Methods of Early Detection of Lung cancEr in PrimarY Care: The MEDLEY Study

Clinical Study Protocol

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2.0 Contents Page

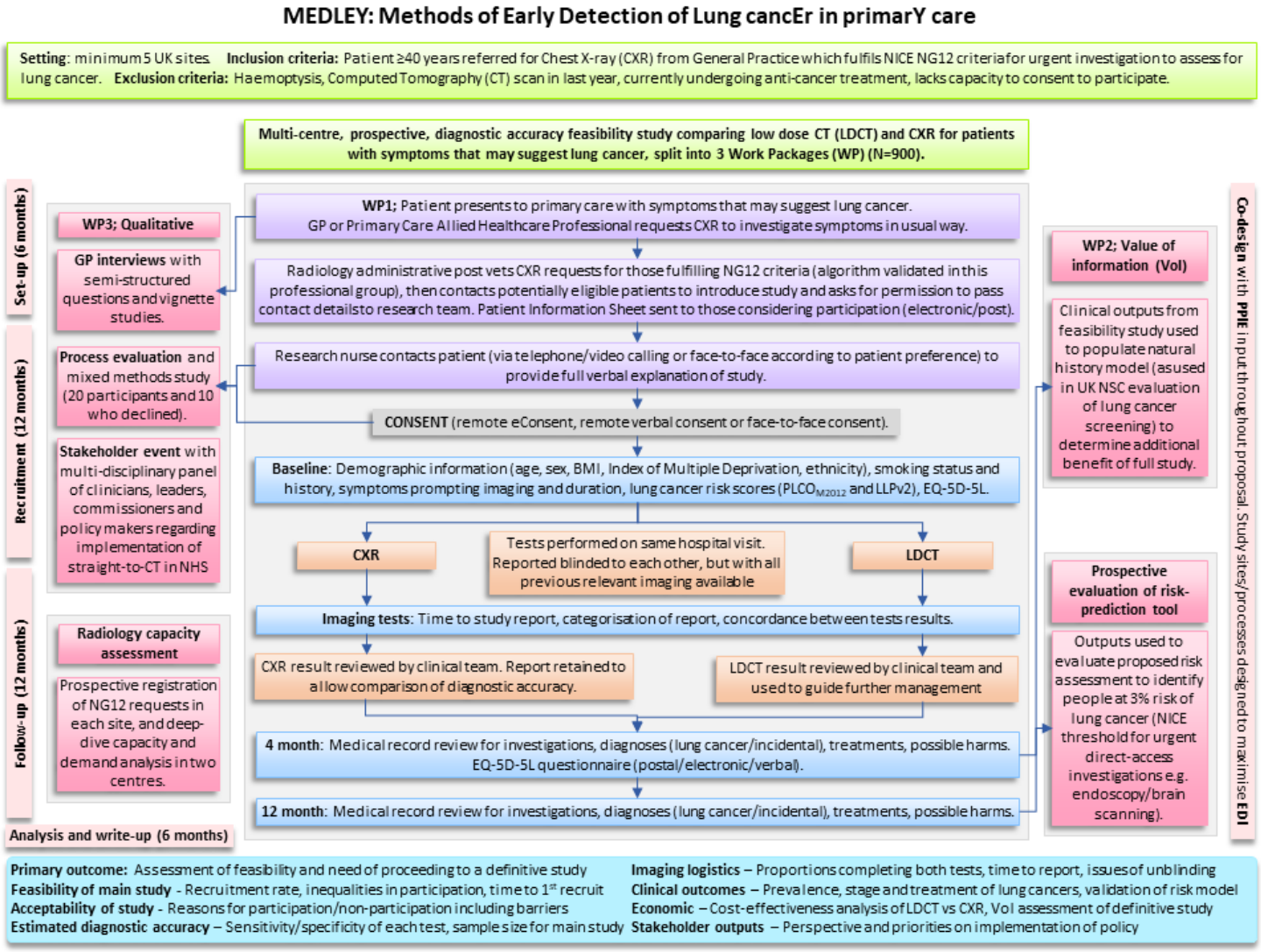
3.0 Glossary of Terms/Definitions

Abbreviation	Explanation
AE	Adverse Event
BMI	Body Mass Index
CI	Chief Investigator
CT	Computed tomography
CRF	Case report form
CTRU	Clinical Trials Research Unit
CXR	Chest X-ray
eCRF	Electronic case report form
eISF	Electronic Investigator Site File
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect parameter information
EVSI	Expected value of sample information
GCP	Good Clinical Practice
GP	General practitioner
HEAP	Health Economics Analysis Plan
HLH	Heart&Lung Health
kVp	Peak kilovoltage
LDCT	Low-dose computed tomography
LLP_{v2}	Liverpool Lung Project [lung cancer risk prediction score developed in the Liverpool Lung Project – version 2]
mAs	Milliampere-seconds
NG12	National Institute for Health and Care Excellence Guideline 12
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PACS	Picture Archiving and Communication System
PI	Principal investigator
PIN	Personal identification number
PIS	Patient Information Sheet
$PLCO_{m2012}$	$PLCO_{m2012}$ Model [lung cancer risk prediction score developed from the Prostate Lung Colorectal and Ovarian (PLCO) cancer screening study and modified in 2012]
PPI	Patient and public involvement
QALY	Quality-adjusted Life Year
QMUL	Queen Mary University of London
RCT	Randomised controlled trial
RDE	Remote data entry
REC	Research Ethics Committee
RUSAE	Related Unexpected Serious Adverse Event
RIS	Radiology Information System
SAE	Serious adverse event
SAP	Statistical analysis plan
SFT	Secure File Transfer
SMG	Study Management Group
SOC	Study Oversight Committee
STARD	Standards for Reporting of Diagnostic Accuracy Studies
VoI	Value of information
WP	Work package

4.0 Study Summary

Study title	Methods of Early Detection of Lung cancEr in PrimarY Care: The MEDLEY Study	
Short title	MEDLEY	
Design	Multi-centre, prospective, diagnostic accuracy feasibility study with blinded outcome assessment, an internal pilot phase and integrated health economic and acceptability work packages	
Participants	Adults aged 40 years and over with a GP referral for chest X-ray with symptoms of suspected lung cancer fulfilling NICE NG12 criteria	
Eligibility for WP1	**Inclusion Criteria**	**Exclusion Criteria**
	Must meet **all** the below: 1. Age 40 years or more at the time the consent form is signed. 2. Have had a CXR requested in general practice which fulfils NICE NG12 criteria (ref) 3. Consent to participate in WP1 (written/verbal/eConsent).	Meet one or more of the below: 1. Present with haemoptysis and/or have a pending urgent suspected cancer referral. 2. Have had thoracic CT or LDCT within the last year 3. Unable to, or chooses not to, receive a LDCT 4. Currently undergoing anti-cancer treatment. 5. Is pregnant* or currently breastfeeding. 6. Previously registered in the MEDLEY study **Assessment of pregnancy potential (or exemption) completed as per national guidelines and/or local Trust policy.*
Planned Sample Size	900	
Intervention	Each participant will receive both a chest x-ray (CXR) and low-dose CT scan (LDCT)	
Follow up schedule	12 months post registration Medical record review at 4 months and 12 months post registration	
	Objective	**Outcome measure**
Primary (WP1)	Establish feasibility and deliverability of a diagnostic accuracy study. Estimate parameters for the design of a potential, future definitive trial.	• Recruitment rate • Proportions of eligible patients consenting to participate • Time from site approach to opening • Sensitivity and specificity of CXR vs LDCT • Estimate of prevalence of lung cancer
Value of Information analysis (WP2)	Undertake a model-based economic evaluation and a value of information analysis with respect to a definitive trial.	• Cost effectiveness of LDCT vs CXR • VoI assessment for a definitive trial
Qualitative study (WP3)	Undertake an embedded qualitative study to obtain views on participation and non-participation, acceptability of trial design, recruitment and imaging requirements, and a stakeholder event to discuss implementation during and post-trial.	• Reasons for participating • Barriers to participation • Acceptability from patient perspective • Acceptability from GP perspective • Perspectives and priorities of key stakeholders
Internal pilot (6 months)	Assess the feasibility of study delivery to maximum target recruitment within the planned timelines.	Number of participants recruited, number of centres open, and recruitment rate/site/month.

5.0 Flow Diagram



6.0 Background

6.1. Lung cancer statistics

Lung cancer is the third most common cancer in the UK and is the leading cause of cancer death [1]. Compared to other common cancers which have seen great improvements in outcomes over recent decades, survival for patients diagnosed with lung cancer remains poor, particularly in the UK [2]. Patients' chances of surviving lung cancer are strongly linked to how early the disease is diagnosed [3]. The most common symptoms of lung cancer, such as cough, are extremely common in general, meaning that early diagnosis of the disease is challenging[4]. Consequently, 70% of patients in the UK have more advanced disease (stage III/IV) by the time their cancer is identified [5].

6.2. How is lung cancer diagnosed in usual care?

Patients who have symptoms that may suggest lung cancer typically access care from general practice. NICE guidance (NG12) outlines the investigations that patients with such symptoms should receive from primary care. For all symptoms, aside from haemoptysis which accounts for less than 5% of presentations, NICE recommends patients should be investigated with chest x-ray (CXR) and those with suspicious findings referred onwards for further investigation such as computed tomography (CT)[6]. The guidance does not include recommendations on actions to take if CXR is negative; the test is therefore relied upon to triage possible lung cancer cases. CXR is cheap, quick and convenient for patients. The main downside of CXR is that it misses about 20% of lung cancers[7], causing delays to diagnosis [8].

6.3. The role for LDCT

Low-dose computed tomography (LDCT) produces more detailed images than CXR and exposes patients to less radiation than conventional CT. Although LDCT has been shown to be more accurate than CXR in asymptomatic patients [9] its accuracy compared to CXR in symptomatic patients is unknown [10]. LDCT scans take longer to acquire and interpret and are more expensive (£90 vs £27) than CXR [11]. LDCT is much more likely to lead to findings of incidental abnormalities, unrelated to patients' symptoms, or nodules which then require further tests and/or follow up, the majority of which are subsequently found to be benign [9, 12]. Such findings can lead to unnecessary anxiety and inconvenience for patients [13, 14]. The most robust comparison of LDCT and CXR is from a screening study in asymptomatic patients, undertaken in the US [9]. Sensitivities were determined with reference to cancers presenting within 12 months of each test. These were reported as 94% for LDCT (95% CI 91 to 96%) and 73% for CXR (95% CI 73 to 74). However, accounting for the additional cancers detected on LDCT which were probably present in the CXR arm at the time of screening but presented beyond the 12-month follow-up period, CXR sensitivity may be as low as 47% (136/284) even accounting for overdiagnosis [15]. A systematic review of CXR in symptomatic patients reported sensitivity between 77% and 80%, based on presentations of lung cancer within one year of the test [7]. This estimate will also be affected by cancers present at the time of the CXR but not presenting for several years [15]. As well as uncertainty about the difference in sensitivity between CT and CXR in symptomatic patients, there are no published data about the stage distribution of the cancers missed on CXR but that LDCT would detect (subsequently termed CT-extra cancers). Screening studies report increased proportions of early stage lung cancers detected by CT (70% stage I/II in NLST and 77% in NELSON) [9, 16]. However, the stage distribution of CT-extra cancers in symptomatic patients may be less favourable. Lung cancers that cause symptoms tend to be larger, and may be located in parts of the lung poorly evaluated on CXR (e.g. the central hilar regions). Tumour size and central location both predict earlier metastatic spread, so these symptomatic cancers that are

identified on CT, but not on CXR, may be more advanced than screen detected cancers, thereby limiting the improvements in outcomes that might be expected.

6.4. The need for MEDLEY

A definitive comparative diagnostic accuracy trial of CXR and LDCT in symptomatic patients would require very large numbers of patients to be recruited, due to the low prevalence of lung cancer, and would be costly. MEDLEY is a feasibility study which will consider how best to address these challenges, provide evidence to indicate if a definitive trial is warranted and how it should be designed and conducted, and give vital insight on how we diagnose lung cancer in the future.

6.5. Why is this research needed now?

Lung cancer is the UK's leading cause of cancer death. Incidence of lung cancer is three-fold higher in deprived compared to affluent areas. Consequently, lung cancer is a key driver of health inequalities and a leading cause of premature mortality; particularly in less affluent regions such as the North of England, Scotland, and Northern Ireland [17-19]. This inequality must be addressed. Chances of survival are much better if the disease is identified early. Patients who are diagnosed with stage I disease have an 88% chance of surviving to one year versus only 23% of those diagnosed at stage IV[20]. Lung cancer outcomes in the UK have persistently lagged behind those of other high-income countries [2] and are partly related to the greater proportion of UK patients diagnosed with late-stage disease[21] which may reflect more limited availability of CT [22]. The UK has fewer CT scanners than similar countries [22] along with chronic shortages of radiologists and radiographers [23, 24]. CXRs requested by GPs are the most common radiological investigation –1,818,905 were performed in 2021/22 in England [25]. Existing NHS services are unlikely to be able to cope with changing the patient pathway from CXR to LDCT. A recent service evaluation in Leeds Teaching Hospitals of 750 GP CXR requests demonstrated that 31% patients fulfil NG12 criteria for urgent CXR. We estimate this would translate to an extra 564,000 CT scans per year additional to the 684,000 CT chest/abdomen performed annually in England – an 83% increase[25]. This would be unlikely to be deliverable given the current workforce shortages in radiology [23, 26]. Our analysis of a national primary care dataset (228,855 CXRs) and data from a large teaching hospital (62,439 CXRs) indicates that simple stratification based on age and smoking status can be used to identify patients who have a 3% or greater risk of clinical diagnosis of lung cancer within two years of imaging [27]. This could provide a simple but robust means to prioritise patients at higher risk for LDCT, consistent with the present NICE 3% risk threshold for cancer testing (e.g. with endoscopy or brain scanning) [6], but requires prospective testing.

England's health service has an aspiration of diagnosing 75% of cancers in stage I or II and improving early diagnosis is crucial to prospects of meeting that goal [28]. Transitioning from CXR to LDCT without adequate evaluation could lead to additional cost, workload, and potential delays for other service-users with limited confidence of feasibility or actual benefits for patients. The Health Services Safety Investigation Body has recommended that research be undertaken to ascertain if LDCT should be used as a first line test for symptoms that may suggest lung cancer to reduce diagnostic delay and improve outcomes [29]. This feasibility study is the first step in this research pathway.

7.0 Aims and Objectives

7.1. Aims

a) Establish whether a trial comparing the accuracy of LDCT to standard of care CXR in patients referred for imaging from primary care with symptoms that may suggest lung cancer, is feasible and acceptable to patients, GPs, and secondary care clinicians.

b) Determine if the costs of undertaking such a trial would be justified by the value of the additional information this would yield.

c) Assess the deliverability, acceptability, and impact of changing the pathway of initial investigation for patients with suspected lung cancer from CXR to LDCT across the NHS for patients, clinicians, NHS healthcare services and policymakers.

7.2. Primary Objectives

a) To undertake a feasibility study to establish the feasibility of a definitive trial based on the barriers and facilitators of a definitive trial, and to estimate parameters for the design of a potential, future definitive trial.

b) To obtain estimates of diagnostic accuracy of CXR and LDCT and establishing if these estimates are consistent with those from asymptomatic populations in RCT settings and symptomatic populations using retrospective data.

c) To undertake a model-based economic evaluation of changing the initial investigation for patients with suspected lung cancer from CXR to LDCT (either for all patients, or for a targeted subgroup of patients), and a value of information analysis with respect to a definitive trial.

d) To undertake an embedded qualitative study to obtain views on participation and non-participation, acceptability of trial design, recruitment and imaging requirements, and a stakeholder event to discuss implementation during and post-trial.

8.0 Study Design

The study is a multi-centre, prospective, diagnostic accuracy feasibility study with an internal pilot phase and integrated health economic and acceptability work packages. The study comprises three integrated Work Packages (WPs):

- WP1 is a multi-centre, prospective, diagnostic accuracy feasibility study with blinded outcome assessment (i.e., CXR is interpreted without access to LDCT and vice versa) and an embedded internal pilot phase to evaluate the feasibility of recruitment and therefore the deliverability of the study (see section 8.4).
- WP2 is a value of information study incorporating data generated from WP1.
- WP3 is qualitative study of acceptability, feasibility and deliverability which will be integrated with the delivery of WP1.

8.1. WP1

WP1 aims to recruit 900 participants with symptoms that may suggest lung cancer who have been referred from primary care for CXR from at least five UK centres. Patients will be recruited from secondary care sites and will follow a standard care pathway. All patients will receive a LDCT as well as a CXR, and both LDCT and CXR will be reported by independent consultant radiologists. The LDCT will be used to guide clinical care by the secondary care team and the report will be sent to the referring GP. All participants will be followed up for a maximum of 52 weeks. Outcomes are defined in section 14 grouped as i) feasibility of deliverability; ii) qualitative acceptability; iii) estimates of diagnostic accuracy; iv) imaging logistics; v) clinical outcomes; vi) economic outcomes. Those outcome measures informing the decision criteria to progress to definitive trial are stated in sections 14.1 and 14.2. The reference standard will be cancer diagnosis within 12-months of clinical follow-

up, but cancer diagnoses resulting from the paired LDCT (i.e. MDT approved diagnosis within 3 months of LDCT) will also be reported as a contemporaneous reference standard.

8.1.1. Blinding

Independent reporting of LDCT and CXR imaging for each participant is critical to the integrity of the study as the research question is proposing LDCT to be a replacement for, not adjunct to, CXR. As such radiology reporting and decision making for each imaging technique must be made without influence/bias from the other imaging technique completed at the same timepoint. To ensure blinding to the other imaging modality, LDCT and CXR images for the same participant will be reported by a Consultant Radiologist who will not have access to the results of the other imaging report for that participant, but will have access to relevant previous imaging such as previous thoracic CT or CXR (if carried out).

Separation of imaging in this way, together with ensuring availability of old images, is technically challenging for NHS radiology reporting systems. To address this issue both LDCT and CXR reporting will be outsourced to a third-party provider (Heart&Lung Health), which can ensure a robust, blinded radiology review system.

8.2. WP2

Value of information (VoI) analyses [30] are able to quantify the economic value of gathering additional information based on the expected improvement in decision making that the new information would provide. The most relevant VoI analysis for research design and prioritisation is the expected net benefit of sampling, which combines the expected value of sample information (EVSI) with the expected research costs of obtaining the sample information. EVSI analyses are the most complex of VoI analyses, typically requiring substantial computational investment.

A prerequisite for VoI analyses is an economic evaluation (a cost–utility analysis). WP2 will begin with the adaptation of an existing model for cost–utility analysis of lung cancer screening by LDCT [31] to the diagnostic setting and reimplementation in the statistical programming language R (which is necessary to achieve greater computational efficiency and allow parallelisation in a high performance computing environment). The adaptation of the model will include the incorporation of economic data gathered in WP1.

The model will be used to undertake EVSI analyses and preliminary expected net benefit of sampling analyses.

8.3. WP3

The qualitative work package will assess the acceptability and feasibility of conducting a diagnostic accuracy trial as well as the concept of a direct GP LDCT pathway for suspected lung cancer. The qualitative study will encompass semi-structured, in-depth patient interviews with approximately 30 purposively selected patients (10 of which will have declined to participate in WP1), semi-structured interviews and vignettes with 15 General Practitioners (GPs) and a national stakeholder event co-hosted with significant bodies such as the British Thoracic Oncology Group and NHS representatives.

This will provide findings relevant to the design of a feasible larger-scale trial, ensuring the trial design is informed by a broad spectrum of stakeholder insights and real-world applicability.

8.4. Internal Pilot

The study will include a five month internal pilot phase, occurring within the first five months of recruitment. The aim of the internal pilot is to assess the feasibility of study delivery to maximum

target recruitment within the planned timelines. The progression criteria to main study include number of participants recruited, number of centres open, and recruitment rate/site/month.

Progression Criteria	Red	Amber	Green
% Threshold	<50%	50%	100%
Study recruitment	<50%	50-99%	≥ 100%
Recruitment rate/centre/month	<6.67/centre/ month	6.67-13.33/centre/month	13.33/centre/month
Number of centres open	<3	3-4	5
Total number of participants recruited	<100	100-199	200

At the end of the internal pilot phase, if any of the green criteria are not met, remedial actions will be submitted to the funder for discussion. . Not all criteria are required to be green for study delivery to be considered viable. An independent Study Oversight Committee will review supplementary data on sample size assumptions, and their recommendations will feed into the pilot phase progression report to the funder.

9.0 Eligibility

Eligibility waivers to inclusion/exclusion criteria are not permitted.

9.1. Inclusion Criteria for WP1

Patients meeting ALL the following criteria will be considered for enrolment into the study.

1. Age 40 years or more at the time the consent form is signed.
2. Have had a CXR requested in general practice which fulfils NICE NG12 criteria [6]
3. Consent to participate in WP1 (written/verbal/eConsent).

9.2. Exclusion Criteria for WP1

Patients will be excluded from this study for ANY of the following reasons:

1. Present with haemoptysis and/or have a pending urgent suspected cancer referral.
2. Have had thoracic CT or LDCT within the last year
3. Unable to, or chooses not to, receive a LDCT
4. Currently undergoing anti-cancer treatment.
5. Is pregnant* or currently breastfeeding.
6. Previously registered in the MEDLEY study

*Assessment of pregnancy potential (or exemption) completed as per national guidelines and/or local Trust policy.

9.3. Patient, GP, and Stakeholder Eligibility for WP3

For patients:

1. Met the first two inclusion criteria listed in Section 9.1.
2. Consent to participate in WP3 (written/verbal/e-consent informed consent)
   Note: patients who decline to participate in WP1 will still be given the opportunity to take part in WP3 (see section 10.4)
3. Do not meet exclusion criteria 1, 2, 4, or 5 in Section 9.2

For GPs:

1. Consent to participate in WP3 (written/verbal/e-consent informed consent).

2. Current practicing General Practitioner.
3. Either
    a) Has referred a patient for a chest X-ray who was subsequently consented to WP1
    OR
    b) Has referred a patient meeting NG12 criteria for CXR

For stakeholders:

1. Consent to participate in WP3 (written/verbal/e-consent informed consent).
2. Relevant professional background, including:
    - Clinician in respiratory medicine, radiology, and radiography
    - senior leaders invited from professional organisations (e.g. Royal College of Radiologists, UK Lung Cancer Coalition)
    - commissioners (e.g. Integrated Care Boards)
    - policy makers (e.g. NHS England)
    - patient advocacy groups.

10.0 Recruitment

10.1. Recruitment Setting

10.1.1. Recruitment Setting for WP1

Patients are referred from primary care to their local secondary care radiology department for a CXR. The study will recruit patients from secondary care acute hospital trust radiology services in the UK.

Research centres will be required to have obtained local ethical and management approvals and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the study.

The proposed study pathway will correspond to the standard care pathway with the exceptions of consent, data collection, and LDCT.

10.1.2. Recruitment Setting for WP3

Patients who have been approached to take part in MEDLEY WP1 will provide optional consent to take part in WP3 at the point of joining the study, or at the point of declining participation.

Qualitative and stakeholder components of the study will involve professionals working from other settings, particularly primary care (GPs). The aim will be to recruit GPs who have referred a patient who had registered to WP1 in the first instance, but this can be opened up to other GPs who have referred a patient meeting NG12 criteria for CXR outside of the study if required.

10.2. Eligibility Screening for WP1

Participating research sites will be required to complete a non-registration log of all patients who have been referred from general practice for CXR who fulfil the NG12 criteria and are considered potentially eligible for the study on the basis of their X-ray request but not recruited into the study. Documented reasons for ineligibility or declining participation will be collected and closely monitored by the CTRU as part of the regular review of recruitment progress. Non-registration logs should be returned to CTRU on a monthly basis. The following anonymised data will be collected on the non-registration log:

- Age
- Sex
- Index of multiple deprivation (according to participant's postcode)

- Ethnicity
- Date screened

Patients who are not registered either because they are ineligible or because they decline participation will also have the following recorded:

- Reason not eligible OR
- Reason declining participation
- Main language
- Whether or not the patient agrees to take part in WP3 including contact details and preferred method to receive further information

10.3. WP1 Informed Consent and Eligibility

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996. The assessment of eligibility will be confirmed and the informed consent process will be undertaken by the PI or registered healthcare professional who is approved by the PI as detailed on the Authorised Personnel Log.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with standard routine care at the participating site including the collection of identifiable participant data. Participants must remain free to withdraw at any time from all or some aspects of the study without having to give reasons and without prejudicing their further treatment. Participants must be provided with a contact point where they may obtain further information about the study.

Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

Informed consent can be taken either (i) face-to-face on a paper form (written consent), (ii) as remote e-consent using REDCap, (iii) as remote verbal consent over the telephone. The mode of informed consent used will depend on the patient preference. Consent can be provided on the same day as NICE guidance stipulates imaging should be undertaken urgently (within 14 days) and as many centres now offer 'walk-in' appointments, patients typically proceed to have their CXR within a day or two of their consultation in primary care. There is minimal risk to the participant from the additional LDCT. The burden for participants is also minimal as there are no in person follow ups, imaging can be completed on the same day (or within 7 working days of each other), and each investigation is expected to take no more than 15 minutes.

Patients who provide informed consent who subsequently permanently lose capacity will be withdrawn from the study. Data collected up until the point of CTRU becoming aware of loss of capacity will be used in the analysis.

Note: If the patient withdraws between consent and registration the original GP CXR request will remain active, the patient will be advised to attend for that investigation, the report would be returned to the GP for actioning, and the PI will have no responsibility for actioning the result.

Consent forms do not need to be returned to CTRU for patients who are not registered.

(i) written or witnessed verbal consent face-to-face

For participants who choose to complete in-person consent, a paper copy of the consent form will be completed with the researcher. Witnessed verbal consent may be used for patients who have capacity to consent but are unable to physically sign the paper form. Patients may prefer to speak to the researcher in person or may feel more comfortable asking questions about the study face-to-face. The researcher may also feel this method is most appropriate after the initial telephone call, because of difficulties communicating over the telephone including language barriers or difficulty hearing. An in-person interpreter or telephone interpreting service could be used when completing consent this way.

(ii) remote e-consent using REDCap

Patients who choose to consent using remote eConsent will provide verbal consent for their initials, date of birth, email address and phone number to be disclosed to CTRU through the REDCap system. If the patient does not consent to this disclosure, they will be unable to use remote e-consent and a convenient time will be arranged to complete a remote verbal or paper consent process.

Assenting patients receive a link to a questionnaire (REDCap) prior to the eConsent telephone/video call. The researcher will discuss the study and what it involves, and each point on the consent form, with the patient. The patient will complete all questions and add a signature (by clicking a button to confirm completion of the form), then submit. The researcher will open the form and complete sign-off. The participant will receive an electronic copy of the consent form, or the researcher may download and post a copy if requested. Patients may prefer to receive things electronically, and not want to make the extra trip to hospital to see a researcher face-to-face. This process is efficient, and both the patient and researcher receive a completed copy within a short time frame. It also reduces paper resource use at the research site. If patients do not have access to, or feel confident using a computer and/or REDCap, face-to-face or verbal consent over the phone would be more appropriate. REDCap is also only available in English, which limits this form of consent.

(iii) remote verbal consent over the phone

For those not wishing to attend the hospital for face-to-face consent and unable to complete remote electronic consent (e.g. device accessibility) or preferring not to, the researcher will complete the consent form with the patient over the telephone. Each statement on the consent form will be read to the patient, with the researcher initialling and signing the consent form on behalf of the patient. A copy of the consent form signed on behalf of the patient will be posted/emailed to the patient. Patients may not have access to, or feel confident using a computer and/or REDCap but may also not want to make the extra trip to hospital to see a researcher face-to-face. Telephone interpreting service can be used when completing consent this way.

10.4. WP3 consent

10.4.1. Population

WP1 participants will be asked for optional consent to be contacted by a researcher about taking part in a qualitative interview at the point of entering until the target sample size has been reached. Participants will remain free to decline to take part in an interview at any time by revoking consent without giving reasons and without prejudicing further treatment. This includes withdrawing their data up to one week after the interview has taken place.

Patients who decline to participate in WP1 will also be offered the opportunity to take part in WP3, in order to understand reasons for non-participation. At the time of discussing participation for WP1

patients who decline to participate will be asked if they may be contacted in the future regarding another part of the study. Patients who give this consent to be contacted again, despite having declined to participate in WP1, will be contacted and asked if they wish to consent to WP3.

Assenting patients will receive a WP3 information sheet via their preferred method (postal/email) and will be contacted by telephone to provide an opportunity to ask any questions and discuss the study details with the qualitative researcher. An interview time and date will be mutually agreed on, accommodating preferences for either a telephone or video interview. Verbal consent to be interviewed will be taken by the qualitative researcher at the start of the call using a separate verbal consent form and recorded. Recording will stop after verbal consent and restart for the formal interview.

10.4.2. GP and stakeholders

GPs who have referred patients will be contacted by a researcher about taking part in a qualitative interview. If the target sample size is not reached, other GPs who have not referred patients involved in the study will also be contacted through local Clinical Research Network contacts until the target sample size is reached. GPs will be free to decline to take part in an interview at any time without giving a reason.

GPs will be contacted via email with a WP3 participant information sheet attached. An interview time and date will be mutually agreed on, accommodating clinical priorities and preferences for either telephone or video interview. Verbal consent to be interviewed will be taken by the qualitative researcher at the start of the call using a separate verbal consent form and recorded. Recording will stop after verbal consent and restart for the formal interview.

We will compile a list of potential stakeholders, drawing on network contacts and key connections through the British Thoracic Oncology Society and the Roy Castle Lung Cancer Foundation. All stakeholders will be invited to our event via email with an information sheet. Potential participants will be able to ask questions via email or telephone prior to the event. Arrival at the event will indicate consent to participate.

10.5. WP1 Registration

Informed consent for entry into the study must be obtained prior to registration.

Following confirmation of informed consent and eligibility participants will be registered into the study by an authorised member of staff at the study research site. Registration will be performed centrally using the CTRU automated, secure, 24-hour registration system which can be accessed via the web. To register using the web-based system a staff site email address, site code and Personal Identification Number (PIN) will be required. Authorisation codes and PINs will be provided by the CTRU to access the registration service. These codes will only be issued once a site has been fully approved and all the necessary documentation has been received at CTRU.

The following information will be required at registration:

- Participant details, including initials, sex and date of birth
- Site code for research site
- Confirmation of eligibility
- Confirmation of written informed consent and date
- Confirmation of completion of the baseline questionnaire (where applicable - paper/telephone administration only)

- Whether the participant requires an electronic link to complete the baseline questionnaire and preferred method of receipt and contact details (email/text) (where applicable)
- Preferred method of follow up questionnaire administration (where applicable - electronic/postal/verbal)
- Decision regarding optional consent to be contacted for WP3 including phone number and preferred method to receive further information

Once registration is complete, the system will allocate a participant ID number which will be shown on screen.

After registration the research site will:

- Add the unique participant ID number to the consent form if completed on paper
- Return a copy of completed paper consent forms, contact details form and paper baseline questionnaires (where applicable) to CTRU via secure file transfer
- Send the GP letter notifying the participant's GP of their participation in the study
- Arrange the CXR and LDCT appointments for the participant, including creation of new CXR/LDCT requests under the named responsibility of the local PI.
- Cancel the GP CXR request. **Note: Responsibility for actioning test results will transfer to the local PI at this point**

11.0 Treatment/Intervention Details

Participants will receive LDCT (technology being assessed) in addition to current standard of care (which includes CXR). At the time of study registration, two new requests will be generated for LDCT and CXR by the local participating centre MEDLEY study team and the original CXR request (made by GP) will be cancelled by the MEDLEY study team. These will be requested under the name of the local Respiratory Physician PI, and that Respiratory team will take responsibility for reviewing and actioning results from the LDCT report and CXR report as per local standard of care practice.

11.1. LDCT

CT image acquisition protocol

Subject position:

Participants should lie supine on the CT table with arms above their head and thorax in the midline of the scanner. Subject comfort should be optimised, and maximal inspiration rehearsed prior to the scan to minimise motion during the CT. Imaging should be performed during suspended maximal inspiration. No intravenous contrast material will be administered.

Localiser:

Sites should use their standard scanogram scout view (scanogram) to localise the start and end positions of the scan. The frontal localiser should be performed in the PA projection and at the lowest possible setting to minimise breast dose.

Volumetric CT scan:

The lung parenchyma (lung apices to bases) must be scanned in its entirety in a single cranio-caudal acquisition. The field of view selected as the smallest diameter as measured from widest point of outer rib to outer rib large enough to accommodate the entire lung parenchyma. Thin detector collimation (≤1.25mm) will be used.

Exposure factors:

Radiation exposures will be as low as possible while maintaining good image quality. The acquisition parameters will be set to ensure that the calculated radiation dose delivered to each individual is below 2 mSv (based on the median standard 70kg adult). This will be done by ensuring that the kVp and mAs settings are varied according to participant body habitus. The height and weight of participants will be used to enable accurate selection of exposure factors. Medical physics input should be obtained when setting up LDCT scanning protocols, and a standardised protocol should be used.

11.2. CXR

A PA projection radiograph will be acquired at maximum inspiration according to local hospital protocols for adult patients.

11.3. Categorisation of image reporting

Imaging reports for all study LDCT and CXRs will be added to hospital records via the Radiology Information System (RIS) either automatically or through manual transfer of the report text. The reports will comprise a summary category (LDCT 1-6 and CXR 1-6) and free text report. Computer-aided detection/artificial intelligence will not be used to analyse LDCT or CXR images.

- LDCT 1: Likely cancer – for urgent review in clinic
- LDCT 2: Indeterminate finding - requires follow-up CT (e.g. nodule)
- LDCT 3: Significant other respiratory finding requiring further clinical evaluation
- LDCT 4: Significant other non-respiratory finding requiring further clinical evaluation
- LDCT 5: No action required
- LDCT 6: Other
- CXR 1: Likely cancer – urgent CT scan recommended
- CXR 2: Indeterminate finding - requires follow-up chest X-ray (e.g. pneumonia)
- CXR 3: Non-malignant finding – CT scan recommended (e.g. ILD)
- CXR 4: Non-malignant finding – other investigation/clinical evaluation recommended (e.g. heart failure)
- CXR 5: No action required
- CXR 6: Other

The PI or delegated members of the team will review each imaging report for all registered participants at least weekly to action results. The LDCT result will primarily guide management, but the CXR report will also be reviewed in case of the rare scenario where an abnormality is noted on the CXR that is not seen on the LDCT (e.g. humeral lesion). If a participant has only completed one imaging modality, this will be used to guide management. A standardised letter will be sent to the GP, with a copy to the patient, (see section 12.8) including:

a) What actions have been arranged in Secondary Care (maybe none)
b) What actions are needed in Primary Care (maybe none)
c) The full text of the LDCT report (for information) OR CXR report if LDCT not completed
d) Comments from the clinical review meeting (maybe none)

11.4. Responsibility for further management

Actions required within secondary care (e.g. referral to the lung cancer service, referral to another hospital service, repeat imaging such as CT) will be arranged by the PI or delegated team as per local standard of care practice. Actions for Primary Care (e.g. antibiotics for a chest infection, repeat CXR

to ensure resolution of consolidation) will be clearly stated in section (b) of the letter. Coronary artery calcification, aortic valve calcification and emphysema will all be managed as per the hospital's normal policy for routine CT imaging. There is no requirement to follow the Targeted Lung Health Check protocol for these findings.

11.5. Withdrawal and opt-out

In the event a patient withdraws consent prior to registration, no further data is required to be submitted.

In the event a participant does not attend one or both of their imaging appointments they will continue to complete the follow up schedule unless unwilling to do so and eCRFs will continue to be collected unless consent for collection of follow up data is withdrawn.

Participants should not be withdrawn from the study unless it is harmful for them to continue, or the participant wishes to be withdrawn. The PI, or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the study are defined and documented using the Early Study Completion CRF in order that the correct processes are followed by the CTRU and site.

Participants may 'opt out' of one, multiple or all of the components listed below.

a) Completing a CXR
b) Completing a LDCT
c) Completing questionnaires
d) Receiving phone calls
e) Consent for their data to be used in future research
f) Consent to be contacted to take part in qualitative interviews
g) Collection of data from medical records

Participants who opt out of both components (a) and (b) i.e., non-attendance at both imaging appointments, will be contacted by telephone in the first instance to see whether it is feasible to rearrange an appointment within 14 days. If the participant is not contactable then a non-attendance letter will be sent to the participant and to the GP to inform them that no imaging has been performed (see below).

For participants who opt out of (a) the MEDLEY CXR request will be cancelled, the LDCT is outsourced for reporting as per protocol, and the PI will review the result and generate a standard MEDLEY output letter which will be sent to the participants' GP.

For participants who opt out of (b) the MEDLEY LDCT request will be cancelled, the CXR is outsourced for reporting as per protocol, the PI will review the result and generate a standard MEDLEY output letter which will be sent to the participants' GP.

In both of the above cases , clinical responsibility remains with the local PI.

For participants who opt out of components (a) - (f) (in any combination), data will continue to be collected as per the protocol schedule and all of the participants' data will be used in the analysis. Participants who opt out of all components (a) – (g) listed above will be considered a full study withdrawal, no further data will be collected past the point of withdrawal and data collected up to the point of withdrawal will be used in the analysis.

In line with the principles for handling end of participation events in clinical trials research (PeRSEVERE) (https://ukcrc-ctu.org.uk/page-persevere/), a letter will be posted/emailed to the participant, in the following circumstances;

(i) The participant does not attend either of their imaging appointments and it has not been possible to contact them by telephone.
The letter will emphasise the importance of contacting their GP to arrange a new CXR appointment and provide contact details for more information or any questions.

(ii) The participant has completed their imaging and subsequently opted out of one or more of (c) – (g) above.
The letter will thank them for their involvement in the study, confirm their position in the study going forward, offer the opportunity to follow progress and outcomes of the study and requesting feedback on their reasons for withdrawing if they are happy to do so.

12.0 Assessments/Samples/Data Collection

12.1. WP1&2 Submission of Study Data

Consent forms

Where paper consent forms have been completed, a scanned copy of the completed Informed Consent document will be returned to CTRU via the CTRU secure file transfer system (SFT).

Non-registration

Non-registration data will be collected via remote data entry (RDE) on electronic case report forms (eCRFs). Access to the live database will be provided by CTRU to site staff following site authorisation to start recruitment where (i) self-delivered RDE guidance training has been completed and (ii) the member of staff has the relevant delegated duty assigned on the authorised personnel log.

Registration, baseline and follow up data

Registration data is submitted via the CTRU 24-hour system. The baseline eligibility checklist is completed on paper and a scanned copy returned to CTRU via the CTRU SFT, all other baseline data is collected via RDE on eCRFs. Access to the live database will be provided by CTRU to site staff following site authorisation to start recruitment where (i) self-delivered RDE guidance training has been completed and (ii) the member of staff has the relevant delegated duty assigned on the authorised personnel log.

Participant questionnaires

Baseline questionnaires may be administered by the research team in person/on paper or over the telephone/on paper ***prior*** to registration. Scanned copies of paper questionnaires will be returned to CTRU via the CTRU SFT. Where electronic questionnaire administration of the baseline questionnaire is required, this will be indicated during registration and will be administered by the CTRU after registration. Non-responders to the electronic baseline questionnaire will receive 1 reminder.

Postal and electronic follow up questionnaires will be administered by CTRU using the preference indicated at registration. Telephone follow up questionnaire administration will be completed by the research team and a scanned copy of the paper form returned via CTRU SFT. Non-responders will receive 1 reminder.

Participating sites will be expected to maintain a file of essential study documentation (electronic Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the study.

Where central collection of reports is undertaken by the CTRU for central monitoring purposes it is the responsibility of site to obliterate all personal identifiable data prior to sending to the CTRU and use the study number plus date of birth and initials to identify the participant.

12.2. Schedule of Events

Please see next page.

Study visit	**Consent**	**Baseline**	**LDCT imaging appointment**	**CXR imaging appointment**	**HLH LDCT upload**	**HLH CXR upload**	**HLH LDCT report transfer**	**HLH CXR report transfer**	**Post-imaging clinical review of report**	**Follow up**	
Timeline	on or before day 0	Day 0	First test (LDCT) within 10 working days of GP CXR request, + additional 5 working days for CXR if unable to arrange on same day as LDCT		Within 2 working day of image acquisition		Within 2 working day of report being available[1]		Within 10 working days of report being available[2]	4m post baseline +/- 2 weeks	12m post baseline +/- 2 weeks
Informed consent	X										
Eligibility checks		X									
Contact details form		X									
EQ-5D questionnaire		X[3]								X[4]	
Demographics, medical history, & baseline clinical assessments		X									
Registration in Gen24		X									
Arrange CXR and LDCT appointments		X									
Cancel GP CXR request		X									
Send GP letter		X									
LDCT[5]			X								
CXR[6]				X							
RUSAE reporting			X	X							
Send patient/GP non-attendance letter (where applicable)			X	X							
Manual transfer of scans to HLH record from local PACs **OR** check automatic transfer via HL7 has been successful					X	X					
Manual transfer of scan report from HLH into local record OR check automatic transfer to RIS has been successful							X	X			
Review reports & initiate standard care									X		
Send GP patient result letter									X		
Medical record review										X	X
eCRF completion		X			X	X	X	X	X	X	X

[1]If the interval between HLH image upload and completion of reporting by HLH exceeds 5 working days please notify CTRU.

[2]If there is a delay between LDCT and CXR acquisition/report availability , the LDCT report should be reviewed first, followed by separate review of CXR report once available.

[3]administered by site in person/by telephone. If participant requires this to be sent electronically this will be administered by CTRU. Note: if electronic administration is required, contact details must be sent to CTRU on the day of the baseline visit.

[4]administered by CTRU if participant completing on paper/postal or electronic. Administered by site if participant requires telephone administration.

[5]Low-dose CT must be completed **prior** to chest X-ray.

[6]Patient should have both scans on the same day or within 5 working days of each other.

12.3. Eligibility and Baseline Assessments

The following information will be collected at the baseline assessment:

- Data relating to the clinical assessment of eligibility
- Formal confirmation of eligibility

For participants that complete formal eligibility to proceed to registration the following baseline data will be recorded prior to registration:

- Demographic information
- Relevant medical history and clinical assessments
    - BMI,
    - index of multiple deprivation,
    - ethnicity,
    - mental health diagnoses,
    - smoking status and history,
    - symptom(s) prompting imaging and duration,
    - Other parameters needed for lung cancer risk scores ($PLCO_{M2012}$/LLP_{v2}),
    - Name of General Practitioner who referred patient for chest X-ray and name of practice
- Questionnaire
    - health-related quality of life (EQ-5D-5L) in person/on paper/telephone/electronic administration (where applicable).

12.4. WP1 Registration

Registration will be completed at the baseline visit prior to booking the imaging appointments by a member of the research team after consent using the CTRU 24 hour system.

Following registration, the LDCT and CXR appointments will be arranged. Note: the LDCT must be completed before the CXR and within 10 working days of the GP CXR request, and there will be a maximum of 5 working days between the imaging tests.

The following information will be recorded **after** registration:

- Participant ID number
- Date of LDCT appointment
- Date of CXR appointment

12.5. LDCT and CXR appointments

Within 2 working days of the date of the participant's scheduled imaging appointment (s), the following information will be recorded:

- Whether the participant has attended the schedule appointment
- Related Unexpected Serious Adverse Events

If non-attendance at 1 or both of the imaging appointments, processes followed as per section 11.5.

12.6. HLH LDCT and CXR image upload

Within 2 working days of the image acquisition the following information will be recorded:

- Confirmation imaging was completed successfully

- Confirmation that letter has been sent for participants who don't attend either imaging appointment (where applicable)
- Confirmation of upload of images to Heart and Lung Health

Members of staff at recruiting centres, who are detailed on the authorised personnel log as responsible for this activity, will be provided with access to forward cases to the third-party system, and will be responsible for ensuring CXR and LDCT images are forwarded within 2 working days of image acquisition. Where available, old imaging will be transferred to HLH alongside the LDCT and CXR images acquired as part of MEDLEY. If available, the previous 3 thoracic CT scans and the previous 5 CXRs should be uploaded (of which 1 CXR should be over 1 year old).

12.7. HLH LDCT and CXR report transfer

Once reported by the HLH radiologists, reports will be returned to the relevant hospital PACS system. Depending on the local site arrangement, these results may automatically return to the hospital Radiology Information System (RIS), or need manually transferring by the study team from the hospital PACS into RIS within 2 working days of the report being available. The following information will be recorded:

- Duration between study upload to HLH and availability of completed report on HLH system
- Confirmation reports have been added to participant notes
- Radiological categorisation

12.8. Clinical Review/Action Meeting

The MEDLEY team at each centre will ensure the imaging results are received, reviewed and actioned in a timely manner (see Section 11.3 for further details). The study team will action any results reported by HLH according to local practice, which may include but not be limited to following up on findings or booking further tests and treatments. The clinical review of reports is strongly advised to take place within 5 working days of the reports being available and no more than 10 working days after the reports are available. A letter must be sent to the participant's GP using the standard template provided (see section 11.3). In addition, the following information will be recorded in the Clinical Review/Action Meeting eCRF:

- Clinical categorisation of LDCT report or CXR report if LDCT not completed
- Requirement for further review and outcome
- Actions (investigations/treatments)
- Confirmation that GP letter is sent

12.9. WP1&2 Follow Up Assessments

All participants will be followed up for a maximum of 52 weeks.

Month 4 Record Review and Questionnaire

A member of the research team will review the participant's medical records and record the following (relating to clinical activity resulting from MEDLEY imaging findings):

- Investigations
- Diagnoses (lung cancer (including stage), indeterminate nodules, and incidental findings) and date
- Treatments
- Possible harms

Participants will also complete an EQ-5D-5L via their preferred method of administration.

Month 12 Record Review
A member of the research team will review the participant's medical records and record the following:

- Investigations
- Diagnoses (lung cancer (including stage), indeterminate nodules and incidental) and date
- Treatments
- Possible harms

12.10. Site level imaging data

As the ability of the radiology services to meet demand for LDCT depends on a number of complex factors, in one or more sites we will collate some additional data which may include staffing levels, number of operational x-ray and CT machines, planned elective capacity, but also the non-attendance and cancellation rates, equipment unavailability due to breakdown and maintenance, cancelled lists for other reasons (e.g. staffing), as well competing priorities as any emergency or surveillance CT activity that takes place on elective CT lists. We will collate this for at least two non-consecutive months.

We will capture data from selected participating site(s) on site-level imaging capacity according to established methodology[32-36]:

- Total number of CT examinations (chest and other) undertaken per week
- Total number of CXR examinations (GP requested and total) undertaken per week
- Number of full-time equivalent radiographers and radiologists on rota per week.
- Proportion of CXR requests received that fulfil NG12 criteria on one day per week (week 1 = Monday, week 2 = Tuesday etc.)

12.11. WP1&2 Questionnaires

Consenting participants will complete an EQ-5D-5L questionnaire (See section 16.1.1) at baseline and 4 months via their preferred method. Non-responders will receive 1 reminder.

12.12. WP1 Protocol Deviations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

12.13. Definition of End of Study

The end of the study is defined as the date of last data item for the last participant remaining in the study.

12.14. WP3 Qualitative Data collection

WP3 data collection will be completed by the qualitative research team at QMUL.

Data on participants' and patients' experiences and views on recruitment methods, the acceptability of the interventions, and their perceptions of trade-offs between LDCT and CXR, such as accuracy versus radiation exposure and logistical concerns will be collected through semi-structured

interviews. Interviews will be recorded and transcribed verbatim by a QMUL approved transcription service.

GP data collection will use both semi-structured questions and vignettes. These interviews will explore GP perspectives on the implementation of LDCT, risk-based patient selection, and the impact on their workload. GPs will be asked to state their preferences for different scenarios depicted in the vignettes, and to explore these in detail.

Using the World Café methodology, the stakeholder event will facilitate discussions across multidisciplinary panels, capturing qualitative insights on LDCT's acceptability and the feasibility of scaling up for a definitive trial.

13.0 WP1 Safety Monitoring/SAEs

13.1. General Definitions

A Serious Adverse Event (SAE) – means an untoward occurrence that:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability,
- consists of a congenital anomaly or birth defect,
- is otherwise considered medically significant by the Investigator.

A Related Unexpected Serious Adverse Event (RUSAE) means an SAE occurring to a research participant that in the opinion of the Chief Investigator was:

- 'Related' that is, it resulted from the administration of any of the research procedures, and
- 'Unexpected' that is, the type of event is not listed in the protocol as an expected occurrence.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol section 12.4 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

13.2. Operational Definitions for (S)AEs

13.2.1. Expected AEs/SAEs – Not reportable

LDCT and CXR are low-risk with well-known safety profiles and as such, adverse events will only be reported if they meet the seriousness criteria (12.1), are related to the intervention, and occur on the day the intervention is received. AEs and SAEs which are not related to the study intervention (e.g., as a result of further investigations or treatment later in the patient pathway) are NOT reportable.

13.2.2. Recording & Reporting related SAEs and RUSAEs

All SAEs and RUSAEs occurring on the day of imaging must be recorded on the SAE/RUSAE Form and sent to the CTRU within 24 hours of the research staff becoming aware of the event. Once all

resulting queries have been resolved, the CTRU will request the original form should also be posted to the CTRU and a copy to be retained on site.

For each SAEs /RUSAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to study drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be sent to the CTRU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All RUSAEs will be reviewed by the CI and will be subject to expedited reporting to the Sponsor (dependent on Sponsor processes) and the main REC by the CTRU on behalf of the CI within 15 days.

13.3. Responsibilities

Principal Investigator / Authorised individual:

1. Checking for SAEs when participants attend their imaging appointments.
2. Judgement in assigning:
   - Seriousness
   - Relatedness
   - Expectedness
3. To ensure all RUSAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow-up information as soon as available.
4. To report RUSAEs to local committees in line with local arrangements.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment.
2. Undertake RUSAE review.
3. Review all events assessed as Related / Unexpected in the opinion of the local investigator . In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the main REC.

CTRU:

1. Expedited reporting of Related / Unexpected SAEs to the main REC and Sponsor within required timelines.
2. Preparing periodic safety reports to the SOC as appropriate.
3. Notifying Investigators of Related / Unexpected SAEs which compromise participant safety.

Study Oversight Committee (SOC):

In accordance with the study Terms of Reference for the SOC, periodically reviewing safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

14.0 Outcome Measures

Outcomes are grouped according to type and those marked with an asterisk (*) will inform the decision to proceed to, and/ or inform the design of a definitive trial.

14.1. WP1 Quantitative outcomes

Outcomes are grouped according to type.

14.1.1 Outcomes relating to feasibility and deliverability of a definitive trial

- (*) Recruitment rate: number of participants recruited per centre-month
- (*) Proportions of eligible patients who consent/do not consent to participate, including assessment of non-participant characteristics associated with possible inequalities in participation
- (*) Time from site approach to opening, from opening to recruiting first participant, and duration of site recruitment

14.1.2 Estimates of diagnostic accuracy

- To inform sample size calculation for a definitive trial:
  - (*) Sensitivity & specificity of CXR using contemporaneous LDCT as a reference standard
  - Comparative sensitivity and specificity of LDCT and CXR using lung cancer diagnoses within one year (given the shorter follow-up this being a feasibility study) as reference standard
  - Sensitivity of CXR reported by cancer stage using contemporaneous LDCT as a reference standard
  - (*) Correlation/discordance between LDCT and CXR test results: proportions of paired tests that agree/disagree on presence of lung cancer.

14.1.3 Imaging logistics

- (*) Proportions of recruited participants not undergoing imaging with LDCT & CXR
- Time from CXR request to imaging & report, and reporting time by radiologist
- Incidences of unblinding (CXR)
- Total number of CT examinations (chest and other) undertaken per week
- Total number of CXR examinations (GP requested and total) undertaken per week
- Number of full-time equivalent radiographers and radiologists on rota per week.
- Proportion of CXR requests received that fulfil NG12 criteria on one day per week (week 1 = Monday, week 2 = Tuesday etc.)

14.1.4 Clinical outcomes

- (*) Prevalence of lung cancer among recruited patients
- Stage & histology of lung cancer at diagnosis
- Prevalence of indeterminate pulmonary nodules requiring CT surveillance
- Prevalence of incidental findings
- Subsequent investigations because of imaging (lung cancer and incidental findings)
- Eventual treatments for diagnoses resulting from imaging (lung cancer and incidental findings)
- Harms of investigation or treatment (including but not limited to invasive investigations or surgery for benign disease)

- Prospective validation (discrimination and calibration) of risk stratification to select patients for LDCT

14.2. WP2 Economic Outcomes

- Cost-effectiveness analysis of LDCT versus CXR, adapted from our model previously constructed on LDCT for asymptomatic patients by MEDLEY co-applicants and used in the recent UK NSC evaluation of lung cancer screening (35) evaluating strategies where all CXRs are replaced by LDCT, and also a targeted LDCT strategy (based on the 3% threshold).
- (*) Value of information assessment (including expected value of sample information) for a definitive trial considering total replacement of CXR with LDCT as well as targeted use of LDCT
- EQ-5D-5L at baseline and 4 months from all participants (including conversion to utility values with a suitable value set/tariff)
- Projected use (and cost) of subsequent investigations under counterfactual assumptions where only one imaging test (CXR or LDCT) is used

14.3. WP3 Qualitative outcomes

- Reasons for participating/not participating, barriers to participation and whether these contribute to disparities in recruitment
- Acceptability from patient perspective of:
  - Recruitment strategy
  - Trial design and imaging requirements
  - Proposed risk stratification of patients to receive LDCT instead of CXR
- Acceptability from GP perspectives including identifying site-level barriers and considering the impact of further investigations, treatments and additional diagnoses resulting from LDCT
- Perspectives and priorities of key stakeholders on post-trial implementation of instituting LDCT instead of CXR for lung cancer detection in routine primary care across the health system.

15 WP1 Statistical Considerations

15.1 Statistical Analysis Plan (SAP)

Statistical analysis is the responsibility of the CTRU Statisticians. A full statistical analysis plan (SAP) will be written according to published recommendations [37] before formal analyses are undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures and guidelines and will be finalised and agreed by the appropriate members of the research team and reviewed by the Study Oversight Committee (SOC). Any changes to the finalised analysis plan, together with reasons for changes will be fully documented. All analyses will be conducted using SAS version 9.4, unless stated otherwise.

Progression to the main study will be assessed after 5 months of recruitment, allowing for a 1-month decision period by the funder. Blinded interim reports will be presented to the SOC containing descriptive information. This will include data on recruitment, follow-up, safety and data quality.

A single final analysis will be conducted after the study is closed to recruitment and follow-up and when the full database has been cleaned and locked.

The main study population will include all participants registered to the study, regardless of post-registration activity.

A per protocol population, for pre-specified analyses, will consist of registered participants who complete both the LDCT and CXR tests within a maximum of 5 working days of each other (including

participants with indeterminate results) and have either a positive or negative cancer diagnosis at the end of the 12-month follow-up period.

15.1.1 Screening, flow of patients and baseline characteristics

The flow of participants and sites through the study will be presented in a modified Standards for Reporting of Diagnostic Accuracy Studies (STARD) diagram [38, 39], which will include numbers of potentially eligible patients, not eligible (with reasons), completing each of the index tests, positives/negatives on each test and reference standard results (with reasons where no reference standard is available).

Summary statistics will be presented for baseline participant characteristics by arm using means, standard deviations, medians, minimum, maximum, quartiles and range for continuous variables and counts and percentages for categorical variables.

In line with the STARD guidelines [39], the following items will also be reported:

- Distribution of lung cancer staging data
- Distribution of alternative diagnoses in participants without lung cancer
- Time interval and any clinical interventions between LDCT, CXR and the reference standard (cancer diagnosis within 12-months of clinical follow-up)

15.1.2 Analysis of outcomes

Continuous variables will be summarised using simple descriptive statistics, means, standard deviations, medians and ranges. Categorical variables will be summarised using counts and percentages, with proportions and confidence intervals reported as appropriate.

15.1.3 Feasibility outcomes

The monthly recruitment rate of participants to the study will be calculated by centre and overall. Point and precision estimates will be obtained for the recruitment rate using a log-linear Poisson regression model, with an offset term for total recruitment duration.

The number of participants who consent and who do not consent to participate in MEDLEY will each be divided by the number of patients screened who are eligible to take part in the study. A confidence interval for the proportion will be calculated using the exact method.

Centre performance will be summarised descriptively:

- Time from site approach (defined as date of issuing formal site selection email) to opening (defined as date of Sponsor Green Light to recruit email)
- Time from site opening to recruiting first participant
- Duration of site recruitment

15.1.4 Diagnostic accuracy

Crosstabulations of the results of each test will be reported (positive/negative/indeterminate). Sensitivities and specificities will be calculated for each test using the numbers of lung cancer cases or non-cases respectively and reported together with appropriate 95% confidence intervals.

15.1.5 Imaging logistics

The proportions of recruited participants not undergoing imaging with CXR alone, LDCT alone and both CXR and LDCT will be reported together with appropriate 95% confidence intervals.

15.1.6 Clinical outcomes

An estimate of the prevalence of lung cancer in the MEDLEY study population will be reported as a percentage together with an appropriately derived 95% confidence interval. The prevalence will be estimated based on confirmed cancer diagnoses after 12 months of follow-up.

15.1.7 Risk stratification strategy

The strategy developed by the MEDLEY team [27] will be reviewed using the MEDLEY study data. Incidence of lung cancer will initially be investigated according to the age and smoking status of MEDLEY participants. Comparisons between the data observed in MEDLEY will be drawn with data from the initial development of the risk strategy.

15.2 Sample Size

Based on realistically recruiting 5 participants per site per week (i.e. 20 per site per month) and allowing staggered opening of sites, it is estimated that 900 participants can be recruited to MEDLEY within a 12-month recruitment timeframe. Recruiting a total of 900 patients will permit estimation of a per-centre-month recruitment rate for a full diagnostic accuracy trial and relevant trial sample size parameters with acceptable precision. For the recruitment rate, using generalised linear modelling theory, and working with the log-likelihood and Hessian for a one-parameter Poisson model, 900 participants gives a 2-sided 95% confidence interval for relative precision as (1/1.068 to 1.068) times the estimated rate. For example, with 20 participants per centre-month recruited, then a 95% confidence interval for the true recruitment rate would be (18.7 to 21.4) per centre-month. Based on 2021/22 -level data, between 250-579 CXRs per week per site are requested [25]. Our unpublished analysis indicates 31% of CXRs fulfil NG12 criteria, and experience with the Yorkshire Lung Screening Trial demonstrates 50% of eligible patients are recruited. Hence the average recruitment rate of five/week/centre is realistic.

Sensitivities of CXR and LDCT will be estimated. We anticipate that prevalence of lung cancer detected will be at least 1.7%. This is based on the proportion of those who were diagnosed with lung cancer within two years following investigation with CXR and with similar characteristics as participants who will be recruited to MEDLEY [40]. Although the follow up period for MEDLEY will be one year, rather than two years, the number of cancers detected will exceed that which would be identified on CXR alone and it is likely that a substantial proportion of cancers not detected on CXR would take longer than two years to be diagnosed [41].

As a feasibility study, MEDLEY has not been designed for any pre-specified precision (which would be the design criteria for a definitive trial). With a prevalence estimated as 1.7%, an estimated sensitivity of 90% would have an 95% exact confidence interval covering values as low as 72% (estimated using the Clopper-Pearson exact method). Other metrics including specificity of CXR/LDCT, proportions of concordant/discordant imaging results, proportions completing imaging, and proportions completing questionnaires would all have 2-sided 95% confidence intervals +/- 3.3% (estimated using the normal approximation method) assuming that a minimum of 97% of participants are included in estimates of specificity, and assuming a worst-case estimate of 50% where estimated variance is maximised.

We have used simulation to predict how precisely we will estimate the proportion of CXR requests that fulfil NG12 criteria. Assuming that there will be at least 169 centre-weeks of recruitment and that for each of these, GP CXR requests will be assessed for NG12 and those eligible contacted until 5 potential recruits are identified, we expect to estimate the proportion of requests fulfilling NG12 with a 95% confidence interval width of 2.4%, with the interval width being below 3.0% with 90%

probability. The simulation incorporated uncertainty in the population proportion of CXR requests fulfilling NG12 criteria (Beta distribution with parameters 31 and 69) and the proportion of CXR requests which do fulfil NG12 criteria resulting in a potential recruit (Beta distribution with parameters 5 and 5).

15.3 Site-level imaging data

Using these data, we will estimate the number of CT slots required to meet a range of demand percentiles, both before and after including the patients redirected from the CXR pathway. This will include the 85th percentile (which is typically used to describe the capacity required for an urgent service with variable demand). This will take into account capacity necessary to set aside ('carve-out') for emergency and surveillance procedures. We will, therefore, be able to ascertain the number of additional weekly slots required to meet the demand from the redirected patients, at any given demand percentile.

We will estimate the maximal capacity of the sites currently with respect to CT, how many additional CT tests would be required if all GP CXR requests that fulfil NG12 criteria were converted to LDCT, and alternatively the number of additional scans if conversion to LDCT was restricted to those who met a proposed 3% risk threshold.

16.0 WP2 Economic Evaluation and Value of Information Analysis Plan

A health economic analysis plan (HEAP) will be developed and reviewed by the Study Oversight Committee (SOC).

The objective of the health economic analysis is to determine whether replacing CXR with LDCT for some or all primary care referrals for suspected lung cancer is a cost-effective use of limited NHS resources. The economic evaluation will generally follow the NICE reference case for economic evaluations, in particular:

- Health effects will be captured by the quality-adjusted life year (QALY), with a preference for this to be measured among patients using the EQ-5D-5L and valued by a representative general population sample of the UK population via the time trade-off method.
- Costs will be included from the perspective of the NHS and publicly funded personal social services.
- A cost-effectiveness threshold of £20,000 to £30,000 per QALY will be used.
- A lifetime time horizon will be used.
- Future costs and QALYs will be discounted by 3.5% per year.

16.1. Collection and analysis of economic data

16.1.1 Health-related quality of life

We will collect EQ-5D-5L at baseline and 4 months. Standard descriptive and graphical analyses will be conducted as per the EuroQol manual [42]. We will calculate utility values using the most appropriate value set, which could come from the second UK EQ-5D-5L valuation study or crosswalk to the EQ-5D-3L. If both of these are available for use then the base case analysis will be dictated by the NICE position statement. We will examine differences between measures at baseline and 4 months, stratified by lung cancer status, e.g., comparing EQ-5D-5L utility at the two timepoints using the paired t-test.

16.1.2 Resource use

For each participant, we will assemble relevant data on their use of healthcare resources, including the initial imaging reports, subsequent investigations for lung cancer, subsequent investigations for incidental findings, and subsequent imaging of pulmonary nodules of indeterminate risk.

As all participants will have received CXR and LDCT, but each of these investigations will be reported independently, we will develop and apply rules to determine which healthcare resources would be used if only one of the imaging technologies had been used. For example, if the reports are LDCT1 (likely cancer – follow up in clinic) and CXR1 (likely cancer – urgent CT scan), then in the LDCT-only counterfactual there would be the cost of LDCT plus subsequent cancer investigations, while in the CXR-only counterfactual there would be the cost of CXR plus a (standard-dose) CT scan plus subsequent cancer investigations.

We will statistically summarise:

- actual resource use for participants in MEDLEY
- counterfactual resource use if only CXR used
- counterfactual resource use if only LDCT used.

16.1.3 Unit costs

Unit costs will generally be sourced from recognised sources, e.g., NHS National Cost Collection and the PSSRU Unit Costs of Health and Social Care.

As cost-effectiveness results are expected to be very sensitive to the unit costs for CXR and LDCT, we will also undertake pragmatic literature reviews and microcosting exercises to accurately estimate the unit costs for these imaging techniques.

16.2 Adaptation of lung cancer screening model

An existing Microsoft Excel economic model for cost–utility analyses of lung cancer screening will be adapted to create an economic model for the lung cancer diagnostic setting.

The model will be translated into R, with the following expected benefits:

- Improved ability to test and validate the model
- Greater flexibility (e.g., the Excel model limits the number of individuals that can be simulated in a single run)
- Improved speed of execution
- Ability to parallelise execution on a high-performance computing cluster

The structure of the model will need to be updated for use in the diagnostic setting:

- No need for subsequent imaging (except as indicated by, e.g., indeterminate nodules)
- Patients will be symptomatic and will have been referred for suspected lung cancer, which affects the pre-test probability of lung cancer (and the stage distribution of lung cancers presenting) and health-related quality of life
- Detail around the testing process will be enhanced

Various data collected from MEDLEY will be combined with data identified through pragmatic literature review and incorporated into the model:

- Distributions of patient characteristics in the diagnostic setting (age, sex, smoking status, $PLCO_{m2012}$ lung cancer risk prediction)

- Health-related quality of life (EQ-5D-5L utility)
- Prevalence and stage distribution of lung cancer in the diagnostic population
- Subsequent investigations

16.3 Cost-utility analysis

Following adaptation of the model, a cost-utility analysis will be conducted.

Population: Patients referred from primary care with suspected lung cancer (NG12) excluding those with haemoptysis (for whom CT is already the primary investigation).

Competing options:

- CXR all: All patients receive CXR as the primary investigation
- LDCT stratified: A simple decision rule will classify patients according to their pre-test probability of lung cancer, with higher risk patients receiving LDCT as the primary investigation and lower risk patients receiving CXR as the primary investigation
- LDCT all: All patients receive LDCT as the primary investigation

Analysis details (in line with NICE reference case):

- Perspective: NHS and publicly funded personal social services
- Time horizon: Lifetime
- Discount rate: 3.5% for costs and QALYs
- Cost-effectiveness threshold: £20,000 per QALY

Parameters in the model will be subject to uncertainty and probabilistic analyses will be undertaken. Cost-effectiveness acceptability curves and distributional plots for incremental net benefit will be produced.

A budget impact analysis will not be conducted, but the results will be shown based on the expected annual population affected and the costs will be disaggregated so that the contribution of the primary investigation on costs can be seen.

16.4 Value of information analyses

We will conduct value of information analyses following the cost-utility analysis. These analyses estimate the value that can be obtained through obtaining more information about parameters of the economic model which then lead to being able to make a better policy decision. All value of information analyses will be calculated based on the incident population (the number of people referred from primary care for investigation for possible lung cancer meeting NG12 criteria) for 10 years, a willingness-to-pay of £20,000 per QALY, and discounting at 3.5% per year.

16.4.1 Expected value of perfect information (EVPI)

The EVPI is an upper bound for the value which can be obtained by reducing parameter uncertainty, as it gives the expected value of *immediately* obtaining perfect information about every parameter in the model, even those for which information is extremely difficult to gather (e.g., parameters relating to how lung cancer develops, which is typically unobserved).

16.4.2 Expected value of perfect parameter information (EVPPI)

EVPPI is similar in concept to EVPI, except that model parameters are divided into two groups, with perfect information immediately being obtained for the parameters in one group, and no additional information being obtained for the parameters in the other group. Different partitions of parameters

can be undertaken, including calculating the value of perfect information for a single parameter while all other parameters remain subject to uncertainty. The HEAP will prespecify which partitions of parameters will be analysed.

16.4.3 Expected value of sample information (EVSI)

EVSI analyses are distinguished from EVPI and EVPPI because they require assumptions about how information can actually be gathered. The analyst must select particular study designs which could be adopted and how the findings from these studies would be integrated with existing knowledge. For example, an EVSI analysis could estimate the value of a larger version of the MEDLEY study, giving information on the relative diagnostic accuracy of CXR and LDCT, as well as the prevalence of lung cancer in the population and how this relates to observable characteristics such as age, sex, smoking status (and risk prediction such as $PLCO_{m2012}$). These future studies are repeatedly simulated, with each simulated study dataset then being integrated into the economic model to estimate whether the additional information improved decision making, and if so by how much.

Possible target study designs for the EVSI analyses will be identified in the HEAP, but which of these is taken forward for EVSI analysis will be informed by the findings of the EVPPI analyses. EVSI analyses will explore how the value to decision makers of future studies is influenced by sample size.

17 WP3 Qualitative Analysis

17.1 Analysis

Interviews will be recorded and transcribed verbatim using a QMUL approved transcription service. The qualitative data obtained from patient and GP interviews, and the notes from the stakeholder event will be analysed using a framework approach to applied thematic analysis, with the assistance of NVivo software for managing and coding the verbatim transcripts. The analysis will commence with an initial thorough reading of the transcripts, allowing for the identification and development of early, data-driven codes. These preliminary codes will then be applied within a skeletal framework, which is specifically designed to address the analytic aims of understanding the factors influencing trial participation, evaluating the acceptability of the recruitment strategy, and assessing the acceptability of implementing low-dose computed tomography (LDCT) in comparison to chest X-rays (CXR). The coding framework will be refined iteratively through an ongoing process, led by the postdoctoral qualitative researcher in discussion with sub-study leads (Quaife & Black). This researcher will engage in regular discussions with the broader research team to challenge, refine, and support the interpretation of the data, ultimately leading to the development of the final thematic framework.

17.2 Qualitative study sample size

It is anticipated that up to 30 patients (10 of which will have declined to participate in WP1) will be identified to take part in semi-structured interviews to ensure diverse representation across various demographics and risk factors associated with lung cancer. The sample will include both patients who have been registered to WP1 and those who declined to participate.

18 Study Monitoring

18.1 Study Oversight Committee

A study Monitoring Plan will be developed and agreed by the Study Management Group (SMG) and Study Oversight Committee (SOC) based on the study risk assessment; this may include on site monitoring. The SOC will also review the safety and ethics of the study. Detailed reports will be

prepared by the CTRU for the SOC at regular intervals. The SOC will be provided with detailed reports containing the information agreed in the data monitoring analysis plan.

18.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the study is at analysis. However missing data items will not be chased from participants (although missing questionnaires sometimes are). The Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

18.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the SOC and, where applicable, to individual NHS Trusts.

19 Quality Assurance and Ethical Considerations

19.1 Quality Assurance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research, and through adherence to CTRU Standard Operating Procedures (SOPs).

19.2 Serious Breaches

Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the Research Ethics committee SOP) A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the study subjects, or the scientific value of the research. In the event of doubt or for further information, the Investigator should contact the study team at the CTRU.

19.3 Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996 or later. Informed written consent will be obtained from the patients prior to registration into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a Research Ethics Committee (REC) prior to entering patients into the study. The CTRU will provide the REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

20 Data Protection and Confidentiality

The data controller for WP1 is University of Leeds. Participating sites will be data processors for any study data processing (while remaining data controllers of data processing required for patient care). Queen Mary University of London and University of Exeter will also be data processors for the study.

All data processing for the study will be in accordance with the 2018 Data Protection Act and in line with the principles of the UK General Data Protection Regulation. Personal data will be processed under a lawful basis of 'task in the public interest' (GDPR Article 6, 1(e)) and special categories of personal data (in this case, data about health, racial or ethnic origin) will be processed for scientific research purposes (GDPR Article 9, 2(j)).

All potential study participants are provided with detailed information about how their data will be processed before any personal data is processed for the study. Any material changes to how data will be processed will be communicated to study participants in a timely manner (prior to the changes, if reasonably possible).

Personal data will only be processed for specified, explicit and legitimate purposes, and will be adequate, relevant and limited to those purposes. Data will be stored and transferred securely for all processing. The study will undergo an information governance risk assessment at the CTRU to ensure its proposed processing is compliant with data protection laws.

Confidentiality of participant data will be maintained at all times, with access to data granted only to those who need it for legitimate reasons (i.e to conduct the study, or to ensure the study has been conducted lawfully). Participants will allow access to their confidential data through the informed consent process. In general, for data transferred between participating centres and CTRU, patients will be identified in the study by their initials, date of birth and a study-specific ID number. Sites are responsible for maintaining this pseudonymisation on any data sent to the CTRU. Any exceptions (e.g. collecting unredacted consent forms at the CTRU for central monitoring of informed consent) will only be for legitimate reasons and will be explained fully to participants in advance of data processing. Where central monitoring of source documents, or copies of source documents, is required by the CTRU, the participant's name must be obliterated by site before sending. Any breach of confidentiality or of participants' personal data will be handled and reported (if required) in line with relevant laws.

Data transferred between CTRU and University of Exeter will be pseudonymised and will include participant study ID number and age but will not include initials or date of birth.

Recording of qualitative interview consent and the formal interview will be made separately. Interview recordings will be saved securely at QMUL until transcription has been completed and then will be deleted. Transcription will be completed by a QMUL approved transcriber with a signed confidentiality agreement in place with QMUL. Qualitative interview transcripts will be retained for potential re-use in secondary analysis studies. QMUL will only keep contact details whilst required to run the study.

Data will be made available for secondary research once the main study objectives are complete. See Section 23.2 (data sharing for secondary research purposes) below. Transcripts will be held at QMUL in a secure archive and can be shared upon reasonable request and the appropriate ethical permissions.

Study data will be retained for a minimum of 15 years. When there is no longer a lawful basis for retaining the data, it will be securely destroyed.

Note: the economic model for the lung cancer diagnostic setting developed as part of this study will not contain any participant level data and will not be subject to the destruction period detailed above.

20.1 Archiving

At the end of the study, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. Transcriptions and consent recordings will be retained for the duration of the study and then a minimum of 5 years at QMUL. Data will be securely destroyed after five years. This is to comply with the UK Policy Framework for health and social care research, the Data Protection legislation and Barts Health NHS Trust (Barts Health) and Queen Mary University of London (Queen Mary) Policies on the Retention and Disposal of Records (based on Department of Health recommendations on records retention).

Note: the economic model for the lung cancer diagnostic setting developed as part of this study will not contain any participant level data and will not be subject to the archiving period detailed above.

21 Statement of Indemnity

This study is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical study and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care. The sponsor has not made any arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

22 Study Organisational Structure

22.1 Individuals and Individual Organisation

Chief Investigator (CI) – As defined by the UK Policy Framework for Health and Social Care Research, the CI is responsible for the design, management, and reporting of the study.

Study Sponsor – The Sponsor is responsible for study initiation management and financing of the study as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the study contract.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the study in accordance with the UK Policy Framework for Health and Social Care Research and CTRU SOPs. The CTRU will provide set-up and monitoring of study conduct to CTRU SOPs, including, registration design and service, database development and provision, protocol development, CRF design, study design, source data verification, monitoring schedule and statistical analysis for WP1 of the study. In addition the CTRU will support REC submissions and study set-up, ongoing study management including training, monitoring reports and promotion of the study. The CTRU will be responsible for the day-to-day running of the study including study administration, database administrative functions, data management, safety reporting and all statistical analyses.

University of Exeter – Researchers at the University of Exeter will have responsibility for the Value of Information analysis for WP2 of the study.

Queen Mary University of London – Researchers at Queen Mary University of London will have responsibility for providing information to participants, taking consent, and carrying out qualitative interviews for WP3 of the study.

22.2 Oversight / Study Monitoring Groups

Study Management Group (SMG) – The SMG, comprising the CI, CTRU team, other key external member of staff involved in the study will be assigned responsibility for the clinical set-up, on-going management, promotion of the study, and for the interpretation and publishing of the results. Specifically the SMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the SOC, (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment and follow-up procedures, (viii) auditing consent procedures, data collection, study end-point validation and database development.

Study Oversight Committee (SOC) – The SOC, with an independent Chair, will provide overall supervision of the study, in particular study progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a patient representative. The CI and other members of the SMG may attend the SOC meetings and present and report progress. The Committee will meet 6 monthly as a minimum.

23 Publication Policy and Data Sharing

23.1 Publication Policy

The study will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main study publication, giving details of roles in planning, conducting and reporting the study.

To maintain the scientific integrity of the study, data will not be released prior to the first publication of the analysis of the primary endpoint, either for study publication or oral presentation purposes, without the permission of the Study Oversight Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the study until the first publication of the analysis of the primary endpoint.

23.2 Data Sharing for Secondary Research

Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all study participants (excluding any study-specific participant opt-outs)

will be made available for secondary research purposes at the end of the study, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete.

Data will be shared according to a controlled access approach, based on the following principles:

- The value of the proposal will be considered in terms of the strategic priorities of the CTRU, Chief Investigator and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request.
- We encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets.
- The timing and nature of any data release must not adversely interfere with the integrity of the study or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual study or research project basis, a reasonable period of exclusivity will be agreed with the study or research project team.
- Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. We will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. We will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants.
- Any data release must be in line with any contractual obligations to which the CTRU is subject.
- The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project.
- The research project must have clear objectives and use appropriate research methods.
- The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate IT security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure.

Data will only be shared for participants who have given consent to use of their data for secondary research.

Data will only be made available in such a way that data recipients cannot identify individuals by any reasonably likely means, and we will only share data for projects that are clearly in the public interest and compatible with the original purpose of the data processing.

Requests to access study data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

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25 Additional Information/Appendices

25.1 Appendix 1 – Summary of protocol amendments