Health Research Authority

Targeted Abdominal CT in Conjunction with Lung Cancer Screening – A Pilot Study (TACTICAL1)

FULL TITLE: Targeted Abdominal CT in Conjunction with Lung Cancer Screening – a pilot study (TACTICAL1): a randomised controlled pilot study of adding abdominal non-contrast CT to Lung Cancer Screening CT Thorax amongst high lung cancer risk ever-smokers aged 55-70.

Protocol Version: 2.1

Date: 21 July 2026

RESEARCH REFERENCE NUMBERS

ISRCTN:	ISRCTN13013437
IRAS Number:	357376
REC Reference:	25/NW/0185
SPONSORS Number:	University of Cambridge G128732
FUNDERS Number:	Yorkshire Cancer Research RA\2024\R2\107
ROO Grant Number:	G128732

This protocol has regard for the HRA guidance

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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......./...../.....

.....

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Position:

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LIST OF ABBREVIATIONS

Define all unusual or ‘technical’ terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AAA	Abdominal aortic aneurysm
AE	Adverse Event
ANCCT	Abdominal Non-Contrast Computed Tomography
AR	Adverse Reaction
CA	Cancer Alliance
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTU	Clinical Trials Unit
HNY	Humber and North Yorkshire
GCP	Good Clinical Practice
HUTH	Hull University Teaching Hospitals NHS Trust
IRM	Imaging Review Meeting
ISRCTN	International Standard Randomised Controlled Trials Number
LCS	Lung Cancer Screening
LDCT	Low Dose Computed Tomography scan
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
PACS	Picture Archiving and Communication System
PI	Principal Investigator
PIS	Participant Information Sheet

PPIE	Patient and Public Involvement and Engagement
RCC	Renal Cell Carcinoma
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SoC	Standard of Care
SOP	Standard Operating Procedure
SRCP	Secure Research Computing Platform
TMF	Trial Master File
TMG	Trial Management Group
WYH	West Yorkshire and Harrogate

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1. OVERVIEW

1.1. TRIAL SUMMARY

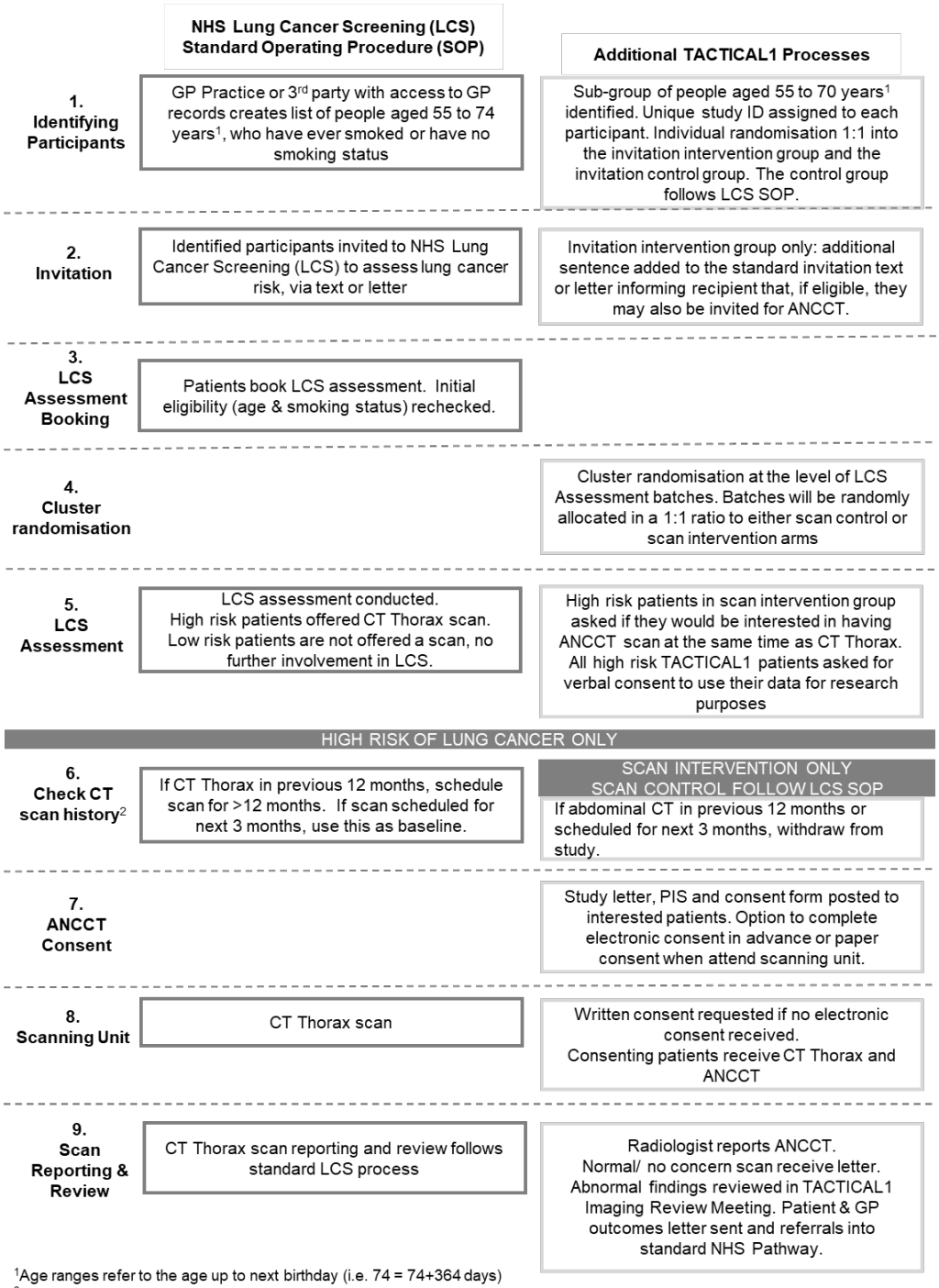
Trial Title	Targeted Abdominal CT in Conjunction with Lung Cancer Screening – a pilot study (TACTICAL1): a randomised controlled pilot study of adding abdominal non-contrast CT to Lung Cancer Screening CT Thorax amongst high lung cancer risk ever-smokers aged 55-70.
Short Title	TACTICAL1
Trial Design	A pilot study of adding abdominal non-contrast CT scanning (ANCCT) to NHS Lung Cancer Screening (LCS) Low Dose CT scan (LDCT) thorax amongst high lung cancer risk ever-smokers aged 55-70 in the first round of a West Yorkshire and Harrogate Cancer Alliance's LCS and a Humber and North Yorkshire Cancer Alliance's East Riding LCS programme. There are two points of randomisation: 1. at the individual level to receive an invitation letter for LCS (standard of care; invitation control) versus invitation letter for LCS with potential for an additional abdominal scan (invitation intervention) 2. those randomised at an individual level to the invitation intervention arm at 1) to be randomised at the cluster level, to being offered a CT Thorax only during the LCS assessment (standard of care in LCS; scan control) or offered both CT Thorax and ANCCT during this assessment (scan intervention). This pilot study includes a process evaluation.
Trial Participants	For the individual level randomisation: be invited to the first round of West Yorkshire and Harrogate's LCS or Humber and North Yorkshire Cancer Alliance's LCS (i.e. have been identified as a smoker or ex-smoker and registered as living within the LCS catchment area), and aged 55-70 years 364 days old at the date of invitation. For the cluster level randomisation: to have made an appointment for the LCS assessment and be eligible to attend for lung screening.
Primary Objectives	1. To evaluate how the invitation to being offered the potential for an additional ANCCT, if eligible, affects uptake to the LCS. 2. To assess whether participants can be successfully randomised using a cluster randomisation approach to having a CT Thorax only or having both CT Thorax and

	ANCCT scans. This is to pilot this randomisation approach with the near-future aim of a fully powered study. 3. To evaluate how adding ANCCT to the existing LCS process affects scanning throughput, and therefore, how this would impact service provision of LCS. 4. To evaluate acceptability of the additional processes required to add the ANCCT to the existing LCS process.
Planned Sample Size	Total in invitation control group (WYH + HNY LCS) = 1568+1568= 3136 people. Total in invitation intervention group (WYH + HNY LCS) = 1568+1568= 3136 people. Total in scan control group = 130-168 per site = 260-336 people. Total in scan intervention group = 130-168 per site = 260-336 people.
Follow up duration	6 months. Only undertaken for those in the scan intervention group who are reviewed at the Imaging Review Meeting (IRM) with a finding requiring further action.
Planned Trial Period	November 2024 (start of planning phase) – October 2027 (FPFV)

1.2. LCS PROCESS FLOW WITH ADDITIONAL TACTICAL1 PROCESSES

Figure 1 details the points of interaction of TACTICAL1 with the existing LCS process which are then described in more detail in section 8.

Figure 1:



[1]Age ranges refer to the age up to next birthday (i.e. 74 = 74+364 days)
[2]*In some LCS this check happens before the LCS call; in others it happens after the appointment has been made.*

1.3. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Yorkshire Cancer Research, Jacob Smith House, 7 Grove Park Court, Harrogate, HG1 4DP, Tel: 01423 501269, Fax: 01426 527929 Email: hq@ycr.org.uk	Grant funding for all study costs including study staff support.
CRUK Major Centre: Cancer Research UK Cambridge Centre [C9685/A25177 and CTRQQR-2021\100012] Contact: Karen Barker karen.barker@cruk.cam.ac.uk and NIHR Cambridge Biomedical Research Centre (NIHR203312) Contact: Lauren Basham lauren.basham@nhs.net	Funding for Chief Investigator Professor Grant Stewart.

1.4. ROLE AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUP

There will be one trial committee for this pilot study – the Trial Management Group (TMG), which will include the Chief Investigator, Project Manager, Site Principal Investigators, LCS Programme Managers from the Sites and any other person deemed to be relevant to the agenda. The TMG will oversee the day to day running of the trial, providing clinical, scientific and practical advice and monitoring the progress of the trial regularly.

1.5. KEY WORDS

Screening

NHS Lung Cancer Screening

Kidney Cancer

Abdominal Cancers

Lung Cancer

Abdominal Aortic Aneurysms (AAA)

2. BACKGROUND

Early detection of cancer allows the best chance of survival[1] [2]. For lung cancer, screening exists in the USA and was approved in 2023 in the UK by National Screening Committee and is subsequently being rolled out as a targeted screening program for high-risk ever-smokers aged 55 to 74 years 364 days[3] [4]. The Lung Cancer Screening (LCS) programme (formerly known as the Targeted Lung Health Check, (TLHC)) is delivered by Cancer Alliances on behalf of NHS England.

Adding extra tests to the LCS could help detect other diseases that might not have their own cost-effective screening programs due to low prevalence[5] [6]. One such disease is kidney cancer, which shares smoking as a risk factor with lung cancer[1], is the ninth most common cancer in men and 14th in women[1]. It is highly treatable if caught early (95% disease-free at 10 years)[7]. However, 87% of people with small kidney masses show no symptoms[1], making kidney cancer a silent disease at the curable stage. Due to this, both participants and researchers have made early kidney cancer detection a research priority[8] [9] and this led to the Yorkshire Kidney Screening Trial (YKST), which tested whether adding an abdominal non-contrast CT (ANCCT) scan to lung cancer screening to detect kidney cancer and other serious abdominal conditions could be effective[10].

In YKST, people attending the second round of lung cancer screening in the Yorkshire Lung Screening Trial (YLST) were offered an ANCCT scan in addition to their low dose CT thorax. Out of 4,438 participants, 97.1% (4309/4438) were eligible, and 93.3% (4019/4309) accepted the ANCCT, demonstrating high participant acceptability and willingness to attend screening.

Interviews with 20 participants who took up the offer of the ANCCT, five who declined, and eight healthcare professionals involved in the study showed that adding the ANCCT was generally acceptable[11]. It was found that giving participants prior notice about the scan and clear pathways for downstream management of findings will be important if it is to be offered more widely[10]. Responses from the 76% (380/500) of participants responding to a post-scan survey showed that there were no significant psychological, social, or financial differences between those with normal scans and those with abnormal scans requiring no further action. People needing further investigations or referrals had higher scores on the negative psychological consequences questionnaire than those with normal scans at 3 months, but no differences were seen at 6 months. Thus, it was demonstrated that screening for kidney cancer and other abdominal malignancies using abdominal CT alongside the thoracic CT within lung cancer screening is unlikely to cause significant lasting psychosocial or financial harm to participants with incidental findings[12].

The additional administration and procedures for YKST (including sharing the participant information video, taking consent, collecting baseline information) added 13.3 minutes to the established YLST scanning unit process but subsequent analysis identified potential ways to significantly reduce the time needed on the scanning unit to only a few minutes. Such a reduction in time will be essential to ensure that adding an ANCCT to the existing LCS scanning unit process does not impact throughput.

Overall, 5.3% of YKST participants had serious findings, including 0.25% with kidney cancer, 0.25% with other abdominal cancers, and 1.5% with abdominal aortic aneurysms (AAA). This combined

prevalence is in the range of established UK screening programmes. Non-serious (incidental) findings are key to understand in development of a new screening approach as these have the potential for harm, including overtreatment and psychological harms. However, only 340 (8.5%) participants who were eventually confirmed to have a non-serious finding requiring further evaluation (by referral to specialists or further investigations) beyond the original screening scan.

Analysis was then conducted using data from YKST, to evaluate if this targeted screening approach is likely to be cost effective in the setting of the NHS LCS programme. The results of our economic modelling study estimated that adding an ANCCT to the CT Thorax in a population aged 55-74 years, 364 days, (the age range used in LCSs) would be cost effective, resulting in an ICER of £11,851 and net monetary benefit of £47.48 per person, assuming a £20,000/QALY cost-effectiveness threshold[13]. At this threshold there is 96.8% probability that adding ANCCT is cost-effective as an add-on to the lung screen. Analysis of results by age and sex indicates that cost-effectiveness is generally higher if younger people are screened, screening is not cost-effective for people aged over 70, and screening is harmful (negative QALYs) for men aged over 75 and women aged over 79. We used this information to define the age range for future studies evaluating screening with ANCCT in addition to LCS. Screen-detection of AAA contributes most to the cost-effectiveness of screening, with detection of kidney cancer and colon cancer also contributing highly (and cancer screening remains cost effective if AAAs are removed from the model). In summary, YKST has shown that offering an additional ANCCT to participants attending for the second round of a lung cancer screening within a clinical trial setting is feasible, acceptable and cost-effective. The findings from these studies have also moved the original concept from solely screening for kidney cancer to consider multiple abdominal cancers and serious non-cancerous conditions such as AAA and highlighted several ways to improve the acceptability and efficiency of the approach. We therefore refer to this as “upper abdominal screening” rather than solely kidney cancer screening.

We now seek to demonstrate, in a pilot RCT, if this process can be rolled out into the LCS environment with a near-future view goal of undertaking a definitive RCT to assess stage shift of the major diseases identified and/or disease specific survival improvement with screening.

3. RATIONALE

TACTICAL1 aims to test the co-designed end-to-end processes required to deliver combined screening in a working LCS and evaluate how these processes work to ensure that they do not negatively impact participant uptake of the LCS assessment nor the throughput on the scanning unit, and that they are acceptable to both participants and healthcare professionals.

Furthermore, TACTICAL1 will aim to test the cluster randomisation process for participants being randomised to being offered a CT Thorax only (standard of care in LCS) or being offered both CT Thorax and ANCCT. This is to pilot this randomisation approach with the near-future aim of a fully powered study.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

4.1. Primary objectives

1. To evaluate how the invitation to being offered an additional ANCCT, if eligible, affects uptake to the LCS.
2. To assess whether participants can be successfully randomised using a cluster randomisation approach to being offered a CT Thorax only (standard of care in LCS) or offered both CT Thorax and ANCCT. This is to pilot this randomisation approach with the near-future aim of a fully powered study.
3. To evaluate how adding ANCCT to the existing LCS process affects scanning throughput, and therefore, how this would impact service provision of LCS.
4. To evaluate acceptability to participants and healthcare professionals of the additional processes required to add the ANCCT to the existing LCS process.

4.2. Secondary objectives

1. To evaluate uptake of the ANCCT amongst those participants cluster randomised to be offered it.

4.3. Table of primary outcome measures/endpoints

The primary outcome measures and endpoints are:

Primary Objectives	Primary Outcome Measures	Primary Endpoints and Success Criteria
To evaluate how the invitation to being offered the potential for an additional scan of the abdomen, if eligible, affects uptake to the LCS	Attendance rate at the LCS phone call of those receiving the TACTICAL1 invitation letter offering an additional ANCCT, if eligible, versus those sent the standard LCS invitation letter.	Attendance rate of the invitation intervention group to the LCS phone call is non-inferior to the attendance rate of the invitation control group and if so, whether it is superior.
To assess whether participants can be successfully randomised using a cluster randomisation approach to being offered a CT Thorax only or being offered both CT Thorax and ANCCT. This is to pilot this randomisation approach with the near-future aim of a fully powered study.	Successful cluster randomisation of participants into scan control and scan intervention groups.	Successful cluster randomisation of participants into scan control and scan intervention groups as demonstrated by groups of similar size and demographics.
To evaluate how adding ANCCT to the existing LCS process affects scanning throughput, and therefore, how	Number of participants scanned per day.	Average number of participants scanned per standard LCS scanning day is no different when adding the ANCCT.

this would impact service provision of LCS.	Time and motion study to evaluate impact, from invitation to scan, of adding ANCCT processes to the existing LCS processes, and impact on overall throughput of LCS Data from daily short questionnaire completed by scanning unit staff capturing perceived impact of TACTICAL activities on throughput.	A recommended standardised protocol, including a process map, detailing each task, the incremental time taken for TACTICAL1 tasks and an accompanying description of the most time efficient ways to perform the task. Activities or behaviours to avoid highlighted. Data from daily short questionnaire completed by scanning unit staff shows perceived impact of TACTICAL activities on normal LCS processes is no different when ANCCT is added for at least 80% of days.
To evaluate acceptability to participants and healthcare professionals of the additional processes required to add the ANCCT to the existing LCS process.	Qualitative and quantitative acceptability to participants and health care professionals of the key processes in combined thorax and abdominal screening, including: a. Additional sentence added to the LCS invitation, informing of possible ANCCT b. Checking eligibility for ANCCT on the participant record system at the same time as LCS eligibility checks c. Cluster randomisation of LCS assessments d. Scan reporting e. Imaging review meeting, onward referral process and participant communication	Over 75% of participants are satisfied or very satisfied with their scanning unit experience. All those involved in the LCS including LCS assessors, scanning unit staff and HCPs, report the additional processes required to add the ANCCT to be acceptable.

4.4. Table of secondary outcome measures/endpoints

The secondary outcome measures and endpoints are:

Secondary Objectives	Secondary Outcome Measures	Secondary Endpoints and Success Criteria
To evaluate uptake of the ANCCT amongst those participants randomised to be offered it.	The proportion of participants accepting the offer of ANCCT	At least 80% of participants offered the ANCCT, accept the invitation and attend the scan.

5. TRIAL DESIGN

The study is a pilot study of adding non-contrast ANCCT to the LCS CT Thorax scan amongst high lung cancer risk ever-smokers aged 55-70 years 364 days in the first round of a West Yorkshire and Harrogate Cancer Alliance LCS and a Humber and North Yorkshire Cancer Alliance LCS. The study has two randomisations:

(i) Individual randomisation to receive an invitation letter for LCS (standard of care; *invitation control*) versus invitation letter for LCS with potential for an additional abdominal scan (*invitation intervention*). This is to ensure that mentioning the additional scan is not detrimental to LCS uptake.

(ii) Cluster randomisation to being offered a CT Thorax only during the LCS assessment (standard of care in LCS; *scan control*) or offered both CT Thorax and ANCCT during this assessment (*scan intervention)*. This is to pilot this randomisation approach with the near-future aim of a fully powered study.

The study includes an embedded process evaluation.

6. TRIAL SETTING

The study will take place within two LCS programmes:

1. One LCS within the Humber and North Yorkshire Cancer Alliance (HNY).
2. One LCS within the West Yorkshire and Harrogate Cancer Alliance (WYH).

7. PARTICIPANT ELIGIBILITY CRITERIA

7.1. For the individual level randomisation to invitation control or invitation intervention

7.1.1 Inclusion criteria

To be randomised at the individual level to receive an invitation letter for LCS (standard of care; invitation control) versus invitation letter for LCS with potential for an additional abdominal scan (invitation intervention):

- Be eligible to be invited to the first round of a West Yorkshire and Harrogate LCS or a Humber and North Yorkshire Cancer Alliance LCS (i.e. have been identified as a smoker or ex-smoker and registered as living within the relevant LCS catchment area).
- Be registered with a GP in England.
- Be aged 55-70 years 364 days old at the date of invitation.

7.1.2 Exclusion criteria

- None

7.2. Eligibility criteria for the cluster level randomisation to scan intervention or scan control

7.2.1 Inclusion criteria

To be eligible for the cluster level randomisation the participant must:

- Have been individually randomised to the invitation intervention arm
- Have booked in for a LCS assessment

To receive the CT Thorax plus ANCCT, the participant must:

- Have been randomised to the scan intervention cluster
- Be invited to attend for a LDCT Thorax based upon scores on either $PLCO_{M2012}$ or Liverpool Lung Project (LLP) risk prediction models ($PLCO_{M2012}$ risk of ≥1.51% over six years or LLPver2 five-year risk of ≥2.5%)[14] during the LCS assessment.
- Have attended the lung scan appointment
- Have given electronic or written informed consent to participate

7.2.2 Exclusion criteria

Existing LCS exclusion criteria:

- Participant does not have capacity to give consent (standard criteria for assessing capacity apply).
- Weight or physical size exceeds restrictions for scanner (>200kg).

- Participant unable to lie flat.
- Poor physical fitness such that treatment with curative intent would be contra-indicated.
- Participants who have had a full CT Thorax that meets the image reconstruction parameters of the programme in the last 12 months are not excluded from the lung screening programme, but would have their CT Thorax appointment deferred until 12 months have elapsed since that last scan, provided they still meet all inclusion criteria and have no exclusion criteria – if the deferred appointment is within the timeframe for TACTICAL1, they remain eligible but if deferred appointment is outside the timeframe for TACTICAL1 they would not be eligible.

Additional TACTICAL1 exclusion criteria:

- Had an abdominal CT in the previous 12 months or has one booked within the next 3 months.
    - For HNY, this is checked before the LCS assessment. Therefore, participants will be excluded before the LCS assessment.
    - For WYH, this is only checked after the LCS assessment. Therefore, anyone having had an abdominal CT in the previous 12 months or with one booked within the next 3 months will be excluded at this point (see 8.6).

7.3 Eligibility criteria for the process evaluation

7.3.1 Health care professionals

Healthcare professionals involved in the delivery of LCS in any of the study areas who agree to take part.

7.3.2 Participants

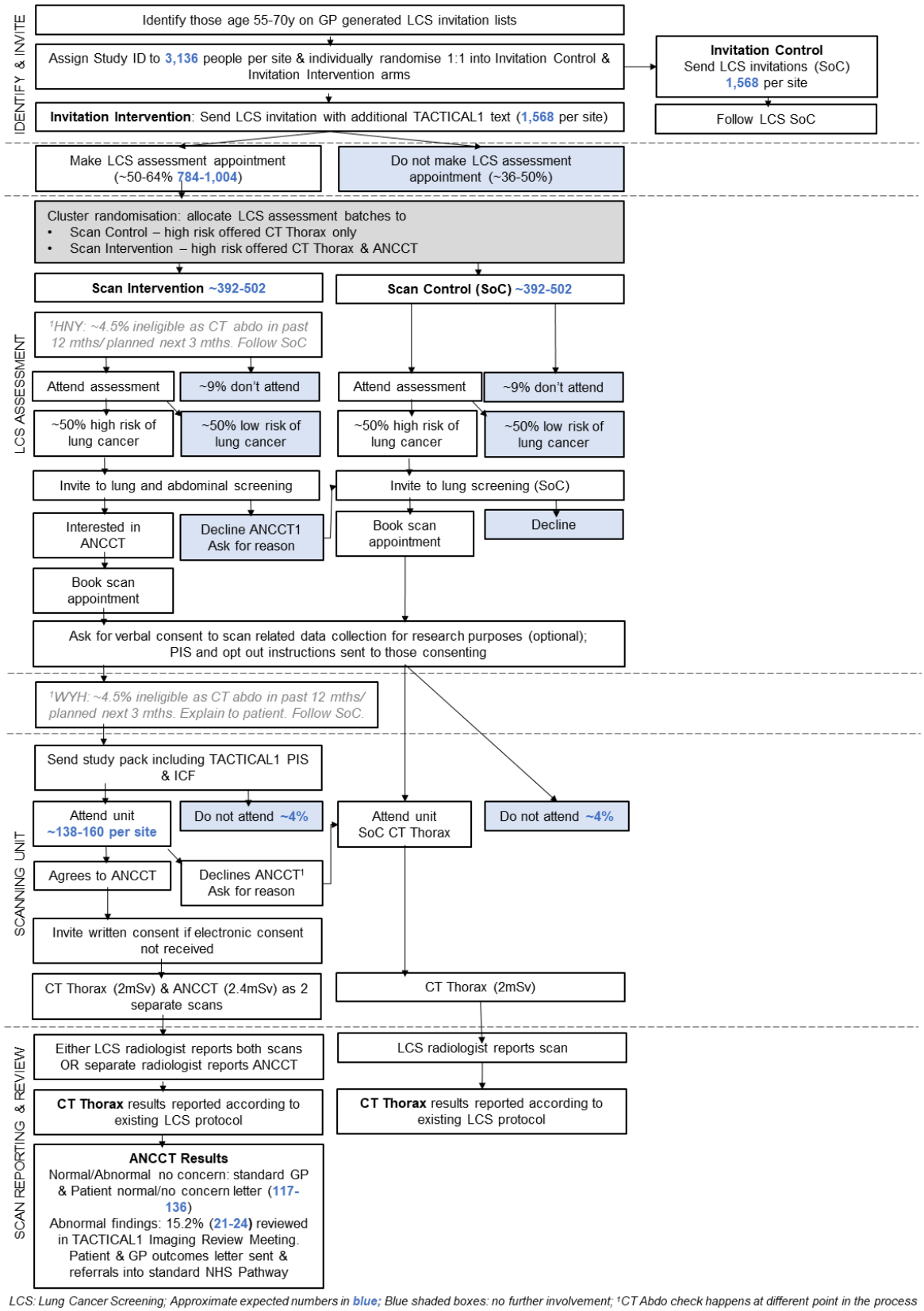
People individually randomised to the invitation intervention arm who attend the LCS assessment or the scanning unit within the study period and who agree to be interviewed.

8. TRIAL PROCEDURES

There are 3 major elements to the logistics of TACTICAL1:

1. **Adding ANCCT to the LCS process**. From invitation to completion of the ANCCT, the existing NHS LCS programmes run by the HNY and the WYH Cancer Alliances will be leveraged (figure 1, steps 1-8). These LCS are part of the NHS England's national programme and as such, follow NHS England's standard protocol[14].
2. **Downstream processes from the scan.** Reporting of the ANCCT, informing participants of results, dealing with abnormalities and making appropriate referrals into the existing NHS standard pathway of care are new TACTICAL1 specific processes, separate to the LCS (figure 1, step 9).
3. **Additional non-clinical TACTICAL1 research processes.** Observations, questionnaires and time-and-motion studies of the end-to-end process together with HCP and participant invitations to and conducting of qualitative interviews on acceptability of the process are additional non-clinical TACTICAL1 activities undertaken by the TACTICAL1 research team.

The participant pathway through the research study is shown in figure 2:



LCS: Lung Cancer Screening; Approximate expected numbers in blue; Blue shaded boxes: no further involvement; [1]CT Abdo check happens at different point in the process

8.1. Identifying Participants

The Cancer Alliances will work in their normal manner and in accordance with the LCS criteria and methodology as detailed in the NHS Standard Protocol for LCS[14], to identify participants who are eligible to be invited to the LCS.

A TACTICAL1 sub-group will be created which excludes those who are over 70 years old. These individuals have been excluded from the TACTICAL1 study as YKST data suggests upper abdominal screening is not cost-effective in those aged over 70 years[13].

The study team will assign a unique study ID to each participant on the TACTICAL1 list.

8.2. Individual randomisation to invitation control or invitation intervention

The study team will individually randomise identified participants, into the invitation control and intervention groups until there are 1568 in each group for both the WYH LCS and the HNY LCS. Each site will be provided with a set of two randomisation lists of length 1568 that will allocate participants in a 1:1 ratio to intervention and control.

8.3. Invitation to LCS

Those randomised to the invitation control group are invited to NHS LCS to assess lung cancer risk via letter or text message, following the normal process (no change to standard letter used in each area).

Those randomised to the invitation intervention group will have additional text included in the standard LCS letter or text explaining that, if eligible, they may also be offered a scan of their abdomen at the same time as their lungs.

8.4. LCS Assessment Booking

Interested participants follow the instructions in the invitation letter or text to book their LCS assessment. Age and smoking status are rechecked to ensure eligibility.

8.5. Cluster randomisation to scan control or scan intervention

Participants in this second stage of trial will be randomised at the level of LCS assessment batches, using a cluster randomisation design. A LCS assessment batch is defined as a group of individuals scheduled to have a LCS assessment within the same administrative cycle. Each batch will be randomly allocated in a 1:1 ratio to one of two arms, to being offered 1) a CT Thorax only during the LCS assessment (standard of care in LCS; scan control) or 2) offered both CT Thorax and ANCCT during this assessment (scan intervention). Randomisation will be performed centrally using a computer-generated randomisation sequence, stratified by screening centre to ensure balance across different locations. Allocation concealment will be maintained until the point of LCS assessment and all individuals within a batch will receive the same invitation, if they are high risk, based on their batch allocation. The clusters will typically be batches of approximately 100 LCS assessments.

Cluster randomisation by LCS assessment batch was chosen for pragmatic and operational efficiency, aligning with the real-world delivery of the screening programme. This approach is based on the AgeX trial (NCT01081288) of breast screening age range in England where small clusters of participants are randomised to determine which women are offered an additional screening invitation before age 50 and which are not, and which women are offered additional screening after the age of 70 or not[15].

Randomising entire batches ensures that all individuals within a given LCS assessment cycle receive the same offer, simplifying administrative processes and reducing the risk of contamination between study arms. This approach also reflects how LCS assessments are typically issued in routine practice, allowing the trial to be seamlessly integrated into existing workflows without disrupting service delivery. Moreover, batch randomisation supports the scalability of the intervention and mirrors successful models used in large screening trials, such as the AgeX trial.

8.6. LCS Assessment

During the LCS assessment call, participants answer some initial screening questions to assess their risk of lung cancer and their ability to attend for LCS (eg ability to lie flat) to determine whether they are eligible for lung screening or not.

For the scan control batches, those who are ‘high risk’ following the LCS assessment will:

- have an appointment booked for LCS in the normal way by the LCS assessor.
- be asked for their verbal consent to having their data used for research purposes (for further information see section 8.5.1).

For the scan intervention batches, those who are ‘high risk’ following the LCS assessment will:

- be told that there is a study called TACTICAL1 and as part of this they are eligible to have an ANCCT at the same time as their lung scan and asked if they are interested in this.

If the participant is interested in having an ANCCT:

- the LCS assessor will book the appointment in the normal way and highlight that it is a TACTICAL1 appointment.
- The participant will be asked for their verbal consent to having their data used for research purposes (for further information see section 8.5.1).
- The LCS assessor will explain to the participant that they will receive a letter in the post or email (depending upon the participant’s preference) together with more information about the ANCCT scan and the study, together with a consent form and instructions about how to provide their consent for this additional scan, which can be done either prior to their appointment (electronically or on paper) or on the day of the scan.

If the participant declines the invitation for the ANCCT

- The LCS assessor will ask them if they are happy to give a reason for declining (using the pre-code list generated using reasons given for declining in YKST; table 1)
- They will also ask if they would be willing to be contacted for a short interview to understand more about why they would not like the ANCCT and verbal consent to be contacted will be collected if they agree. Participants who complete an interview will be offered a £25 shopping voucher as a token of appreciation for their time and contribution to the research.
- The assessor will resume the standard process for the lung scan invitation.
- The participant will be asked for their verbal consent to having their data used for research purposes (for further information see section 8.5.1).

Table 1: YKST reasons for declining invitation to ANCCT

Participant believes they are OK/ no abdominal concerns
Participant reports they have had their abdomen checked recently/ already being monitored
Participant feels they currently have too many other ongoing health issues
Participant feels they are too old
Claustrophobia regarding the scanner
Radiation concerns
Participant is too busy/ doesn't have enough time
Cancer apprehension
Not wanting to see into the future
Do not want to give a reason
Other (specify)

The outcome of the LCS assessment will be recorded by the study team in the study database.

8.6.1. Verbal consent to data being used for research purposes

During the LCS assessment, the assessor will ask people if they are happy for their CT scan and related data to be used for research purposes. If the participant has questions about this, the assessor may be able to answer these, but will also reassure people that they will be a patient information sheet (PIS (data)) explaining the use of their data for research purposes – what data will be used, how it will be collected and stored, who will use it, and how their confidentiality will be protected. People who provide verbal consent for their data to be used for research purposes will be sent this written information. This gives them the opportunity to rescind their consent for the use of their data, if they wish to, following consideration of the information. To rescind their consent, they can

either telephone or email the TACTICAL1 research team at University of Cambridge. They do not need to give a reason why.

People who do not provide verbal consent during the call for their data to be used for research purposes will have this recorded and will not receive this written information. Their data will not be used for TACTICAL1 research purposes.

8.7. Check CT history

As part of the standard LCS process, the LCS team review medical records to see if the participant has had a full CT Thorax in the last 12 months. In these participants, LCS is deferred until 12 months have elapsed since that last scan, provided they still meet all inclusion criteria and have no exclusion criteria. This may be outside the study recruitment period; and as such they would not be eligible for TACTICAL1. The LCS team also checks to see if the participant has a CT Thorax booked or planned over the next 3 months. If they do, the participant is excluded from TACTICAL1 and this planned scan is used as the LCS baseline scan.

In addition to these standard LCS eligibility checks, for TACTICAL1, medical records will be reviewed to ensure any participant in the scan intervention arm has not had an abdominal CT in the preceding 12 months or does not have an abdominal CT planned or booked for the next 3 months. This will be done at the same time and by the same person that is checking the CT Thorax history, as part of the standard LCS process. It may be before or after the LCS assessment, depending upon the standard practice within each Cancer Alliance.

If the participant has had an abdominal CT in the previous 12 months or has one planned within the next 3 months, they will not be eligible for an ANCCT scan but will still be eligible for the lung scan if they meet all LCS criteria.

In those LCS services where the SoC review of medical records to confirm eligibility is done before the LCS assessment, those not eligible for ANCCT as part of LCS will not be offered this.

In those LCS services where the SoC review of medical records to confirm eligibility is done after the LCS assessment (ie after the participant has accepted the invitation to participate in TACTICAL1), the LCS assessor will explain to the participant during the call that their participant records will need to be checked to see if they have had an abdominal CT in the previous 12 months and if so, they may not be eligible to take part in the study. If they are not eligible, a member of the LCS will contact them to explain why they have been withdrawn.

The outcome of the abdominal CT history check will be recorded by the study team in the study database.

8.8. ANCCT Consent

Those agreeing to have an ANCCT scan as part of TACTICAL1 will be asked to give written informed consent of this. We have taken this approach because it is an additional procedure which may result in a diagnosis for participants, and because it involves radiation.

Following the LCS assessment, participants who have expressed interest in having an ANCCT scan will be sent a study pack by the study team either by post or email, depending up on the participant's preference. The study pack includes a participant information sheet (PIS (scan)) about the ANCCT scan and a consent form. The PIS (scan) will include contact details for the study team so that participants can contact them with any questions they may have. The PIS (scan) will contain instructions on how to provide consent. Participants can complete the paper consent form in advance of their LCS appointment and bring it along to their appointment. Alternatively, participants can provide electronic consent in advance of their LCS appointment via the study website address (a website address and a QR code will be provided for this in the PIS (scan)).

If participants do not provide electronic consent in advance of the LCS appointment or bring a completed paper consent form to their appointment, consent can be sought before the appointment by a member of the scanning unit team who has been appropriately trained in obtaining consent for research studies and using a paper consent form. A paper copy of the PIS (scan) will be available for participants to read if they have not already read it.

8.9. Scanning unit

For each scanning day, the study team will check which participants on the appointment list are in the scan intervention arm (i.e booked to have the ANCCT and CT Thorax) and check whether the participant has completed the electronic consent form.

When participants from the scan intervention arm attend the scanning unit, the study team will check their list to see if they have completed the online consent form and/or brought back a hard copy consent form. If they have not done this, they will be asked if they would still like to have the ANCCT and if yes, asked to complete a paper consent form. Participants who do not want to have an ANCCT scan will be asked if they wish to proceed with the standard LCS CT Thorax. Before proceeding with the ANCCT scan, the study team will confirm with those who completed the online consent form prior to attending the scanning unit, that they still wish to proceed with the scan.

8.9.1. CT Image Acquisition Protocol

All participants in this trial will undergo a single low dose CT Thorax, with one cohort also receiving an ANCCT. Only the ANCCT that is required by this study is additional to routine care. The CT Thorax and ANCCT will be conducted as two separate scans during the same appointment.

For the ANCCT, the abdomen will be scanned from just superior to the most superior aspect of the diaphragm to the top of the pelvic brim in a single craniocaudal acquisition and transaxial images of a maximum of 1mm thickness will be generated, with further reconstructions as necessary.

The effective dose for the low dose CT scan of the thorax is 2mSv, taken from the standard protocol for targeted lung health checks in the UK[14], which is indicative of the maximum dose for a standard 70 kg adult. This is approximately consistent with a DLP of around 75 mGy.cm using the effective dose conversion factor from Shrimpton et al[16].

There is no national DRL for an ANCCT only scan. The national DRL for a kidneys-ureters-bladder (KUB) examination is a DLP of 290 mGy.cm. Using a DLP to effective dose conversion factor of 0.018mSv/mGycm, this equates to an effective dose of 5.2mSv. An ANCCT alone reduces the typical DLP to approximately 135 mGy.cm, which would yield an effective dose of 2.4 mSv. It should be noted that this is calculated for an average sized patient, and doses for smaller or larger patients will differ from this.

The total protocol dose is approximately 4.4 mSv, which is less than two years of average natural background radiation in the UK. The radiation dose to be used in the ANCCT alone represents the approximate background environmental radiation exposure over 12 months

Participants lie supine on the CT table with arms above their head and thorax in the midline of the scanner. Subject comfort is optimised and maximal inspiration rehearsed prior to the scan to minimise motion during the CT. Imaging is performed during suspended maximal inspiration. No intravenous contrast material will be administered. The standard scan projection radiograph is used to localise the start and end positions of the scan.

The abdominal CT images will be transferred from the mobile unit to the hospital's Picture Archiving and Communication System (PACS) system at the same time, and via the same process, as is used for the CT Thorax.

8.10. Scan reporting and review

The CT Thorax are reported by radiologists in accordance with the LCS standard protocol. The ANCCT will either be reported at the same time by the same radiologist or in parallel by a different radiologist, depending upon site preference.

Participants will be triaged according to their findings with outcome driven actions outlined in Table 2. Those with normal scans or abnormal findings of no concern (for example benign cysts, small stones (<5mm), anatomical variants) will be sent a 'normal' letter by the site research team, using templates based upon those used in YKST. The remaining participants will be discussed in an Imaging Review Meeting (IRM), attended by a research nurse and a consultant. Participants will be referred into the standard NHS Standard Care Pathway, with participant results letters, GP letters and referral letters written and sent by the site research team as appropriate.

The IRM will take place no later than 15 days after the scan and results letters will be sent to participants no later than 28 days after the scan.

Table 2: Outcome driven actions

Outcome	Reason	Action	Communication
Normal	No action required	Discharge	GP / participant: letter communicating result
Abnormality of no concern (e.g. anatomical variant,	Abnormality not requiring further	Discharge	GP / participant: letter detailing findings and including standard

benign cyst, small renal stone <5mm)	investigation or treatment		additional information on the abnormality of no concern if appropriate e.g. stone advice leaflet
Abnormality of possible or immediate concern to be reviewed at Imaging Review Meeting			
Abnormality of possible concern	Finding requiring further elective investigations or treatment	According to recommendations by radiologist and disease specific specialist. Further tests and referrals to be coordinated by Consultant Urologist and their delegates.	GP / participant: letter explaining findings, need for further investigations or onward referral, date repeat scan.
Abnormality of immediate concern	Abnormality requiring immediate further investigation for possible abdominal cancer or AAA	**Fast Track 2 week wait appropriate speciality.** Coordinated by Consultant and their delegates. For AAA 7cm+: Direct same-day referral to on-call Vascular Specialist	Participant contacted by relevant speciality administrative team scheduling appointment

8.10.1. Quality Assurance

Ten percent of all normal ANCCT selected at random will be second-read by a different radiologist. Any ANCCT where there is discordance following the second read will be discussed in the image review meeting for resolution.

9. Payment

There is no payment to participants.

10. Consent

All invitation intervention participants who are high risk for lung cancer will be asked for their verbal consent to allowing their CT scan and related data to be used for research purposes. Those providing verbal consent will be sent a patient information sheet (PIS (data)) which includes instructions on how to rescind consent if they change their mind. See section 8.5.1.

Participants interested in having the ANCCT will be sent a participant information sheet (PIS (scan)) and a consent form in their study pack either by post or email, depending upon the participant's preference. The PIS will contain instructions on how to provide consent, including a website address and QR code for those who would like to provide electronic consent.

Those who prefer to provide written consent can either bring the completed paper consent form when they come for their appointment or complete a paper consent form provided by the study team when they attend the scanning unit.

If a participant attends the LCS assessment and is high risk and interested in having an ANCCT but the preferred scanning date is less than 1 week from the assessment call, they will be asked if it is possible to email them the PIS (rather than post). If they do not want to receive an email, they will be asked to attend the scanning unit 20 minutes before their appointment time to enable them to read the PIS and decide whether they would like to consent to the ANCCT.

Additional consent will be obtained for those invited to participate in the process evaluation part of the study (see section 13).

As participants in TACTICAL1 will be approached at the point of their LCS first consultation to consider participation in TACTICAL1, no mental capacity and consultee declaration is relevant per se as this will be under the guidance of the LCS protocol.

11. Baseline data

The following demographic data is collected as standard practice by the LCS service:

- Biological sex
- Age
- Education
- Smoking status
- Ethnicity
- Index of Multiple Deprivation (IMD)
- Postcode area

At the first individual level randomisation (invitation control versus invitation intervention), each participant is assigned a unique study ID. The LCS service will record uptake to the LCS assessment. The LCS will provide (to the TACTICAL1 study team) aggregate level data on uptake by each of the demographic factors per invitation group.

Necessary participant consent and data sharing agreements will be established to allow Humber and North Yorkshire Cancer Alliance and West Yorkshire and Harrogate Cancer Alliance to share consenting participants' individual level baseline data, together with the participant's study ID, with the University of Cambridge study team. This data will be uploaded to the study database, stored on a secure University of Cambridge server.

For the second, cluster level randomisation, participants are asked for consent for their CT scan and associated data to be used for research purposes. This data will include participant level data on the above socio-demographic characteristics, along with their cluster (scan control or scan intervention), outcome of the LCS assessment, attendance for LCS (or LCS plus ANCCT), and final outcome of the

screening. This data will be uploaded to the study database, stored on a secure University of Cambridge server.

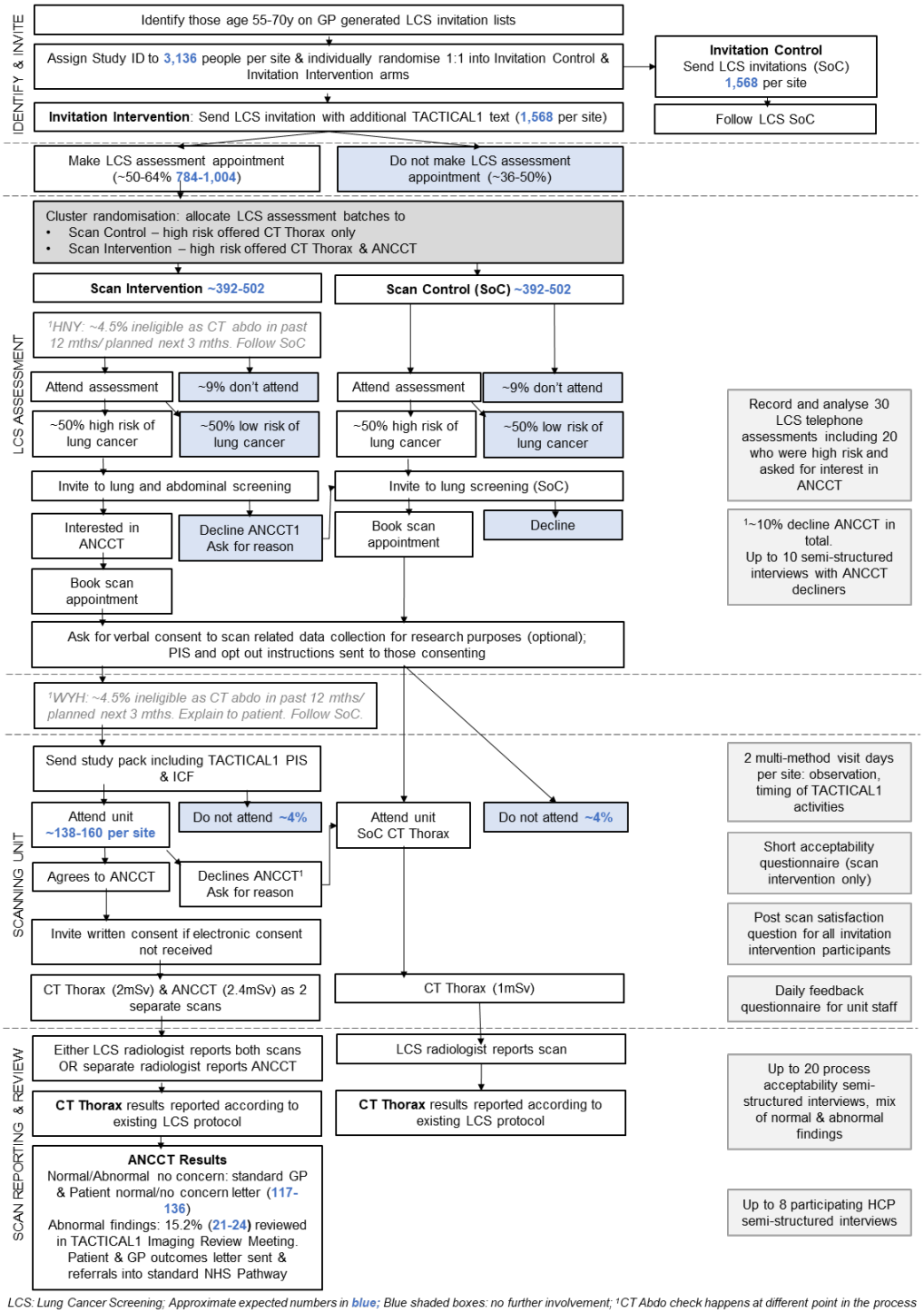
12. Long term follow-up assessments

There will be a 6 month follow up for all participants in the scan intervention group who are reviewed at the IRM with a finding requiring further action. No long-term follow-up assessment will be undertaken for all other participants.

13. Process Evaluation

Figure 3 below shows, in light grey shaded boxes on the right, the different steps which will be used to evaluate the overall acceptability of the process including any impact on LCS throughput.

Figure 3



LCS: Lung Cancer Screening; Approximate expected numbers in blue; Blue shaded boxes: no further involvement; [1]CT Abdo check happens at different point in the process

13.1. Analysis of LCS assessment calls

The research team will either obtain a license to record the LCS assessments for those in the invitation intervention group at HNY and WYH or arrange for the researcher to listen in to the live calls. The LCS assessors will inform participants who they call that calls will be recorded or listened to for training and research purposes. They will also ask for verbal consent for a researcher to listen to their recording and analyse it to suggest improvements to the process. For those consenting, LCS assessors will note anonymised details of the call that can be analysed and will pass these details onto the researcher at the end of the working day. The researcher will listen to enough of these from the invitation intervention group to ensure that they hear 20 from the scan intervention group who were high risk and interested in having an ANCCT, and 10 from the scan control group who are high risk for lung cancer and are only offered the lung scan.

Analysis will include anonymised notes of process issues and time taken for the extra processes required to assess/ arrange for the ANCCT, together with call data showing number of LCS assessments and proportion of TACTICAL1 calls.

13.2. Participant semi-structured interviews

13.2.1. Participants declining scans

High-risk participants in the invitation intervention group, who are not interested in having the ANCCT will be asked by the LCS assessor if their contact details can be passed onto a researcher to arrange a follow-up interview at a convenient time. If agreed, the researcher will send a PIS (interview) and ICF to return in a freepost envelope. Any participant who had expressed an interest in having the ANCCT during the LCS assessment but declines to consent to the scan when they attend the scanning unit for their lung scan will be asked by the scanning unit staff if their contact details can be passed onto a researcher to arrange a follow-up interview at a convenient time. If agreed, the scanning unit staff will give the person a PIS (interview) and ICF to either complete and return whilst on the scanning unit or to return in a freepost envelope at a later date. Participants who complete an interview will be offered a £25 shopping voucher as a token of appreciation for their time and contribution to the research.

The semi-structured interview will explore topics including, if/how the invitation and material for the ANCCT affected their decisions about the lung scan, and what they would recommend with respect to materials in a large-scale programme. Up to 10 people will be interviewed and, if sufficient numbers, they will be purposively sampled for variation in age and sex.

Interviews will be recorded and held online using teleconferencing software or via telephone, according to participant preference. For those who have not returned the written consent form before the interview, verbal consent will be taken using the consent form as a structured script, with the interviewer signing on behalf of the participant, offering to send them a copy afterwards.

13.2.2. Randomised participants following their scan results

A subset of study participants who consented to have the ANCCT and to be contacted about an interview on the main study consent form, will be sent a separate interview invitation pack containing a

participant information leaflet and copy of the interview consent form after their scan. Participants who complete an interview will be offered a £25 shopping voucher as a token of appreciation for their time and contribution to the research. Up to 20 will be purposively selected across sites to include those with normal, benign findings and findings that need follow-up. They will be invited to take part in an interview with a member of the research team between 4 and 8 weeks after their scan so that they will have been given their scan results.

These semi-structured interviews will include topics such as satisfaction with the end-to-end process, the time given to consent to the scan and the information given to consent, as well as ideas on how to improve this. Exploring these after results might give a more reflective account that includes the impact of any diagnoses. The interviews will be conducted over teleconferencing software or telephone and consented through an optional section in the ANCCT consent form, following the process described above in section 10.

13.2.3. Healthcare professional semi-structured interviews

All healthcare professionals participating in this study will be invited to participate in an interview with a member of the research team at the same time as being invited to take part in the study via an invitation letter, PIS (HCP) and ICF. Of those consenting, up to 8 will be purposively selected for variation in role and site, to include LCS managers, LCS assessors, scanning unit staff, radiographers, study teams, radiologists and urologists.

The semi-structured and recorded interviews will be conducted remotely using teleconferencing software with the procedure and consent process as described in section 10.

The interviews will take place at the end of the study and will be based on a topic guide that includes questions on the perceived impact of adding the ANCCT and its processes onto the existing LCS process, and barriers, enablers or suggested strategies for a larger scale programme.

13.3. Multi-method visit days

Some quantitative and qualitative data will be collected during day-long visits by a researcher to sites where core study activities take place. Combining a mix of data, both observed and through questions, will allow a more valid exploration of the TACTICAL1 processes than by either method alone. This will be analysed in conjunction with a daily record of the number of CT Thorax only and CT Thorax and ANCCT scans completed each day, together with the number of participants not attending.

13.3.1. Scanning unit observations

As part of the process evaluation, a researcher will spend two days at each of the HNY and WYH scanning units at a time when ANCCT scan appointments have been booked. On entry to the scanning unit, staff will inform participants that there is a researcher present to take anonymised notes about the process and obtain verbal consent for them to observe. If they decline, the researcher will not observe that participant. If they consent, the researcher will stay and observe.

The researcher will time the various activities of the scanning unit staff for participants, including the total time for those needing a lung scan and those needing an additional ANCCT. They will also time the consent process, record the number of participants who consented in the scanning unit and remotely, time the duration for consent for those consenting in the scanning unit, and time the duration of the various scans. They will make anonymised field notes of any barriers, facilitators and strategies for the process, focussing on the addition of the ANCCT and the consent procedures. They will also record the number of scans done of each type, and how many accepted the ANCCT out of those offered.

Throughout each day, at convenient times such as breaks, the researcher will conduct up to five informal interviews with scanning unit staff and five with participants, exploring how they felt the additional activities introduced by the ANCCT affected throughput (for staff), and what could be done to improve the process (for staff and participants).

13.3.2. Daily feedback questionnaires for scanning unit staff

Paper questionnaires will be provided to scanning unit staff for them to complete one each at the end of every scanning day. They will focus on throughput, any delays and causes, and perception of feasibility. Only one to two different staff each day will need to fill these in to capture all necessary data. These will be site specific but anonymised and scanned and sent by study teams to the research team via secure nhs.net to nhs.net email.

13.3.1. Pre-scan questionnaire for scan intervention participants

Each scan intervention participant will be asked to complete a short questionnaire at the same time as they give their consent, to provide feedback on the information they received about the ANCCT and the time allowed to decide whether to participate. The questions use a Likert scale. The participant study ID will be written on the questionnaire by the scanning unit staff or electronically for those providing their consent online. Scanning unit staff will collect hard copies of the questionnaires and send them via post to the research team.

13.3.2. Post scan questionnaires for invitation intervention participants who attend the scanning unit

Each invitation intervention participant who attends the scanning unit (whether they be scan intervention or scan control participants) will be provided by scanning unit staff with a simple satisfaction question, using a Likert scale, to share their feedback on the scanning unit experience. The participant study ID will be written on the questionnaire by the scanning unit staff for all those participants who have either consented to the ANCCT and/ or to having their data used for research purposes. Scanning unit staff will collect these and send them via post to the research team.

14. Withdrawal criteria

Consented participants wishing to withdraw from the study will be able to do so at any time. If a participant asks to withdraw from the study, either before or after the scan or qualitative interview, researchers will ask if the participant is willing to share their reason for withdrawing, although it will be made clear to the participant that they are not required to share this information if they do not wish.

If the participant still wishes to withdraw from further trial activity a member of the research team will request that the participant allows us to retain any data that has been collected and stored up to the point of withdrawal.

If the participant explicitly states they do not wish to contribute further data to the study, and desires that their existing data should not be used in the analysis, their preference will be recorded on the withdrawal CRF and action taken within the database to ensure their data is excluded from the analysis. If it is not possible to exclude the participant from the analyses they will be contacted and told why.

15. End of trial

The trial will end following the 6 month follow up for those with abnormal findings and following the normal or letter of no concern for those with normal findings.

16. Safety

16.1. Assessment and management of risk

The main risks of participating in this study are those associated with undergoing non-contrast CT based screening for abdominal pathology. Specifically:

- risks of investigations and/or treatment for abnormal findings on ANCCT
- risk of harm by detection and treatment of indolent cancers (over-diagnosis)
- psychological worry resulting from the screening findings
- risk of radiation induced cancers as a result of screening.

16.2. Risks of investigations and/or treatment for abnormal findings on CT scan

Potential harms might include morbidity or very rarely mortality from invasive investigations (such as biopsy), or harms from treatments such as surgical treatment. Particular concern relates to those participants who receive harm whilst undergoing investigation for an abnormality which subsequently turns out to be benign. For example there is a risk of participants found to have a small renal mass undergoing surgical resection for a benign lesion. As such, biopsy of small renal masses will be discussed with all participants in the shared decision-making process. It should be noted that in this

pilot study it is estimated that only 3 people will be found to have a small renal mass and thus exposed to this risk.

16.3. Risk of harm by detection and treatment of indolent cancers (over-diagnosis)

Over-diagnosis is when cancers or other conditions that would not have otherwise caused the participant harm during their lifetime are detected and treated. In TACTICAL1 we will seek to minimise over-diagnosis by ensuring participants have a detailed work-up of any renal mass or other tumour (usually by biopsy or radiological assessment) to ensure the aetiology of the lesion is understood before deciding on treatment be it observation, surgical excision or tumour ablation (i.e. cryotherapy or radiofrequency ablation). It should be noted that in this pilot study it is estimated that only 4 people will be found to have a small renal mass or other tumour and thus exposed to this risk.

16.4. Psychological worry resulting from the screening findings

Psychological worry about screen-detected findings has been raised as a potential harm, specifically relating to the detection of small indeterminate lesions which are relatively common findings. However, data from YKST suggests that overall there was no clinically significant psychosocial impact on screening participants in the long term.

16.5. Risk of radiation induced cancers as a result of screening

Radiation induced cancers are a recognised harm of LDCT screening. The radiation dose to be used in the CT thorax plus ANCCT represents less than the approximate background environmental radiation exposure over 24 months. For participants at high-risk of abdominal cancers undergoing CT screening, the harms from radiation-induced cancers are significantly outweighed by lives saved through earlier detection of pre-existing cancers and other serious findings. Nevertheless, this potential harm should still be discussed with participants prior to consent for an ANCCT scan and is included in the Participant Information Sheet that participants will be given.

16.6. Serious Adverse Events

A Serious Adverse Event (SAE) will be any untoward medical occurrence that takes place whilst a participant is on the mobile unit that:

- Results in death
- Is life-threatening* (subject at immediate risk of death)
- Requires in-participant hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

*‘Life-threatening’ in the definition of ‘serious’ refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as a participant admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

SAEs will be recorded and reported from the time that participants enter the scanning unit to the time they leave the scanning unit. All SAEs should be reported to the TACTICAL1 Project Manager and CI within 1 working day of the TACTICAL1 team becoming aware of the event.

Any unexpected SAEs or SAEs that are related to participation in the study, will be reported to the sponsor research_governance@medschl.cam.ac.uk within one working day of the research team being notified. This clinical review for causality will be completed by a clinician on the TMG (this will be the Chief Investigator whenever possible). SAEs that are both unexpected and related to participation in the study should also be reported by the CI to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event. Information on SAEs will be summarised for trial oversight committees, funder and other progress reports, as required.

17. STATISTICS AND DATA ANALYSIS

The primary and secondary outcome measures and endpoints are detailed in section 4.

17.1. Sample size for intervention letter versus control letter

The TACTICAL1 sample size calculation is derived to test the first element of the study, the non-inferiority test of the intervention invitation against the control invitation on the primary outcome of making the LCS assessment appointment (see figure 2).

Let:

p_C = Proportion of participants responding in the control group (lung scan invitation only).

p_I = Proportion of participants responding in the intervention group (lung + ANCCT invitation)

D = p_I - p_C = Difference in proportions

Delta_NI = the non-inferiority margin of -5%, the pre-specified threshold below which a lower response rate in the intervention arm would be considered unacceptable.

The null hypothesis H0 = Delta <= - Delta_NI

The alternative hypothesis is HA = Delta > - Delta_NI

If we assume the current control uptake is 50% and the non-inferiority margin is -5% and the difference in proportions is zero, for a one-sided 2.5% alpha and 80% power we need to randomise 3136 people in a 1:1 ratio.

Data from the Cancer Alliances suggests that 50-64% of those invited for a LCS assessment will make an appointment, around 8-9% will not attend the assessment and of those being assessed, approximately 50% will be expected to be high risk and therefore invited to screening. The anticipated number who would receive the CT Thorax and ANCCT, once decliners, those ineligible and non-attenders are accounted for would be ~138-160 per site.

17.2. Sample size for qualitative component

We also plan to recruit up to 30 participants (20 having ANCCT and lung scan, and 10 having declined the ANCTT scan) and 8 healthcare professionals involved in the screening process for qualitative semi-structured interviews. For the qualitative interviews with participants, we will draw on the principles of information power[17] when deciding when to cease data collection but previous experience and our prior knowledge of key processes from YKST, suggest these sample numbers will be sufficient to achieve our objectives. Where numbers permit, we will purposively sample participants for to include a range of ages, sex and abdominal findings.

For the qualitative interviews with healthcare professionals, there are approximately 12 closely involved in the screening process. We will approach them all and if needed, purposively sample for a range of roles.

We will also analyse 30 LCS assessments and four scanning unit days/ combined scan consultations to provide a range of staff and sites whilst being practical to complete. Combining with the interview data and the range of data collected from the visit days (questionnaires, informal interviews) in a mixed-methods analysis, there should be sufficient information power to answer our rather focussed objectives[11,17].

17.3. Statistical analysis plan

17.3.1. Primary analyses

Primary Outcome Measure 1: Attendance rate at the LCS phone call of those receiving the TACTICAL1 invitation letter offering an additional scan of the abdomen, if eligible, versus those sent the standard LCS invitation letter.

Descriptive analyses will first be used to summarise the attendance rate at the LCS phone call of those sent the invitation letter versus those sent the control letter. A non-inferiority test will be conducted using a one-sided 97.5% confidence interval approach. The primary analysis will involve a difference-in-proportions test comparing the response rates between the control and intervention groups. If the lower bound of the confidence interval for is greater than -5% then non-inferiority will be concluded. If non-inferiority is demonstrated, a subsequent superiority test will be conducted to assess whether the proportion in the intervention group is significantly higher than in the control group, using a one-sided test at the 2.5% level. As this is a hierarchical testing approach, no adjustment for multiple comparisons is required when proceeding from non-inferiority to superiority testing.

For each of the two sites, we will present aggregated data on the proportion of those in the invitation control group and invitation intervention group who attend for a LCS risk assessment. The proportions will be reported with 95% confidence intervals.

We will additionally report the proportion of participants in each group by age, sex, smoking status, ethnicity, education level and socio-economic status.

Primary Outcome Measure 2: Successful cluster randomisation of participants into scan control and scan intervention groups.

Successful cluster randomisation of participants into scan control and scan intervention groups will be demonstrated by groups of similar size and demographics. Baseline characteristics of those randomised will be compared.

Primary Outcome Measure 3: Number of participants scanned per day, time and motion study to evaluate impact, from invitation to scan, of adding ANCCT processes to the existing LCS processes, and impact on overall throughput of LCS plus data from daily short questionnaire completed by LCS and Scanning unit staff capturing perceived impact of TACTICAL activities on throughput.

A comparison of the number of scans performed in a day over the study period will be made with the number of scans in a period immediately before and/or after the study. The mean number of scans performed per day will be compared using an un-paired T-test.

The time impact from invitation through to scan of adding ANCCT processes to the existing LCS processes, and impact on overall throughput of LCS will be assessed through analysis of the LCS assessment calls, the field notes taken during observations on the scanning unit visit days, together with data from daily short questionnaire completed by Scanning unit staff on the number of scans undertaken.

Primary Outcome Measure 4: Qualitative and quantitative acceptability to participants and health care professionals of the key processes in combined thorax and abdominal screening, including:

Data on the acceptability to participants and health care professionals of the key processes in combined thorax and abdominal screening will come from qualitative and quantitative assessment.

The qualitative (verbatim transcripts made from the recordings of semi-structured interviews, text from observational field notes, reflective memos, field notes from informal interviews) data will be thematically analysed based on Braun and Clarke's Principles[18]. Quantitative (Likert scores from questionnaires, time for activities) data, calculated as described above, will be combined with the qualitative with a convergent mixed-methods approach[19]. The qualitative and quantitative data will be combined through a narrative and via 'joint display': creating a visual map of the process and highlighting key additional steps, their impact and strategies to overcome any barriers[19]. Analysis will

be supported by NVivo software and relevant theories will be incorporated as necessary through abduction[20].

Over 75% of participants responding that they are satisfied or very satisfied with the process will be taken to be acceptable.

17.4. Planned recruitment rate

The recruitment to TACTICAL1 will be relatively short (~4 months). For the first individual level randomisation (invitation control, invitation intervention), 3,124 people need to be invited in each Alliance at a rate of about 1,000 per month.

17.5. Economic evaluation

The modelling base case in the YKST cost effective analysis made certain assumptions which are being evaluated in TACTICAL1. If TACTICAL1 demonstrates that these assumptions are correct, then the modelled cost-effectiveness is feasible. If they are not correct, then provided costs are below the modelled maximum justifiable costs which formed part of the sensitivity analyses, then cost-effectiveness can still be concluded[13].

If costs are different to the assumptions, it will be possible to calculate the new estimated net monetary benefit.

18. Data Management

18.1. Data storage and access

Research data collected and generated during the project will be managed according to recommended good practice, as described by the Digital Curation Centre. (https://www.dcc.ac.uk/dmps).

A log of study data for all participants will be maintained by each site and at intervals throughout the study all personally identifiable information will be removed and the log will be via email to researchers in Cambridge or uploaded onto the study database, hosted on a secure University of Cambridge server. Where consent has been provided, the study ID will also be shared as a unique identifier.

A record of participant's electronic consent will be automatically stored in the study database on a secure University of Cambridge server. Paper copies of consent forms received on the scanning unit will be scanned and emailed from nhs.net to nhs.net email to researchers in Cambridge where they will then also be stored on the secure University of Cambridge server or scanned and uploaded directly onto the secure study database. The original paper copies will be destroyed.

Electronic versions of consent forms from healthcare professionals and participants for the qualitative interviews will be stored on the secure University of Cambridge server. Any paper copies will be treated as above.

The completed short daily feedback questionnaires from the scanning unit will be stored at each site within a locked cupboard and posted to the researchers in Cambridge at regular intervals using tracked post. No personal identifiable data will be included on those questionnaires. Data from the completed participant questionnaires will be entered into a database by a member of the study team. The questionnaire will include the study ID and no personal identifiable data.

For the qualitative interviews, contact details, along with the age, sex and result of the ANCCT (normal/ no concern/ potentially significant finding) of participants consenting to their details being passed onto the research team to potentially be contacted about taking part in the interview study will be sent to the research team within the University of Cambridge via secure nhs.net to nhs.net email accounts and subsequently stored on the secure University of Cambridge server. Recordings of interviews will be uploaded to the secure University of Cambridge server immediately following the recording of the interview. Interviews will then be deleted from the audio recorder or online video platform. No audio or video interviews will be emailed.

An external company will transcribe the interviews verbatim. Interviews will be transferred to the company via a secure and encrypted file transfer service and all those able to access the files will sign a confidentiality agreement. Before transfer, each participant will be given a qualitative study ID number and all recordings will be anonymised with that study ID number. The key to the ID numbers will be stored for up to 1 year on the secure University of Cambridge server only accessible to members of the research team.

All transcripts will be redacted to remove personal identifiers and any information that could lead to identification of individuals or organisations. These pseudonymised transcripts will be stored a university server. Direct quotes will be used in subsequent reports and publications. To ensure confidentiality no names will be presented with quotes and quotations will have all proper names removed.

The original recordings will be retained in the secure University of Cambridge server for the duration of the study and then destroyed along with all other personal identifiable information after 12 months.

Anonymised field notes from observations and informal interviews, along with anonymised staff and participant questionnaires, will be stored on a university server. They will be labelled with a pseudonym indicating the site, role and date.

The secure University of Cambridge server is an ISO:27001 accredited Safe Haven and controlled by a multi-factor authentication and monitored.

All study staff will understand the principles of confidentiality and will hold current Good Clinical Practice (GCP) certificates.

18.2. Data anonymisation

All potentially eligible participants will be allocated a unique study ID number before the first randomisation into the invitation control and invitation intervention groups. They will be identified by this number on all study related documentation throughout the course of the study and data analysis

process. All study data will be link-anonymised at source wherever possible, or as soon as possible afterwards if applicable. The link file connecting the unique study ID number with personal data will be stored securely and separately to the trial data by the relevant Trust or GP Federation. Interviewees will be given a pseudonym, so they remain anonymous in the reporting of the qualitative data. All personal data will be kept for the minimum period of time required by this study and future studies. The study data will then be fully anonymised and securely archived or destroyed.

18.3. Minimisation of missing data

We will attempt to minimise the quantity of missing data, prioritising the primary outcome measures.

18.4. Archiving

All study documents will be retained for a maximum of 10 years following the conclusion of the study. Following the submission of the end of study report the Sponsor will arrange for archiving of the Trial Master File in accordance with the Sponsor's process.

Following the end of the retention period the Sponsor will notify the Chief Investigator in writing that the required retention period has completed and that documents will now be destroyed. A copy of the instruction to the archivist to destroy the records will be requested.

19. ETHICAL AND REGULATORY CONSIDERATIONS

19.1. Research Ethics Committee (REC) review and reports

Before the start of the TACTICAL1 trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. information letters. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the NHS R&D departments before they can be implemented in practice at sites). The Chief Investigator will notify the REC of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC, within one year after the end of the trial.

19.2. Peer review.

TACTICAL1 has been funded by Yorkshire Cancer Research. As part of this funding process three rounds of peer review were undertaken by an expert panel of four cancer researchers and PPIE representatives.

19.3. Public and Participant Involvement

Effective participant and public involvement is key to the success of this project. Abdominal screening will only result in meaningful participant benefit if the very real issues around acceptability are

addressed through dialogue with participants. The overarching aim of earlier identification of kidney cancer and abdominal cancer and the role of screening in this paradigm has been driven by participants and the public since our group started to develop this research programme in 2014. This has been a consistent theme emphasised by the NCRI Renal and Bladder Cancer Clinical Studies Group (until disbanded in 2023) as evidenced by entries in their annual reports. Research gap analysis work including PPI representatives has further emphasised that a major research need is to 'identify an inexpensive, highly sensitive and specific biomarker/tool to enable early diagnosis and screening for kidney cancer'[21].

PPI was crucial to the development of the YKST study, which developed preliminary data for TACTICAL1. To inform YKST, we held a PPI workshop at University of Cambridge. Two particularly engaged individuals, continued to work with us throughout YKST, reviewing the funding application, protocol, ethics application, participant facing materials and the results.

Findings from YKST's (a) 500 person 'Participant Harms' survey and (b) 25 participants plus 8 health care professional acceptability interviews have been key in defining TACTICAL1 objectives[11,12].

Subsequently, input from our three lay advocates and a 10-strong PPIE panel has helped shape TACTICAL1 initial design. The three PPIE representatives named in this protocol will continue to provide input into the co-design process, review all participant facing materials, sit on the TMG and provide the lay perspective on the interpretation and communication of findings. The proposed TACTICAL1 Participant and HCP acceptability interviews would further enrich the PPIE feedback and together be critical in informing next steps.

19.4. Regulatory Compliance

The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

Before any site can enrol participants into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as relevant[22].

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended[23].

19.5. Indemnity

NHS indemnity (for negligent harm) will cover Trust employees, both substantive and honorary, who are working in the course of their NHS employment and in respect of conducting research projects which must have received HRA Permission. The University of Cambridge will provide site and staff insurance cover for University of Cambridge staff who are working on this study.

19.6. Amendments

Any substantial amendments to the study protocol will be submitted to REC. The Chief Investigator will be responsible for the decision to amend the protocol, and will decide whether any amendment is substantial or non-substantial following discussion with the sponsor. A full amendment history will be tracked in the protocol appendix.

20. DISSEMINATION POLICY

20.1. Dissemination policy

The results will be disseminated at clinical meetings, by publication in peer-reviewed journal and to policy makers. A summary of study published findings will be made available to participants on request via the University of Cambridge's Urological Malignancies Virtual Institute website.

All publications and presentations relating to the trial will be authorised by the TMG and the funder. We will publish the main trial results in peer-reviewed journals and present at national and international scientific meetings. The uniform requirements for manuscripts submitted to biomedical journals (http://www.icmje.org/) will be respected. All clinicians, researchers and PPI members will be acknowledged where they have been involved in written papers. With the assistance of our collaborators and participant representatives we will disseminate the trial findings to a wide NHS and general audience.

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22. APPENDICIES

Appendix 1 – Amendment History

Amendment No.	Protocol Version No.	Date Issued	Authors of Changes	Details of Changes Made
NSA001	2.0	28/11/25	Jessica Kitt	1. Participants can now be offered the choice of receiving PIS (data), PIS (scan) and the e-consent for the scan via email or post rather than just post. 2. The researcher can now either listens to a selection of the LCS assessment calls in real time using a second headset or listen to recordings. The LCS assessors will ask for verbal consent for a researcher to listen to their call for training and research purposes. 3. If a patient attends the LCS assessment and is high risk and interested in having an ANCCT but the preferred scanning date is less than 1 week from the call, they will be asked if it is possible to email or text them the PIS (rather than post). If they do not want to receive an email or text, they will be asked to attend the scanning unit 20 minutes before their appointment time to enable them to read the PIS and decide whether they would like to consent to the ANCCT.
Modification 3	2.1	21 Jul 2026	Carley Batley	1. Adds incentive for patients to complete interviews.