymised data. Total anonymization was discussed but the patients felt that some form of decryption should be possible by NAAASP in the case that the research identified important information of clinical relevance to the men included in the study. The committee felt that the information governance safeguards should prevent release of the data to commercial companies without the consent of the men involved in the study and that any outputs of the research should not be commercially exploited.

The project was re-discussed with the NIHR Leicester Biomedical Research Centre's PPI group in June 2018 with respect to the new datasets to be linked with, and the new linkage process established (substantial amendment 1). A further public engagement event was held in October 2018 where the project and processes were discussed with a group of 65 men and partners/family members at the Leicester NAAASP patient education forum for men with small AAAs. All those present approved of the revised data linkage process and the project overall.

In late 2018, in response to a request from the HRA CAG a further round of public engagement was undertaken to broaden the geographical and demographic reach of our activities. This public engagement process was based around the provision of information

about the research online and the dissemination of a link to the study website (www.le.ac.uk/vass) via paper flyers to research participants included with annual materials sent to participants in other studies in this disease area and social media.

The study website holds information about the study methods and processes described in our previous protocol which we used as an example of our data sharing process. We created a short video explaining the previous data linkage process for web page visitors to view as well as providing written information about the research. Embedded in the website was a short survey for visitors to complete if they wish to do so. It is via this survey that we assessed public opinion on the acceptability of data sharing for research, including the issue of obtaining pseudonymised data for research.

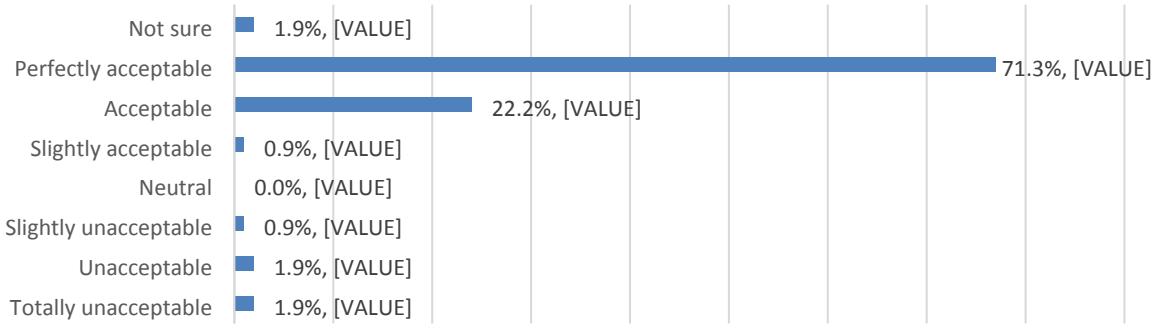
The information on the website and the survey were designed with our NIHR BRC PPI group. One issue identified during this process was that public understanding regarding the terminology used to describe the various stages of de-identification. For example, our PPI group did not understand the term 'pseudonymisation' without explanation. This makes designing and presenting information about this research in a concise and engaging manner somewhat challenging. The resultant materials and survey therefore represented the study in the way that was deemed relevant and accessible by our PPI group. This resulted in the use of some terminology that would not be used by information governance experts.

The survey was closed on 1/2/19, after receiving 110 responses (48 women (44.4%) and 60 men (55.6%)). Sixty (55.6%) of the respondents were resident in the East Midlands, with all but 2 others being resident in other regions of England. 62.1% of respondents were 50 years or older.

The questions we asked were as follows:

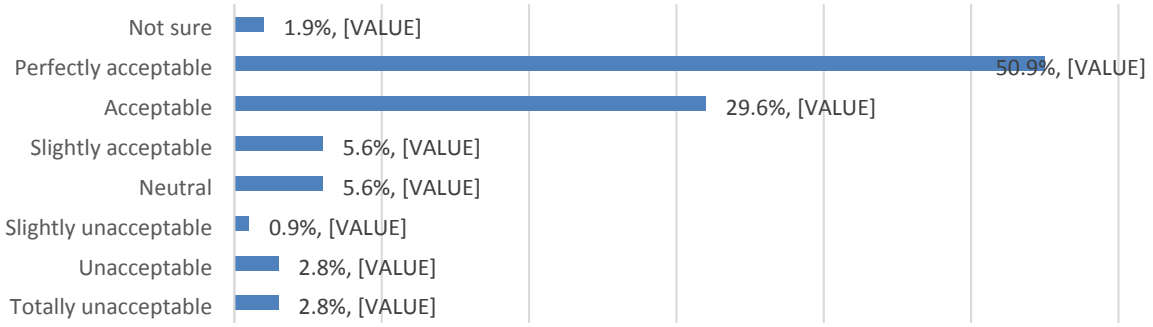
"Question 1: The NHS gathers information about people when they attend their GP or a hospital. This information is gathered in order to provide medical care for you. This information can be effectively anonymised by removing all identifiable information such as name, address and date of birth. Do you think it is acceptable for medical researchers at UK academic institutions such as the University of Leicester to be able to use anonymised NHS data for medical research?"

The responses to this question are shown below. In this and the following figures the bars represent the percentage of responses in each category. The numbers at the end of each bar represent percent and number of responses in that category:



“Question 2: Each part of the NHS stores its own set of information. By combining information about people from different parts of the NHS we can perform more sophisticated medical research but this requires the transfer of NHS numbers between different NHS bodies. In the research we are proposing, the NHS numbers for men who have been screened for abdominal aortic aneurysms would be securely transferred from the NHS Abdominal Aortic Aneurysm Screening Programme to NHS Digital, the central data repository for the NHS. Do you think it is acceptable for different parts of the NHS to share peoples' NHS numbers for medical research purposes?”

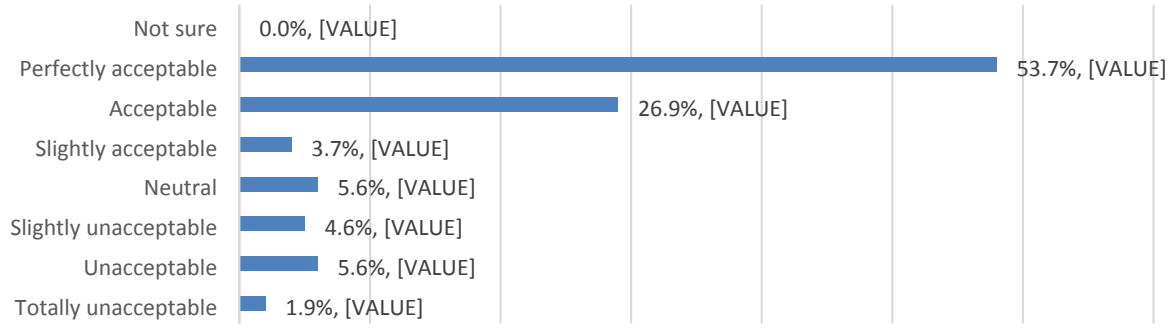
Responses:



“Question 3: In this research we are planning to use information gathered by the NHS Abdominal Aortic Aneurysm Screening Programme for medical research. When men are invited for AAA screening they are asked by the NHS AAA Screening Programme if they give their permission to be contacted about research. The

Screening Programme asks for this permission using the following text: "To contact you, asking whether you will allow us to use your personal information for research purposes". In our research we are not going to use any personally identifiable information (name, address, date of birth). What we want to do is to use data from the screening programme that has had all personally identifiable information removed before it is transferred to us at the University of Leicester. We want to do this research without contacting all the men who have been screened in the past to ask if this is OK. Do you think it is acceptable to undertake this research without re-contacting men who have been invited for abdominal aortic aneurysm screening?"

Responses:



This PPI work is supportive of the research proposed in this protocol.

2.2 Objectives

The aim of this research is to determine the clinical and economic effectiveness of targeted AAA screening in comparison to the current NAAASP strategy.

The main objectives of our research are as follows:

1) Link individual mens' NAAASP screening records to their individual primary care records and prepare the linked dataset for analysis.
2) Determine the primary care record risk factors for screen-detected AAA and establish targeted AAA screening criteria. This will include the development of a multivariable AAA risk prediction model for screen-detected AAA. The feasibility of using primary care risk factors as criteria for AAA screening cohort selection will be assessed by measuring if men with screen-detected AAA are represented in primary care records, how contemporary their primary care record entries are in relation to screening invitation dates and how complete their primary care records are for the risk factors identified.
3) Undertake in-silico trials of targeted AAA screening. The diagnostic accuracy (AAA diagnosis) of targeted AAA screening based on AAA risk factors and the primary care risk model will be compared with whole population screening. The long-term harms, benefits, clinical and economic outcomes of targeted screening compared to whole population screening will be estimated using a discrete event simulation model.

Alongside these objectives we will undertake a qualitative study to explore the ethical issues around targeted screening. This will be used to help frame the results of our research in a publicly relevant manner.

2.3 Study design

In this research to undertake a quantitative analysis of targeted AAA screening we will link individual patient screening outcome data for over 3,100,000 men screened for AAA between 2013 and 2024 by the NAAASP to individual mens' primary care records available in the Clinical Practice Research Datalink (CPRD). This dataset will be used to determine the clinical outcomes of targeted AAA screening strategies had these been used. An established statistical model of AAA screening will be used to compare the long-term harms, benefits, clinical effectiveness and cost effectiveness of targeted screening with the current population screening strategy.

This research will be conducted in 3 separate work packages:

Work package 1 (WP1): Linkage of 2013 to 2024 AAA screening individual patient screening outcome data with primary care records from the CPRD. Dataset cleaning and processing of primary care coded data into research-ready 'clinical' data.

Work package 2 (WP2): Identification/confirmation of AAA risk factors for screen-detected AAA in primary care records. Establishment of hypothetical targeted screening strategies based on these risk factors, including building a primary care risk prediction model for screen-detected AAA.

Work package 3 (WP3): In-silico diagnostic accuracy trials of the hypothetical targeted screening strategies identified in work package 3. Update an established discrete event simulation model of AAA screening. Use the outputs from the in-silico trials as new model parameters to estimate long-term changes in benefits, harms and cost-effectiveness of targeted screening vs whole population screening.

A complementary qualitative study of the ethics and acceptability of targeted screening for AAA will be run alongside the above three work packages.

2.3.1: Dataset preparation (work package 1)

Work package 1 consists of 2 tasks:

- Task 1.1 - Individual mens' data from the NAAASP will be linked with individual primary care records.
- Task 1.2 - The linked dataset will be prepared for analysis, including the conversion of coded primary care data into clinically meaningful research-ready data.

In order to describe this work package, it is first necessary to describe the data sources for this linkage.

NHS AAA Screening Programme data:

We have permission from the NAAASP to link screening outcomes data for the screening years 2013/14 to 2023/24 (inclusive) to primary care data. The NAAASP records screening invitation dates, screening attendance dates and screening outcomes (aortic diameter) for all men invited for AAA screening. NHS number is used as a unique identifier in the dataset. Data is currently available for 11 screening years (2013 to 2024). In the 6 years from April 2013 to March 2019 the NAAASP invited 1,736,038 men for screening and detected 15,191 AAAs (**Table 1**, above). With five additional year's data, we expect to have screening records for over 3,100,000 men invited for screening and over 31,000 men with AAAs.

Proportion of AAA screening records with primary care data available for linkage:

Primary care data will be obtained from CPRD. CPRD records consist of electronically coded records of registrations and consultations in primary care. Detailed descriptions of both CPRD GOLD and CPRD Aurum have previously been published(52, 53) and additional details are available on the CPRD website.(54) CPRD has provided data for over 2400 peer-reviewed publications to date. Coding of clinical events in CPRD has been both technically and clinically validated.(55-58) There are published methods for generating clinical events from coded primary care data such as CPRD.(59) Within the NIHR Leicester Biomedical Research Centre we have developed in-house algorithms to convert coded primary care data to research ready clinical data(60) and used these in recent research outputs.(61)

CPRD consists of two distinct databases, CPRD GOLD and CPRD Aurum. CPRD GOLD is based on data collected from GP practices using the Vision software system and CPRD Aurum consists of data from practices using the EMIS Web system. As of 4th February 2020 CPRD contained complete primary care records for 8,910,236 people in the GOLD database and 20,105,159 people in the Aurum database. 99.2% of records in the Aurum database are from people registered in England whilst 23.7% of the records in the GOLD database are from England. At the time of submission the total number of records in the combined CPRD databases that are available for linkage, and from people registered in England is estimated to be 22,064,085.

Calculating total coverage from overall figures in CPRD is complicated since the total number of records in CPRD includes both people currently registered with a GP and those previous registered (who may have died or transferred to a different practice). The total number of records in CPRD for people currently registered at a practice contributing to CPRD is 13,257,430 (10,265,548 in CPRD Aurum and 2,991,882 in CPRD GOLD). Allowing for the different geographical coverage of each database for England, this represents a current population coverage of 19.6% (13,265,430 records for England's total population of 55,464,000 June 2019 population estimate).

Based on the above, we estimate that CPRD will contain current records for a similar proportion of men invited for AAA screening in England as the overall population coverage as a minimum (19.6%). This coverage may change by the time this research is due to start. CPRD is continuing to recruit additional GP practices to add to their databases. At present CPRD contains records from a total of 1139 English practices but has a total of 1467 practices in England signed up to share data with CPRD. This means CPRD is likely to expand by up to one third its size again in the near future (a further 10% population coverage). Counter to this increase is the need to consider individuals who have exercised

their right not to have data included in data sharing for research under the national data opt out, currently at just under 3% of the population.(62)

Considering both the increase in data availability due to CPRD expansion and the decrease due to the national data opt out we estimate that at least 20% of men invited for screening between 2013 and 2024 will be currently registered with GP practices contributing to CPRD. The overall percentage of records available for linkage will be higher as records from deceased or men transferring out of CPRD practices will be available in addition.

Several other primary care datasets were considered for use in this research but discounted and/or were unavailable for linkage:

- NHS Digital General Practice Extraction Service (GPES). In our original HRA protocol we specified that the NHS Health Checks GPES extract would be used in this project. Access to this dataset for research has been withdrawn.
- The Health Improvement Network (THIN) is completely anonymised at source and cannot be linked with external datasets such as the NAAASP.
- The QResearch research governance process does not permit linkage with external datasets at this time.
- All attempts to discuss linkage with TPP's ResearchOne research group were unsuccessful.

Work package 1, task 1.1 - Data linkage:

We will undertake data linkage using an adaptation of the CPRD's established pathway and patient level data-flow model for non-standard linkages.(63) Adaptation of the previously established pathway was necessary due to the data controller for the NAAASP data set changing from Public Health England (PHE) to NHS England (NHSE) in 2021. The other important change necessitating a new data flow schema to be established was the merger of NHS Digital with NHS England in 2023. Under the previously established CPRD pathway for bespoke linkages NHS Digital acted as a trusted third party to receive individual participant data from the provider of the dataset to be linked. NHS Digital then linked the data to CPRD identifiers using a bridging file of NHS identifiers linked to CPRD identifiers, before pseudonymising the dataset and passing it to CPRD for linkage to CPRD data. This data flow now no longer relies on using NHS Digital as a trusted third party and that approach is no longer relevant as the provider of the dataset to be linked is NHSE, and NHS Digital has now merged into NHSE.

In this revised data flow model the only flows of identifiable data are under existing NHSE arrangements - from NECSWS, the clinical informatics system provider for the NAAASP to NHSE. NHSE are the data controller for this flow and NECSWS is a data processor Linkage of CPRD identifiers held by NHSE to NAAASP data, and de-identification will be undertaken by the South Central and West Data Services for Commissioners Regional Office (SCWDSCRO). DSCROs are part of NHSE, and whilst originally established to analyse,

prepare and de-identify NHSE data for distribution to regional commissioning teams, they are able to undertake data management work for NHSE as specified here.

The data linkage process/flow therefore involves the following organisations:

NHSE – NHS England, data controller for the NAAASP dataset
NECSWS – NEC Software Solutions, data processor for the NAAASP dataset
SCWDSCRO – South Central & West Data Services for Commissioners Regional Office, part of NHSE
CPRD – Clinical Practice Research Datalink, data controller for the CPRD dataset

UoL – University of Leicester, data controller

Approvals and agreements already in place for the processes involved in this linkage are:

NHSE-CPRD:

- NHSE data sharing framework contract (DSFC): CON-323906-Z3V7K
- NHSE data sharing agreement (DSA) NIC-15625-T8K6L-v1.2

CPRD HRA/CAG approval:

- CAG: 21/CAG/0008; REC: 05/MRE04/87; IRAS: 286947

An additional data sharing agreement between NHSE and CPRD, and contracts between CPRD and UoL will be required prior to data linkage commencing. NECSWS is already contracted by NHSE to manage the NAAASP clinical system, including data extraction for research purposes.

Data flow:

Data flow is shown in Figure 1 below. Where existing approvals exist (primarily CPRD CAG approval) this is indicated in the figure. Numbers in the figure correspond to the steps detailed in the written data flow description provided on the pages immediately after the figure.

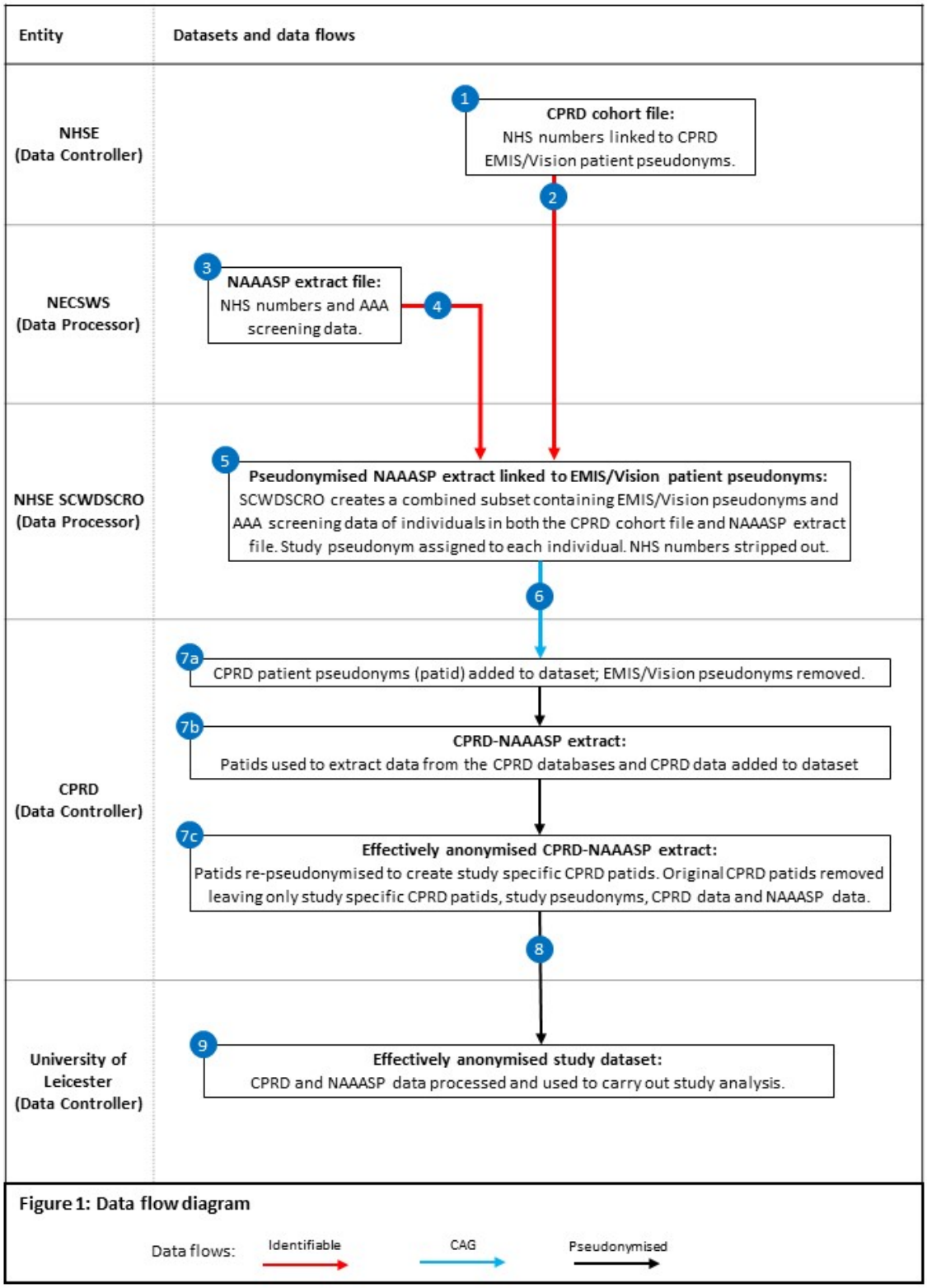


Figure 1: Data flow diagram

Data flow process:

1) CPRD cohort file containing NHS numbers and GP software (EMIS/Vision) patient pseudonym for all people included in the CPRD dataset held by NHSE.
2) NHSE will share the CPRD cohort file with the SCWDSCRO.
3) NECSWS will extract data from the NAAASP database according to the study data specification (below).
4) NAAASP extract file sent to SCWDSCRO.
5) SCWDSCRO:
   - Links the CPRD cohort file and NAAASP extract on the basis of NHS number;
   - Filters the NAAASP extract to remove men not in CPRD;
   - Adds CPRD identifiers (GP software (EMIS/Vision) patient pseudonyms) to the remaining records in the NAAASP extract;
   - Generates a new study pseudonym for each individual in the dataset;
   - Removes the NHS numbers from the filtered NAAASP extract file but retaining the study pseudonym and GP software (EMIS/Vision) patient pseudonyms. The study pseudonym will be retained so that the research team at the University of Leicester can check for individuals with multiple records in CPRD/NAAASP data.
6) SCWDSCRO will pass the data file from #5 to CPRD.
7) CPRD:
   a. Uses the GP software (EMIS/Vision) patient pseudonyms to add CPRD patient pseudonyms (patid) to the dataset; removes the GP software (EMIS/Vision) patient pseudonyms from the dataset;
   b. Adds CPRD data to the dataset: Patids used to extract data from the CPRD primary care/standard linked databases which is added to the dataset;
   c. Re-pseudonymises dataset: Creates a new pseudonymised CPRD patid (study-specific CPRD patid); Removes patids from the dataset leaving only study specific CPRD patids, study pseudonyms, CPRD data and NAAASP data.
8) CPRD passes the effectively anonymised NAAASP data, CPRD primary care and standard linked data to the University of Leicester.
9) UoL process the study dataset to undertake the academic analysis.

Individual project data flows:

The following table (Table 2) lists all the data flows for the project. Numbers in the table relate to the steps in the data flow diagram and process described above (Figure 1).

	Dataset	From	To	Identifier(s)	Privacy category
2	CPRD cohort file	NHSE	NHSE (SCWDSCRO)	• NHS number • EMIS/Vision patient pseudonym	Personally identifiable
4	NAAASP extract	NECSWS	NHSE (SCWDSCRO)	• NHS number	Personally identifiable
6	Pseudonymised NAAASP extract linked to EMIS/Vision patient pseudonyms	NHSE (SCWDSCRO)	CPRD	• EMIS/Vision patient pseudonym • Study pseudonym	Pseudonymised
8	Effectively anonymised CPRD-NAAASP extract of data for men in the NAAASP extract	CPRD	UoL	• Pseudonymised CPRD patid • Study pseudonym	Effectively anonymised

Table 2: Project data flows

Datasets:

Datasets created/transferred for each step of the process are listed and described below (Table 3). Numbers in the table below correspond to the dataflows listed in the flow diagram and process.

Step	Dataset	Description
1	CPRD cohort file	A file containing NHS numbers linked to EMIS/Vision patient pseudonym for CPRD contributing practices.
3	NAAASP extract	A subset of the overall NAAASP dataset. This is to be extracted by NECSWS as per the project data specification document (see NHSE-CPRD data sharing agreement). Note: Each individual represented in the dataset can have multiple rows of data.
5	Pseudonymised NAAASP extract linked to EMIS/Vision patient pseudonym	A subset of the NAAASP extract. This will contain AAA screening data for every man in the NAAASP dataset who is linked to a CPRD patient in the CPRD cohort file. A study pseudonym will be added for each individual in the dataset. NHS numbers will be removed leaving only EMIS/Vision patient pseudonym and study pseudonyms.
7	Effectively anonymised CPRD-NAAASP extract of data for men in the NAAASP extract	A combined dataset of the CPRD data extract for each individual in the pseudonymised NAAASP extract, and NAAASP data. EMIS/Vision patient pseudonyms replaced by study-specific CPRD patient pseudonyms (re-pseudonymised CPRD patid). Data specification according the project CPRD protocol.
9	Effectively anonymised study dataset	NAAASP outcome data linked to CPRD records for study analysis

Table 3: Datasets used in the project

The data specification for the NAAASP extract is provided below (Table 4). Any processing by NHSE/CPRD prior to receipt by UoL is listed in the table. This includes detail of which data fields will be passed directly through to UoL by CPRD.

Screening Data (NAAASP) fields to be extracted (Table 4):

Minimum dataset table	Field Code	Description of field content	Privacy category	Rationale for inclusion	Processing after transfer to NHSE
AAA Demographics	1.1.1	NHS NUMBER	Personally identifiable	To enable linkage with CPRD record key by NHS Digital	Not shared. Removed by NHSE after linkage with CPRD pseudonyms. CPRD pseudonym removed by CPRD and replaced with study specific pseudonym before passing to University of Leicester (UoL)
AAA Demographics	1.3.1.3	Year of Birth	Minimised	To calculate age at time of screening and therefore determine whether man is part of primary cohort or self-invited	Passed through to UoL
AAA Demographics	1.5	Ethnicity	Personally identifiable	Ethnicity may influence attendance for screening. Ethnicity is required to check for potential inequality introduced through targeted screening.	Passed through to UoL
AAA Appointments	2.1.4	Appointment Date	Non-identifiable	Fact and date of screening are secondary outcomes.Appointment history provides important data for health economic assessment. Appointment history also enables the analysis of what happens to men with AAA who enter the surveillance programme.	Passed through to UoL
AAA Appointments	2.1.8	Appointment Test Date/Time	Non-identifiable	Attendance for screening is a secondary outcome.	Passed through to UoL
AAA Appointments	2.1.11	Appointment Type	Non-identifiable	Appointment type required as number and attendance of surveillance appointments required for health economic analysis	Passed through to UoL
AAA Appointments	3.2.2	Clinic Type	Non-identifiable	Type of appointment required for health economic assessment	Passed through to UoL
AAA Screening	3.2.4	Clinic Site Name	Non-identifiable	Screening programme required to adjust analysis of attendance as different regional programmes have variation in invitation methods	Passed through to CPRD but processed by CPRD prior to transfer to UoL. CPRD will only pass through screening programme names for those where the base population is >1m. Screening programmes where base population is <1m will be aggregated and anonymized.
AAA Screening	3.8.5	Conclusive Test (Y/N)	Non-identifiable	Screening outcome required to assess diagnostic accuracy of targeted screening	Passed through to UoL
AAA Screening	3.12.1	Max Longitudinal Measurement	Non-identifiable	Screening outcome is the primary endpoint. The performance of targeted screening algorithms to detect AAA	Passed through to UoL

Minimum dataset table	Field Code	Description of field content	Privacy category	Rationale for inclusion	Processing after transfer to NHSE
				include or exclude men with abnormal, but non- aneurysmal aortae is an important secondary endpoint so actual diameter is required.	
AAA Screening	3.12.3	Max Transverse Measurement	Non-identifiable	Screening outcome is the primary endpoint. The performance of targeted screening algorithms to detect AAA include or exclude men with abnormal, but non- aneurysmal aortae is an important secondary endpoint so actual diameter is required.	Passed through to UoL
AAA Screening	3.23.1	Surveillance discharge decision	Non-identifiable	Discharge from surveillance is a secondary endpoint. Targeted screening algorithms that only identify men who complete surveillance if an AAA detected avoid the psychological harm of un-necessary surveillance.	Passed through to UoL
AAA Screening	3.25.2	Measurement Banding	Non-identifiable	Field required for validation of screening measurement outcomes	Passed through to UoL
AAA Referral	5.6.1	Requested Date	Non-identifiable	Referral for surgery is an important endpoint in AAA screening. A secondary analysis of the performance of targeted screening algorithms to detect only men who are referred for surgery will be performed.	Passed through to UoL
AAA Referral	6.13.1	Surgery Declined Yes/No	Non-identifiable	AAA repair and reasons for non-repair is an important endpoint in AAA screening. A secondary analysis of the performance of targeted screening algorithms to detect only men who undergo surgery will be performed.	Passed through to UoL
AAA Referral	6.13.2	Unsuitable for Surgery Yes/No	Non-identifiable	AAA repair and reasons for non-repair is an important endpoint in AAA screening. A secondary analysis of the performance of targeted screening algorithms to detect only men who undergo surgery will be performed.	Passed through to UoL
AAA Referral	7.7	Surgery Method Description (AAA)	Non-identifiable	Type of AAA repair is an important endpoint in AAA screening and informs health economic analysis	Passed through to UoL
AAA Referral	7.19.1	Date of Surgery (NVR)	Non-identifiable	AAA repair and reasons for non-repair is an important endpoint in AAA screening. A secondary analysis of the performance of targeted screening algorithms to detect only men who undergo surgery will be performed.	Passed through to UoL

Work package 1, task 1.2 - Data integration and preparation:

Following the completion of the linkage process, the combined dataset will contain effectively anonymised individual patient records detailing the results of the invitation to screening and primary care data. Data cleaning in preparation for analysis represents a considerable task. This dataset will contain data for just over 600,000 men (at least 20% of the men invited for screening). Data for both men attending and men not attending for AAA screening will be available. The CPRD data will not be precisely matched to the time of screening invitation and the coded primary care data from both the GOLD and Aurum datasets will need to be processed and harmonised into research-ready 'clinical' data.

CPRD datasets contain multiple files that detail patient demographic and registration details, the details of all consultations, referrals and therapies and other administrative data relating to individual patients. Each file is linked to a unique identifier for each patient. CPRD GOLD and CPRD Aurum have different file formats and raw data is coded differently in each dataset but can be processed to generate the same clinical variables. CPRD provide code browsers and codelists for both datasets to facilitate the generation of research data from coded data. In addition, in the NIHR Leicester Biomedical Research Centre GENVASC study(60) we have developed scripts and codelists to process coded primary care data into research-ready clinical data. These scripts can be applied to all currently available primary care coding standards such as Read version 2 and SNOMED that are used by both CPRD Aurum and CPRD GOLD. These local scripts are based on the codelist definitions used in the NHS Quality Outcomes Framework (QOF) rulesets which will ensure the applicability of this research to future NHS use. Using these processes, primary care data will be used to identify men with a primary care record indicating a history of smoking and other AAA risk factors (primarily hypertension and hyperlipidaemia(64)) that was recorded prior to the date of screening (and therefore could have been used to identify that man for a targeted screening strategy).

Records for men who only have primary care data from times after screening will be retained in the dataset but flagged for later sensitivity analyses. Some men will have records that include data from both before or after the date of invitation for screening. Data recorded after the invitation for screening will be flagged. Data processing will focus on established AAA risk factors that are available in primary care records.

2.3.2. The development of targeted AAA screening strategies (work package 2)

At the completion of work package 1, we will have an individual patient dataset of AAA screening outcomes and primary care data. The aim of work package 2 is to analyse the study dataset and determine what the main risk factors for screen-detected AAA are in primary care data and thus develop hypothetical targeted screening strategies for testing in work package 3. This work package will consist of one main task.

Work package 2, task 2.1 – Confirmation and/or identification of primary care risk factors for screen-detected AAA and the development of a primary care risk model for screen-detected AAA

Known and putative AAA risk factors (smoking, hypertension, hyperlipidaemia, diabetes (protective factor) will be tested for association with screen-detected AAA to determine their potential for use as sole criteria for targeted screening. Since it is unlikely that targeted screening based on a single risk factor will identify a large enough proportion of men with AAA to be publicly acceptable, multivariable risk modelling will be used to determine the potential for combinations of clinical variables to use as criteria for targeted screening. Such a multivariable predictive risk model for AAA This would be applied at the time of screening cohort identification using electronic health records and therefore would not need to be restricted to a small number of simple clinical predictor variables. If the final model is based on a small number of variables, adaptation for clinical and public use will also be considered. The target population for the model will be the same as the population in which it is developed ensuring the relevance of the model to future clinical practice/applicability.

The primary care-NAAASP dataset will take the form of a cross-sectional cohort study. The dataset will be of adequate size to develop and validate an AAA risk model. The outcome of interest will be the diagnosis of an AAA at screening (aortic diameter 3.0cm or more).

The dataset will be split into a training (calibration) dataset and testing (validation) dataset. Individual records will be assigned at random to training and testing datasets on a 4:1 ratio keeping a balanced split of AAA positive and negative patients in both datasets. The dataset will contain a large number of potential predictor variables. All variables will be considered for inclusion in the model and reviewed by the investigators. Continuous variables (e.g. lipid levels) will not be categorized prior to inclusion in the model. Categorization will be considered if the final risk model is simple and has the potential to be adapted for self-use by patients. Non-linear effects and interactions between variables will also be considered with variable selection techniques and clinical judgements used to select a parsimonious model. An appropriate imputation strategy will be considered accounting for the nature of the ?.

Variables will be tested for association with the diagnosis of AAA at screening. Binary logistic regression modelling with statistical variable selection will be applied to the development dataset. Appropriate model selection strategies with 10-fold cross-validation will be employed to identify predictors associated with the diagnosis of AAA at screening. Receiver operating characteristic curve analysis will be performed. According to our PPI group's clear priorities to maintain disease detection rates sensitivity will be considered as the major criterion for model performance. This success criterion and/or the success threshold may be revised depending on the outputs from work package 1. Model validation will be performed

in the validation dataset. Finally, sensitivity analyses to test variable selection assumptions will be performed. The TRIPOD checklist will be used to present results(65).

We will also investigate the options for developing a predictive risk model for AAA in a machine learning framework particularly accounting for the novel and advanced strategies of variable selection and incorporating complex non-linear relationship between predictors. The machine learning-based strategy will include an integrated approach to dimension reduction, feature selection and classification using advanced techniques like tree-based modelling, support vector machine and neural network or an ensemble of best performing models. The training and testing datasets and the model fitting and validation of the identified predictive risk model will be similar.

2.3.3. Clinical and cost-effectiveness modelling of targeted AAA screening (work package 3)

Work package 3 consists of the following three tasks:

- Task 3.1: Review and update an established discrete event simulation model of AAA screening
- Task 3.2: Conduct in-silico trials of targeted vs population screening for AAA to determine the diagnostic accuracy of targeted screening
- Task 3.3: Model the long-term effectiveness of targeted vs population screening using discrete event simulation modelling

Work package 3, task 3.1 – Review and update the AAA screening discrete event simulation (DES) model

In the NIHR HTA 'Screening Women for aortic ANeurysm' (SWAN) project(9) a new statistical model of AAA screening was developed. This discrete event simulation (DES) model allows individual screening parameters to be varied and the effect on clinical and economic effectiveness to be assessed over a 30-year time horizon. MJS and MJB were co-investigators on the SWAN project and have access to the relevant IP and computer program to be able to apply the SWAN DES model in this project. A full description of the model is given in the HTA report from the SWAN project.(9) In the SWAN project the DES was first parameterised for men and successfully validated against empirical screening programme data for men from the MASS trial as well as the previously used Markov model of AAA screening. The DES has recently been used by MJS and MJB in a commissioned review for the National Screening Committee to estimate the clinical and economic effects of varying surveillance intervals for men with small AAA in the NAAASP. This report has been published as part of a National Screening Committee authored public consultation document.(66)

Before using the DES in this project we will update relevant model parameters that may have changed over time or be affected by targeted screening strategies. A full list of the DES model parameters, including those that we will review and update is shown in Table 5. All the parameters for men have been established during the process of the SWAN project (Table 5). Where model parameters may be affected by the AAA risk factors used as the basis of hypothetical targeted screening programmes in WP3, additional clinical data will be sought to update model parameters according to the risk factors. If additional clinical data is not available sensitivity analysis will be used to model potential uncertainty.

The SWAN DES model – technical details:

The SWAN model aggregates data from multiple simulated individuals and estimates events from screening until 30 years after screening to enable long-term economic modelling. Each simulated individual has a particular set of characteristics, with the chances of an individual having a given characteristic defined by the parameters entered into the model. For example, the prevalence of AAA is one parameter entered into the model. If set at 1%, an average of 1 in 100 simulated individuals will have an AAA. The uncertainty in the parameter estimates can also be accounted for using probabilistic sensitivity analyses.

Parameter	Data source	Update required?	Data availability
Screening			
Re-invitation proportion	Parameters will be measured as outcomes from in-silico trials	N/A	Generated as part of project
Attendance proportion			
Non-visualisation proportion			
AAA size distribution at screening			
Prevalence proportion			
Proportion of AAAs detected			
AAA growth & rupture			
AAA growth	Published analysis(67)	Yes	Data available in publication
AAA rupture	Published analysis(67)	Yes	Data available in publication
Surveillance			
Surveillance intervals	NAAASP	No	
Dropout rate from surveillance	NAAASP	Yes	Available via NAAASP/published
Incidental detection rate	MASS trial	No	MASS is best available data
Delay from 5.5+cm scan to consultation	NAAASP	Yes	Available via NAAASP/published
Consultation scan	RESCAN for CT vs. US AAA diameters	No	
Decision at consultation: proportion returned to surveillance	NAAASP	Yes	Available via NAAASP/published
Decision at consultation: non-intervention proportion	NAAASP	Yes	Available via NAAASP/published
Decision at consultation: proportion elective surgery	NAAASP	Yes	Available via NAAASP/published
Delay from consultation scan to elective surgery	NAAASP	Yes	Available via NAAASP/published
Elective operations			
Proportion receiving EVAR vs. open repair	NAAASP and NVR	Yes	Available NAAASP/NVR/published
EVAR 30-day operative mortality	NVR	Yes	Available via NVR report
Open repair 30-day operative mortality	NVR	Yes	Available via NVR report
Re-intervention rate after successful EVAR	EVAR1	No	
Re-intervention rate after successful open repair	EVAR1	No	
Long-term AAA mortality rate after successful EVAR	EVAR1	No	
Long-term AAA mortality rate after successful open repair	EVAR1	No	
Emergency operations			
% operated after rupture	IMPROVE trial	No	
Proportion receiving EVAR vs. open repair	NVR	Yes	Data available from NVR
EVAR 30-day operative mortality	NVR	Yes	Data available from NVR
Open repair 30-day operative mortality	NVR	Yes	Data available from NVR
Re-intervention rate after successful EVAR	IMPROVE trial	No	
Re-intervention rate after successful open repair	IMPROVE trial	No	
Long-term AAA mortality rate after EVAR	IMPROVE trial	No	
Long-term AAA mortality rate after open repair	IMPROVE trial	No	
Costs			
Invitation, re-invitation	NAAASP	Yes	Available via NAAASP
Screening scan	NAAASP	Yes	Available via NAAASP
Surveillance scan	NAAASP	Yes	Available via NAAASP
Consultation for elective surgery	NHS Reference costs	Yes	Routinely available
Elective EVAR repair	NHS Reference costs	Yes	Routinely available
Elective open repair	NHS Reference costs	Yes	Routinely available
Emergency EVAR repair	NHS Reference costs	Yes	Routinely available
Emergency open repair	NHS Reference costs	Yes	Routinely available
Surveillance after operations	NHS Reference costs	Yes	Routinely available
Re-intervention after EVAR	NHS Reference costs	Yes	Routinely available
Re-intervention after open repair	NHS Reference costs	Yes	Routinely available
Miscellaneous			
Non-AAA mortality rate	ONS	Yes	NOMIS extract tool for ONS
Overall QoL / utilities	Population norms	Yes	Kind et al, 1998
QoL harms of screening	MASS trial	No	Already in model
QoL harms of surgery	MASS trial	No	Already in model
Discounting rates	NICE guidelines		Keep same discounting rates

Table 5: Parameters used in the AAA screening discrete event simulation model

By modelling the results for many millions of individuals the numbers of clinical events and economically relevant costs can be estimated with a good degree of accuracy for a follow-up period of 30 years after screening. In this project, the clinical events for each simulated individual will be calculated under the scenario of targeted screening being offered and compared to the scenario of the current NAAASP screening process. The model provides outputs in terms of the number of clinical events, life-years gained with screening and incremental cost-effectiveness ratios (cost per quality-adjusted life-year gained). The screening strategy can be varied in the model which thus allows new screening strategies to be compared with the existing programme.

Work package 3, task 3.2 – In-silico trials of risk factor/risk model based targeted screening

The linked NAAASP-primary care dataset will be used to test the targeted AAA screening strategies developed in work package 2. This will conform to the following clinical trial structure:

Population: Men in the year of their 65th birthday (current AAA screening population)
Intervention: Risk-factor targeted invitation for AAA screening
Comparison: Whole population screening
Outcome: Diagnostic effectiveness of targeted screening

The full range of targeted screening strategies to be tested will be determined in work package 2. As a minimum we expect to test targeted screening based on smoking history (current or ex-smoker) and other cardiovascular risk factors (e.g. hypertension, diabetes and hyperlipidaemia). Each of these risk factors will be examined as criteria for screening, both in isolation and in combination. The primary outcome for these in-silico trials will be diagnostic effectiveness (sensitivity and specificity, positive and negative predicative values, likelihood ratio, diagnostic odds ratio and area under the receiver-operator characteristic curve). Secondary outcomes will be those required to re-parameterise the DES model (re-invitations, attendance, non-visualisation, AAA size distribution at screening, AAA prevalence at screening and proportion of AAAs detected).

For each screening strategy, individuals will be categorized into invited and non-invited groups. In each of these groups, the actual screening outcomes will be known. Ultrasound has a sensitivity and specificity of over 99% as a diagnostic test for AAA. Therefore, the true detection rate will be known for each group and the overall proportional detection rate for each hypothesized screening strategy can be calculated. The primary analysis will be based on invitation for screening but because attendance rates may be different for the targeted groups compared to the overall population, analyses based on only those who attend for screening will also be performed.

Sample size calculations:

In the 6 screening years from 2013 to 2019 inclusive, 1,736,038 men were invited for AAA screening by the NAAASP, 1,380,052 men attended for AAA screening and 15,191 AAA were detected. Extrapolating the screening cohort numbers for the additional two years that

will be available by the project start date, we expect to have screening data available for over 3.1 million men in total, and over 31,000 men diagnosed with AAA. Allowing for a minimum of 20% data availability in CPRD, linked data will be available for just over 610,000 men, with over 6,000 AAA cases.

Since 2011, and funded by the British Heart Foundation, we have been recruiting men from the NAAASP into a prospective cohort study of men with AAA, the UK Aneurysm Growth Study. In this contemporary AAA cohort based on the NAAASP, 85% of men with AAA are self-reported ex- or current smokers, a figure higher than the 45% reported in Office for National Statistics reports(13). We therefore expect our most basic model of targeted screening based on smoking status alone to have a sensitivity for AAA detection of between 45% and 85%. Our risk models based on combinations of risk factors would have a higher sensitivity for the detection of AAA. Our sample size of 6,000 AAA cases has adequate power to estimate sensitivities of 70% and above with a marginal error of +/- 1.25% and sensitivities of 85% and above with a marginal error of +/- 1.00% (Hajian- Tilaki(68) method, α=0.05) (**Table 6**).

Sensitivity	Marginal error						
	2.00%	**1.75%**	**1.50%**	**1.25%**	**1.00%**	**0.75%**	**0.50%**
70%	2017	2634	3585	5163	8067	14342	32269
75%	1801	2352	3201	4610	7203	12805	28812
80%	1537	2007	2732	3934	6147	10927	24586
85%	1225	1599	2177	3135	4898	8708	19592
90%	864	1129	1537	2213	3457	6147	13830
95%	456	596	811	1168	1825	3244	7299

Table 6: Sample sizes to estimate sensitivity of targeted AAA screening strategies when compared to non-targeted screening as a gold standard diagnostic test. Calculations based on the method of Hajian-Tilaki(68). Shaded cells shown those combinations of sensitivity and marginal error for which our sample size of 5,000 cases has adequate power.

For the purposes of developing an overall risk stratification model using primary care data (work package 2), with 6,000 men with AAA (events), we have adequate sample size to build and validate a model with over 20 predictor variables (based on a 4:1 training:testing split). This is based on a conservative events per variable ratio of at least 50:1 to avoid over-

fitting(69) and to allow for statistical variable selection(70). We expect the proposed predictive risk models will include far fewer predictors than 10, and therefore, the study will have adequate power for the development, validation and testing of the risk stratification model.

Work package 3, task 3.3 – Long-term effectiveness modelling of targeted vs population screening:

The outcomes for each screening strategy (based on either AAA risk factors or the primary care AAA risk algorithm developed) will be used to populate the AAA screening discrete event simulation model to estimate long-term clinical and economic effectiveness of targeted AAA screening.

The outcomes of targeted screening from the in-silico trials (task 3.2) stage will be used to re-parameterise the discrete event simulation model. The trial outputs from each targeted screening scenario examined will be compared for their effect on long-term clinical and cost-effectiveness. Our PPI work with public groups has identified that the key study outputs to be reported are clinical events. The SWAN screening model calculates absolute numbers of clinical events for varying screening scenarios and this requirement can be satisfied through the use of this model.

Results for targeted screening strategies will be compared with the reference case scenario of whole-population invitation for screening. Model parameters other than screening outcomes may require revision as the risk factors/model being used for the hypothetical targeted screening programme being studied could feasibly influence important parameters such as surveillance drop-out rates and operative mortality. For example, a screening strategy based on smoking status or diabetes would require adjustment of growth parameters accordingly. Generating estimates for such parameters based on AAA risk groups may be challenging due to the paucity/inaccuracy of data available for such an exercise, particularly when risk factors may be used in combination. If suitable clinical data is available it will be used but if not relevant parameters will be varied in a series of sensitivity analyses.

Clinical results will be presented as changes to the number of clinical events, principally proportional AAA detection and AAA mortality but including the effect of quality-adjusted life years. The model outputs allow an assessment of incremental harms of screening due to individual clinical events such as AAA rupture and AAA repair. Cost effectiveness results will be presented as the difference in incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (INMB) between targeted screening and whole population screening.

Sensitivity/additional analyses:

In the methodological and analysis phases of this project there are several areas where alternative methodologies exist or variable clinical definitions are used. In order to explore

the strength and clinical applicability of our results, we will conduct a range of sensitivity analyses.

The interpretation and processing of coded primary care datasets can be complex. There are several different proposed methods for establishing smoking status for example(59, 71). The effect of varying the methods for calculating smoking status, hypertension and hyperlipidaemia will be examined as preliminary sensitivity analyses. We will use CPRD codelists and our established in-house methods and compare these with the methods available in CALIBER(71) and those described in ClinicalCodes.org(59). Additional sensitivity analyses will be conducted for coding variations in any strong predictors of AAA identified in the risk prediction modelling exercise.

Additional analyses relating to the management and delivery of both AAA screening and vascular surgical services will be considered on a case-by-case basis. Where the research team have capacity to undertake additional analyses these will be performed (for example the effect of clinical variables obtained from CPRD on AAA growth rates).

2.4 Qualitative sub-study: Understanding the ethics and acceptability of targeted screening for abdominal aortic aneurysm

To explore ethical issues and public acceptability of targeted screening we will undertake a qualitative study of targeted screening. This will assist us with the framing of results from the project and feed into the quantitative data analyses described above. The key question that this work package will address is what degree of underdiagnosis is acceptable in AAA screening programmes if costs need to be reduced to maintain viability for the NHS. Secondarily, we will establish what are the particular qualities of the screening programme that the public value, and whether there is potential for stigmatisation with targeted screening approaches. As well as being an important independent output from research the results of this study will be used to suggest success criteria for the later quantitative work packages. These success criteria will be reviewed and confirmed with input from the PPI group. The results will also be used to frame research outputs such as our evidence review submission to the National Screening Committee. This study will take place in two stages, firstly a qualitative literature review will be undertaken to identify issues associated with targeted screening and establish themes and topic guides for the second stage of this research where two waves of focus group discussions or interviews will be used to explore the ethics and acceptability of targeted AAA screening. If required, focus group discussions will be replaced by individual participant interviews, either to follow-up with focus group participants or with additional participants who could or preferred not to attend focus group meetings.

Literature review

A literature review will be conducted to develop themes to be discussed in the later focus groups. The aims of the literature review are to 1) identify existing literature on the subject of attitudes towards targeted screening, 2) identify ethical issues relating to targeted screening in general and 3) determine if conclusions have been drawn in previous research as to aspects of screening that present personal value to individuals, including the balance between healthcare costs and clinical benefit/value of screening. Preliminary themes will be established and will be used to develop topic guides for focus group discussions. Preliminary themes will also provide the contextual background to the qualitative output resulting from the quantitative research components of this project.

Methods: The review will be registered on PROSPERO and conducted using Cochrane principles. The ApaPsycInfo, MEDLINE, CINAHL, Scopus, Web of Science and Google Scholar will be searched for articles published in the 20 years prior to the search date using terms relating to targeted screening, screening, AAA screening, qualitative/mixed methods and medical ethics (autonomy, beneficence, non-maleficence and justice). English language studies reporting the outcomes of qualitative and mixed-methods studies (where possible if data collected and analysed using qualitative methods can be identified) of targeted screening and AAA screening will be included in the review. If there is inadequate data from studies of targeted screening or AAA screening the review will be expanded to include studies of related screening programmes. Those involving neonates, children and young people will be excluded. Reference lists of retrieved articles will be searched to identify additional studies. Articles identified in the literature search will be obtained and titles/abstracts screened for inclusion in the full review. A version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for qualitative studies (https://casp-uk.net/) will be used to conduct a methodological quality appraisal of the retrieved articles. Eligible papers will be reviewed by two members of the research team and translated to

EndNote for deduplication. The following contextual data will be extracted: population, setting, country, method and analytic approach. After having applied the RETREAT framework, considering the foreseen high number of retrieved results, thematic synthesis was deemed the most suitable method for the qualitative evidence synthesis. After the screening of sources for title and abstract, the corresponding sections (findings, discussion, and conclusion) will be coded 'line-by-line' to develop 'descriptive themes' focusing on patients' experiences and perceptions of screening, as well as on reported acceptability, from which interpretive themes will be elaborated. The results of the synthesis will be reported in accordance with the ENTREQ framework to enhance the transparency in the reporting process (78). The resulting data will again be reviewed by members of the research team and the PPI group. The primary outcomes for the review will be new interpretations and conceptual insights into the acceptability and ethics of targeted screening and AAA screening.

Focus groups

Themes identified in the literature review will be used to develop topic guides for focus group discussions and/or interviews (topic guides submitted as substantial amendment 4, May 2023). People will be invited to join the study from four categories 1) men previously invited for screening who attended for screening; 2) men previously invited for screening who did not attend; 3) men who will be invited for screening in the next 5 years (men aged 59 to 63) and 4) members of the public. Men who have attended for screening represent those who have directly benefitted from screening. In this group we will include men diagnosed with AAA in screening. Men who did not attend for screening may be a challenging group to recruit but will provide important insight into the value of AAA screening and the decision-making process around attendance for screening. Men shortly to be invited for AAA screening will be used to explore factors that may influence them to attend and their overall views on being excluded from screening. Members of the public are lay individuals without personal or family experience of AAA or AAA screening representing societal diversity. Members of the public will provide insight into the general public's views of, and attitudes towards, AAA screening from those who are not directly benefited by AAA screening. Two waves of focus groups or interviews will be convened for each category; categories will include three focus groups of approximately 6-8 participants. Focus groups may be substituted by individual participant interviews where necessary or where this is preferred by the participant.

Participant recruitment:

Participants will be invited from established local cohort studies where the cohort consent includes contact for future research. In addition, mailing lists owned by the University Hospitals of Leicester NHS Trust communications team for the purposes of sharing information with members of the public who have opted in to being contacted for research purposes will be used and clinical mailing lists held by the NHS clinical services (where men have indicated their willingness to be contacted for research). Participants will be also recruited with the support of the Be Part of Research online platform for NIHR- funded studies. This is a UK-wide registry for all health and care specialties, when registering,volunteers specify the type of study and the condition they are interested in and provide consent to be contacted about research opportunities. Potential participants will also be contacted via conventional media engagement, social media and a press release to notify them about the study. In particular, we will use our Centre for Black and Ethnic Minority

Health as an avenue for recruitment to ensure diversity in our groups, particularly as ethnicity is a potential criterion for targeted AAA screening. Recognizing that recruitment of men who have not attended for AAA screening may be challenging, we will adapt an approach we have previously used successfully in this group where men were invited by the local AAA screening unit using postal invitations. Flyers, posters, letters of invitation and emails (using the text from the letter of invite) will all be used.

Qualitative methods:

Focus groups/interviews will be semi-structured and will systematically explore the themes identified in the literature review. Whilst all identified themes will be covered in the overall process it may be that some are more appropriate for participant/focus group category than another. The themes will be reviewed by the project team to determine if this is the case and if so, themes will be selected for particular categories. The theme of NHS cost saving vs underdiagnosis in targeted screening will be explored in all groups irrespective of the literature review results/ category. Informed consent will be sought from participants. After an introduction to the clinical concept of AAA screening and the current whole population screening approach, the aims of the research will be presented to the focus group/participant. This introduction will be tailored for each of the group categories. Meetings will be audio-recorded and transcribed verbatim. Interviews/focus groups will be recorded on an encrypted voice recorder. Recordings will be deleted from the voice recorder as soon as they have been transferred to the University's servers. No personal details will be stated within the recordings and a participant ID will be referenced.

Focus group and interview data will be analysed using a reflexive thematic approach assisted by NVivo software. This analytic method consists of six phases: 1) familiarisation with the dataset by listening to the recordings, reading and re-reading the transcripts while annotating analytic ideas an insights, 2) identification of relevant fragments of data for which researchers will develop preliminary 'code labels', 3) grouping and merging codes to develop broader teams, 4) theme development, 5) reviewing and refining themes, and 6) writing-up the results (73). Whilst coding and theme development will be informed by relevant sociological theories of screening and the findings of the literature review, qualitative data analysis will principally have an inductive orientation, grounded in the data, in order to explore the plurality of participants' views and experiences, a deductive approach. To help ensure that a non-biased result is achieved, outlier data collected will also be analysed. Also, an independent researcher who is not part of the study team, will also be asked to review the analysis to help minimise bias towards assumed outcomes.

Mindful of the possible harms of screening (74-76), but also that one of the potential benefits of targeted screening is in the reduction of psychological harms in screen-negative men, when analysing the data we will be alert to the potential for screening to have had positive or negative consequences. Similarly, we will specifically look for the potential for stigmatisation of invited groups in targeted screening.

Qualitative results will be presented to and discussed with the PPI group in order to obtain their views on the research findings. Together, the research team and the PPI group will craft a policy approach based on the findings with the aim of developing a set of public acceptability thresholds for the diagnostic accuracy of targeted screening to take forward into the outputs from the project as a whole.

Section 3 - Study Participants

3.1 Description

Main study: Men screened for AAA within the NHS AAA Screening programme in England for the period covering 2013-2024; specifically, screening years 2013/14, 2014/15, 2015/16, 2016/17, 2017/18, 2018/19, 2019/20, 2020/21, 2021/22, 2022/23 and 2023/24.

Qualitative sub-study: Men previously invited for AAA screening and men who will be invited for AAA screening in the next 5 years.

3.2 Inclusion Criteria

Main study:

1. All men invited to the NHS AAA screening programme in England between the period of 2013/14 to 2023/24 inclusive

Qualitative sub-study:

1. Men
2. 60-70 years old
3. Invited for AAA screening previously
   OR
4. Eligible for invitation to AAA screening in the next 5 years (age 60-64)
5. Members of the public without expert knowledge or experience of AAA or AAA screening.

3.3 Exclusion Criteria

Main study:

1. All men who do not consent for their data to be used for the purposes of research at the time of screening (NAAASP opt-out). The NAAASP will apply this opt-out at the time of dataset preparation.
2. All men who have opted out of NHS data sharing via the national opt-out scheme managed by NHSE . NHSE will apply this opt-out at the time of linking the NAAASP dataset to CPRD identifiers.

Qualitative sub-study:

1. Women
2. Men who fall outside of the age range of 60-70 years
3. Men who do not have the capacity to consent (as defined by the Mental Capacity Act 2005)

3.4 Study Procedures

Informed Consent

Main study:

This research will be primarily conducted under a Section 251 approval obtained by the Clinical Practice Research Datalink (Appendix 1). No individual participant consent will be sought.

Qualitative sub-study:

Informed consent will be obtained from each individual study participant prior to them taking part in the study. To ensure that participants are capable of giving consent for themselves, the researcher will assess participants' capacity in line with the guidance provided within the Mental Capacity Act 2005. All potential study participants will be provided with a detailed Participant Information Sheet produced for the study. The Participant Information Sheet will provide details regarding the purpose and nature of the research, what the research involves, the benefits, risks and burdens associated with participation, and the alternatives to taking part. Individuals expressing an interest in study participation will then be able to discuss the study further with the researcher and ask any questions they may have – including any further information they may require relating to the objectives and nature of the study, any possible risks associated with their participation, and the option to withdraw from the research if they change their mind. Those participants who are still interested in participation after this discussion, and meet the study's eligibility criteria, will be interviewed following a full written informed consent process. This will include signing of a consent form by participants demonstrating that they understand what their participation involves and that they have agreed to participate. Participants will have the option to provide consent electronically by signing an electronic consent form and returning it to the designated members of the team via email.

Section 4 - Codes of Practice and Regulations

4.1 Ethics

Main study: This study has Health Research Authority Confidentiality Advisory Group Section 251 approval to establish a legal and ethical basis for linking data without the consent of those patients (appendix).

Qualitative sub-study: The qualitative sub-study will be undertaken under approval from the Health Research Authority. Whilst many of the study procedures fall outside of NHS research participant identification may take place on NHS premises (e.g. poster placed in AAA screening clinic) so this sub-study is included in this protocol (formal NHS CCC will not be required for the purposes of advertising the research). Where possible Recruitment of study participants will be via non-NHS community sources/sites and media publicity. Prior permission for study promotion and direct approach to potential study participants at the community organisation sites will, therefore, be obtained from the relevant community organisations.

4.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines.

4.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

4.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

4.5 Approvals

The Investigator is responsible for submitting all substantial and non-substantial amendments to the Sponsor for review and then to the relevant regulatory authorities for approval. All approvals will be confirmed prior to implementing any amendments.

4.6 Participant Confidentiality

Main study:

All data will be handled according to the data sharing agreements between the NHS AAA Screening Programme and the respective primary care data holders. All data will be stored on the secure research server known as the Research File Store (RFS) at the University of Leicester. The RFS is a secure and

resilient server that adheres to current information governance standards and is centrally managed by the University of Leicester to ensure it is updated to meet future changes in data security standards. Data will only be accessed from a secure computer, in a locked office within a controlled access building and floor. Security of the system shall be governed by the corporate security policy of The University of Leicester (ISP available at: http://www2.le.ac.uk/offices/itservices/resources/cis/iso/Policy-Documents/Published%20PDFs/InfoSec%20Policy%20Overview.pdf). Only those researchers named on this application will have access to the data requested. Other Ethical Considerations

None.

The researchers will fully adopt all IG policies of the University of Leicester, no data will be transferred outside of the University of Leicester and no identifiable data will be used.

4.7. Data Handling and Record Keeping

Data flow including how we will avoid using identifiable data has been discussed in section 2.3 (Study design).

All data will be stored on the secure research server known as the Research File Store (RFS) at the University of Leicester, described below. Data will only be accessed from secure computers on the wired University of Leicester network.

4.8. RFS – "The Research File Store"

University of Leicester holds Cyber Essentials certification for its research storage service (Research File Store, RFS, or R: drive) accessed from its fully managed desktop/laptop service. The University of Leicester Cyber Essentials certification number is QGCE597 and can be validated on the National Register of Cyber Essentials Certified Companies.

The RFS is based on enterprise class storage. There are no removable media or systems in the solution. The RFS is housed in two secure data centres which are access controlled via swipe card and pin and monitored via CCTV. Access is restricted to essential IT Services staff. Any third-party access is supervised. The RFS is backed-up nightly to an enterprise-class backup facility in a further secure, access- controlled data centre. Backups are retained for a year in line with Backup Retention schedule.

RFS data destruction

At end of life, all RFS servers, storage systems and desktop PCs are disposed of under the University Estates Division's managed waste disposal contract to ensure the University's compliance with its WEEE obligations. This contract engages a third-party organisation to securely wipe all disks. The contracted company uses specialised software to provide secure data destruction to U.S. DoD 5220.22-M, U.S. DoD 5220.25, U.S. DoD 5200.28M and HMG (CESG) IS5 baseline and enhanced.

Section 5 - Study Governance

Data Management meetings will be held at least every 6 months.
The goal of these meetings will be to review:

- The data sharing agreements,
- Maintenance of essential documentation – i.e., ensure all named persons are up to date with all training,
- Risk management – review possible data risks,
- Access control – ensure only people who are named and require access can access the data,
- Review of Compliance – review of all of the above.

Minutes and records of the above will be kept in a data management file in a locked office.

Section 6 - Financing and Insurance

This research is funded by the NIHR HS&DR programme (NIHR130075).
There will be no NHS treatment or service support costs.

Section 7 - Project Management

Data management meetings will be held every 6 months as described in section 6. Minutes and records of the above will be kept in a data management file in a locked office. Project management meetings to discuss the research described in section 2 will be held monthly.

Section 8 - Publication Policy

The data will be published open access in scientific journals and presented at meetings nationally and internationally.

Section 9 - References

1. Thompson SG, et al. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. Br J Surg. 2012;99(12):1649-56.10.1002/bjs.8897
2. Multicentre Aneurysm Screening Study G. Multicentre aneurysm screening study (MASS): cost effectiveness analysis of screening for abdominal aortic aneurysms based on four year results from randomised controlled trial. BMJ. 2002;325(7373):1135
3. Takagi H, et al. Abdominal Aortic Aneurysm Screening Reduces All-Cause Mortality. Angiology. 2017:3319717693107.10.1177/0003319717693107
4. Glover MJ, et al. Cost-effectiveness of the National Health Service abdominal aortic aneurysm screening programme in England. Br J Surg. 2014:n/a-n/a.10.1002/bjs.9528
5. Thompson SG, et al. Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. Health technology assessment (Winchester, England). 2013;17(41):1-118.10.3310/hta17410
6. NAAASP. NHS AAA Screening Programme (online). Available: aaa.screening.nhs.uk/ Accessed January 2017.
7. DeFrank JT, et al. The psychological harms of screening: the evidence we have versus the evidence we need. J Gen Intern Med. 2015;30(2):242-8.10.1007/s11606-014-2996-5
8. Choke E, et al. Changing epidemiology of abdominal aortic aneurysms in England and Wales: older and more benign? Circulation. 2012;125(13):1617-25.10.1161/CIRCULATIONAHA.111.077503
9. Thompson SG, et al. Screening women aged 65 years or over for abdominal aortic aneurysm: a modelling study and health economic evaluation. Health Technol Assess. 2018;22(43):1-142.10.3310/hta22430
10. Johansson M, et al. Benefits and harms of screening men for abdominal aortic aneurysm in Sweden: a registry-based cohort study. The Lancet. 2018;391(10138):2441-7.10.1016/S0140-6736(18)31031-6
11. Johansson M, et al. Estimating overdiagnosis in screening for abdominal aortic aneurysm: could a change in smoking habits and lowered aortic diameter tip the balance of screening towards harm? BMJ. 2015;350:h825.10.1136/bmj.h825
12. LeFevre ML. Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(4):281-90.10.7326/m14-1204
13. Office for National Statistics.
14. Owens DK, et al. Screening for Abdominal Aortic Aneurysm: US Preventive Services Task Force Recommendation Statement. Jama. 2019;322(22):2211-8.10.1001/jama.2019.18928
15. Spencer CA, et al. The potential for a selective screening strategy for abdominal aortic aneurysm. J Med Screen. 2000;7(4):209-11.10.1136/jms.7.4.209
16. Lindholt JS, et al. High-risk and low-risk screening for abdominal aortic aneurysm both reduce aneurysm-related mortality. A stratified analysis from a single-centre randomised screening trial. Eur J Vasc Endovasc Surg. 2007;34(1):53-8.10.1016/j.ejvs.2006.12.031

17. Golledge J, et al. Atherosclerosis and Abdominal Aortic Aneurysm Cause, Response, or Common Risk Factors? Arteriosclerosis Thrombosis and Vascular Biology. 2010;30(6):1075-7.10.1161/atvbaha.110.206573
18. Lee AJ, et al. Smoking, atherosclerosis and risk of abdominal aortic aneurysm. Eur Heart J. 1997;18(4):671-6
19. Wahlgren CM, et al. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. J Vasc Surg. 2010;51(1):3-7; discussion 10.1016/j.jvs.2009.08.036
20. Tang W, et al. Lifetime Risk and Risk Factors for Abdominal Aortic Aneurysm in a 24-Year Prospective Study: The ARIC Study (Atherosclerosis Risk in Communities). Arterioscler Thromb Vasc Biol. 2016;36(12):2468-77.10.1161/atvbaha.116.308147
21. Forsdahl SH, et al. Risk Factors for Abdominal Aortic Aneurysms A 7-Year Prospective Study: The Tromso Study, 1994-2001. Circulation. 2009;119(16):2202-8.10.1161/circulationaha.108.817619
22. Kobeissi E, et al. Blood pressure, hypertension and the risk of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort studies. European journal of epidemiology. 2019;34(6):547-55.10.1007/s10654-019-00510-9
23. Stackelberg O, et al. Lifestyle and Risk of Screening□Detected Abdominal Aortic Aneurysm in Men. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2017;6(5):e004725.10.1161/JAHA.116.004725
24. Carter JL, et al. Sex-Specific Associations of Vascular Risk Factors With Abdominal Aortic Aneurysm: Findings From 1.5 Million Women and 0.8 Million Men in the United States and United Kingdom. J Am Heart Assoc. 2020;9(4):e014748.10.1161/jaha.119.014748
25. Jahangir E, et al. Smoking, sex, risk factors and abdominal aortic aneurysms: a prospective study of 18 782 persons aged above 65 years in the Southern Community Cohort Study. J Epidemiol Community Health. 2015;69(5):481-8.10.1136/jech-2014-204920
26. De Rango P, et al. Diabetes and Abdominal Aortic Aneurysms. European Journal of Vascular and Endovascular Surgery. 2014;47(3):243-61.
27. Lederle FA. The Strange Relationship between Diabetes and Abdominal Aortic Aneurysm. European Journal of Vascular and Endovascular Surgery. 2012;43(3):254-6.10.1016/j.ejvs.2011.12.026
28. Sweeting MJ, et al. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. Br J Surg. 2012;99(5):655-65.10.1002/bjs.8707
29. Jones GT, et al. Comparison of three targeted approaches to screening for abdominal aortic aneurysm based on cardiovascular risk. Br J Surg. 2016;103(9):1139-46.10.1002/bjs.10224
30. Alund M, et al. Selective screening for abdominal aortic aneurysm among patients referred to the vascular laboratory. Eur J Vasc Endovasc Surg. 2008;35(6):669-74.10.1016/j.ejvs.2007.12.014
31. Mani K, et al. Screening for abdominal aortic aneurysm among patients referred to the vascular laboratory is cost-effective. Eur J Vasc Endovasc Surg. 2010;39(2):208-16.10.1016/j.ejvs.2009.11.004
32. Hernesniemi JA, et al. The prevalence of abdominal aortic aneurysm is consistently high among patients with coronary artery disease. J Vasc Surg. 2015;62(1):232-40 e3.10.1016/j.jvs.2015.02.037

33. Koshty A, et al. Coronary Artery Disease as a Relevant Risk Factor in Screening of Abdominal Aortic Ectasia and Aneurysm. The Thoracic and cardiovascular surgeon. 2018.10.1055/s-0038-1676336
34. Salem MK, et al. Should Asian men be included in abdominal aortic aneurysm screening programmes? Eur J Vasc Endovasc Surg. 2009;38(6):748-9.10.1016/j.ejvs.2009.07.012
35. Jacomelli J, et al. Editor's Choice - Inequalities in Abdominal Aortic Aneurysm Screening in England: Effects of Social Deprivation and Ethnicity. Eur J Vasc Endovasc Surg. 2017;53(6):837-43.10.1016/j.ejvs.2017.03.006
36. van de Luijtgaarden KM, et al. Risk of abdominal aortic aneurysm (AAA) among male and female relatives of AAA patients. Vasc Med. 2017;22(2):112-8.10.1177/1358863x16686409
37. Cosford PA, et al. Screening for abdominal aortic aneurysm. Cochrane Database Syst Rev. 2007(2):CD002945.10.1002/14651858.CD002945.pub2
38. Moll FL, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.10.1016/j.ejvs.2010.09.011
39. Benson RA, et al. Screening results from a large United Kingdom abdominal aortic aneurysm screening center in the context of optimizing United Kingdom National Abdominal Aortic Aneurysm Screening Programme protocols. J Vasc Surg. 2016;63(2):301-4.10.1016/j.jvs.2015.08.091
40. Thompson SG, et al. Screening men for abdominal aortic aneurysm: 10 year mortality and cost effectiveness results from the randomised Multicentre Aneurysm Screening Study. Bmj. 2009;338:b2307.10.1136/bmj.b2307
41. Ashton HA, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet. 2002;360(9345):1531-9
42. Lesjak M, et al. Screening for abdominal aortic aneurysm: does it affect men's quality of life? Australian Journal of Primary Health. 2012;18(4):284-8.10.1071/py11131
43. Wanhainen A, et al. Low quality of life prior to screening for abdominal aortic aneurysm: A possible risk factor for negative mental effects. Ann Vasc Surg. 2004;18(3):287-93.10.1007/s10016-004-0021-x
44. Lucarotti ME, et al. Psychological morbidity associated with abdominal aortic aneurysm screening. Eur J Vasc Endovasc Surg. 1997;14(6):499-501
45. Spencer CA, et al. Is screening for abdominal aortic aneurysm bad for your health and well-being? ANZ J Surg. 2004;74(12):1069-75.10.1111/j.1445-1433.2004.03270.x
46. MacSweeney ST, et al. Pathogenesis of abdominal aortic aneurysm. Br J Surg. 1994;81(7):935-41
47. Lederle FA, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Annals of internal medicine. 1997;126(6):441-9
48. Brown LC, et al. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. Ann Surg. 1999;230(3):289-96; discussion 96-7
49. Wang S, et al. Activation of AMP-activated protein kinase alpha2 by nicotine instigates formation of abdominal aortic aneurysms in mice in vivo. Nat Med. 2012;18(6):902-10.10.1038/nm.2711

50. Sidloff D. AGES. Circulation. 2013;in press.
51. Bath MF, et al. Patients with Small Abdominal Aortic Aneurysm are at Significant Risk of Cardiovascular Events and this Risk is not Addressed Sufficiently. Eur J Vasc Endovasc Surg. 2017;53(2):255-60.10.1016/j.ejvs.2016.10.013
52. Wolf A, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International journal of epidemiology. 2019;48(6):1740-g.10.1093/ije/dyz034
53. Herrett E, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.10.1093/ije/dyv098
54. CPRD databases. [Available from: https://cprd.com/primary-care.
55. Gallagher AM, et al. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. Pharmacoepidemiology and drug safety. 2019;28(5):563-9.10.1002/pds.4747
56. Hagberg KW, et al. Validation of autism spectrum disorder diagnoses recorded in the Clinical Practice Research Datalink, 1990-2014. Clinical epidemiology. 2017;9:475-82.10.2147/clep.S139107
57. Iwagami M, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2017;32(suppl_2):ii142-ii50.10.1093/ndt/gfw318
58. Reeves D, et al. Can analyses of electronic patient records be independently and externally validated? The effect of statins on the mortality of patients with ischaemic heart disease: a cohort study with nested case-control analysis. BMJ open. 2014;4(4):e004952.10.1136/bmjopen-2014-004952
59. Springate DA, et al. ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. PLoS ONE. 2014;9(6):e99825.10.1371/journal.pone.0099825
60. Genvasc. [Available from: https://www2.le.ac.uk/projects/bru/our-research/research-themes/genetics-and-biomarkers/genvasc.
61. Lawson CA, et al. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. The Lancet Public health. 2019;4(8):e406-e20.10.1016/s2468-2667(19)30108-2
62. National data opt-outs. 2018 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/care-information-choices/mi-june-2018.
63. linkage Cdffn-s. [
64. Forsdahl SH, et al. Risk Factors for Abdominal Aortic Aneurysms. A 7-Year Prospective Study: The Tromsø Study, 1994–2001. 2009;119(16):2202-8.10.1161/circulationaha.108.817619
65. Collins GS, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 2015;350:g7594.10.1136/bmj.g7594
66. National Screening Committee. NSC public consultation on proposal to extend AAA surveillance intervals [Available from: https://www2.le.ac.uk/departments/cardiovascular-sciences/people/bown/nsc-report-on-aaa-surveillance-intervals and https://legacyscreening.phe.org.uk/aaa.

67. Oliver-Williams C, et al. Safety of Men With Small and Medium Abdominal Aortic Aneurysms Under Surveillance in the NAAASP. Circulation. 2019;139(11):1371-80.10.1161/circulationaha.118.036966
68. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. Journal of biomedical informatics. 2014;48:193-204.http://dx.doi.org/10.1016/j.jbi.2014.02.013
69. Peduzzi P, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. Journal of clinical epidemiology. 1995;48(12):1503-10
70. Wynants L, et al. A simulation study of sample size demonstrated the importance of the number of events per variable to develop prediction models in clustered data. J Clin Epidemiol. 2015;68(12):1406-14.10.1016/j.jclinepi.2015.02.002
71. Denaxas SC, et al. Data resource profile: cardiovascular disease research using linked bespoke studies and electronic health records (CALIBER). Int J Epidemiol. 2012;41(6):1625-38.10.1093/ije/dys188
72. Gale NK, et al. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology. 2013;13(1):117.10.1186/1471-2288-13-117
73. Braun V. & Clarke V. Thematic Analysis. A practical guide. London (GB): Sage Publications; 2023.
74. Heath I. Role of fear in overdiagnosis and overtreatment--an essay by Iona Heath. BMJ. 2014;349:g6123.10.1136/bmj.g6123
75. Hicks LK. Reframing overuse in health care: time to focus on the harms. J Oncol Pract. 2015;11(3):168-70.10.1200/jop.2015.004283
76. Moynihan R, et al. Preventing overdiagnosis: how to stop harming the healthy. BMJ. 2012;344:e3502.10.1136/bmj.e3502
77. Sidloff DA, et al. Cardiovascular Risk in Patients Screened for AAA. European Journal of Vascular and Endovascular Surgery. 2017;54(5):666.https://doi.org/10.1016/j.ejvs.2017.08.027

78. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Medical Research Methodology. 2012;12(1):181.

Section 10: Appendices:

1) Health Research Authority Confidentiality Advisory Group approval for linkage to take place by the Clinical Practice Research Datalink for distribution to the research team