UK Lung Screening Trial

UKLS

Study Sponsors / Co-sponsors

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UKLS Trial Team

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*Non independent Members listed in section 21

Table of Contents

Glossary

ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
AR	Adverse Reaction
CEO	Chief Executive Officer
CF	Consent Form
CI	Chief Investigator
COM	Central Operations Merseyside Primary Care Agency
CRF	Case Report Form
CT	Computed Tomography
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DM	Data Manager
DMC	Data Monitoring Committee
DVD	Digital Video Disc
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GP	General Practitioner
HA	Health Authority
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IRAS	Integrated Research Application System
ISF	Investigator Site File
LCTU	Cancer Research UK Liverpool Cancer Trials Unit
LDCT	Low Dose Computed Tomography
LECMC	Liverpool Experimental Cancer Medicine Centre
LFT	Liver Function Test
LLP	Liverpool Lung Project
MDT	Multidisciplinary Team
MinIP	Minimum Intensity Projections
MPR	Multi-planar reformations
MREC	Multi-centre Research Ethics Committee
MST	Mean Sojourn Time
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NLST	National Lung Screening Trial
NRES	National Research Ethics Service
PET-CT	Positron Emission Tomography - Computed Tomography
PI	Principal Investigator
PIS	Patient Information Sheet
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
R&D	Research & Development
RCPath	The Royal College of Pathologists
RLBUHT	The Royal Liverpool and Broadgreen University Hospitals NHS Trust
RSA	Research Site Agreement
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SHA	Strategic Health Authority
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Coordinator
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 Study Protocol Approval

I, the undersigned, hereby approve and authorise this clinical study protocol:

Signature: _____ **Date:** _____

Professor John Field – Chief Investigator
Director of Research
Roy Castle Lung Cancer Research Programme
University of Liverpool

Signature: _____ **Date:** _____

Signed on behalf of the University of Liverpool (Co-Sponsor)
Mrs Lindsay Carter
Research Co-ordinator
University of Liverpool
Foresight Building
Liverpool
L69 3GL

Signature: _____ **Date:** _____

Signed on behalf of the Royal Liverpool and Broadgreen University Hospitals NHS Trust (Co-Sponsor)
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This protocol has been approved by:

- The Chief Investigator
- The Trial Management Group

2 Protocol Statements

2.1 General Information

This document describes the UKLS trial and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial. However, centres entering participants for the first time are advised to contact the coordinating centre (Cancer Research UK Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the LCTU.

2.2 Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, Research Governance Framework for Health and Safety Care and the LCTU Standard Operating Procedures (SOPs).

2.3 UK Registration

This study will have National Research Ethics Service (NRES) approval and each centre must undergo Site Specific Assessment (SSA) by the relevant Trust Research and Development (R&D) department and NHS sites must be granted R&D approval from each Trust where the trial will be carried out. In addition the trial will have approval from the National Information Governance Board for Health and Social Care for screening potential participants from the local PCT databases.

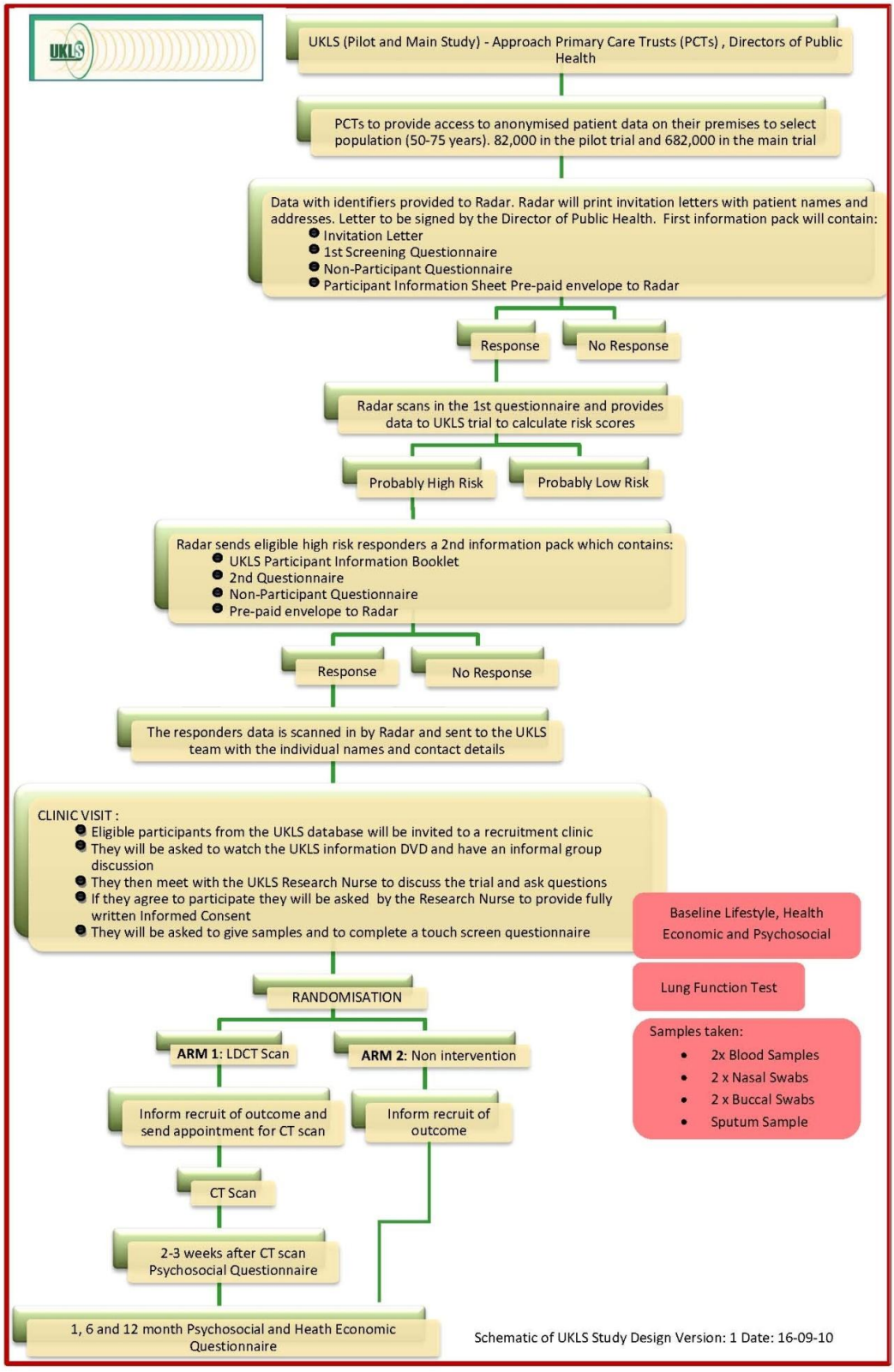
3 Protocol Summary

Title:	UK Lung Screening Trial (UKLS)
Design:	Randomised controlled screening trial
Sample Size:	Maximum 4,200 participants from the UK for the Pilot Trial Maximum 32,000 participants from the UK for the Main Trial.
Study Period:	Pilot: 14 months. Main Trial: 10 years
Main Inclusion Criteria:	1. Risk criteria based on the LLP Risk Prediction Model (includes age, sex, smoking duration, history of previous pneumonia, history of previous cancer, family history (early/ late onset) exposure to asbestos – algorithm 2. Males and females aged between 50 to 75 years old 3. Fully informed written consent given
Main Exclusion Criteria:	1. Unable to give consent 2. Co-morbidity which would unequivocally contra-indicate either screening or treatment if lung cancer were detected. 3. A CT scan of the chest performed within one year of the invitation to be screened. 4. Any condition precluding written informed consent 5. Inability to lie flat 6. Weight greater than 200 kg (too large for CT scanner)
Number of Sites:	The pilot trial will have two participating centres: • Liverpool Heart and Chest Hospital • Papworth Hospital Both centres will predominately use their own fixed site CT. However, the feasibility of using mobile CT units will be trialled at 1 site for a 6 week period in the pilot The main trial will take place at a further 5 sites still to be determined. The Royal Brompton Hospital will act as a second reading centre for all the CT scans in the both the pilot and main trial.
Study Duration:	10 years
Description of Intervention:	Low dose Computed Tomography (CT) of the lungs
The objectives of the Pilot UKLS	1. Will the proposed method of recruitment (based on the protocol of a two-stage postal survey of risk directly

study:	aimed at the general population) deliver the required numbers? This entails estimating: a. Response rates to questionnaires. b. Proportion of subjects approached who are eligible. c. Proportion of eligible subjects who consent to randomisation. d. Proportion of subjects randomised to LDCT who comply with intervention. 2. How many subjects need to be approached to obtain the required full trial population? 3. Do the recruitment, randomisation and scanning protocols work in practice? Is the recruit's journey from initial survey to LDCT scanning logistically efficient? 4. Are both fixed and mobile CT units practicable for trial purposes - is one preferable to the other in terms of cost/convenience? 5. Testing of staff training programmes. 6. Testing of QA procedures, for radiology and technology, including radiation dose aspects. 7. Do questionnaires or consent/information procedures or documentation need revising? 8. Review recruitment in hard to reach groups 9. UKLS database capable of capturing all of the required information from the recruitment phase to CT screening, investigations and treatment. 10. Collection of blood *sputum specimens at the recruitment phase, and QC. 11. Provide Screening data for HTA review at Month 12 of the pilot for review and decision whether to fund the Main UKLS trial. 12. Management of UKLS through the LCTU
Main Study Primary Objectives:	1. To establish the impact of pre-clinical detection of lung cancer mortality by comparing lung cancer mortality between the control group and the screened groups combined. 2. To establish if there is a lung cancer mortality benefit from CT screening 3. Establish total mortality benefit 4. Cost effectiveness of a national lung cancer screening programme.
Main Study Secondary Objectives:	1. To determine the physical morbidity associated with lung cancer screening 2. To determine the resource implications of screening and the resulting intervention 3. To assess the feasibility of population screening for lung cancer as reflected by uptake of invitations and compliance rates with annual screening 4. Establish a blood and tissue bank for the future assessment of early detection diagnostics and novel

	tumour biomarkers

Schematic UKLS Study Design:



4 Background Information

4.1 Introduction

Lung cancer kills more people worldwide than other malignancy. Currently 33,500 individuals die each year in the UK from lung cancer. The number of deaths has fallen in the past years and this is likely to be due to a decline in tobacco smoking, and possibly greater public awareness. However, there is now a large ex-smoking population in the USA and Europe, who remain at high risk of developing lung cancer, which is dependent on their smoking duration prior to tobacco cessation. This group of individuals now exceeds current smokers in both the USA and Europe and will continue to do so over the next two to three decades. Screening to detect the disease before patients develop any symptoms is a control measure urgently requiring evaluation as surgical resection at an early stage of the disease remains the only realistic option for a cure.

Chest radiography & sputum cytology lung cancer screening: The earliest lung screening trial was undertaken in London with over 55,000 individuals randomised to chest radiography every 6 months for three years or chest radiography at the beginning and end of the three year period [1]. No mortality difference was found between the two groups. Three major trials in the USA and one in Czechoslovakia were developed in the 1970's. The results of these large trials were disappointing as none of these studies showed any reduction in lung cancer mortality utilising chest radiography, with or without sputum cytology. One current trial which has 'usual care' only in the control arm is the lung component of the NCI PLCO (Prostate, Lung Colorectal & Ovarian) screening trial. In this trial, smokers are offered annual chest radiography for three years, and non-smokers two annual repeat screens; the results of this study are expected in 2010.

Low Dose CT lung cancer screening: Low dose computed tomography (LDCT) offers a major advance in imaging technology, which was introduced in the late 1990s [2]. This is more sensitive than chest radiography and has enabled detection of lung tumours smaller than one centimetre. Randomised trials of this technology as a screening tool have not as yet been completed. However, there have been a number of demonstration projects. Early studies of note include, the Early Lung Cancer Action Project (ELCAP) [3] in 1000 high-risk smokers; the Mayo Clinic project with 1520 individuals aged 50 years having annual sputum cytology and spiral CT screening [4], the Milan study [5] and a three-year mass screening programme using a mobile CT unit in Japan [6]. The ELCAP (observational) was later expanded to an international collaboration including 30,000 subjects.

The EU-US Spiral CT Collaboration was initiated in 2001 in Liverpool. Subsequent meetings throughout Europe resulted in the development of collaborative protocols which provided a mechanism for different trial groups to work together with the ultimate aim to pool results; the concept of which was formulated in the 'Liverpool Statement 2005'. [7]

The first major lung cancer RCT screening trial utilising LDCT was the National Lung Cancer Screening Trial (NLST), which is a combination of two trials, one set up by the US National Cancer Institute (NCI) and the other by the American College of Radiology Imaging Network (ACRIN). The NLST started in 2002 and completed enrolling in 2004. This study has over 50,000 former and current smokers randomised to annual LDCT or annual chest radiograph for three years. The major

objective of this was to determine whether LDCT reduces lung cancer mortality compared to a chest radiography arm. In November, 2010, the Director of the National Cancer Institute reported that the National Lung Screening Trial (NLST) showed that spiral CT screening when compared to chest X-ray evaluation resulted in a 20% reduction in lung cancer-related mortality. (http://www.cancer.gov/newscenter/pressreleases/2010/NLSTresultsRelease).

The NELSON RCT trial was launched in 2003 in the Netherlands and Belgium, [8] and now incorporates centres in Denmark. This trial is designed to compare lung cancer mortality in a group randomised to LDCT screening compared to a control group, without screening. A great deal of attention was focused on the selection of a high risk population to thus reduce the cost but retain the power of the study. Potential study participants were approached by letter with a questionnaire on their smoking exposure and whether they wished to be included in the trial. The questionnaire was initially sent to 335,441 men and women aged 50-75 years old. Based on this dataset the selection criteria were developed, depending on duration of smoking, duration of smoking cessation in ex-smokers, number of cigarettes smoked per day and the mean estimated expected lung cancer mortality rate. In this trial, LDCT screening takes place in years 1, 2 and 4, with 10 years of follow-up. The trial has 20,000 individuals, randomised in equal numbers to LDCT or 'usual care'. A number of small trials have been initiated, in anticipation of combination with partner studies, or a future meta-analysis. These include the ItaLung and Dante Trials in Italy [9, 10] and the French randomised pilot study, Depiscan, comparing LDCT and chest radiography recently reported its baseline findings [11].

The evidence required to justify (or rule out) the provision of screening as a service is a randomised controlled trial of LDCT screening with usual care as the control regimen and lung cancer mortality as the endpoint. To date, we do not have the results of any randomised trials which can provide adequate evidence to justify the instigation of a National Lung Cancer Screening Programme. The results of the NLST and NELSON studies are eagerly awaited. The unanswered question which remains in the UK is whether either of these studies will provide adequate information on their own to justify the implementation of a UK National Screening Programme. Although the combined US study is large and should have precise results, the use of an active screening regime in the control group may raise problems of interpretation. The NELSON study has adequate power for a substantial benefit in a high risk group, but a lower baseline lung cancer mortality or smaller benefit than anticipated may jeopardise a conclusive result.

The UK National Screening Committee has determined 22 criteria for the viability, effectiveness and appropriateness of a screening programme (http://www.nsc.nhs.uk/uk_nsc/uk_nsc_ind.htm) ; 20 of which are relevant to LDCT lung cancer screening. Black *et al.,* [12] have undertaken a systematic review of the literature in order to ascertain whether there was evidence for any clinical effectiveness utilising LDCT for lung cancer screening. This review was undertaken at the time when there was a paucity of real data and thus the conclusions were drawn from two small trials with very variable results. Not surprisingly, their conclusion stated that there was insufficient evidence at the time to support LDCT screening. This remains the case.

The objective of the RCTs is to assess whether LDCT screening and treatment of early lesions will decrease lung cancer mortality compared to a control group without screening. Additionally, a UK trial would aim to test the intervention against the

criteria outlined by the UK Screening Committee, especially those concerning cost effectiveness. A useful aid to cost-effectiveness is the ability to select a population at sufficiently high risk to give a substantial harvest of tumours in return for the screening activity. The group selected should also be of sufficiently high risk that the benefits of the screening will outweigh the likely harms.

It is important to measure the psychological impact of any new form of screening. A range of studies of different types of screening indicate that false positive and abnormal screening results are associated with short-term increases in anxiety and worry. Negative psychological effects are possible in lung cancer screening, although it is not known how sustainable these effects will be, or how they compare with adverse effects from other forms of cancer screening. The very act of participation in the lung screening trial may cause anxiety, as well as anxiety awaiting the outcome of the CT screen. In the case of individuals who require further tests due to suspicious nodules, there is the potential for further sustained anxiety.

A review of CT screening conducted for the Health Technology Assessment (HTA) Programme examined six recent economic evaluation models of CT screening, constructed by Japanese and US researchers [13]. The review concluded that these models provided an insufficient basis for assessing CT screening in the UK, for three reasons. Firstly, the quality of reporting was described as “poor” in all cases, a lack of transparency in reporting precluding any assessment of scientific plausibility. Secondly, all of the models had been driven by assumptions about, for example, lung cancer aetiology, disease progression, screening effectiveness, survival and the like, and most of these assumptions remained “uncorroborated” by evidence. The proliferation of assumptions generated very wide confidence intervals about the estimated cost effectiveness ratios. Finally, none of the published models had been populated with UK economic data. However, an evidence-based screening regimen potentially applicable to the UK has been modelled more recently, and the incremental cost effectiveness ratio of a single screen amongst a high-risk male population has been calculated. On the basis of reasoned speculations as to how test parameters and costs might behave under screening, the model generates cost effectiveness ratios well within the range of values currently considered acceptable in England [14].

4.2 Rationale

The objective of the UKLS trial is to assess whether LDCT screening and treatment of early lesions will decrease lung cancer mortality compared to a control group without screening. Additionally, a UK trial would aim to test the intervention against the criteria outlined by the UK Screening Committee, especially those concerning cost effectiveness. A useful aid to cost-effectiveness is the ability to select a population at sufficiently high risk to give a substantial harvest of tumours in return for the screening activity. The group selected should also be of sufficiently high risk that the benefits of the screening will outweigh the likely harms.

The most efficient way of controlling cost will be to screen only those individuals who are at high risk of developing the disease. There has been increasing interest in developing methods for individual risk prediction for lung cancer. Models have been developed for use within high risk groups [15], and for the general population [16], based mainly on age and smoking. The predictive accuracy of lung cancer risk models may be further improved by the addition of other epidemiological risk factors [17]. The Liverpool Lung Project (LLP) [18] has recently developed a method to calculate absolute risk of lung cancer over a defined period, based on age, sex,

smoking duration, family history of lung cancer, history of non-pulmonary malignant tumour, history of pneumonia and occupational exposure to asbestos [19]. The LLP risk questionnaire has been validated in the Harvard case control, then EUELC case control and the LLP cohort studies. The LLP risk model has distinctive strengths. Firstly, the predictor variables are all explicitly defined and can be readily assessed at the time of patient presentation and secondly, patients can be assigned to their appropriate risk class on the basis of information from the initial history alone.

The screening process confers potential harms as well as potential benefits. In a randomised trial and in any future national screening service, the screening would be provided only to those whose risk was sufficiently high that the likely benefits outweigh the likely harms.

4.3 Objectives

The overall aim of the trial is to provide data required for an informed decision about the introduction of population screening for lung cancer. This involves establishing the impact of screening on lung cancer mortality, determining the best screening strategy and assessing the physical and psychological consequences and the health economic implications of screening. A further objective is to create a resource for future improvements to screening strategies.

4.4 Potential Risks and Benefits

4.4.1 Potential Risks

Any screening programme has the potential to cause harm. Even if evidence for a beneficial effect of lung cancer screening is established, for any one individual it is always possible that more harm than good will result from participation; for example, a cancer may be detected which was not destined to cause harm and investigations and treatments offered may produce serious side effects or even death.

1) The very act of participation in the lung screening trial may cause anxiety, as well as anxiety awaiting the outcome of the CT screen. In the case of individuals who require follow-up CT screens, there is the potential for further anxiety. In order to reduce this anxiety, we will provide an informative Participant Information Booklet, further information on our UKLS web site and also provide a telephone number for anxious patients to call at their "Pilot Site". The UKLS utilises a Research Nurse for recruitment for morning sessions, however the Research Nurse will be available each afternoon session to answer calls or make appointments to see anxious patients. If a patient is extremely anxious the Respiratory Consultant associated with the Pilot CT screening Trial Site, will provide an appointment to see these individuals. In such cases we will also inform the recruit's GP of their concerns, in order that they may have further support.

2) Adverse psychological consequences of screening: It is important to measure the psychological impact of any new form of screening. Our group has extensive experience in defining and measuring such harmful effects; the proposed pilot will provide the opportunity to test a draft measurement instrument. Negative psychological effects are possible in lung cancer screening, although it is not known how sustainable these effects will be, and how they compare with adverse effects from other forms of screening. Hence, ideally invitees should be fully informed of this risk, and receive adequate information on interpreting screening results. These considerations have shaped our draft invitation materials for the UKLS pilot.

3) Recruits may be concerned about the exposure to radiation from a CT scan. The amount of radiation delivered by one low dose CT scan of the chest to a standard-sized adult is approximately 1 mSv (in clinical practice a routine chest CT examination may be up to 10 mSv). 1 mSv is approximately equivalent to 5 months' worth of natural background radiation. The International Committee on Radiological Protection advises that there may be a small chance that low amounts of radiation may cause cell damage that will manifest itself as cancer many years after the exposure. In the UKLS protocol the radiation dose will almost invariably be less than 1 mSv. According to the Twelfth COMARE deliberations there is no threshold below which there is no deleterious effect from radiation. The risk of cancer induction for one low dose CT scan (UKLS protocol) is estimated at 1 in 20,000 for a healthy 50-year-old (this is additional to the lifetime likelihood of developing cancer of approximately 1 in 4). We will make the above information clear to all potential participants during the consent process.

4) Diagnostic workup may cause anxiety in recruits: Diagnostic work-up of patients with suspicious nodules may include bronchoscopies, biopsies, staging CT with contrast, PET scan, and surgical resection. The great majority of suspicious nodules will not grow and will be regarded as benign. This will be made clear to subjects recalled for additional investigation. The detection of such nodules is an unavoidable part of the screening programme. The Participant Information Booklet will provide a detailed explanation of why follow-up CT is needed in a relatively high proportion of subjects and associated risks. Modelling based on preliminary results from other screening trials has indicated that clinical work-up will only occur in a very small proportion of the CT screened population (estimated at 1.5% of which 70% will have lung cancer). The proportion of subjects that undergo these tests is kept low by application of the UKLS care pathway that ensures subjects are filtered by less invasive tests (repeat CT) until the probability of malignancy is sufficiently high to warrant invasive tests or resection. This requires strict adherence to the CT screening protocol and the rigorous training of the radiologists and radiographers.

5) Overdiagnosis: This is a major issue of any screening trial and can only be assessed in the Main UKLS Trial. The main outcome measure of overall, all-cause mortality will not be influenced by this bias. The pilot will have insufficient power to detect differences in mortality as a result of screening and therefore this bias will only be compensated for in the main trial.

6) Treatments: A significant increase in lung cancer diagnosis and treatment through screening inevitably leads to treatment complications and costs. Lung cancer resection carries a significant complication and mortality rate, influenced by a range of patient characteristics and co-morbidities. A feature of lung cancer surgical treatments is their ongoing capacity to compromise quality of life. Accordingly, the pilot will provide an opportunity to develop and test clinical monitoring forms for all treatments provided to patients with screen-detected cancers – and to examine the associated organisational and training issues.

4.4.2 Known Potential Benefits

There are no completed and reported randomised controlled trials (RCT) in lung cancer screening available to assess the benefits of lung cancer screening compared to no intervention at all. However, evidence from preliminary data from a wide range of international observational studies indicates that the technology is clearly effective in detecting disease before patients develop symptomatic lung

cancer [20]. Surgical resection at an early stage of the disease remains the only realistic option for a cure. Thus the obvious next stage of research is a randomised trial to estimate the effect of the screening on mortality from lung cancer.

5 Selection of Centres/Clinicians

Each participating Centre (and investigator) has been identified on the basis of:

- National Thoracic Centre in an NHS setting with large case load of lung cancer patients
- Lead clinicians in Radiology, Respiratory Medicine, Pathology and Surgery with a specific interest in the management of early lung cancer
- Population with a high risk of developing lung cancer within the vicinity of the Centre
- Support from the Trust's CEO. All the Clinical leads indicating an enthusiasm to participate in the study
- Ensuring that sufficient time, staff and adequate facilities are available for the trial
- Providing information to all supporting staff members involved with the trial or with other elements of the patient's management
- Discussion and agreement to UKLS trial costings
- Agreement to utilise the UKLS Protocols and Care Pathway
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing-up to Good Clinical Practice (GCP) and other regulatory documentation
- Centre fitting demographic considerations for undertaking a lung cancer screening trial

5.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment (SSA) by local Research and Development (R&D) department
b. Signed Research Site Agreement (RSA)
c. Receipt of evidence of completion of (a) & (b) by LCTU
d. Completion and return of 'Signature and Delegation Log' to LCTU
e. Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
f. CV including a record of ICH GCP training – Other personnel on the delegation log
g. Signed Clinical Study Protocol Receipt Form
h. Provision of Patient Information Sheet, Consent Form and other required documentation on trust headed paper
i. ARSAC Approval for performing the CT scans

5.2 Centre/Clinician Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

6 Trial design – Main UKLS Trial

6.1 Primary Endpoint(s)

- To establish the impact of pre-clinical detection of lung cancer lung cancer mortality by comparing lung cancer mortality between the control group and the screened groups combined
- To establish if there is a lung cancer mortality benefit from CT screening
- Establish total mortality benefit
- Cost effectiveness of a national lung cancer screening programme

6.2 Secondary Endpoint(s)

- To determine the physical morbidity associated with lung cancer screening
- To determine the resource implications of screening and the resulting intervention
- To determine psychosocial consequences of lung cancer screening
- To assess the feasibility of population screening for lung cancer as reflected by uptake of invitations and compliance rates with annual screening
- Establish a blood and tissue bank for the future assessment of early detection diagnostics and novel tumour bio-markers.

6.3 UKLS Trial Design

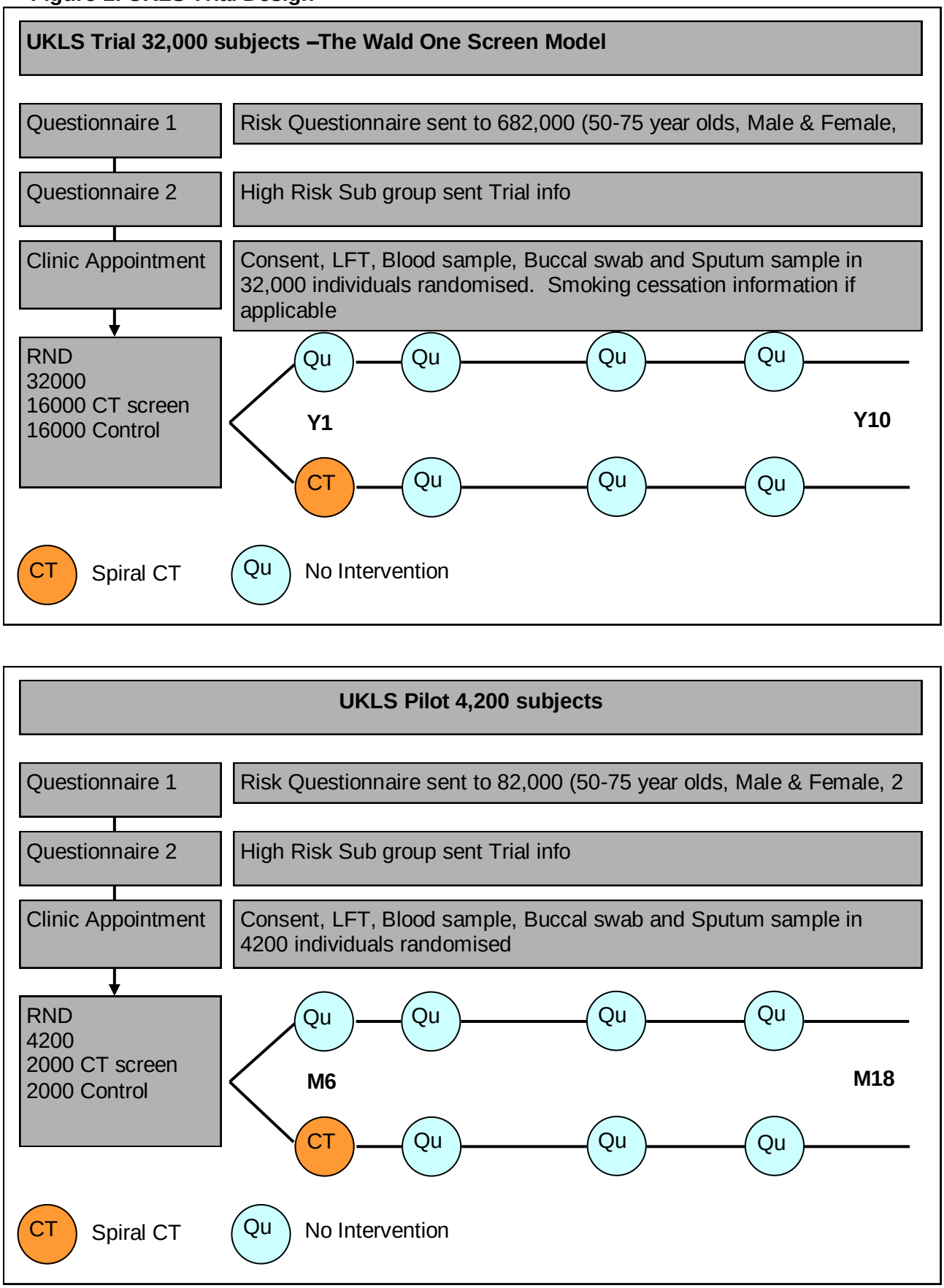
The 'Wald Single Screen Design' has been chosen for the UKLS trial. The study arm is offered a single CT scan (with appropriate further workup where necessary), the control arm is given usual care, and both arms are followed up for lung cancer incidence and mortality. The details of this design are provided in Figure 1: UKLS Trial Design.

1. Individuals 50-75 years of age will be selected at random from NHS / SHA records and approached with an invitation letter, Participant Information Sheet and first questionnaire (Appendix A: Invitation Letter, Appendix B: Participant Information Sheet and Appendix C: first UKLS Questionnaire). The responses to the first UKLS questionnaire will be analysed, based on the Liverpool Lung Project [19] five year predictive risk model.
2. The high risk individuals will be contacted with a further second questionnaire (Appendix D: second Approach Letter, Appendix E: second Questionnaire, Appendix F Not Wishing to Participate and Appendix G: Participant Information Booklet) regarding specific questions on their medical history and also provided with detailed information about the UKLS Trial.
3. Individuals responding to the second questionnaire will be invited to one of the recruitment centres. They will be shown a UKLS Information DVD outlining the study in groups of 6-8 people. This will be followed by an informal group discussion with the chance to ask questions and gain further information. They will then meet with the Research Nurse and if the individual agrees to participate they will go through the consenting process.
4. After gaining fully informed written consent the Research Nurse will undertake a Lung Function Test. The recruit will also be asked to provide blood samples, buccal swab, nasal brushings and sputum specimens. The

recruit will also be asked to complete a touch screen lifestyle/medical history questionnaire and a baseline psychosocial and health economics questionnaire. All smokers will be provided with smoking cessation advice sheets and a list of local NHS Stop Smoking services.

5. The recruits will then be randomised into either CT screen group or the control group.
6. In total 4,000 individuals will be recruited into the Pilot UKLS trial with 2,100 randomised into the screened group. In total 32,000 individuals will be recruited into the main UKLS trial with16,000 randomised into the screened group.
7. Participants will then complete follow-up psychosocial and health economics questionnaires two weeks after being notified of their CT results, or notification that they are on the control arm of the trial.

Figure 1: UKLS Trial Design



7 STUDY POPULATION

7.1 Inclusion Criteria

1. Risk criteria based on the LLP Risk Prediction Model (includes age, sex, smoking duration, history of previous pneumonia, history of previous cancer, family history (early/ late onset) exposure to asbestos – algorithm)
2. Males and females aged between 50 to 75 years old
3. Fully informed written consent given

7.2 Exclusion Criteria

1. Unable to give consent
2. Co morbidity which would unequivocally contraindicate either screening or treatment if lung cancer were detected
3. A CT scan of the chest performed within one year of the invitation to be screened
4. Any condition precluding written informed consent
5. Inability to lie flat
6. Weight greater than 200 kg (too large for CT scanner)

7.3 Patient Withdrawal from Trial Intervention

In consenting to the trial, participants are consenting to all trial procedures, follow-up and data collection. If voluntary withdrawal from intervention occurs, the participant should be asked to allow for the LCTU to keep information on them that has been collected and stored.

Participants may be withdrawn from treatment for any of the following reasons:

a. Participant withdraws consent.
b. Intercurrent illness preventing further treatment or follow-up.
c. Any change in the participant's condition that justifies the withdrawal of the participant in the clinician's opinion.

If a participant wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up or, failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up.

7.4 Withdrawal from Trial Completely

Participants who autonomously withdraw from the trial for reasons other than those listed above, have previously consented to follow-up in the trial. Data up to this time can be included. They may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the participant explicitly states their wish not to contribute further data to the study, the LCTU should be informed in writing by the responsible physician and an end of study CRF should be completed.

7.5 Loss to Follow-up

If any of the study participants are lost to follow-up, contact will initially be attempted through the PI at each centre. If this is unsuccessful, the patient's GP will be asked to provide follow-up information to the recruitment centre. This will be described in the Participant Information Booklet and consent obtained.

7.6 Co-enrolment Guidelines

Participants registered onto UKLS are not restricted to enter any other clinical trials or studies.

8 Enrolment and Randomisation

8.1 Screening

Potential participants will be invited to take part in the trial from the age/sex registers of Health Authorities (HAs) geographically related to the collaborating centres. Local HAs will be contacted during the set-up phase of the trial for permission to access their registers. This will ensure that invitations to participate in the trial can be sent to the correct age groups. Inviting un-biased cohorts of people is central to the trial design, as uptake needs to be documented in order to comprehensively answer the questions of whether a national lung cancer screening programme is feasible.

The enrolment plan has been discussed in detail with the PCTs. The preferred plan will be for HAs to provide details of participants (name, address, NHS number and GP details) electronically to Radar, the data management organisation that will send participants the invitations and questionnaires.

The process of invitations begins with Radar sending the first questionnaire to selected participants.

The initial information packs will include:

- Invitation letter
- Participant information sheet
- First questionnaire
- Refusal questionnaire
- Pre-paid envelope to send completed documents back to Radar

If the HAs provide contact details of eligible participants in electronic format, the data will be imported to the Radar database. Each participant on the list will be automatically allocated a random seven digit unique number which will be their own unique reference number for the life of the trial.

Once the initial invitation and questionnaire have been sent out to the potential participants, the data from these questionnaires will be returned to Radar using the pre-paid envelopes. Radar will use postcodes to compute Index of Multiple Deprivation (IMD) scores of all approached participants and send this IMD data along with their age, gender and unique 7 digit identifying number to the UKLS team. Radar will scan the questionnaire data and send the data to the LCTU and it will be imported into the UKLS database. The Risk Algorithm, based on the LLP risk model will be built into the UKLS database and will check which participants are ‘high risk’ according to the selection criteria and thus eligible for the trial.

Participants with a high risk score and have expressed an interest in participating in lung screening, will receive a second information pack. The second information pack will be sent by Radar (which will elucidate inclusion/exclusion parameters) and will include:

- Second Invitation Letter
- UKLS Patient Information Booklet (PIB)

- Second questionnaire
- Refusal questionnaire
- Pre-paid envelope to send completed documents back to Radar

The replies are returned to Radar, where the questionnaires will be scanned and the information on eligible participants sent to the LCTU and imported in the UKLS database. The participants that respond to the specific inclusion/exclusion criteria questions and indicate an interest in lung screening will be invited to attend the local pilot recruitment centre.

8.2 Recruitment

In the pilot study, recruitment will take place at two centres, Liverpool Heart and Chest Hospital and Papworth Hospital. The main trial will have seven recruitment centres; the remaining five are still to be selected. As detailed above, if the participants respond positively to the second approach, the UKLS project management team, in conjunction with the recruitment centre, will invite them to a 'Recruitment Centre' for a 'Clinic Visit' which will consist of the following:

- Recruits in groups of 6-8 individuals will be shown a UKLS Information DVD (Appendix H: UKLS DVD Outline) which provides a background to the UKLS trial, its design and objectives, randomisation, CT screening, investigations, Care Pathways and the translational studies. The research nurse will hold a group discussion to answer general questions.
- The participant will then proceed to a separate clinic room, where they will meet with the UKLS research nurse to confirm eligibility for the study and to discuss any outstanding issues of the trial in detail. The participant has the opportunity to ask questions at this stage
- If an individual agrees to participate, fully informed written consent to participate in the UKLS study will be taken by the UKLS Research Nurse. (Appendix I: UKLS Informed Consent Form)
- The UKLS Research Nurse will then perform the following:
    a. Lung Function Test assessed by the Research Nurse (FEV1/ FEC recorded)
    b. Phlebotomy; all participants will have up to 24mls of blood taken at the registration visit. Blood samples, buccal swabs, nasal brushings and sputum samples will be labelled as detailed in the SOP, and packaged. The packages will be collected on a daily basis by courier for delivery to the University of Liverpool Experimental Cancer Medicine Centre (LECMC) Good Clinical Laboratory Practice (GCLP) laboratory.
    c. 24 mls of blood will also be collected from participants referred to the Multi-Disciplinary team prior to surgery or investigation as well as at subsequent out-patient follow up visits. These samples will be transported to the University of Liverpool Cancer Research Centre, 200 London Road, Liverpool.
- The participant will then be asked to complete a Touch Screen computer lifestyle, medical history, psychosocial and health economics questionnaire. Assistance will be provided to the participants on how to complete the questionnaire.
- Approximately 2 weeks after the clinic visit, participants will be informed to which arm they have been randomised. All smokers will be provided with

smoking cessation advice sheets and a list of local NHS Stop Smoking services.

8.3 Randomisation

On receipt of the Informed Consent Form, the LCTU utilises the UKLS database management system to randomise individuals. The UKLS database will automatically check eligibility and if eligibility is confirmed will randomise the participant to either the CT screening arm of the trial or the control arm on a 1:1 ratio, using a computer generated random number algorithm. Participants will be notified of their randomised allocation by the LCTU. If the participant has been randomised to the CT arm of the trial the notification letter will include an invitation to have the CT scan and an appointment for the CT scan.

9 Lung cancer Screening

9.1 Introduction

Participants will be randomised to either receive intervention CT scan (Arm A) or to a control arm (Arm B) no intervention.

9.2 Arm A

Participants randomised to Arm A will receive a low dose CT scan.

9.3 Arm B

Participants randomised to Arm B will have no intervention.

9.4 Radiological Protocol for the UK Lung Cancer Screening Trial

9.4.1 CT Equipment Requirements

All participating sites will use 16 or higher (e.g. 64) channel multi-detector CT (MDCT), whether fixed site or mobile, calibrated according to the manufacturer's specifications. For consistency, the same fixed site CT machine should ideally be used throughout the course of the study.

The rationale for using a 16 or higher channel MDCT platform is that the majority of screen detected nodules will be small (3-10 mm) and require optimal spatial resolution for accurate and reproducible evaluation including nodule volume measurement. Only MDCT enables data acquisition within a single breath-hold at the narrow detector collimations and slice thicknesses required multi-detector CT. Although 64 slice CT is considered relatively advanced, by study completion such technology is likely to be the norm. The use of 16 slice or higher MDCT platforms will ensure that the screening CT, the test under consideration, is of the highest quality and the primary endpoint is not compromised by inferior image quality.

During the 14 month period of the Pilot Study during which CTs are acquired, the two sites will use a mobile CT (private sector) for a six week period; the mobile machine will be of the same basic technical specification (i.e. at least 16 channel MDCT).

9.4.2 CT Image Acquisition Protocol (applicable to fixed site and mobile CT)

Preparation

Participants' weight and height will be ascertained prior to scanning to permit selection of exposure factors.

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 to localise the start and end positions of the scan. The frontal localiser should be performed in the PA projection

(tube at gantry bottom, patient supine) and at the lowest possible setting (e.g., 80 kVp, 20 mAs) to minimise breast dose.

***Volumetric CT scan**:* The lung parenchyma (lung apices to bases) must be scanned in its entirety in a single craniocaudal acquisition. The field of view (FOV) selected as the smallest diameter as measured from widest point of outer rib to outer rib large enough to accommodate the entire lung parenchyma (usually no more than 35cm). Thin detector collimation (0.5 – 0.625mm) will be used with a pitch of 0.9-1.1. Scan time should usually be in the region of 5 seconds but must not exceed 10 seconds to avoid respiratory motion artefact. Sufficient delay time must be given after completion of the inspiratory command to ensure inspiration is complete prior to scan commencement. A start delay of 5-7s is usually appropriate, during which breathing commands are given.

***Exposure factors**:* Radiation exposures will be as low as possible whilst maintaining good image quality. The CT dose index (CTDIvol) will be kept below 4 mGy, with the effective radiation dose well below 2 mSv. The kVp and mAs settings will be varied according to participant body habitus:

	Slim subjects (<50 kg BW)	Standard (50-90 kg BW)	Large (>90 kg BW)
kVp setting	100 kVp	120 kVp	140 kVp
mAs settings*	**depending on scanner type adjusted to achieve CTDI given below*		
CTDIvol	0.8 mGy	1.6 mGy	3.2 mGy
Effective dose	<0.5 mSv	<0.8 mSv	<1.4 mSv
Effective dose including scout view (0.2mSv)	<0.7 mSv	<1.0mSv	<1.6mSv

If available, adaptive filtering should be used to optimise image quality, especially in the shoulder region and lung apices. Dose modulation packages should be used according to local practice.

***Image reconstruction**:* should rely on thin collimation and overlapping 1mm-volumetric data. Image reconstruction should be standardised and used for any subsequent follow-up examinations.

The reconstruction parameters will be:

Reconstruction Algorithm	Reconstruction Slice thickness	Reconstruction Increment	Reconstruction FOV
Moderate spatial frequency / soft tissue (eg. GE Standard, Philips B, Siemens B30f).	1mm	0.7mm	Entire lung parenchyma

9.4.3 Image Interpretation

Image interpretation is performed on 3D CT workstations which permit scrolling through the data set with variable thickness and orientation using multi-planar reformations (MPR), Maximum Intensity Projection (MIP) and Minimum Intensity

Projections (MinIP). Nodule detection is simplified by using MIP of around 10mm thickness. Additional reconstructions of image data may be necessary for clarification. Axial and coronal or sagittal planes should also be reviewed. All three planes are helpful for assigning a nodule to a lung segment (for identification and follow-up). Nodule characterisation is usually based on thin MPR. MinIP may be helpful for evaluating the bronchial tree.

All scan data acquired from trial participants will be archived and retained at the local site. The data will be sent in standardised DICOM 3.0 format in a point-to-point fashion using the secure NHS N3net to a firewall protected server at the central site for second reading and secondary archiving.

9.4.4 Methodology for CT Reading

Establishing and maintaining accurate CT interpretation is crucial for the success of the trial. To this end, all baseline CT studies will be interpreted both locally and centrally (double reading) to optimise the sensitivity and specificity of CT screening.

The pilot study will aim to optimise the method of reporting including the investigation of the effectiveness of different methods of training observers and the appropriateness of radiologists versus non-radiologists as local site readers. This will be undertaken in both the pre-trial training sessions and by continuous assessment in the two centre pilot study.

9.4.5 Local and Central Reading Personnel

Local Site Reading, Reader 1

The pilot trial will investigate the practicality and effectiveness of the use of radiographers as readers. The primary purpose of this reader, once appropriately trained, will be to identify and measure pulmonary nodules using volumetric analysis software (Siemens LungCare), and record them on the UKLS web-based database. A benefit of developing this expertise will be to the local department which will already be faced with the increasingly frequent challenge of dealing with incidentally detected pulmonary nodules on CT.

For the specific tasks of CT nodule detection and categorising nodules into one of the four grades in the Care Pathways, radiological expertise is not required. The requirement to work in an uninterrupted and focused fashion is more important than medical/radiological expertise. Systematic CT reading is time-consuming; subsequently entering information into the UKLS database takes more time. It is likely that a technician or radiographer is a more appropriate reader than a highly trained (and relatively expensive) radiologist who, in a clinical setting, is unlikely to be able to undertake such reading and data entry without interruption.

Local Site Reading, Reader 2 – Consultant

The purpose of the second reader is to act as trainer and mentor to Reader 1 and confirm or refute findings about which Reader 1 is uncertain. As part of the pilot study there will be the opportunity for readers 1 and 2 to read independently, allowing a comparative study of observer performance to be undertaken. Furthermore, the two pilot centres could also read each other's cases to increase the

power of this comparison (projected numbers approx 100 cases/month for 14 months in each of two centres).

Options for local reporting protocol (Pilot) methodology include:

1. Reader 1 then Reader 2 – The technologist (Reader 1) serves as a first reader (flags nodules, enters all data into database), then the radiologist (Reader 2) works as a second independent reader (flags nodules); Reader 1 enters (agreed) nodule data into the database.
2. Reader 2 then Reader 1 – Reader 2 marks any nodule that he/she wants to be entered and the Reader 1 takes care of database entries (time saving).
3. Independent/blinded – followed by consensus or arbitration. Reader 2, the radiologist, serves as a first reader (marks nodules and saves XML file with nodule data), Reader 1, the technologist, serves as a second independent reader (marks nodules) and then takes care of transferring all data into the database.

The third option would have the advantage of allowing Reader 1 to learn "on the fly" and the continuous feedback would show at what point Reader 1 reaches or supersedes Reader 2's detection of nodules.

By the end of the Pilot study there will be a formal review, based on the outcome of the Readers' performance, as to the optimal method of CT reading for the Main trial. It is likely that the Reader 2 (radiologist) will not be required routinely.

The CT readings will have one of three possible outcomes:

Benign/insignificant nodule or no nodules – no further action
Nodules requiring follow up
Nodule requiring other intervention e.g. MDT opinion and staging CT

Central Site Reading, Reader 3

All baseline CTs will be read by a central reader, Reader 3 (consultant radiologist), who will be unaware of the conclusion of the local centre's reader. The central site reading will take place within two weeks of the first, local site, reading. For quality control purposes 10% of follow up CT scans will be read by a central reader. In addition, the central reader will be available to deal with ad-hoc queries on particular cases from the Radiologists at the trial sites.

Arbitration Reading, Reader 4

Occasionally, there will be significant discordances regarding the presence or absence of a nodule, interval growth or significant extra pulmonary finding and these will require review and arbitration by a fourth reader, Reader 4. Such readers will be one of a designated panel of experts, drawn from the UKLS Radiology Group.

The local site reader will receive the central reading report, with discrepancies, if any, highlighted. In case of discordance, the local site reader may find it necessary to change the initial report; in this event, the updated record is submitted to the central site. The site reader sends the final report to the trial participant's general practitioner.

9.4.6 Lung Nodule Characterisation

For each nodule evaluated, various characteristics (listed below) will be entered by the reader in a customised electronic data collection form, integrated with Siemens LungCare software and the calculated sizes and volumes generated by the software will be automatically uploaded into the UKLS Management System (on licence from NELSON investigators) immediately after completion of the reading.

Nodule definitions:

A nodule is characterised as a small approximately spherical, non-linear circumscribed focus of abnormal soft tissue.

A non-calcified nodule is classified as non-calcified in the absence of a benign pattern of calcification.

For all nodules the following characteristics will be recorded on the UKLS database: Maximum dimensions in x, y and z direction, minimum, maximum and mean diameter, size, volume, density, location (central versus peripheral, lung segment, section number and table position), and their surface characteristics.

Nodules will be categorised by:

NUMBER

The characteristics of each nodule will be recorded separately. The number of nodule evaluations per CT examination is unlimited, but if there are if there are more than 20 nodules less than 8 mm in size, the individual characteristics of the nodules will not be recorded separately.

SIZE

Nodules will be categorised as:
(n.b. nodules ≤ 3mm are for the purposes of the trial ignored and not recorded)

Solid nodules

Category 2 (Small). If intraparenchymal with a volume of 15-49 mm^3. If pleural or juxtapleural with a maximal diameter of 3.1 - 4.9 mm.

Category 3 (Medium). If intraparenchymal with a volume of 50-500 mm^3. If pleural or juxtapleural with a maximal diameter 5 - 9.9 mm.

Category 4 (Large). If intraparenchymal with a volume >500 mm^3. If pleural or juxtapleural with a maximal diameter of 10 mm or greater.

Part solid and non-solid nodules (ground glass opacities)

Category 2 (Small). If the maximal non-solid component diameter is less than 5 mm and, in case of a solid component, if this component has a volume <15 mm^3.

Category 3 (Medium). If the non-solid component has a maximal diameter of more than 5 mm or, in case of a solid component, if the component volume is 15-500 mm^3.

Category 4 (Large). If the solid component has a volume >500 mm^3.

POSITION
Nodules will be classified as central or peripheral. They will be defined as peripheral if the distance to the thoracic wall is less than one third of the total distance to the hilum. All nodules will be further categorised as:

i. Intraparenchymal. No contact with the pleura, or fissures
ii. Pleural based. Nodules with contact with the pleura
iii. Juxtapleural. Nodules that are within 2 mm of the pleura

MORPHOLOGY
Nodules will be categorised as benign – Category 1 or not benign – Categories 2 to 4.

Category 1 Nodules will be classified as

Benign if they contain fat, or contain a characteristic benign pattern of calcification.

Sub-pleural lymph nodes will be recorded as such if they fulfil the following criteria: they lie within 5 mm of the pleura (or are within interlobar fissures) are < 8mm in diameter, are smooth bordered and ovoid and at least one interlobular septum radiating from surface is identified.

Category 2 to 4 nodules will be characterised by the following definitions and descriptions. These should be recorded for each nodule.

Solid – a nodule of homogeneous soft tissue attenuation. Solid nodules may have different outlines and these will be classified as smooth, polylobulated, spiculated or irregular. Smooth is defined as a continuous regular outline. Lobulation is defined as areas of bulging of the lesion contour. Spiculation is defined as the presence of strands extending from the lung margin into the lung parenchyma. Irregular is defined as not smooth, polylobulated, or spiculated.

Part-solid – a nodule of both ground-glass and soft-tissue attenuation

Non-solid/Ground glass opacity – a nodule composed of a focal area of hazy increased lung opacity

GROWTH CHARACTERISTICS
Volume doubling time category: < 400 days, 400-600 days, >600 days.

9.4.7 Summary of Categories of Nodules detected during Screening

Category 1 Benign nodules: Nodules fulfilling one of the following criteria; a benign pattern of calcification, fat, measuring less than 3 mm in diameter or volume <15 mm3. Sub-pleural lymph nodes fulfilling the following criteria: they lie within 5 mm of the pleura of the middle and lower lobes, are <8 mm in diameter, are smooth bordered and ovoid and have at least one interlobular septum radiating from surface.

Category 2 If solid and intraparenchymal with a maximal diameter of 3.1 - 4.9 mm or a volume of 15 - 49 mm^3. If solid and pleural or juxtapleural with a max diameter of 3.1 - 4.9 mm. If non-solid or part solid with a max diameter of 3.1 - 4.9 mm. The solid component has a diameter of <3 mm and/or volume of <15 mm^3. All non-solid/ground glass opacities independent of diameter (all to be recorded).

Category 3 If solid and intraparenchymal with a volume of 50 - 500 mm^3. If solid and pleural or juxtapleural with a diameter 5 - 9.9 mm. If non-solid or part-solid with a diameter of the ground-glass component of >5mm. If part solid and the solid component has a volume of 15 - 500 mm^3 or has a max diameter of 3.0 – 9.9 mm.

Category 4 If solid and intraparenchymal with a volume >500 mm3. If solid and pleural or juxtapleural with a diameter of ≥10 mm. If part solid and the solid component has a diameter of ≥10 mm or has a volume >500 mm^3.

Management of newly identified nodules at Follow Up CT

If a new nodule is identified at 3 months the following will apply:

1) Readers will check that the nodule is genuinely new. If the nodule is identified on the baseline scan in retrospect, the volume doubling time will be calculated as if it had been identified and the appropriate algorithm followed as per the original UKLS protocol.

2) If the consensus reading is that the nodule is genuinely new and classified as category 1 or 2, then there will be no change to the existing algorithm and the participant will undergo a scan in 9 months (i.e. 12 months from baseline) (See "9 month" letter).

3) If the consensus reading is that the nodule is genuinely new and classified as larger than a category 2, then the participant will be recommended to have a follow up CT in 3 months. The reasoning behind this is because new nodules that have developed rapidly in this timeframe are likely to be inflammatory and have resolved within 3 months. (See new "incidence 3 month letter")

4) At 3 months, if the nodule has resolved or is stable (VDT>400 days) the participant will continue as per the protocol and have their originally planned CT at 12 months from baseline (See new "6 months" letter)

5) At 3 months, if the nodule has grown significantly (VDT<400 days), the participant will be referred to the MDT.

9.4.8 Reader Training

All readers will require significant training and it is important for the pilot and for the main trial that readers are fully trained before the commencement of recruitment. The non-radiologist (Reader 1) will be required to undergo training on 100 CTs which will comprise a mix of validated cases from the NELSON study (details below). The radiologist (Reader 2) would require at least 30 cases and both readers will receive application training on the Siemens LungCare and UKLS database software.

The training set CTs, derived from NELSON studies, will consist of screening examinations that demonstrate:

1) Imaging findings ranging from normal to overtly abnormal, with the inclusion of focal opacities (including a range of non-solid and other "difficult" lesions) commonly observed in the course of CT screening

2) Examples from which definitions of what constitutes a lung nodule, and nodule characteristics, such as density, margin and volume, can be imparted
3) Cases with deviations from the technical parameters specified by the protocol, including examples of important suboptimal image quality for whatever reason, e.g. motion, beam hardening, under-inflation of the lungs, etc.

Readers will be tested on a different batch of test cases. Reader 1 will be required to read 50 nodules in test conditions and readers 2 and 3 will be required to read 25 nodules in test conditions. A concordance rate of 80% compared to the NELSON standard will be required and all central and local readers will need to achieve this "pass standard" prior to being signed off to read within the trial.

9.4.9 Quality Assurance

As above, all readers prior to reporting will have to undergo training and pass the competency test on validated NELSON cases. Radiologists involved with the reading of CTs (central or local sites) must be registered with the General Medical Council and accredited by the Royal College of Radiologists UK (or equivalent). Radiologists should have a specialist interest in thoracic imaging and have been involved with the supervision and/or performance, review and interpretation of at least 300 chest CT examinations in the previous three years.

9.4.10 Pilot Phase

During the pilot there will be regular feedback of performance to the local centres in comparison to the consensus view. Detailed analysis of individual scores will be made. Development of audit scoring system to grade level of discrepancy will be made:

5 Complete agreement
4 Trivial difference in read – e.g. difference in description of nodule but no change in outcome
3 Minor disagreement – unlikely to be of any clinical significance
2 Moderate disagreement – could be of clinical significance
1 Major error in interpretation - failure to report a significant nodule (e.g. 8mm diameter nodule) with change in outcome

As part of the pilot the development of reference range for discrepancy to trigger a review of a reader/centre will be formulated.

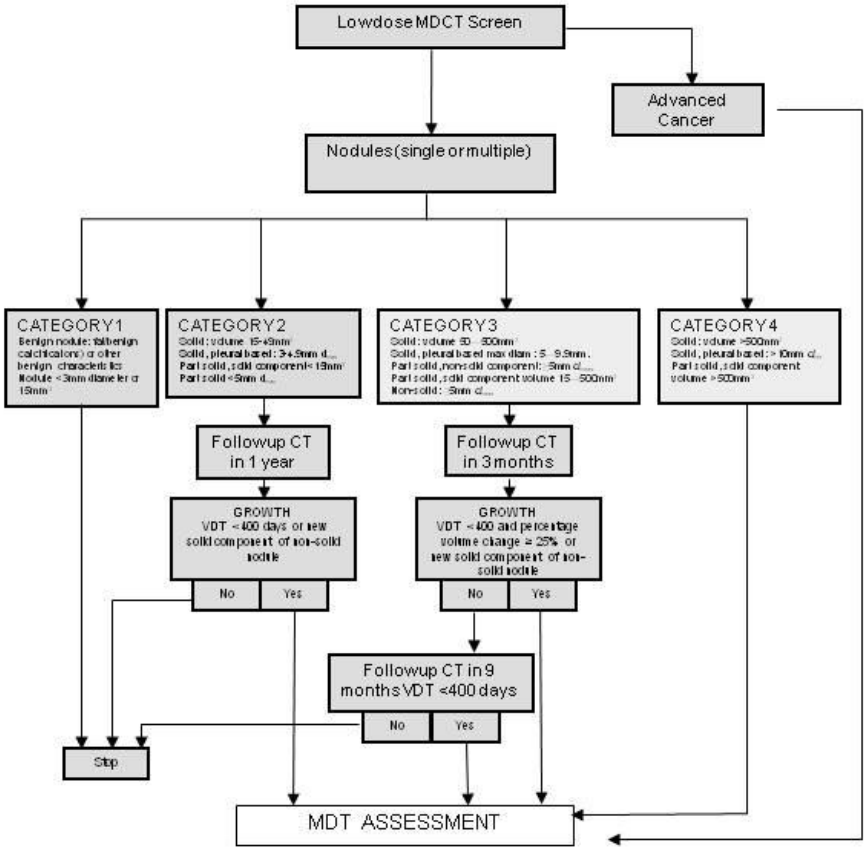
9.4.11 Main Phase

Formal audit will be taken continuously with grading of adequacy of scan and reader concordance. In addition to initial training of readers, annual site visits, central quarterly monitoring meetings and an annual investigators' meeting will be organised.

10 UKLS Care Pathway

Figure 2: UKLS Care Pathway

Figure 1: UKLS Nodule Care Pathway Management Protocol



11 MDT Assessment

The Respiratory Physician will collate all of the clinical information for presentation to the Multidisciplinary Team (MDT). The MDT will determine the best management options for the study participant (who now becomes a patient) by considering the risks and benefits of each option. Risk will be determined by the fitness assessment and the risk of the procedure to the patient. Benefit will relate to the probability that the lesion identified by screening is malignant. The MDT will need to assess fitness for surgical or other radical procedures and the risk of malignancy. The management options (with preferred option) would then be discussed with the patient and patient's preferred option adopted. The MDT will assess fitness from the clinical history and objective testing. The former will include identification of co-morbidities and the latter will be tailored to the individual to include tests relating to co-morbidity (such as cardiac exercise testing for ischaemic heart disease) and those assessing respiratory fitness such as lung function testing and quantitative ventilation/perfusion scanning. The risk that the lesion is malignant will be higher for larger nodules, or those that have shown growth. In these circumstances, or where the CT has shown obvious cancer, the normal work-up employed by the MDT will be adopted. This will usually involve a Positron Emission Tomography - Computed Tomography (PET-CT) scan if the patient is thought to be suitable for radical treatment, fitness assessment as above and a biopsy or immediate resection. For smaller nodules (<1.5cm) the MDT would be helped considerably by being provided with an estimated probability that the nodule is malignant. This is so the MDT can balance the potential risk and benefits of the options of biopsy, surgery or a period of monitoring for signs of malignancy (growth on serial CT). Thus ULKS will provide an estimate of malignancy for smaller nodules.

11.1 The UKLS Care Pathways

Diagnostic workup and treatment algorithms are already available within NHS practice. However, the detail of the UKLS Care Pathways has been amended to cater for the management of nodules of differing sizes. The clinical care pathways comply with current standards and where possible existing clinical protocols are employed such as those recommended by National Institute for Health and Clinical Excellence (NICE). The pilot study will employ the agreed pathways, as detailed in Figure 2: UKLS Care Pathway and Figure 3: NICE Lung Cancer Investigation Care Pathway. These pathways will be modified if deemed necessary by the Steering Committee, and the full study will add to the subjects enrolled in the pilot.

The Care Pathways are summarised in Figure 2: UKLS Care Pathway for individuals who participate in the UKLS Trial. The algorithms are presented according to the findings of the CT. If there are no findings then there is no further active follow-up of the individual.

It is anticipated that some subjects will have significant other diseases and they will be referred back to their GP.

There are significant differences in the way smaller nodules, larger nodules and more obvious lung cancers are managed, thus this forms the major part of the UKLS Care Pathway. The methodology by which the nodules are handled is based on the NELSON protocol, which has been tried and tested in 10,000 individuals [21]. These patients will be discussed at the Trial Centres' MDT meetings and their treatment

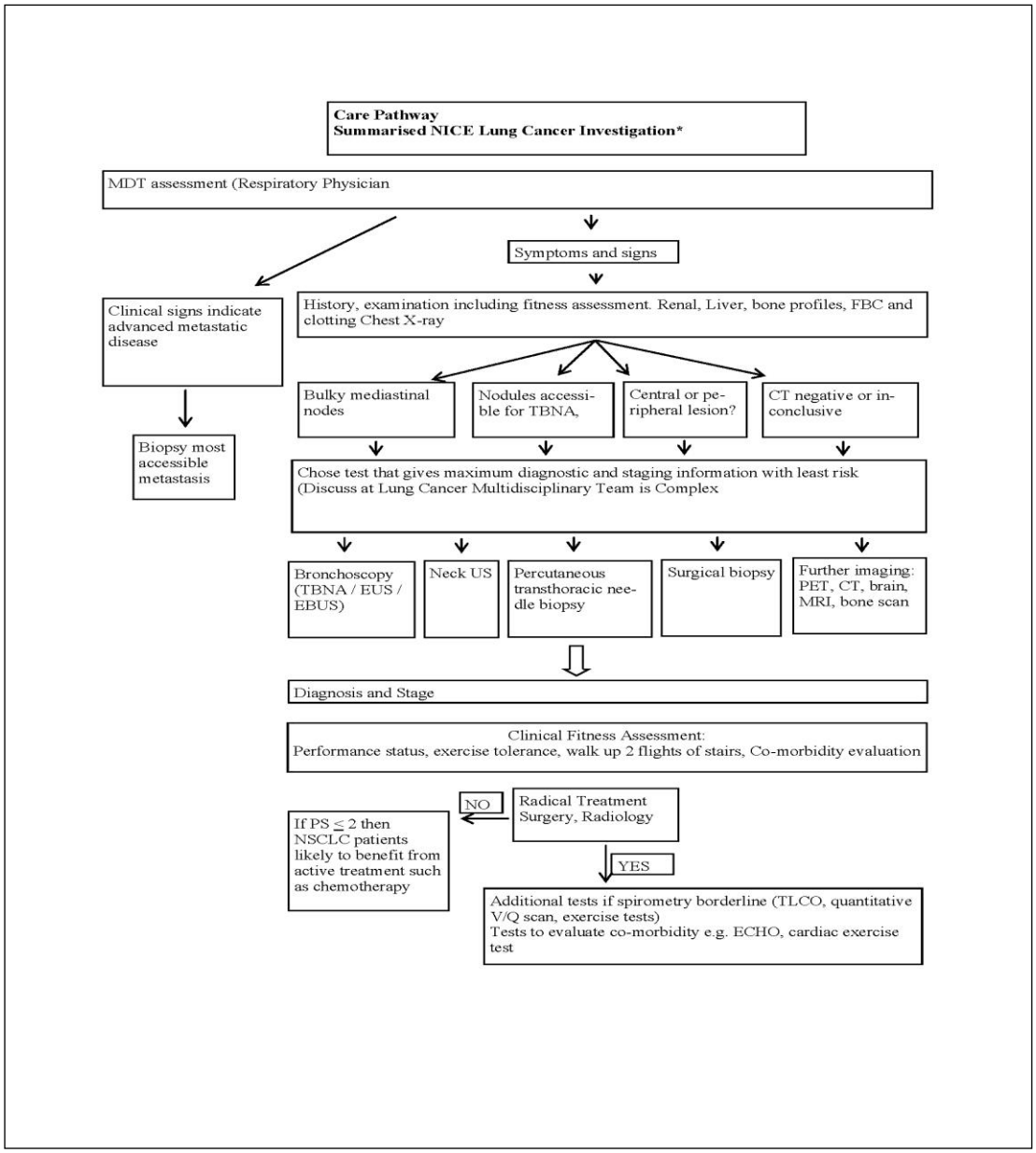
planning will be based on the Care Pathway flow diagram outlined in Figure 2, which is based on NICE guidelines.

Patients will need to be kept informed of their position in the management pathways and given opportunities to have their concerns addressed. The pathways described are according to accepted standards. Appropriately trained personnel will discuss all scan results with subjects.

The follow-up of small nodules and action taken will depend on a discussion of the risks and benefits of three options with the subject – observe for a prescribed period, transthoracic needle biopsy or excision. There will be a recommended approach according to size of nodule and rate of growth, but the subjects together with their doctor will make an informed decision about the approach taken.

In the unlikely eventuality that a participant will require care that falls outside of the UKLS Care Pathway due to unforeseen clinical presentation, the time interval for the repeat CT scan may be reassessed and amended accordingly. This may also effect the decision of *when* to refer the participant to the Multi-Disciplinary Team. On these rare occasions, the decision to work outside of the UKLS care pathway must be taken by the first **and** second read radiologist and documented on the UKLS database.

Figure 3: Summarised NICE Lung Cancer Investigation care pathway



12 Pathological Investigations

The UKLS Pathology protocol provides recommendations for uniform handling of specimens obtained during a CT-screening trial. The primary aim is to provide a pathologic diagnosis to facilitate the management of trial patients who have lung (or associated tissue) lesions biopsied and, in some cases, lung lesions subsequently resected. A secondary aim is, where possible, to provide appropriate tissue for biomarker and other translational research as part of additional studies complimenting the screening project. The pathology/biomarker protocol is intended for the handling of these specimens in a standardised fashion, which is based on current best practice and used by the majority of thoracic pathologists, as outlined in The Royal College of Pathologists (RCPath) guidelines for handling lung cancer resection specimens. The UKLS pathology protocol also includes freezing of tissue samples where available, for translational research. The UKLS pathology protocol is detailed in Appendix J: Pathology Protocol.

The local pathologist is the nominated specialist pulmonary pathologist at the surgical centre where the patient is treated. This pathologist is responsible for the primary diagnosis and reporting of the case, this is the diagnosis on which the patients' subsequent management will be decided. This diagnosis will also be used for evaluation of the 'disease-specific mortality' endpoint within the trial.

Pathological specimens, particularly tumour tissue collected form consented participants who have been referred to the MDT will be transported to the University of Liverpool Cancer Research Centre, 200 London Road, Liverpool where they will be stored securely in line with local policy and SOPs.

13 Surgical Protocols

The Surgical Review group have decided that the NICE guidelines, published in February 2005, provide an entirely appropriate protocol for the selection of patients for lung cancer surgery which derive from the UKLS trial. These patients will be managed through the MDT according the UKLS Pathway.
(http://www.nice.org.uk/nicemedia/pdf/cg024fullguideline.pdf)

14 Assessments and Procedures

14.1 Schedule for Follow-up

Once a participant has been randomised onto the UKLS trial they will be followed up for a period of 10 years. Follow-up information on all participants will be collected indirectly through either Cancer Registry or via The Office of National Statistics (ONS). A subset of participants will be contacted to complete the Psychosocial and Health Economics questionnaires.

14.2 Follow up

All participants randomised onto the UKLS trial will be registered with either the National Health Service Central Register for England and Wales (ONS) or the Cancer Registry. The computerised randomisation for each subject at the registry will be tagged for prompt notification to the study directors in the event of new cases of cancer and deaths from cancer in the study population. The registry will also notify the LCTU of individual subjects who do not appear on the register so that further information required to trace their entry, can be obtained or alternative methods of follow up can be employed.

14.3 Psychosocial and Health Economics

A subset of participants will be asked to take part in the Psychosocial evaluation and Health Economics section of the study. Equal numbers from each study arm will be asked to take part. These participants will be selected at random from the original 4,200 randomised. A brief baseline psychosocial questionnaire will be completed at the clinic recruitment session. Follow-up psychosocial questionnaires will be sent directly to all participants at 1 month post randomisation (i.e. in the screening group, approx. 2 weeks after CT scan results are received – both baseline and follow up scans). These data will be scanned and uploaded onto the UKLS database and analysed.

One objective of the psychosocial evaluation is to assess potential participation bias to the UKLS pilot trial and highlight potential hard to reach groups within this cohort. Analyses will compare the following groups on age, gender and socio-economic status: 1) non-responders, 2) those who complete the non-participation questionnaire (negative responders) and 3) those who complete the UKLS 1st questionnaire (positive responders).

In order to complete these analyses the mail sorting organisation working with UKLS (RADAR) will provide the UKLS study team with data on age and gender of non-responders to the initial approach letter. RADAR will compute the Index of Multiple Deprivation (IMD) scores (a measure of socio-economic deprivation) for all approached individuals using their postcodes and release the IMD information to the UKLS team. The data sent to UKLS is non-identifiable (age, gender and IMD score of each individual).

We have contacted the National Information Governance Board for Health and Social Care (NIGB) who have informed us that we do not need to submit an amendment to them because the proposed analyses are compatible with the purpose of the original NIGB application and there is no flow of patient identifiable information as the UKLS team receive anonymised data from RADAR. Evidence of this can be found within the UKLS Trial Master File.

The Health Economics questionnaire data will be analysed at Nottingham University under the direction of Professor D Whynes.

Psychosocial analysis plan

The primary psychosocial outcome is cancer worry measured using the 6-item revised Cancer Worry Scale [22, 23] adapted for lung cancer. It is hypothesised that trial participants will report increased short-term cancer worry compared to controls, and that those recalled for further tests will report increased cancer worry in the short- and longer-term.

Preliminary analyses
Attrition analyses will first be conducted to examine the sociodemographic (e.g. gender, age, SES, ethnicity) and clinical (e.g. smoking duration, personal and/or familial experience) factors associated with questionnaire non-response at each stage of the psychosocial assessment, using chi-square and independent t-tests as appropriate. Equivalence of trial/control groups in sociodemographic, clinical, and baseline psychological measures will be examined using chi-square and independent t-tests as appropriate. Descriptive statistics will then be used to characterise study participants in terms of sociodemographic and clinical background factors, and to examine the proportion of the sample reporting clinical levels of HADS anxiety/depression and high levels of cancer-specific worry.

Primary analyses
Prior to the main analysis, multivariate assumptions of normality and linearity will be tested. If the outcome data are reasonably normally distributed, repeated measures analysis of covariance will be used to assess any main effects of trial condition on changes in psychological responses (i.e., cancer worry, anxiety, depression, and decision satisfaction) from baseline to four week follow-up, controlling for potential confounding variables such as gender and baseline distress. If the outcome data are not normally distributed, scores may be transformed to produce a more normal distribution using logarithm transformations.

Secondary analyses
Regression analyses will be carried out to examine the predictors of cancer worry, anxiety, depression, decision satisfaction and screening intention at four weeks. Potential predictors include trial condition/CT screening result, gender, age, SES, ethnicity, smoking duration, personal and/or familial experience of lung cancer, lung screening history, screening expectation, and baseline distress measures.

The CARA Model [24] provides a suitable theoretical framework for understanding the role of expectations in predicting psychological responses to screening within the intervention arm. This model suggests that unexpected bad news (i.e. an abnormal CT scan result) will evoke high cognitive effort, a tendency to downplay the accuracy of the information, and a negative emotional response to CT lung screening. Respondents in the intervention arm will be divided according to whether, at pre-screening baseline, they expected to receive a normal/clear result or an abnormal result. A 2 x 2 ANOVA will be used to compare differences in responses to screening results (perceived threat and perceived accuracy) according to consistency between screening expectation (positive vs. negative) and actual result (normal vs. abnormal).

Sub-studies

Participants will be asked to provide up to 24mls of blood, two buccal swabs, nasal swabs and sputum samples as part of their recruitment clinic appointment (subject to appropriate consent as detailed in section 17.3). The samples will be transported to the UKLS biobank held at the University of Liverpool LECMC GCLP facilities for storage.

24 mls of blood will also be collected from participants referred to the Multi-Disciplinary team prior to surgery or investigation as well as at subsequent out-patient follow up visits. Blood collected from participants referred to the Multi-Disciplinary Team will be transported to the University of Liverpool Cancer Research Centre, 200 London Road, Liverpool.

Participants will also be given a sputum collection kit to take home. They will be asked to deposit three morning sputum samples and post the sample back to the UKLS biobank in postage paid Royal Mail Safe Boxes.

15 Statistical Considerations

15.1 Introduction

This study has been designed to have power to detect a significant realistic and clinically worthwhile effect of the intervention. We are particularly interested in the effect in a higher risk population than NELSON, as we feel that if there were a service screening programme in the future, it would probably be neither ethical nor feasible to offer the service to low or medium risk individuals. However, the effect of the screening as estimated in the two trials can be combined in the fullness of time, which gives a safety net for statistical power in case the intervention has a lesser effect than anticipated. The Trial design for UKLS will use the Wald one screen design detailed in section 6.3 UKLS Trial Design.

The reasons for the one screen design are based on:

- It is the most economical approach in terms of the number of CT screening examinations needed for a fully powered trial (see section 15.2 below)
- It will provide early data on rates of cancers in the years following a screen, to inform 'interval' for subsequent screens in a National Screening Programme
- It will produce mortality results in a similar time frame as the other major international multi-centre screening trials, and allow us to synchronise our data with the multi-centre groups for analysis
- The single screen design does not have the problem of long term compliance
- Other screening trials have used this design, including the UK Flexisig Trial, the UK Aortic Aneurysm Screening Trial and the Singapore Breast Screening Trial.

15.2 Sample Size

The sample size/power calculations had the aim of determining a screening schedule which would optimise when and with what study size a significant result is likely in UKLS, with respect to the comparison of lung cancer mortality in the intervention and control group. The question of particular interest is whether a study offering only a single screen to the study group, or one offering multiple screens, is likely to be more efficacious in terms of:

(1) how soon a significant result can be expected; and
(2) resources expended on screening

Without actually carrying out the full trial, the timing and magnitude of the effect on mortality, if any, cannot be known for certain. We can, however, arrive at estimates using published data on the following quantities:

- The incidence of lung cancer in the target population
- Uptake of screening
- The mean sojourn time (MST) of asymptomatic lung cancer (i.e. the duration of the window of opportunity for asymptomatic detection) and its inverse, the rate of progression from asymptomatic to symptomatic disease
- Sensitivity of the screening test, CT scanning
- Survival of asymptomatic lung cancer cases, possibly taking into account length bias/over diagnosis

- Survival of symptomatic lung cancer cases

Single screen design

Although we shall use estimates of instantaneous rates of transition (e.g. from asymptomatic to symptomatic disease, from alive to dead), we shall convert these to discrete time probabilities, to obtain simple deterministic models. Let:

I =Annual incidence rate of lung cancer in target population
λ_1= Instantaneous rate of transition from asymptomatic to symptomatic disease (=1/MST)
λ_2= Instantaneous death rate from lung cancer of asymptomatic cases
λ_3= Instantaneous death rate from lung cancer of symptomatic cases
S =sensitivity of the screening test

We assume a uniform annual incidence and exponential rates of progression to symptomatic disease and death [25]. We first demonstrate how to estimate the cumulative death rates in intervention and control groups for the simple case of a single screen study. In the intervention group, at time point 0, the expected rate of detection of asymptomatic lung cancers in those attending for screening is:

$$P = \frac{IS}{\lambda_1}$$

as shown by Paci and Duffy [26]. Launoy and colleagues [27] have shown that in a programme with a screening interval of r years, the expected proportion of tumours in those attending which are screen-detected is:

$$PS = \frac{S(1 - e^{-\lambda_1 r})}{\lambda_1 r(1 - (1 - S)e^{-\lambda_1 r})}$$

It follows that the cumulative rate of symptomatic cancers arising in the r years after a screen years will be:

$$I_r = I(1 - PS)$$

The number of symptomatic cancers arising in the first year after a screen is I_1. The number arising in the rth year (r=2,3,4…) after a screen is I_r-I_{r-1}. In the control group, and in those who elect not to be screened in the study group, the annual rate of symptomatic cancers is I.

The cumulative rate of lung cancer death by the end of year r from asymptomatic tumours diagnosed in the intervention group at the single screen at the beginning of the study is estimated as:

$$D_1 = P(1 - e^{-\lambda_2 r})$$

The corresponding cumulative death rate in the control group is estimated as:

$$D_0 = I \sum_{i=1}^{r} (1 - e^{-\lambda_3 (i-0.5)})$$

This uses the approximation of time of diagnosis as the midpoint of the relevant year. For the symptomatic tumours arising after the screen in the intervention group, the expected cumulative death rate is:

$$D_0 = \sum_{i=1}^{r} (I_j - I_{j-1})(1 - e^{-\lambda_3(r-j+0.5)})$$

where we define I_0 as 0.

We now require estimates of the various quantities. Let us first suppose that we shall be selecting a fairly high risk group for the trial, with a minimum annual incidence of five per thousand and an average annual incidence of seven per thousand. Thus I=0.007. From a recently published overview, we have estimates λ_1=0.49 and S=0.96 [28]. Five-year survival from lung cancer in the UK has been reported as 6% [29], corresponding to λ_3=0.56. Henschke et al [30] report 85% 10-year survival of 412 stage I screen-detected cases. Assuming that the 72 screen-detected cases in their series with stage II or worse disease had zero ten-year survival, this would give an overall ten-year survival of 72%. Hypothesising further that this is artificially high as a result of length bias/overdiagnosis, we assume a ten-year survival of 50%. Thus we are estimating the effect of screening on mortality from the 'real', life-threatening tumours, rather than inflating the incidence of the intervention group and retaining the very high survival rate. This gives λ_2=0.07. We assume an uptake rate of 80%, which seems high but reflects the motivated nature of this group, already demonstrated by their positive response at two stages of approach.

WALD Single Screen Design

The resulting estimates of cumulative lung cancer mortality are shown in Table 1, adjusted for the 80% compliance. The Table also shows the relative risks of lung cancer death, and the numbers required per group (assuming equal group size) for 90% power to detect the difference as significant, with 2-sided testing at 5% level. The optimum time of analysis would be at the end of three years, and 16,000 subjects per group would be required (32,000 in all). The time to the result, taking into account the recruitment period, would be more likely to be around five years.

Table 1: Relative risks of lung cancer death by year and number required per group in a trial with a single screen intervention

Year	Cumulative lung cancer mortality (study)	Cumulative lung cancer mortality (control)	RR (intervention vs control)	Number required per group
1	1.0	1.2	0.83	368,000
2	3.1	4.0	0.78	63,000
3	5.3	7.8	0.69	16,000
4	9.2	12.1	0.76	20,000
5	13.4	16.7	0.80	21,000
6	17.9	21.4	0.83	24,000

Annual screening for three years

The calculations of the expected incidence of screen-detected and symptomatic tumours in the intervention group are similar to those for the single screen design, although now there is a mix of screen-detected and symptomatic tumours in the first three years. The cumulative mortality, relative risks and numbers required for 90% power are shown in Table 2.

The optimum power is achieved at 5 years, with 7,000 per arm. One might expect to add one year to this for recruitment.

Table 2: Relative risks of lung cancer death by year and numbers required per group in a trial with three annual screens

Year	Cumulative lung cancer mortality (study)	Cumulative lung cancer mortality (control)	RR (intervention vs control)	Number required per group
1	1.0	1.2	0.83	368,000
2	2.8	4.0	0.69	35,000
3	5.0	7.8	0.65	13,000
4	7.8	12.1	0.64	8,000
5	11.2	16.7	0.67	7,000
6	15.2	21.4	0.71	7,200

Allowing for the 80% compliance rate, the single screen arm would incur screening costs for 12,800 CT scans (80% of 16,000). The 3-screen study would incur 16,800 scans (80% of 3 x 7000). Thus it would seem that the single-screen design, based on an idea by Professor Nick Wald, would be more economical and would return an answer to the basic question earlier. We therefore propose a single screen in the study group vs usual care in the control group, with 16,000 subjects per group. We are aware that this design is not entirely conventional and that in a service screening programme, repeated screening would apply. Also, it has implications for analysis and interpretation (see below). However, in addition to its cost-effectiveness as a design, it has a number of other benefits.

The modelling has been carried out varying the parameters, and the single screen design has generally been more cost-effective. Also, the estimation of mortality from the rather simple semi-deterministic model above has been checked against a full stochastic model and results were in agreement.

15.3 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (IDSMC). These analyses will be performed at the LCTU. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

15.4 Criteria to proceed from pilot trial to main trial

The crucial factors are the proportion of the initial sample approached that are successfully recruited, the compliance with screening of those randomised to the intervention, and the ability of the centres to cope with the screenees. We propose continuation criteria for each of these in turn, in each case with three possible outcomes: (1) proceed with the main trial as originally envisaged; (2) revise the protocol of the main trial to correct for problems observed in the pilot, and then proceed; and (3) abandon the main trial and follow up the pilot population, for synthesis of their results with those of other European trials.

A. For recruitment, we propose the following criteria for actions (1), (2) and (3) respectively.

1. If recruitment is more than 90% of the 4.9% anticipated, proceed to main trial.
2. If recruitment is 50-89% of the 4.9% anticipated, revise protocol to include, either an expansion of the initial approached population or to include a second contact of non-responders to first approach, or both. Then proceed to main trial as amended.
3. If recruitment is less than 50% of the 4.9% anticipated, abandon the plan for the main trial.

B. For compliance with screening (CT study group) or usual care (Control group), we propose:

1. If compliance is 75% or more, proceed to main trial.
2. If compliance is 50-74%, revise protocol to increase total study size or to make attendance for screening easier or more attractive, or both. Then proceed to main trial as amended.
3. If compliance is less than 50%, abandon the plan for the main trial.

C. Ability of the centres to cope with the screening workload:

1. If centres screen 80% or more of those scheduled within the anticipated time, proceed to main trial.
2. If centres screen 50-79% of those scheduled within the anticipated time, revise protocol to increase the number of centres or enhance support offered to centres or both. Then proceed to main trial as amended.
3. If centres screen less than 50% of those scheduled within the anticipated time, abandon the plan for the main trial.

We do not propose to use the numbers recommended for further diagnostic workup as a criterion to proceed or not, but if the numbers exceed 30% in either centre, we propose to revise the protocol in terms of training and quality control for initial screening.

D. UKLS Database

Successful implementation of the UKLS database and information system in the LCTU, and recruitment centre clinics in both pilot centres as well as the CT Review Centre. Questionnaire, epidemiological and clinical data collection successfully uploaded onto the UKLS database. An earlier version of this database has been used to manage the NELSON trial, thus no major issues are envisaged, which cannot be resolved.

15.5 Analysis Plan

A full analysis plan is in development. It is anticipated that the traditional Poisson regression[31] based on cumulative mortality from lung cancer will be performed, as is traditional in screening and prevention trials. It is appreciated that the relative risk estimated from this will be less extreme than might be achieved by repeat screening. We shall therefore additionally analyse the mortality results by fitting the relative hazard of lung cancer mortality as a function of time since randomisation [32] This will improve statistical power and yield estimates which can be compared with those of other screening trials with multiple screen designs.

In addition, we propose to analyse the screening data in terms of detection and interval cancer rates, compliance rates, and false positives rates. In addition to simple descriptive analyses, we shall estimate sensitivity, specificity, and positive and negative predictive values. We shall use Markov process models to estimate lead times [33].

16 Adverse event reporting

16.1 Definitions

ICH GCP defines an Adverse Event as follows:

Adverse Event (AE)
Any untoward medical occurrence in a research participant

Serious Adverse Event (SAE):
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events***

*'Life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

16.2 UKLS Adverse Event Reporting

It is not anticipated that any participant in the UKLS trial will any suffer any adverse events relating to their involvement. Routine adverse events data will not be recorded as part of the participant follow-up. Adverse Events may occur later in the patient pathway if a nodule is discovered and this will be dealt with according to local practice in the treating centre.

17 Ethical Considerations

17.1 Ethical Considerations

The study will be conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964 and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996)). The study will be conducted in compliance with the Medicines (Administration of Radioactive Substances) Regulations 1978 ('MARS') and the principles of Good Clinical Practice.

Patients will be asked to consent that data recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

This study may be terminated at the request of the Chief Investigator, IDSMC, or the Independent Ethics Committee if, during the course of the study, concerns about the safety emerge.

17.2 Ethical Approval

Ethical approval will be applied for from the Integrated Research Application System (IRAS). This will include approval from the National Research Ethics Service Committee, NHS R&D, National Information Governance Board for Health and Social Care and Administration of Radioactive Substances Advisory Committee (ARSAC).

All participating sites must undergo site specific assessment (SSA) via IRAS conducted by their local R&D department. A copy of all site approval documentation and a copy of the PIS and ICF on local headed paper should be sent to the LCTU before patients are entered. The LCTU should receive notification of positive SSA and ARSAC for each new centre prior to allowing any patient registration.

After the patient has been registered into the study, the clinician is free to withdraw the patient at any stage if he/she feels it is in the best interest of the patient. However the reason for doing so should be recorded and the patient will remain within the study for the purpose of follow-up and data analysis. Similarly, the patient remains free to withdraw at any time from the protocol and study follow-up without giving reasons and without prejudicing further care.

17.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTU co-ordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to participants by staff with experience of taking consent. Participant Information and Consent forms, describing in detail the trial interventions, trial procedures and risks will be approved by an Independent Ethical Committee (IEC) and the participant will be asked to read and

review the document. Upon reviewing the document, the investigator will explain the research study to the patient and their parent/legal representative and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided.

The patient should have the opportunity to discuss the study and think about it prior to agreeing to participate. After being given adequate time to consider the information (at least 24 hours), the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient for their records, a copy placed in the medical records, a copy sent to the LCTU for randomisation purposes with the original retained in the Investigator Site File (ISF).

The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline in this study.

17.4 Data Capture Methods

17.4.1 Radar

Radar is a data capture company that has been selected to manage the UKLS invitation letters and associated questionnaires. Radar have a wealth of knowledge in the field of managing data for large screening projects and have in place clearly outlined data security and disaster recovery policies. Radar is registered and fully compliant under the Data Protection Act.

Radar will take full responsibility for the end to end process for the UKLS project, as outlined in the UKLS Recruitment Pathway (Page 14 – Section 3.0).

Data will be transferred from Radar to UKLS via an external hard drive, encrypted and password protected. Radar are responsible for maintaining security for all data on their equipment and will be automatically backed-up according to Radar's back-up procedure.

Radar will ensure that security is in place on all equipment that data is stored upon.

17.4.2 Questionnaires

The majority of the data collected for the trial will be obtained directly from the participant using lifestyle and psychosocial and Health Economics questionnaires. These questionnaires will form the basis for participant selection. Follow-up questionnaires will also be sent out during the course of the trial to collect further psychosocial data. For the non-screen arm participants will receive a psychosocial questionnaire two weeks after randomisation to the non-screen arm. In the screen arm participants will receive a psychosocial questionnaire two weeks after receiving the result of their baseline scan and any follow up scans required. Data will also be collected during clinic visits. This data will be recorded within patient notes (Source Data) and will be entered onto the UKLS database where necessary.

Timetable of psychosocial measures	Baseline	Follow-up
Demographic and clinical information • Ethnicity • Socioeconomic status / education • Lung screening history (past lung screening; past recall) • Gender* • Age (DOB)* • Smoking – type and frequency* • Family history of lung cancer* * *Could be accessed from 1st screening risk questionnaire*	✓ ✓ ✓ ✓ ✓ ✓ ✓	x x x x x x x
Cancer distress 6 item Cancer Worry Scale (CWS-R) adapted to lung cancer	✓	✓
General distress Hospital Anxiety and Depression Scale (HADS)	✓	✓
Satisfaction with Decision Scale SWD Scale [34] adapted to decision to take part in lung screening study	✓	✓
Screening expectations & perceptions of CT scan results CARA model [24] Feedback expectancy, i.e. expected CT scan result. To be completed by intervention arm only: perceived feedback threat *("How concerned were you by your CT scan result?" where 1 = not at all concerned, 5 = extremely concerned)* and perceived feedback accuracy *("How likely did you think it was that your CT scan result was false or inaccurate?" where 1 = not at all, 5 = a great deal)*	✓ x	x ✓
Screening behaviours • Intention to attend further screening • Use of private CT scans	x x	✓ ✓

Following a Quality Control check and audit of UKLS data captured electronically form the UKLS questionnaires; original copies of the questionnaire will be securely destroyed. Images of every questionnaire will be stored on the UKLS database and affiliated with the relevant participant.

17.4.3 UKLS Database

Discussions have taken place between the UKLS CI and the Steering Committee of the NELSON trial and it has been agreed that the UKLS trial may have use of their database and adapt as required for a fee during the pilot and main trial.

The IT manager for NELSON, Mr Ton de Jongh, has been appointed as the UKLS IT Database Consultant.

The UKLS database will be housed by the University of Liverpool Computer Services Department. The database will be housed on its own server. Access to areas of the database will be allocated on a need to know basis as authorised by the CI.

18 Trial Monitoring

18.1 Trial Monitoring

Central and site monitoring is conducted to ensure the rights and well-being of participants are protected during the course of a study, and that trial procedures, laboratory and data collection processes are of high quality and meet sponsor requirements. A risk assessment for the study will be carried out prior to the start of patient registration, to determine the level and type of monitoring required and subsequent monitoring plan will be developed to document the central (and potentially site) monitoring, at what frequency monitoring will be carried out, and the level of detail at which monitoring will be conducted.

18.2 Risk Assessment

In accordance with the LCTU Standard Operating Procedures and the requirements of the sponsor organisation a study risk assessment will be completed in partnership with the Trial Management Group.

In conducting risk assessments, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

18.3 Source Data

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies; ICH E6, 1.51).

18.4 Monitoring at LCTU

18.4.1 The Green Light Process

The green light process in place at the LCTU means that no patients can be registered at a particular site without the green light being given. It ensures that all approvals must be in place, all contracts/agreements signed and all study-specific and GCP training received by the site research staff before patients can enter the study. The green light will be granted by the trial co-ordinator (TC), once all essential documents are in place.

18.4.2 Site Research Staff

All site research staff involved in the study must be included in the delegation log. The PI at each site signs off on the delegation log only those staff members he/she feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities.

The TC ensures that all delegated staff have documented study-specific training (on the protocol, SAE reporting and consent process) all of which is provided at site initiation (either on site or by teleconference) by the TC and on a continuous basis throughout the study when new staff are added to the delegation log. Sites are supplied with copies of training aids presented at site initiation to provide a constant

reminder of key study issues. Delegated study research staff must also submit their CV and provide the date of their last ICH GCP training. In order to ensure that site research staff maintain up to date ICH GCP training (to be renewed every 2 years as suggested by ICH GCP), an automated email reminder is sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary contracts and evidence of CRB checks must be obtained for staff (when necessary by UK law).

Automated 6-monthly email reminders (from site opening) are sent to sites requesting that an updated delegation log is faxed to the LCTU. On receipt of updated delegation logs, the TC ensures that new staff have submitted their CVs and date of last ICH GCP training, as well as providing them with trial-specific training.

18.4.3 Randomisation

The TC verifies that all site research staff have attended study specific training related to eligibility screening and the informed consent process. Prior to randomisation, the TC/data manager (DM) carry out a check of all consent forms sent to the LCTU. This includes checking that the patient is eligible, the correct versions of the PIS and ICF have been used, and the patient and clinician signatures are present and dated on the same day. LCTU staff receive appropriate randomisation training and there is always office cover to ensure the randomisation procedure is carried out correctly.

18.4.4 Patient Confidentiality

Participant identifiable information is required throughout the trial to contact participants, assess scan, monitor the trial and to collect Office of National Statistics Data. Patient confidentiality is very important and the participant identifiable information will be stored on a database hosted on the secure University server. The steps below have been put in place to ensure data security:

- All desktop computers and servers will require user name and password to gain access
- All computers will only be used either standalone or behind a hardware and software based firewall
- Any internal/external access to the system will only be provided to essential staff
- External access will require user name and password to be provided
- All passwords will be amended on a quarterly basis
- All password complexity is enforced by University Policy
- McAfee antivirus
- Software will operate on all desktop computers, laptop computers and servers
- Any sensitive data sent by, CD, DVD or external Hard Drive will be contained within an encrypted zip file and password protected.
- All retired hardware will have their disk drives either scrambled or physically destroyed.

The UKLS team will have access to this data on a need to know basis and this will be decided by the Chief Investigator. The laboratory and statistical teams will not recover identifiable information of any kind and will recognise participants by a seven digit code number.

Participant names and addresses will be stored by the LCTU for the purpose of approaching participants to take part in the study and for sending subsequent questionnaires during the course of the study. Participant Information Sheets will reflect that this data will be collected and stored. Data for participants that do not give informed consent will be encrypted and only the database developer will have access to this information. For the purposes of the LCTU participants will only be identified by trial number and/or initials only.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

Consent forms sent to the LCTU as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the study risk assessment. Such information will be stored in secure, locked cabinets

18.4.5 Recruitment

The TC will provide monthly recruitment reports, to allow the IDSMC, TSC and TMG to regularly review recruitment across sites. Slow or inconsistent recruitment will trigger further action centrally. The TC may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. TC will check that the trial is being actively promoted at sites and site recruitment schedules will be reviewed during the course of the trial as necessary.

18.4.6 Data Management Plan

Data entered onto the UKLS database at the LCTU will be centrally monitored by the UKLS team to ensure that data collected are consistent with adherence to the protocol. The UKLS database used for this trial includes validation features which will alert the user to certain inconsistent or missing data on data entry.

18.4.7 Statistical Monitoring

The recruitment, diagnoses of lung cancer, deaths from lung cancer and adverse events will be regularly reported to the Independent Data and Safety Monitoring Committee (IDSMC). These will be reported separately for each arm of the trial, but with the committee and investigators (apart from the Trials Unit statistician) blinded as to which arm is which. Only in the event of a safety, ethics or efficacy concern on the part of the IDSMC will the arms be identified.

18.5 Clinical Site Monitoring

18.5.1 Direct access to data

Site monitoring may be deemed to be necessary as a result of central data checks. In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Each PI therefore permits study related monitoring, audits, ethics committee review and regulatory

inspections by providing direct access to source data/documents. As this also affects the patient's confidentiality, this fact is included on the Participant Information Sheet and Informed Consent Form.

18.5.2 Quality Assurance and Quality Control of Data

Central QA for CT scans
There will be a central radiology review at the second reader site at the Royal Brompton Hospital Trust, under the supervision of Professor D Hansell.

Central Monitoring
Protocol compliance and data collection will be evaluated by the LCTU through central monitoring procedures and by the Trial Management Group and Trial Steering Committee.

18.5.3 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until the LCTU informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the trial. The investigator is required to ensure the continued storage of the documents so that the study data can be compared against source data after completion of the study. The, investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTU undertakes to store originally completed questionnaires and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

19 Indemnity

UKLS is jointly sponsored by The Royal Liverpool & Broadgreen University Hospital NHS Trust and The University of Liverpool. It will be co-ordinated by the LCTU in the University of Liverpool. The University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The UKLS Pilot trial has been sponsored by:

The Royal Liverpool and Broadgreen University Hospitals NHS Trust,
Prescot Street,
Liverpool
L7 8XP

The University Of Liverpool
Research and Business Services,
The Foresight Centre,
3 Brownlow Street,
Liverpool
L69 3GL

20 Financial Arrangements

Research Site Agreements between the sponsor and the pilot recruitment centre will be put in place regarding the conduct of the pilot trial. This contract will detail the financial payments that will be made to cover costs of recruitment. Payments for recruitment at recruitment centres will be made on a per patient basis and reviewed by the TMG.

Participants within the UKLS trial may apply for travel expenses to be reimbursed. Guidelines for reimbursement will be provided to recruitment centres prior to starting the trial.

21 Trial Oversight Committees

21.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will consist of the following members:

Professor John Field	-	Chief Investigator
Professor David Hansell	-	Co-Investigator
Dr David Baldwin	-	Co-Investigator
Professor Stephen Duffy	-	Lead Statistician
Professor Paula Williamson	-	Trial Management
Professor Mahesh Parmar	-	Trial Management/Advice
Mr Terry Kavanagh	-	Lay Patient Representative
Dr Ghasem Yadegarfar	-	Trial Statistician
Mrs Beverley Green	-	Project Manager
Dr Seema Chauhan	-	Operational Director, LCTU

The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

21.2 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will consist of the following members:

Prof Ian Jacobs	-	Independent Chairman
Professor Deborah Ashby	-	Independent Statistician
Mr David Ardron	-	Independent Layman
Professor Peter Armstrong	-	Independent Radiologist
Dr Sanjay Popat	-	Independent Lung Cancer Physician
Professor John Field	-	Chief Investigator
Professor David Hansell	-	Co-Investigator
Dr David Baldwin	-	Co-Investigator
Professor Stephen Duffy	-	Lead Statistician
Dr Ghasem Yadegarfar	-	Trial Statistician
Mrs Beverley Green	-	Project Manager
Dr Seema Chauhan	-	Operational Director, LCTU

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

21.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) consists of the following independent members;

Dr Robert Smith	-	Chairman, expert in Cancer Screening
Dr Allan Hackshaw	-	Expert in Statistics
Dr Catherine Hill	-	Expert in Cancer Epidemiology

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to trial opening and then meet at 6-monthly intervals for the

first two years of recruitment. The committee will then decide on the frequency of subsequent meetings, which must take place at least annually. Details of the planned interim analyses and monitoring are provided in section 10.5.

22 Publication

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator), Lead Statistician and the Lead Radiologist and Respiratory Physician involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

23 Protocol Amendments

Protocol Version 2: 10MAY2011

Minor administrative changes were made to this version of the protocol. Appendices were also amended to reflect the changes made to other related trial documentation

Protocol Version 3: 20SEP2011

An increase to the volume of blood collected from participants was made here. The increase was from 20 to 24mls of blood

Protocol Version 4: 16NOV2011

A clarification to the exclusion criteria was made here. Clarification was made that previous Chest CT scans rather than previous CT scans within the last year preclude participants from joining the trial.

Protocol Version 5: 27FEB2012

The increase to the number of participants approached by UKLS from 82,000 to 250,000 was documented within this amendment

Protocol Version 6: 04APR2012

The protocol was amended to reflect nodule management for new nodules identified at the 3 month repeat scan

Protocol Version 7: 18MAY2012

Changes have been made in protocol version 7 to detail elements of psychosocial analysis. Changes have also been made to the nodule care pathway to clarify detail of how nodule growth is measured. The protocol also reflects changes to allow radiological and clinical decisions to be made in order to allow appropriate referrals to the Multi-Disciplinary Team

Protocol Version 8: 17JUL2012

A change to the frequency of blood collected from participants referred to the MDT has been included in this amendment. In addition, the location where tumour tissue is to be stored has been changed.
Clarification has been made to the frequency of psychosocial questionnaires that are sent to participants.

Protocol Version 9: 28MAR2013

Changes have been made in protocol version 9 to remove the requirement for follow up scans to have a second read at the Royal Brompton. However, for quality control purposes 10% of follow up scans will have a second read

Protocol Version 10: 13JUNE2013

Changes have been made in protocol version 10 to allow psychosocial questionnaires to be sent to participants who have received a follow up CT scan two weeks after receiving their results letter, in addition to the psychosocial questionnaire sent to them two weeks after receiving their baseline scan result.

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