

# **NIHR HTA Programme**

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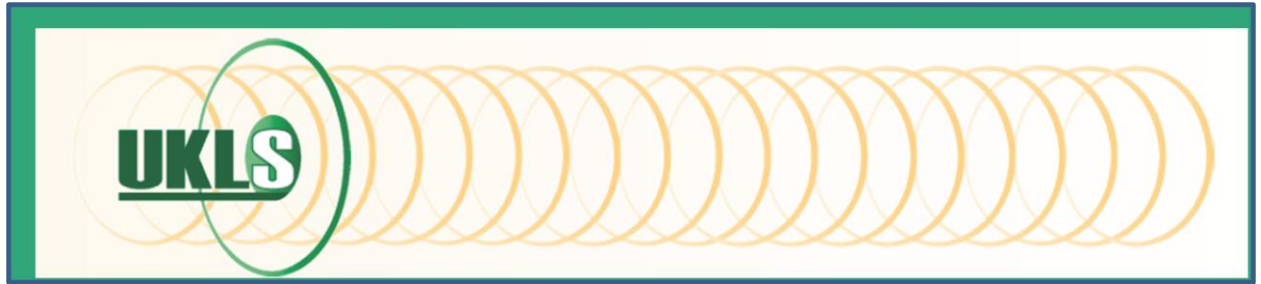
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## UK Lung Screening Trial

UKLS

**CONFIDENTIAL**

### Study Sponsors / Co-sponsors

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## Table of Contents

<b>1</b>	<b>Study Protocol Approval</b>	<b>10</b>
<b>2</b>	<b>Protocol Statements</b>	<b>11</b>
<b>3</b>	<b>Protocol Summary</b>	<b>12</b>
<b>4</b>	<b>Background Information</b>	<b>16</b>
4.1	Introduction	16
4.2	Rationale	18
4.3	Objectives	19
4.4	Potential Risks and Benefits	19
<b>5</b>	<b>Selection of Centres/Clinicians</b>	<b>22</b>
5.1	Centre/Clinician Inclusion Criteria	22
5.2	Centre/Clinician Exclusion Criteria	22
<b>6</b>	<b>Trial design – Main UKLS Trial</b>	<b>23</b>
6.1	Primary Endpoint(s)	23
6.2	Secondary Endpoint(s)	23
6.3	UKLS Trial Design	23
<b>7</b>	<b>Study Population</b>	<b>26</b>
7.1	Inclusion Criteria	26
7.2	Exclusion Criteria	26
7.3	Patient Withdrawal from Trial Intervention	26
7.4	Withdrawal from Trial Completely	26
7.5	Loss to Follow-up	26
7.6	Co-enrolment Guidelines	27
<b>8</b>	<b>Enrolment and Randomisation</b>	<b>27</b>
8.1	Screening	27
8.2	Recruitment	28
8.3	Randomisation	29
<b>9</b>	<b>Lung cancer Screening</b>	<b>30</b>
9.1	Introduction	30
9.2	Arm A	30
9.3	Arm B	30
9.4	Radiological Protocol for the UK Lung Cancer Screening Trial	30
<b>10</b>	<b>UKLS Care Pathway</b>	<b>38</b>
<b>11</b>	<b>MDT Assessment</b>	<b>39</b>
11.1	The UKLS Care Pathways	39
<b>12</b>	<b>Pathological Investigations</b>	<b>42</b>
<b>13</b>	<b>Surgical Protocols</b>	<b>43</b>
<b>14</b>	<b>Assessments and Procedures</b>	<b>44</b>
14.1	Schedule for Follow-up	44
14.2	Follow up	44
14.3	Psychosocial and Health Economics	44
14.4	Sub-studies	46
<b>15</b>	<b>Statistical Considerations</b>	<b>47</b>
15.1	Introduction	47

15.2	Sample Size .....	47
15.3	Interim Monitoring and Analyses .....	50
15.4	Criteria to proceed from pilot trial to main trial .....	51
15.5	Analysis Plan .....	52
<b>16</b>	<b>Adverse event reporting .....</b>	<b>53</b>
16.1	Definitions .....	53
16.2	UKLS Adverse Event Reporting .....	53
<b>17</b>	<b>Ethical Considerations .....</b>	<b>54</b>
17.1	Ethical Considerations .....	54
17.2	Ethical Approval .....	54
17.3	Informed Consent Process .....	54
17.4	Data Capture Methods .....	55
<b>18</b>	<b>Trial Monitoring.....</b>	<b>58</b>
18.1	Trial Monitoring .....	58
18.2	Risk Assessment .....	58
18.3	Source Data .....	58
18.4	Monitoring at LCTU .....	58
18.5	Clinical Site Monitoring .....	60
<b>19</b>	<b>Indemnity.....</b>	<b>62</b>
<b>20</b>	<b>Financial Arrangements.....</b>	<b>63</b>
<b>21</b>	<b>Trial Oversight Committees .....</b>	<b>64</b>
21.1	Trial Management Group (TMG) .....	64
21.2	Trial Steering Committee (TSC) .....	64
21.3	Independent Data and Safety Monitoring Committee (IDSMC) .....	64
<b>22</b>	<b>Publication .....</b>	<b>66</b>
<b>23</b>	<b>Protocol Amendments .....</b>	<b>67</b>
<b>24</b>	<b>References .....</b>	<b>68</b>

## 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)**

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Research Co-ordinator  
University of Liverpool  
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**Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Signed on behalf of the Royal Liverpool and Broadgreen  
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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.



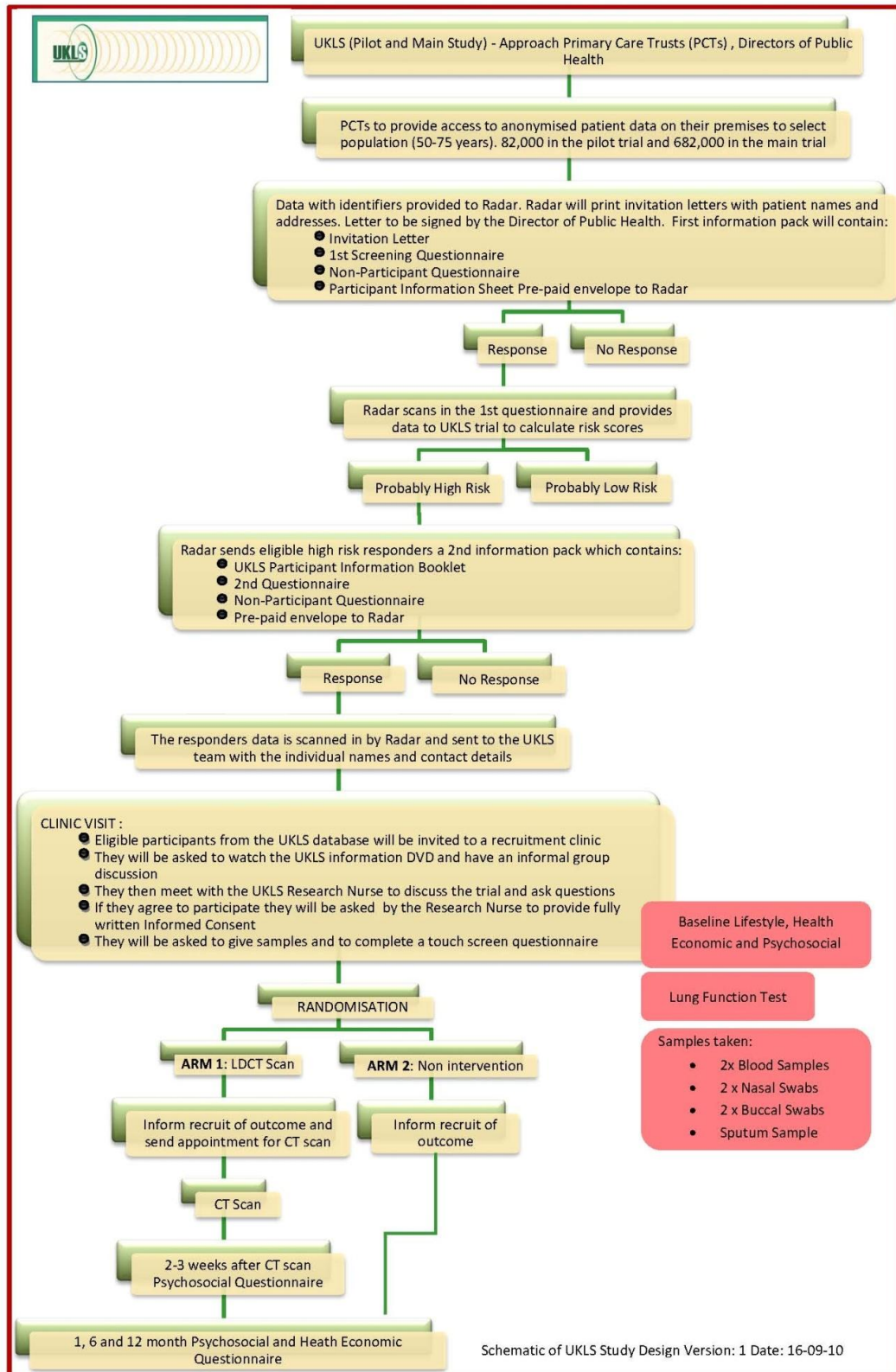
### 3 Protocol Summary

<b>Title:</b>	UK Lung Screening Trial (UKLS)
<b>Design:</b>	Randomised controlled screening trial
<b>Sample Size:</b>	Maximum 4,200 participants from the UK for the Pilot Trial  Maximum 32,000 participants from the UK for the Main Trial.
<b>Study Period:</b>	Pilot: 14 months.  Main Trial: 10 years
<b>Main Inclusion Criteria:</b>	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
<b>Main Exclusion Criteria:</b>	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)
<b>Number of Sites:</b>	The pilot trial will have two participating centres: <ul style="list-style-type: none"> <li>• Liverpool Heart and Chest Hospital</li> <li>• Papworth Hospital</li> </ul> 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.
<b>Study Duration:</b>	10 years
<b>Description of Intervention:</b>	Low dose Computed Tomography (CT) of the lungs
<b>The objectives of the Pilot UKLS</b>	1. Will the proposed method of recruitment (based on the protocol of a two-stage postal survey of risk directly

<b>study:</b>	<p>aimed at the general population) deliver the required numbers?  This entails estimating:</p> <ol style="list-style-type: none"> <li>a. Response rates to questionnaires.</li> <li>b. Proportion of subjects approached who are eligible.</li> <li>c. Proportion of eligible subjects who consent to randomisation.</li> <li>d. Proportion of subjects randomised to LDCT who comply with intervention.</li> </ol> <ol style="list-style-type: none"> <li>2. How many subjects need to be approached to obtain the required full trial population?</li> <li>3. Do the recruitment, randomisation and scanning protocols work in practice? Is the recruit's journey from initial survey to LDCT scanning logistically efficient?</li> <li>4. Are both fixed and mobile CT units practicable for trial purposes - is one preferable to the other in terms of cost/convenience?</li> <li>5. Testing of staff training programmes.</li> <li>6. Testing of QA procedures, for radiology and technology, including radiation dose aspects.</li> <li>7. Do questionnaires or consent/information procedures or documentation need revising?</li> <li>8. Review recruitment in hard to reach groups</li> <li>9. UKLS database capable of capturing all of the required information from the recruitment phase to CT screening, investigations and treatment.</li> <li>10. Collection of blood *sputum specimens at the recruitment phase, and QC.</li> <li>11. Provide Screening data for HTA review at Month 12 of the pilot for review and decision whether to fund the Main UKLS trial.</li> <li>12. Management of UKLS through the LCTU</li> </ol>
<b>Main Study Primary Objectives:</b>	<ol style="list-style-type: none"> <li>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.</li> <li>2. To establish if there is a lung cancer mortality benefit from CT screening</li> <li>3. Establish total mortality benefit</li> <li>4. Cost effectiveness of a national lung cancer screening programme.</li> </ol>
<b>Main Study Secondary Objectives:</b>	<ol style="list-style-type: none"> <li>1. To determine the physical morbidity associated with lung cancer screening</li> <li>2. To determine the resource implications of screening and the resulting intervention</li> <li>3. To assess the feasibility of population screening for lung cancer as reflected by uptake of invitations and compliance rates with annual screening</li> <li>4. Establish a blood and tissue bank for the future assessment of early detection diagnostics and novel</li> </ol>

	tumour biomarkers
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## 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 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](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**

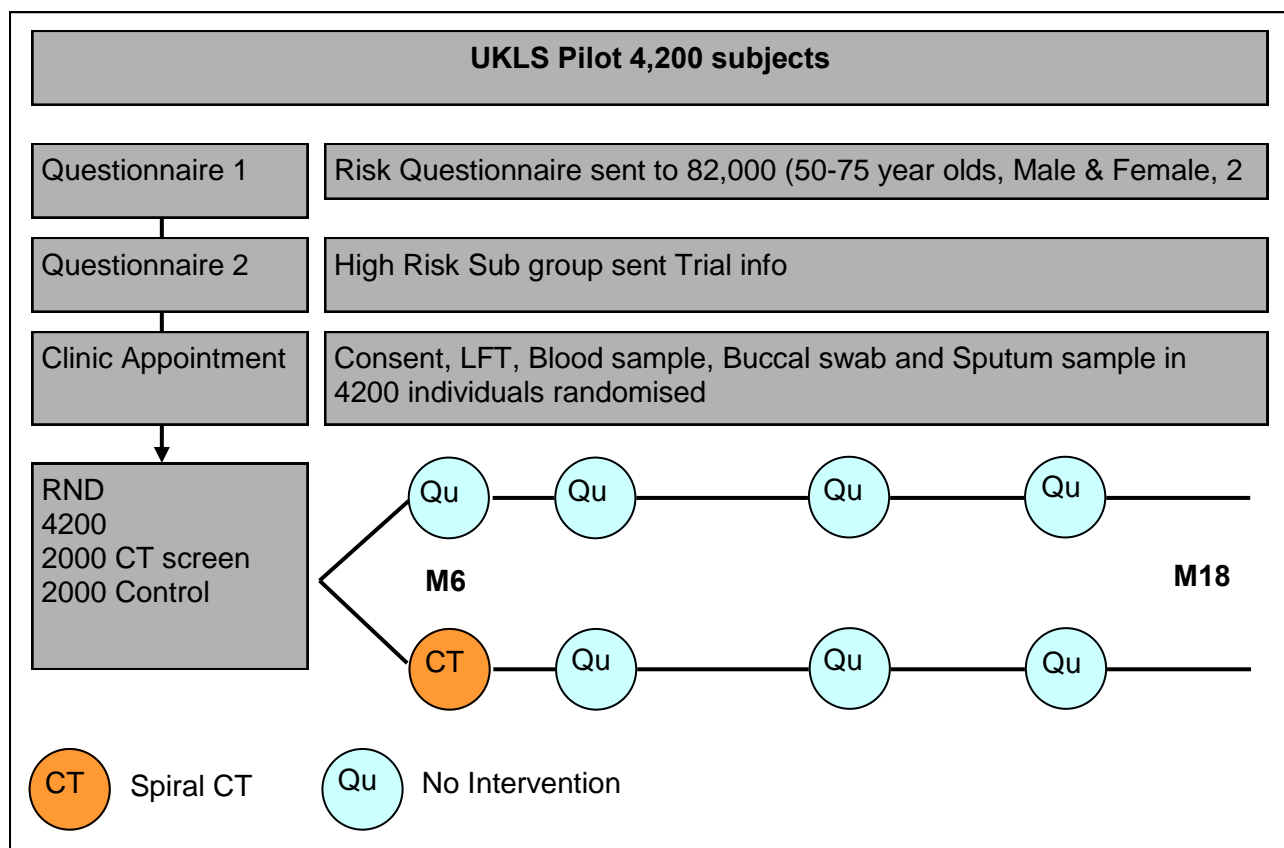
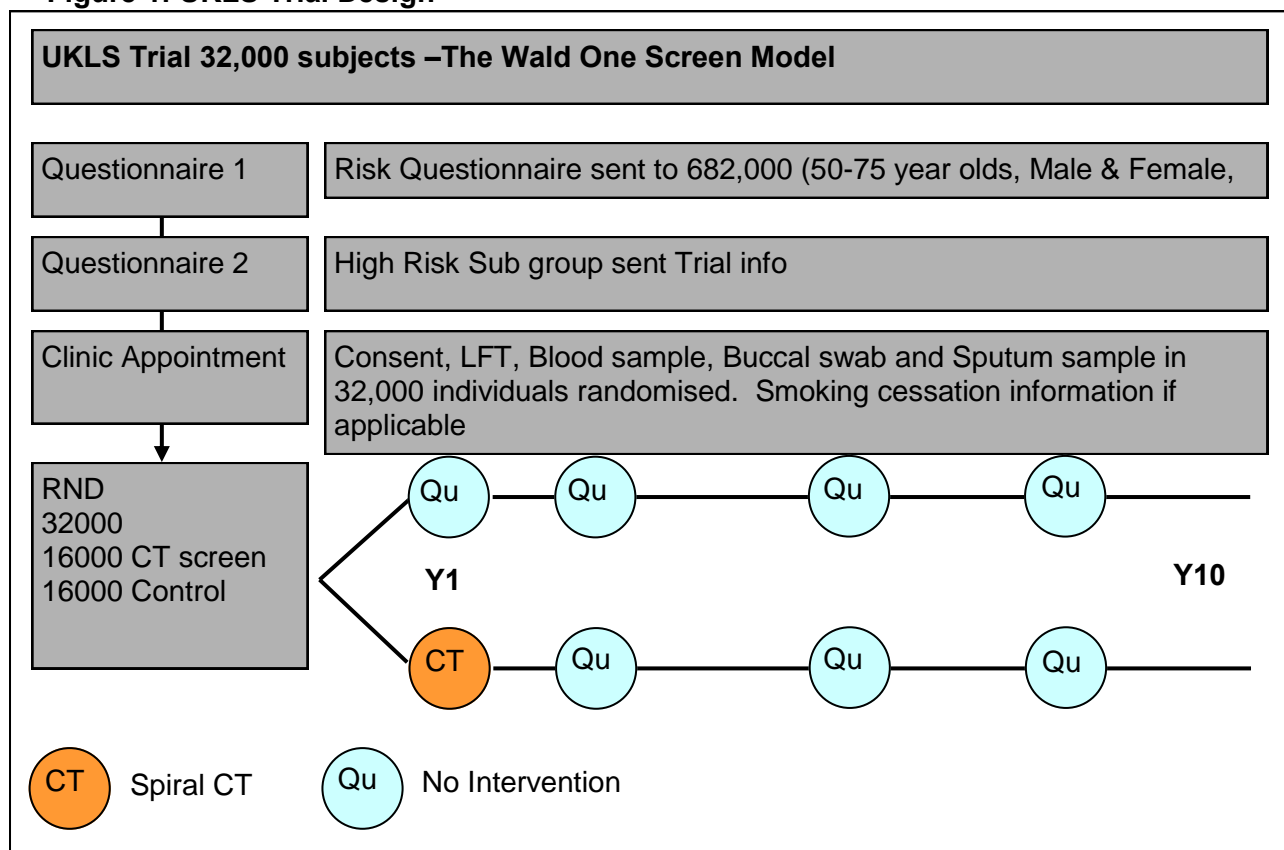
The 'Wald Single Screen Design' has been chosen for the UKLS trial. The study arm is offered a single CT scan (with appropriate further workup where necessary), the control arm is given usual care, and both arms are followed up for lung cancer incidence and mortality. The details of this design are provided 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 with 16,000 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 7 recruitment centres; the remaining 5 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*	<i>*depending on scanner type adjusted to achieve CTDI given below</i>		
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 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 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.

### ***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 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  $\leq 3\text{mm}$  are for the purposes of the trial ignored and not recorded)

### **Solid nodules**

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

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

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

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

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

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

Category 4 (Large). If the solid component has a volume  $>500\text{ mm}^3$ .

#### **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 mm<sup>3</sup>. 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<sup>3</sup>. 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<sup>3</sup>. 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<sup>3</sup>. If solid and pleural or juxtaleural 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<sup>3</sup> or has a max diameter of 3.0 – 9.9 mm.

**Category 4** If solid and intraparenchymal with a volume >500 mm<sup>3</sup>. If solid and pleural or juxtaleural 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<sup>3</sup>.

#### **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.

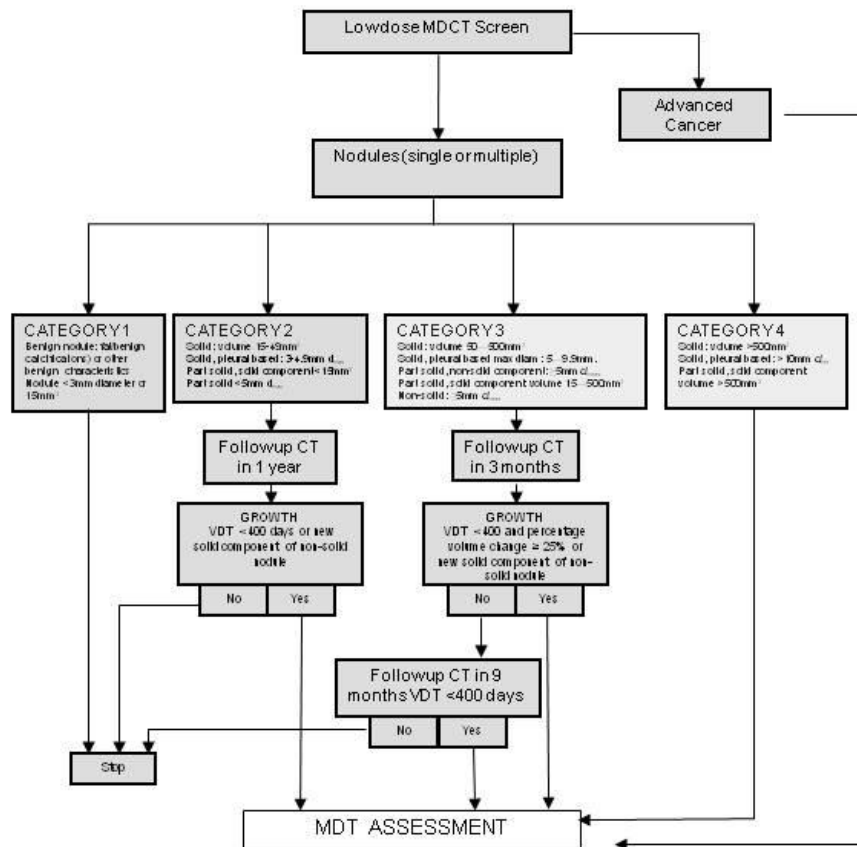
#### **9.4.11 Main Phase**

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 UKLS 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

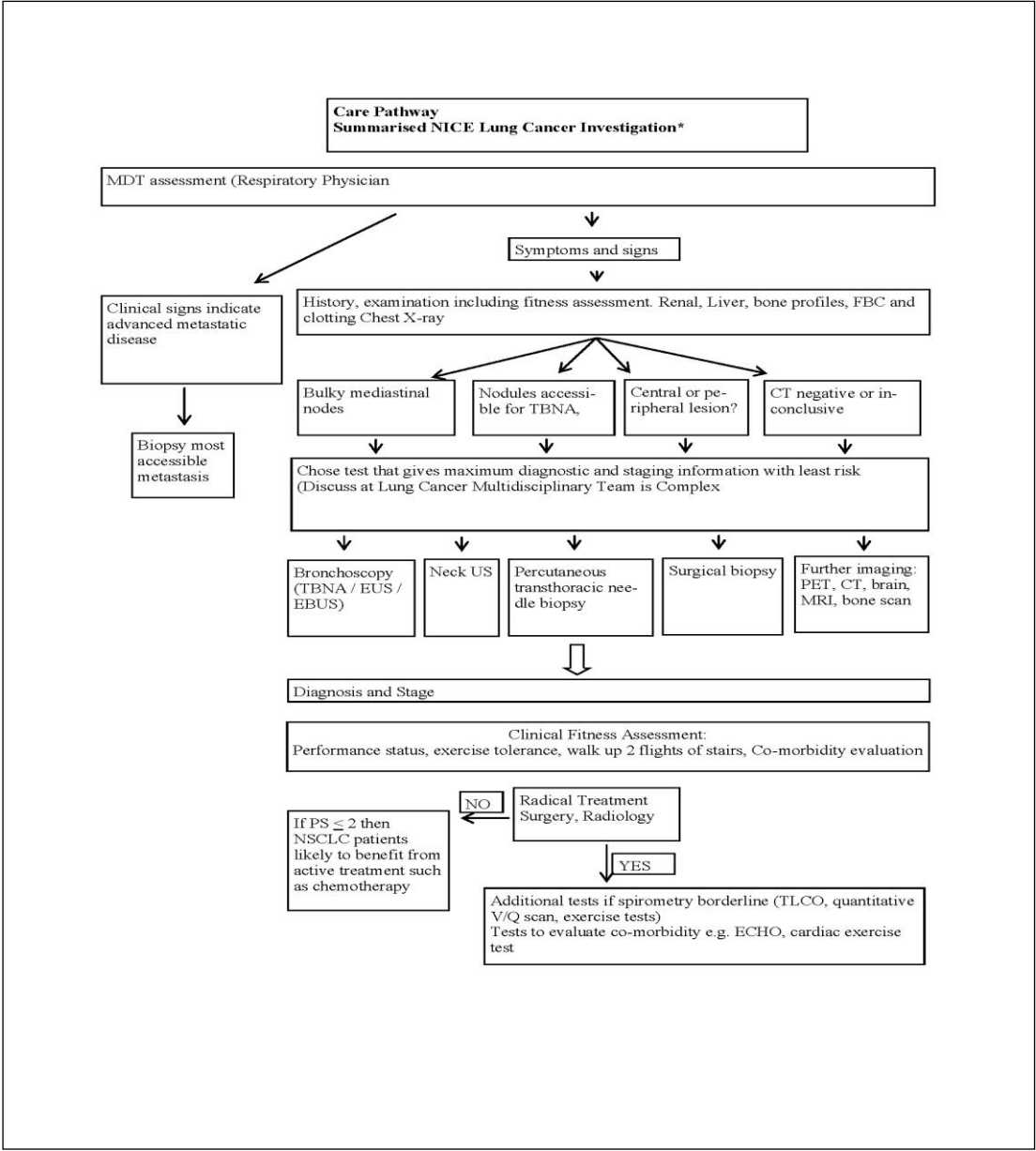
planning will be based on the Care Pathway flow diagram outlined in Figure 2, which is based on NICE guidelines.

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 from 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) and again at 6 and 12 months post randomisation. 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 to be 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 4 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 4 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 3 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

$\lambda_1$  = Instantaneous rate of transition from asymptomatic to symptomatic disease (=1/MST)

$\lambda_2$  = Instantaneous death rate from lung cancer of asymptomatic cases

$\lambda_3$  = 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  $r$ th year ( $r=2,3,4,\dots$ ) 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  $\lambda_1=0.49$  and  $S=0.96$  [28]. Five-year survival from lung cancer in the UK has been reported as 6% [29], corresponding to  $\lambda_3=0.56$ . 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  $\lambda_2=0.07$ . 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.

<b>Table 1: Relative risks of lung cancer death by year and number required per group in a trial with a single screen intervention</b>				
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 3 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.

<b>Table 2: Relative risks of lung cancer death by year and numbers required per group in a trial with three annual screens</b>				
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 18<sup>th</sup> 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. 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
<b>Demographic and clinical information</b> <ul style="list-style-type: none"> <li>• Ethnicity</li> <li>• Socioeconomic status / education</li> <li>• Lung screening history (past lung screening; past recall)</li> <li>• Gender*</li> <li>• Age (DOB)*</li> <li>• Smoking – type and frequency*</li> <li>• Family history of lung cancer*</li> </ul> <p><i>* Could be accessed from 1st screening risk questionnaire</i></p>	✓ ✓ ✓ ✓ ✓ ✓ ✓	x x x x x x x
<b>Cancer distress</b> 6 item Cancer Worry Scale (CWS-R) adapted to lung cancer	✓	✓
<b>General distress</b> Hospital Anxiety and Depression Scale (HADS)	✓	✓
<b>Satisfaction with Decision Scale</b> SWD Scale [34] adapted to decision to take part in lung screening study	✓	✓
<b>Screening expectations &amp; perceptions of CT scan results</b> <b>CARA model [24]</b> 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  ✓
<b>Screening behaviours</b> <ul style="list-style-type: none"> <li>• Intention to attend further screening</li> <li>• Use of private CT scans</li> </ul>	x x	✓ ✓

Following a Quality Control check and audit of UKLS data captured electronically from 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
Mr Christopher Hands	-	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
TBC	-	Trial Statistician
Mr Christopher Hands	-	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.

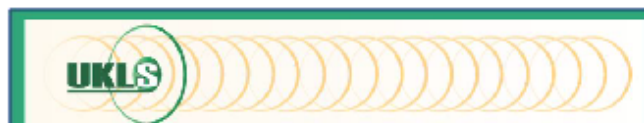


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## Appendix: A – First Invitation Letter Version 4: 27FEB2012



Director of Public Health  
PCT

<name and address to be inserted here>

Name and Address  
DATE

Dear (Name)

We are writing to ask you if you would be willing to help us in our research efforts in setting up a national screening program to screen for lung cancer. Lung cancer kills more people than any other cancer and is very difficult to treat as it is usually diagnosed in its late stages.

We are sorry if we are writing to you at a time when you may already be affected by this disease, however, your name has been chosen at random.

The purpose of this study is to determine whether screening will detect lung cancer at an earlier stage, when treatment is more effective and could therefore help prevent deaths from lung cancer. The Department of Health have given us a large grant for this study.

The study is called the UK Lung Cancer Screening Trial (UKLS). We need to involve 4,000 men and women, half of whom will be screened and the other half will have no screening. The screened group will have a special x-ray called a CT scan. If you are willing to help us, a computer will select the people and later on decide which group you could be in. The results will decide whether the NHS should start a screening programme for lung cancer, alongside those for cervical and breast cancer. Recruitment clinics are being held at Papworth Hospital near Cambridge and Liverpool Heart and Chest Hospital

You have been randomly selected from individuals aged 50 to 75 years of age from your local Primary Care Trusts. We would be grateful if you would read the enclosed UKLS fact sheet and then complete the 'UKLS Questionnaire' and return it in the enclosed envelope.

If the computer selects you to participate based on the questionnaire answers we will send you further information on the UKLS trial.

If you decide not to participate we would be grateful if you could complete the short questionnaire "Not wishing to participate in the UKLS" and return in the enclosed envelope. We will not contact you again. It will not affect your healthcare in any way if you do not take part.

We hope that you will want to take part in the study because it will help us find out if screening can prevent deaths from lung cancer

Yours sincerely,

Director of Public Health – (PCT)

UKLS Contact Details  
<to be inserted here>

## Appendix: B – Participant Information Sheet Version 2: 10MAY2011



### United Kingdom Lung Cancer Screening Trial (UKLS)

**This fact sheet gives an overview of the trial. A more detailed information booklet will be sent if you decide to take part.**

#### **Why do we need a screening test for lung cancer?**

Lung cancer is the most common cause of death from cancer in the UK. The majority of people unfortunate enough to develop this cancer have few symptoms until it has spread outside the lungs. By this time it is difficult to treat and most cases are incurable. In contrast, treatment is more successful and the outlook is good for the small proportion of people diagnosed before the lung cancer has spread. If we are able to find lung cancer at this early stage through screening when treatment is more effective, then we could prevent people dying from lung cancer.

#### **What screening test is being used?**

We will be using a CT (computed tomography) scan. This is an x-ray of the chest.

#### **Am I eligible to take part?**

In order to be eligible to take part you must:

- Be 50-75 years of age.
- Not have had a previous diagnosis of lung cancer.
- Not currently be taking part in any other screening programme for lung cancer.

#### **What does taking part involve?**

- You will need to fill out the enclosed “UKLS Questionnaire” and return to us. A computer will look at your answers and may then select you to take part in the trial.
- You will be sent a more detailed information booklet about the trial and an appointment to attend your local recruitment centre.
- At the recruitment centre you will watch a DVD about the trial and then meet a research nurse. You will be asked to register for the trial and the nurse will then take a sample of blood, a mouth swab or wash and a nose brush. You will be given a pot to take home to send back to us with a deep cough sample.
- A computer will decide whether you are to be in the group to be screened or not to be screened. The groups are chosen at random and are not dependent any information you give us.
- If you are in the screening group you will be sent an appointment for a CT scan.
- If you are not in the screening group you will not be required to attend any further appointments.
- If an abnormality is found by your CT scan, you will be referred for further tests to an NHS specialist.
- You may be asked to complete a number of health related questionnaires after you join the trial.

#### **How long will the study last?**

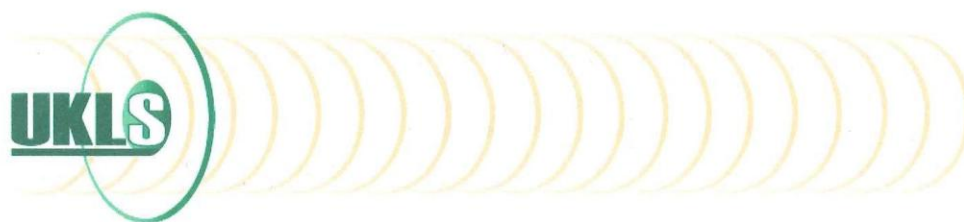
The study will take 10 years to complete. If you agree to take part you will be followed up for 10 years through your medical records.

#### **How do I take part?**

Please fill out the enclosed “UKLS Questionnaire” and return to us in the enclosed envelope.

Thank you very much for taking the time to read this fact sheet. There will hopefully be a great benefit to future generations, both in prevention as well as early diagnosis and improved treatment of lung cancer.

## Appendix: C - UKLS Questionnaire No1 Version 4: Date 27FEB2012



### UK Lung Cancer Screening Questionnaire

All the information you give us is treated as strictly confidential and will only be used in our research

Please complete the questionnaire in black ink and return in the freepost envelope provided

#### HOW TO FILL IN THIS QUESTIONNAIRE

This questionnaire will be processed automatically. For this reason it is important that:

- the questionnaire does not crease;
- this questionnaire is filled out with a **black** or **blue pen** (no red or green felt pen)

#### Example 1:

Gender ☐ Male ☒ Female (you have indicated that you are a female)

If you have ticked accidentally the wrong checkbox, you must shade this box entirely.

Gender ☒ Male ☐ Female (you have now indicated that you are a male)

#### SECTION 1 Questions about your health and job

##### 1. Have you ever been diagnosed with any of the following conditions?

(If yes, please indicate the age at diagnosis for that condition)

			Age at Diagnosis						
	Yes	No	Less than 40	40-49	50-55	56-60	61-65	66-70	70+
Asthma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bronchitis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Emphysema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pneumonia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tuberculosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chronic Obstructive Pulmonary Disease (COPD)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

##### 2. Have you ever had any of the following masses, lumps or tumours that were diagnosed as malignant or cancerous?

	Yes	No
Hodgkins Disease	<input type="checkbox"/>	<input type="checkbox"/>
Leukaemia	<input type="checkbox"/>	<input type="checkbox"/>
Lymphoma	<input type="checkbox"/>	<input type="checkbox"/>
Mesothelioma	<input type="checkbox"/>	<input type="checkbox"/>
Skin growths	<input type="checkbox"/>	<input type="checkbox"/>



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UKLS Questionnaire Number 1 Version 4: 27FEB2012



3. if you have been diagnosed with cancer, please complete the appropriate section

Type of cancer Tumour		Years since diagnosis	
		Within 5 years	Greater than 5 year
Brain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Head/Neck	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oesophagus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lung	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Breast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Colon (Bowel)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. Can you recall any job or activity in which you were exposed to asbestos?

☐ Yes ☐ No

If yes, how many years in total were you exposed to asbestos?

☐ 1 ☐ 2 ☐ 3 ☐ 4+

## SECTION 2 Family history of cancer

1. How many brothers, sisters, sons and daughters (first degree relatives) do you have?

Please skip this question if you are adopted

	1	2	3	4+
Brothers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sisters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sons	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Daughters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Have any of your first degree relatives (including parents) had a diagnosis of cancer?

☐ Yes ☐ No (If Yes, please provide details below. If No please go to section 3)

Type of cancer	Father		Mother		brother		sister		son or daughter
	less than 60 yrs	greater than 60 yrs	less than 60 yrs	greater than 60 yrs	less than 60 yrs	greater than 60 yrs	less than 60 yrs	greater than 60 yrs	
Brain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Head/Neck	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oesophagus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lung	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Breast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Colon (Bowel)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



999999 L This Is Your Personal Identification Number

**SECTION 3 Questions about your smoking history**

**1. Have you ever smoked more than 10 cigarettes per week regularly?**

☐ Yes ☐ No (If No please go to question 5)

**2. How old were you when you first started smoking more than 10 cigarettes each week?**

☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40-49 ☐ 50+

**3. How old were you when you stopped smoking cigarettes?**

☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40-49 ☐ 50+ ☐ Still smoking

**4. Please indicate which types of cigarette and the number you have smoked**

				Number per day					
	Filter	Plain	Hand rolled	0-9	10-19	20-29	30-39	40-49	50+
High Tar	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Low Tar	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Don't know	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**5. Have you ever smoked one or more cigars per day regularly?**

☐ Yes ☐ No (If No please go to question 9 below)

**6. How old were you when you first started smoking one or more cigars per day?**

☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40-49 ☐ 50+

**7. How old were you when you stopped smoking cigars?**

☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40-49 ☐ 50+ ☐ Still smoking

**8. How many cigars did you smoke per day?**

☐ 1-5 ☐ 6-10 ☐ 11-15 ☐ More than 15

**9. Have you ever smoked one or more pipes of tobacco per day regularly?**

☐ Yes ☐ No (If No please go to section 4)

**10. How old were you when you first started smoking a pipe?**

☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40-49 ☐ 50+

**11. How old were you when you stopped smoking a pipe?**

☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40-49 ☐ 50+ ☐ Still smoking

**12. How many ozs did you smoke each day?**

☐ 1/2 ☐ 1 ☐ 2 ☐ More than 2



999999 L This Is Your Personal Identification Number

#### SECTION 4 PREVIOUS X RAYS

1. Have you had a previous X Ray of your chest in the last 12 months

☐ Yes ☐ No

2. Have you had a previous CT scan of your chest in the last 12 months

☐ Yes ☐ No

#### SECTION 5 Lung Cancer Screening

1. If you are invited to have Lung Cancer Screening using a CT scan, how likely is it that you will accept an invitation?

Highly likely ☐  
Quite likely ☐  
Unlikely ☐  
Definitely not ☐

2. If you are a smoker, are you considering giving up smoking?

Yes definitely ☐  
Yes possibly ☐  
Not really ☐  
Definitely not ☐

نقوم بإجراء تجارب فحص سرطان الرئة في منطقتك، وقد حصلنا على التفاصيل الخاصة بك من أمانة الرعاية الأولية (PCT) الخاصة بك. إذا كنت ترغب في معرفة المزيد عن التجارب، وتود كذلك التفكير في المشاركة، يرجى إرسال اسمك وعنوانك باللغة المنخفضة إلى UKLS, University of Liverpool, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

我們現在在你所在之地區進行肺癌普查，並已透過PCT獲得了閣下的個人資料。如閣下希望了解更多詳情及參加是次普查活動，請將姓名、地址及首選語言等資料郵寄至 UKLS, University of Liverpool, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

हम आपके क्षेत्र में फेफड़े के कैंसर का स्क्रीनिंग परीक्षण कर रहे हैं, और आपके व्योरे हमें आपके PCT से प्राप्त हुए थे। यदि आप इस परीक्षण के बारे में और जानना चाहते हैं तो वहां इसमें भाग लेना चाहते हैं, तो अपना नाम, पता और पसंदीदा भाषा निम्नलिखित को भेजें: UKLS, University of Liverpool, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

我们正在您所在地区进行肺癌筛查试验，PCT为我们提供了您的详细资料。如果您想了解更多有关该试验的信息，并可以考虑参与，请将您的姓名、地址和首选语言发送到UKLS, University of Liverpool, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

Waxaannu aaggaaga ka samaynaynaa baarid tijaabo ah oo kansarka sambubbada ah, waxaana xogtaada ina siiyey PCT. Haddii aad jeclaan lahayd in aad wax badan ka ogaato tijaabada oo aad rabi lahayd in aad ka fikirto ka-qaybgelid, fadlan ku soo dir magacaaga, cinwaankaaga iyo luqadda aad doorbiddid halkaan: UKLS, University of Liverpool, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

ਅਸੀਂ ਤੁਹਾਡੇ ਇਲਾਕੇ ਵਿੱਚ ਫੇਫੜੇ ਦੇ ਕੈਂਸਰ ਦੇ ਪ੍ਰਮਾਣਿਤ ਲਈ ਸਕ੍ਰੀਨਿੰਗ ਕਰ ਰਹੇ ਹਾਂ ਅਤੇ ਤੁਹਾਡੇ ਵੱਲੋਂ, ਤੁਹਾਡੇ ਖੋਜ ਵੱਲੋਂ ਉਪਲਬਧ ਕਰਾਏ ਗਏ ਹਨ। ਜੇ ਤੁਸੀਂ ਇਸ ਪ੍ਰਮਾਣਿਤ ਬਾਰੇ ਹੋਰ ਜਾਣਨਾ ਚਾਹੁੰਦੇ ਹੋ ਤਾਂ ਇਸ ਲੇਟਰ ਬਾਰੇ ਵਿਚਾਰਣਾ ਚਾਹੁੰਦੇ ਹੋ, ਤਾਂ ਕਿਰਪਾ ਕਰਕੇ ਅਪਣਾ ਨਾਂ, ਪਤਾ ਅਤੇ ਤੁਸੀਂ ਦੀ ਭਾਸ਼ਾ ਇਥੇ ਭੇਜੋ ਜਾਂ ਓਫ਼ਿਸ, ਓਨਾਜ਼ਕਾਡਸਟਰੀ ਹੀਂ ਜ਼ਬਰਗਸਟਰੀ, ਨੌਰਥ ਥਰੂ, ਰੂਵਰਹੀਰਚਰਡ ਨਜ਼ਦੀਕੀ 1-3 ਬਰਨਲੋ ਸਟਰੀਟ, ਲੀਵਰਪੁਲ, L69 3GL

Okolica, w której mieszkasz, została objęta pilotażowym programem badań przesiewowych w zakresie wczesnej diagnostyki raka płuc. Twoje dane osobowe zostały przekazane przez centrum opieki zdrowotnej PCT. Jeśli chcesz otrzymać więcej informacji na ten temat lub jesteś zainteresowany/-a wzięciem udziału w badaniach, wyślij imię i nazwisko, adres i język, którym chcesz się posługiwać, na adres: UKLS, University of Liverpool, Block C, Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL



999999 L



## Appendix: D – 2<sup>nd</sup> Approach Letter Version 3: 16NOV2011



<Director of Public Health Name and Address  
To be inserted here>

Name and Address  
Date

Dear (Name)

Thank you for replying to our first invitation to participate in the UK Lung Cancer Screening Trial (UKLS). The computer has selected you to enter this screening trial, based on the responses you provided in the first UKLS Questionnaire.

The purpose of this study is to determine whether screening will detect lung cancer at an early stage when treatment is more effective and therefore prevent deaths from lung cancer. The Department of Health have given us a large grant for this study.

We would be grateful if you could read the enclosed UKLS information booklet, which provides you with a detailed description of the study. When you have read the UKLS information booklet, please complete the short questionnaire "I want to participate in the UKLS trial" and return the form in the enclosed envelope.

You will then be contacted within the next 2-4 weeks with an appointment to attend the UKLS recruitment centre in your region. A reimbursement of travelling expenses may be available in certain instances.

If you do not wish to participate in the UKLS trial after reading the information booklet please complete the "Not wishing to participate in the UKLS trial" short questionnaire and return in the prepaid envelope. If you decide not to participate you will not be contacted again. It will not affect your healthcare in any way if you do not take part.

We hope that you will want to take part in the trial because it will help us find out if screening can prevent deaths from lung cancer.

Yours sincerely

UKLS Team  
<UKLS Contact Details to be Inserted Here>

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UKLS Second Approach Letter Version 3: 16NOV2011

**Appendix: E – I Want to Participate in the UKLS Trial Questionnaire Version 2:  
16NOV2011**



***I want to participate in the UKLS Trial Questionnaire***

1. Age 50-55 ☐ 56-60 ☐ 61-65 ☐ 66-70 ☐ 71-75 ☐ 76+ ☐
- 2 Sex M ☐ F ☐
3. What is your height in feet and inches?
- | Feet                     |                          |                          |                          | Inches                   |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 4                        | 5                        | 6                        | 7                        | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       | 11                       | 12                       |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
4. How much do you weigh?
- Stones**
- |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Less than 6              | 6                        | 7                        | 8                        | 9                        | 10                       | 11                       | 12                       | 13                       | 14                       | 15                       | 16                       | 17                       | 18                       | 19                       | 20                       | More than 20             |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
- Pounds**
- |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       | 11                       | 12                       | 13                       |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
5. Do you have any condition that affects your ability to walk?
- Yes ☐ No ☐
6. Do you get out of breath while climbing two flight of stairs slowly
- Yes ☐ No ☐
7. After reading the UKLS information booklet are you still interested in taking part in the study?
- Yes definitely ☐  
 Yes possibly ☐  
 Definitely not ☐

8. If you wish to be considered further for this study, please sign the statement below;

I agree to the UKLS study team having access to my contact details and the name of my GP so I can be contacted again about UKLS. This information will not be shared with anybody else.

Signed \_\_\_\_\_ Date \_\_\_\_\_

Day Time Telephone Number: \_\_\_\_\_  
 Email Address: \_\_\_\_\_

Please return this questionnaire to us using the prepaid envelope provided at UKLS,  
 6 The Stables, Hargate House Farm, Egginton, Road, Hilton, Derby, DE65 5FJ



5549556 X

UKLS I want to participate questionnaire Version 2: 16NOV2011

**Appendix: F – Not Wishing to Participate in the UKLS Trial Questionnaire  
Version 3: 16NOV2011**



***Not wishing to participate in the UKLS Trial Questionnaire***

If you do not wish to participate in the UKLS Trial we would be most grateful if you would complete the following short questionnaire. Please tick the appropriate box for each question below.

- |   |  |   |
|---|--|---|
| <p><b>1. Age</b> 50-55 <input type="checkbox"/></p> <p>56-60 <input type="checkbox"/></p> <p>61-65 <input type="checkbox"/></p> <p>66-70 <input type="checkbox"/></p> <p>71-75 <input type="checkbox"/></p> <p>76 + <input type="checkbox"/></p>  | <p><b>2. Sex</b> M <input type="checkbox"/></p> <p>F <input type="checkbox"/></p>  | <p><b>3. How concerned are you, if at all, about the possibility of getting lung cancer some day? Would you say....</b></p> <p>not at all <input type="checkbox"/></p> <p>somewhat <input type="checkbox"/></p> <p>moderately <input type="checkbox"/></p> <p>very concerned <input type="checkbox"/></p> |
| <p><b>4. Smoking</b></p> <p>Current Smoker <input type="checkbox"/> please go to 4a</p> <p>Ex Smoker <input type="checkbox"/> please go to 4a</p> <p>Never Smoked <input type="checkbox"/> please go to 5</p>   | <p><b>4.a If you are a Current or Ex Smoker</b></p> <p>0-9 per day <input type="checkbox"/></p> <p>10-19 per day <input type="checkbox"/></p> <p>20-29 per day <input type="checkbox"/></p> <p>30 or more per day <input type="checkbox"/></p>   |   |
| <p><b>5. Have you, or any of your friends or family members that are close to you, ever been diagnosed with lung cancer?</b></p> <p>No <input type="checkbox"/></p> <p>Yes, self <input type="checkbox"/></p> <p>Yes, someone close <input type="checkbox"/></p> <p>Yes, self and someone close <input type="checkbox"/></p> <p>Yes, prefer not to say who <input type="checkbox"/></p> | <p><b>6. What is the highest level of education you have?</b></p> <p>Left school at or before age 15 <input type="checkbox"/></p> <p>GCSE or O level or equivalent <input type="checkbox"/></p> <p>A level or equivalent <input type="checkbox"/></p> <p>Further education but not a degrees <input type="checkbox"/></p> <p>Degree or higher (e.g. Masters, PhD) <input type="checkbox"/></p> <p>None of the above <input type="checkbox"/></p> |   |

- 7. If you would like to tell us your reason for not taking part in the UKLS trial, please write it here:**

Thank you for completing this short questionnaire. This information will be kept confidential. We will not contact you again. Please return this to us using the prepaid envelope provided.



999999 X

UKLS Non Participation Questionnaire Version 3: 16NOV2011



**Lung cancer, screening  
and the  
UK Lung Cancer Screening (UKLS) trial**

An information booklet for people thinking about taking part in the UKLS lung cancer screening trial.



**Liverpool Heart and Chest Hospital**



**Papworth Hospital**

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 1 of 13

Contents	Page number
Invitation to take part in the UKLS Trial	3
What is the aim of this booklet?	3
What is lung cancer?	3
Who is at risk of developing lung cancer?	4
What is lung cancer screening?	4
What is the lung cancer screening trial?	5
Why am I being invited to take part?	5
Do I have to take part?	5
What will happen to me if I take part?	6
What are lung function tests?	7
What is the computed tomography (CT) scan?	7
What are the possible side effects of CT scans?	8
When do I get my CT results and what do they mean?	8
What happens if my CT scan finds something?	9
How reliable is lung cancer screening?	9
Are there any risks if I take part?	10
What are the possible benefits of taking part?	10
Where do I need to go?	10
What happens if new information becomes available during the trial?	10
What happens when the trial stops?	11
What will happen to the results of the trial?	11
Will my samples be used for any further research?	11
Will my taking part in the trial be kept confidential?	12
What happens if something goes wrong?	12
Who is co-ordinating and funding the trial?	12
Who has reviewed the trial?	12
I am a smoker but would like to stop smoking. Can I still take part?	12
Where can I get more information?	12
What should I do now?	13

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 2 of 13

### **Invitation to take part in the UKLS Trial**

We would like to invite you to take part in a large national research project which we hope will benefit people at risk of developing lung cancer. Before you decide whether or not to take part, it is important for you to understand why the research is happening and what it will involve. Please take time to read this information booklet carefully and discuss it with your family and friends if you wish.

### **What is the aim of this booklet?**

This booklet tells you about lung cancer, lung cancer screening and how the trial will work. It aims to give you information that will help you choose whether or not you wish to take part in the UK Lung Cancer Screening (UKLS) trial.

### **What is lung cancer?**

Cancer develops when cells become abnormal and grow out of control. Over time they form a clump known as a tumour. Lung cancer develops in the tubes that carry air in and out of the lungs (your airways) or within the lung. It can then spread outside the lung to other parts of the body.

Lung cancer often develops slowly. It is thought that cells first become abnormal at least five years before the cancer can be detected. The reasons for this delay include:

- most tumours grow slowly
- the lungs are large
- the lungs do not feel pain
- some of the symptoms are similar to those of other lung problems such as bronchitis or chronic obstructive pulmonary disease (COPD).

By the time lung cancer is diagnosed, it has often spread outside the lung. If this happens, the cancer can only rarely be cured.

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 3 of 13



The UKLS aims to discover whether finding lung cancer at a very early stage means that it can be treated successfully.

#### **Who is at risk of developing lung cancer?**

Anybody can develop lung cancer, but people who smoke (or used to smoke) are at the greatest risk. The risk increases with the total number of cigarettes you smoke. If you stop smoking, the risk gets less over time.

Passive smoking (breathing in someone else's tobacco smoke) over a long period of time may also cause lung cancer.

Non smokers may develop a particular type of lung cancer (called adenocarcinoma). This can happen in a part of the lung where damage has happened for a number of other reasons (such as breathing in asbestos).

#### **What is lung cancer screening?**

Lung cancer screening uses an advanced x-ray technique, called computed tomography (CT) scanning, in order to find lung cancer before symptoms develop so that early treatment can remove the cancer and deaths from lung cancer may be prevented. More people die from lung cancer in the UK every year than from any other form of cancer. About 40,000 people develop lung cancer each year in the UK and many of these are smokers. However, non-smokers and ex-smokers can also develop lung cancer. Finding lung cancer by screening instead of symptoms may mean that treatment is more effective. Lung cancer screening aims to find changes in the lung at the time of the scan but it cannot prevent you from getting lung cancer in the future.

Only one randomised controlled screening trial (NLST)\* so far has shown that screening by CT scanning is effective. The NLST trial has been recently published and was conducted in the USA. The results showed that the mortality from lung cancer was reduced by 20%. Thus it is likely that in the same population, CT screening is effective. However, populations differ and

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\* National Lung Cancer Screening Trial, USA

there are other questions that remain unanswered, regarding the integration of CT screening into a national programme and which patients benefit most. The unanswered questions led a group of experts from many countries to conclude that further trials (including UKLS) were needed to answer these important questions and to guide the design of future screening programmes.

#### **What is the lung cancer screening trial?**

The United Kingdom Lung Cancer Screening (UKLS) trial is a study of lung cancer screening in the UK. We aim to recruit 4,000 people in the first stage of the trial. If the results of our trial show that CT scanning of the lungs in healthy people is worthwhile then, in the future, CT scanning may be used throughout the country for lung cancer screening. This would be similar to the breast, cervical and bowel cancer screening programmes used today.

#### **Why am I being invited to take part?**

You have provided details about your lifestyle and based on this information we would like to invite you to take part in the UKLS trial. We want to recruit people aged 50 to 75 years old. We have chosen this age group because we believe that if lung cancer screening is shown to be worthwhile, these are the people most likely to benefit.

#### **Do I have to take part?**

No, it is up to you to decide whether or not to take part. If you decide to take part you will be given this information booklet to keep and asked to sign a consent form. You are still free to change your mind or withdraw from the trial at any time and without giving a reason. If you decide not to take part, we will not contact you again and the care you receive from your general practitioner (GP) will not be affected. We would, however, be grateful if you could fill out the attached questionnaire called 'UKLS non-participant questionnaire' and return it to us. This information is very important and will help us to plan future screening programmes.

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 5 of 13



### **What will happen to me if I take part?**

You have already been asked some basic questions about smoking, your lifestyle, occupation and known health problems. The next stage is an invitation to a recruitment clinic.

At the UKLS recruitment clinic, you will be met by the receptionist and invited to watch a DVD which will give you further information about the trial. You will then be met by a UKLS research nurse who will answer any questions you may have and will then ask you to sign a consent form. At this point you will be enrolled into the trial. You will then be asked some more detailed questions about your lifestyle and family history of disease. You will be asked to give your answers on a computer by touching the screen, which will greatly assist us in developing a better way of identifying individuals for lung cancer screening programmes. You will also be asked to blow into a tube a few times (lung function tests) to look at the health of your lungs. A member of the UKLS team will take a sample of blood, a mouth swab or wash and a nose brush. The nasal sampling has a very small risk of causing a nose bleed. You will be given a pot to take home so that you can return a deep cough sample, which will be explained to you at the recruitment visit. Finally, if you are a current smoker, you will be provided with information to help you stop smoking. Your visit to the recruitment clinic should take about an hour. Your GP will be informed that you are a participant in the UKLS trial.

To find out whether CT scanning of the lungs will be beneficial, we need to divide those who join our trial into two groups. Half of the people joining the trial will be offered a CT scan of their lungs and the other half will not. Both groups are equally important because we are going to observe what happens in each group. Then, at the end of the trial, we shall compare what happened to the group who were scanned to what happened to the group who weren't. To run the trial properly, people must be put into a group at random (using a computer), so neither you nor your doctor can choose which group you are

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 6 of 13

put into. You will find out which group you are in about four weeks after you are enrolled.

In this trial we would also like to look at the effect of screening on the well-being of those who take part, so you will be asked from time to time to take part in surveys about your experience of the UKLS.

Regardless of whether you are in the screening or non-screening group, we will check on your health through your medical records over the next 10 years. If for any reason during the trial, you lose the capacity to consent, we will retain all the previously collected data and specimens, however, we will not contact you again with any questionnaires or follow-up appointments.

#### **What are lung function tests?**

Lung function tests (also known as pulmonary function tests) are used to look for the cause of breathing problems (like shortness of breath) and are also used to see how well treatments for breathing problems, such as asthma medicines, are working. They can be used to check for conditions such as asthma, lung tissue scarring, sarcoidosis, and COPD (chronic obstructive pulmonary disease). The tests may also be used to check whether a condition is getting worse.

Lung function tests measure:

- How much air you can take into your lungs. This amount is compared to that of other people your own age, height, and sex;
- How much air you blow out of your lungs and how fast you do it;
- How well your lungs deliver oxygen to your blood; and
- How strong your breathing muscles are.

#### **What is the computed tomography (CT) scan?**

If you are part of the screening group, you will have a CT scan of your lungs. This scan of the chest uses x-rays and a computer to produce pictures of the

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 7 of 13

lungs (it's also known as CAT scanning). During the CT scan you lie down on the scanner and hold your breath for a few seconds while pictures of your lungs are taken. Your appointment should take about 15-30 minutes. All of the CT scan pictures are stored in a computer and read by a radiologist. You will be told about the results of your scan by a clinical member of the UKLS team within four weeks of the scan. If no abnormalities are found, you will not need any further tests but we will contact you to fill out questionnaires so that we can find out about your future health and how you felt about being screened. If any important abnormalities are found you would be given an appointment to see a chest specialist at your local NHS hospital. The specialist may advise follow-up with another CT scan or other tests. If the lung specialist thinks you might have lung cancer, they will discuss treatment options with you. Your GP will be kept informed of your participation in the UKLS trial and of all scan results and any treatment recommendations, and will be able to discuss them with you.

#### **What are the possible side effects of CT scans?**

Because CT scanning uses x-rays to obtain pictures, you will be exposed to some radiation which you would otherwise not receive. However, the dose of x-rays used for the screening CT scan is less than you normally receive in a year from the natural surrounding environment and the risk of it causing harm is therefore very low. If an abnormality is detected, you may need follow-up CT scans and if lung cancer is strongly suspected, further tests will be required. The radiation dose for follow-up CT scans would be higher than for the first but the risk is still low and the benefits of detecting lung cancer at an early stage must be considered.

#### **When do I get my CT results and what do they mean?**

You should receive a results letter from the UKLS trials team within four weeks of having your CT scan. There are three types of results that you could receive;

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 8 of 13

A **normal result** means no tumour or nodule was found. We expect that most people will receive a normal result. A normal result does not guarantee that you do not have or will never develop lung cancer in the future, so staying aware of any symptoms of lung cancer in the future is very important.

An **unclear result** means that your screening CT scan was not quite normal and further tests are needed. Getting an unclear result may not mean you have cancer, just that you will most likely need a follow-up CT scan. If you receive an unclear result you will be invited back to the hospital to have another CT scan. Most people will then receive a normal result.

An **abnormal result** means that the CT scan may have found signs of a cancerous nodule in your lungs. It is not a diagnosis of cancer, but it does mean that you will be offered a follow-up CT scan and other tests. Sometimes scans show other conditions that are not lung cancer but do require medical attention. If this is the case, your GP will be informed and contact you to ensure the abnormality is dealt with appropriately.

#### **What happens if my CT scan finds something?**

You will be cared for through the NHS and given an appointment with a lung cancer specialist doctor to discuss having a more detailed examination of your lungs. This will involve some further tests and the specialist team will explain what is required. If lung cancer is found, a doctor will discuss treatment options with you and your wishes will be taken into account. If you have to undergo any investigations or treatment procedures, we will collect any left-over tissue specimens for future research.

#### **How reliable is lung cancer screening?**

In some cases lung cancer could be present but may not be found by CT scanning. Cancers in the main airways in the middle of the chest may be

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 9 of 13



difficult to identify on CT and not all small cancers in the lung are recognised, even by the most skilled radiologists.

#### **Are there any risks if I take part?**

Sometimes non-cancerous abnormalities are found by screening which you would otherwise have never known about.

If you need an operation to remove a lung abnormality or need to have a lung biopsy any possible risks will be fully explained to you by an NHS specialist before the procedure is undertaken.

#### **What are the possible benefits of taking part?**

As we do not know whether early diagnosis of lung cancer with CT scanning will be beneficial, it is not possible to tell you whether you are likely to benefit from entering the trial or not. Even if the trial is of no benefit to you personally because you have normal lungs it may benefit others taking part in the UKLS trial, as well as people in the future.

#### **Where do I need to go?**

There are two centres taking part in the trial:

1. The Liverpool Heart & Chest Hospital NHS Foundation Trust, Thomas Drive, Liverpool, L14 3PE;
2. Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, CB23 3RE.

Both centres have dedicated rooms for the trial. When you arrive, you will be directed to a waiting room and met by the trial receptionist. If you attend the Papworth clinic, you might be offered screening in our on-site mobile screening unit.

If you provide evidence that you receive benefits, some support may be available to you for reasonable travel expenses.

#### **What happens if new information becomes available during the trial?**

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 10 of 13

Sometimes during the course of a research study a new technique or new information becomes available which is relevant to the study. This is unlikely to happen in this trial because the type of CT scanner being used will be up-to-date and of high quality. However, should such a situation arise, the research nurse will tell you about it and discuss with you whether you wish to continue in the study or whether it would be in your best interests to withdraw.

**What happens when the trial stops?**

Your records will be under the care of the trial centre for 20 years and your GP will continue your normal care during and after the trial.

**What will happen to the results of the trial?**

The main results of this trial are not likely to be available for several years but early results relating to the number of lung cancers found by screening should be known after the first two years. Once carefully analysed, the results will be published in medical journals. If you would like a summary of the results as they become available please inform the research nurse at your trial centre.

**Will my samples be used for any further research?**

If you agree to take part in this trial you will be asked to give a blood sample, a sample of spit, a mouth swab or wash and a nose brush. These samples will be stored at the University of Liverpool Biobank and will be used in future research projects with ethical approval. This may allow researchers to identify biological and genetic factors that affect the risk of future lung disease. This may be useful in developing future screening tests or in understanding more about the causes of lung cancer or other lung diseases. The UKLS research team will be responsible for keeping the samples safely and making sure that any information remains confidential. Results of any studies undertaken on your sample will not be fed back to you personally or placed in your medical records, as the tests are for research only. The research results will not have any implications for you personally. All future use of the samples will have to be approved by an Ethics Committee.

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 11 of 13

**Will my taking part in the trial be kept confidential?**

If you consent to take part in this trial, your medical records and CT scan results may be inspected by authorised representatives within the trial and by the Department of Health regulatory authorities. Your name will not be disclosed outside the trial. You will not be identified in any publication or report of the trial.

**What happens if something goes wrong?**

Your legal rights are not affected by giving your consent to take part in this trial.

**Who is co-ordinating and funding the trial?**

The trial will be co-ordinated by the Liverpool Cancer Trials Unit (LCTU). It is funded by the Department of Health - Health Technology Agency.

**Who has reviewed the trial?**

The trial has been reviewed by the Department of Health – Health Technology Agency, the Multi-Centre Research Ethics Committee (MREC) and by the Local Research Ethics Committees of the two centres involved.

**I am a smoker but would like to stop smoking. Can I still take part?**

Yes and we would encourage you to stop smoking. Even if you stop smoking at any point in the future you are still able to take part in the trial. Just let us know the date you stopped smoking when you send back your next follow-up questionnaire. The UKLS team will provide you with NHS stop smoking materials or you can contact the NHS on 0800 022 4 332 or go to <http://smokefree.nhs.uk>.

**Where can I get more information?**

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 12 of 13

Please feel free to telephone the research nurse on 0800 195 8557 in the UKLS Project management office if you would like more information or have questions you would like to ask.

More information about the trial can be found on the UKLS website [www.UKLS.org](http://www.UKLS.org)

**What should I do now?**

We hope that you are encouraged to join the trial. If you would like to take part, please return the enclosed 'UKLS participant questionnaire'. If however you decide not to take part, please fill in the 'UKLS non-participant questionnaire'.

*Thank you for reading this UKLS information booklet and we do hope you will want to participate in this very important Lung Cancer Screening Trial, which may prevent deaths from lung cancer.*

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*Lung cancer, screening and the UK Lung Cancer Screening (UKLS) trial*

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UKLS Participant Information Booklet Version 4 15July2011 Page 13 of 13



## Appendix H– UKLS Recruitment DVD Version 1: Date 15-09-10

### Will I be screened or not?

- Half of the people taking part in the trial will be screened and the other half will not be screened.
- A computer will decide which group you are put into.
- You will find out which group you are in 4 weeks after you are enrolled.

### What is the computed tomography scan (CT)?

- The CT scan is a special type of x-ray of the lungs.
- You lie down on the scanner and hold your breath for a few seconds while pictures of your lungs are taken. **Picture of scanner.**
- Your appointment should last about 15-30 minutes.
- You will be told your scan results within 4 weeks of your appointment.

### What are the possible side effects of CT scans?

- Low dose of radiation – less than you normally receive in a year from the surrounding environment.
- If an abnormality is found, follow-up CT scans may be needed, so you would be exposed to more radiation.

### When do I get my CT results and what do they mean?

- You will receive your results within 4 weeks of your CT scan.
- Possible results:
  - Normal result – no tumour or nodule found. No further tests needed.
  - Unclear result – scan not quite normal. Further tests needed.
  - Abnormal result – may have signs of a cancerous nodule. Further tests needed.

### What happens if my CT scan finds something?

- You will be given an appointment with an NHS lung cancer specialist.
- You may need further tests:
  - Bronchoscopy (where the doctor can look into your airways);
  - Biopsy (where a small tissue sample can be taken).
- Your GP will be told your results.

### How reliable is lung cancer screening?

- Sometimes lung cancer is not found by CT scanning.
  - Because they might be in the middle of the chest and difficult to see.
  - Because they might be too small to see.



#### **Are there any risks if I take part?**

- Sometimes non-cancerous abnormalities are found by screening which you would otherwise have never known about.
- If you need an operation to remove a lung abnormality or need to have a lung biopsy any possible risks will be fully explained to you by an NHS specialist before the procedure is undertaken.



#### **What are the possible benefits if I take part?**

- It is not possible to tell you if you are likely to benefit from entering the trial.
- If the trial is of no benefit to you personally, it may benefit other taking part and well as people in the future.



#### **What happens if new information becomes available during the trial?**

- This is unlikely to happen in this trial because the type of CT scanner being used will be up-to-date and of high quality.
- However, should such a situation arise, the research nurse will tell you about it and discuss with you whether you wish to continue in the study or whether it would be in your best interests to withdraw.



#### **What happens when the trial stops?**

- Your records will be under the care of the trial centre for 20 years
- Your GP will continue your normal care during and after the trial.



#### **What will happen to the results of the trial?**

- Early results relating to the number of lung cancers found by screening should be known after the first two years.
- The main results of this trial are not likely to be available for several years.
- Once carefully analysed, the results will be published in medical journals.
- If you would like a summary of the results as they become available please inform the research nurse at your trial centre.



#### **Will my samples be used for any further research?**

- You will be asked for a blood sample, a sample of spit a mouth swab or wash and a nose brush.
- Your samples will be stored at the University of Liverpool Biobank.
- They will be used for future research projects with ethical approval.
- Any future research results will not be sent to you directly or placed in your medical records.



### Will my taking part in the trial be kept confidential?

- Your name will not be released outside the trial.
- You will not be identified in any publication or report of the trial



### What happens if something goes wrong?

- Your legal rights are not affected by giving your consent to take part in this trial.



### Who has reviewed the trial?

- The trial has been reviewed by the
  - Department of Health – Health Technology Agency
  - Multi-Centre Research Ethics Committee (MREC)
  - Local Research Ethics Committees of the two centres involved.



### I am a smoker but would like to stop smoking. Can I still take part?

- Yes, if you would like to stop smoking at any point you are still able to take part in the trial.
- Just let us know the date you stopped smoking when you send back your next follow-up questionnaire.
- The UKLS team will provide you with NHS stop smoking materials or you can contact the NHS on 0800 022 4 332 or go to <http://smokefree.nhs.uk>.



### Where can I get more information?

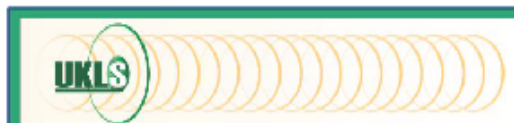
- If you would like more information or have questions you would like to ask, please feel free to telephone the research nurse on
  - Liverpool XXXX between YY Hrs and ZZ Hrs
  - Papworth XXXX between YY Hrs and ZZ Hrs
- More information about the trial can be found on the UKLS website [www.XXXXX](http://www.XXXXX).



### Thank you!

- Thank you for watching this video.
- We do hope that you still want to join the trial which may prevent deaths from lung cancer.

## Appendix I – UKLS Consent Form Version 3: Date 09FEB2012



Identifying Number:

### UKLS Consent Form For Providing Personal Data

Please Read Carefully and Initial Each Section

Please initial  
boxes

I have read the participant information booklet version 4 dated 15<sup>TH</sup> July 2011 for the UKLS study regarding the use of data, samples and tissue and been given a copy to keep. I have been given the opportunity to discuss the study, ask questions and I understand why the research is being done. I know how to contact the Research Nurse if I have further questions at any time.

☐

I understand that I am free to withdraw from the study at any time, that I do not have to give a reason for withdrawing and that this will not affect my future medical care.

☐

I understand that any information retained about me will be treated confidentially and stored securely.

☐

I agree to provide data about my lifestyle, medical, occupational and family history. I understand that medical notes and data collected during the study may be looked at by individuals from regulatory authorities or the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.

☐

I give permission for my medical and related records (eg. medical registers) to be examined and information taken from them for confidential use in the UKLS trial and then stored.

☐

I agree that information held and maintained by The Health & Social Care Information Centre, and other agencies keeping patient medical records, may be used to help contact me or provide information about my health status for confidential use in the UKLS trial.

☐

I give permission to be contacted in the future, even after the research project has ended.

☐

\_\_\_\_\_  
Name of Participant

\_\_\_\_\_  
Signature

\_\_\_\_\_  
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Researcher

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UKLS Consent Form Version 3: 09FEB2012

Page 1

Appendix J – UKLS

95



may be found pathologically, yet only one was evident on the CT or targeted by the surgeon. It is thus important to correlate exactly the pathology of the radiological (index) lesion.

Autopsy-based information is the best source for the disease characterisation and determination of cause of death, therefore the clinical researchers should be encouraged to request, or arrange to request, an autopsy whenever a study patient dies. This will be of vital importance to clearly ascertain the cause of death since it is important to be able to record disease specific mortality, defined by the WHO as "the disease or injury that initiated the train of events leading directly to death." In this context the definition encompasses, in addition to the deaths directly attributable to the pathologic disease entity, those extremely rare deaths that may occur as a result of procedures performed for diagnosis and treatment for lung cancer. In addition, those equally rare RCT deaths due to diagnostic procedures that are initiated as a result of screening but do not result in a diagnosis of lung cancer, must be identified and classified correctly. Equally it will be important to record whether a patient who does have a diagnosis of cancer, and who subsequently dies, has an unrelated cause of death ascertained, if there is such a cause. False attribution of death to lung cancer will skew results. All of these comments will depend on permission for autopsy being granted or the interests of HM Coroner being satisfied where appropriate.

#### **BRONCHIAL AND NEEDLE CORE BIOPSY**

1. Record site of biopsy for correlation with CT
2. Fixation should minimally be 2-3 hours, maximally 24 hours
3. Fixation time should be recorded
4. Because of the small size of the biopsies, frozen sections are not recommended for final diagnosis.

**LOBECTOMY/PNEUMONECTOMY SPECIMEN** for carcinoma. (Preoperative diagnosis is known) – except the sampling of fresh tissue for banking, all this is standard practice. CT scans must be available when the lung resection specimens are cut, to facilitate lesion identification and correlation. Frozen section analysis of resection margins if requested by surgeon.

All lymph nodes identified at the sample's hilum are taken for histological examination – all tissue processed.

A small transaxial cut in the pleura at a non-involved site towards tumour, allows access to palpable lesions for fresh tissue sampling. This approach should avoid interference with sites where there is a question of involvement of resection margin(s) or visceral pleura. It is best to avoid large airways as intact airways facilitate specimen inflation for fixation. Frozen section examination, at the time of sampling, of the tissue taken for banking, ensures the quality (tumour present) of the banked material. Optionally, imprints of fresh tumour can be made, air dried for 24 hours and then stored at -80 C. A sample of 'normal' lung tissue should also similarly be examined at frozen section prior to storage. Peribronchial inflation of the specimen with neutral buffered 10% formalin ensures adequate specimen fixation after 18-24 hours. Very large tumours may require 48 hours' fixation but fixation time should be limited to what is required as prolonged fixation may degrade the molecular integrity of the tumour. Fixation time should be recorded. Depending on the pathologist's experience and comfort with anatomic-CT correlation, the specimen should be cut in parallel 1cm thick parasagittal or coronal sections. Digital photographs of the specimen slices should be taken to illustrate the relevant pathology present. Measure tumour size in 3 dimensions (if possible before fixation), the distance of the tumour from the pleura, and the bronchial resection margin. For small tumours (< 3cm), whole mount, sledge blocks are not recommended as they limit flexibility of tissue use and are not suitable for immunohistochemistry. If the lesion is known to be an adenocarcinoma or appears to have a BAC component grossly, more than 4 tissue blocks of lesions over 3cm in maximum diameter are recommended. Any additional

satellite tumour masses, or other lesions (possible synchronous localised BAC, AAH lesions etc) should be blocked up in their entirety after their location in the resection specimen is recorded. Whilst the size of each lesion in the gross sample should, if possible, be recorded, this may be easier in the tissue sections. If the latter is used for lesion measurement, this fact should be recorded. Ten random sections of non-neoplastic lung are blocked and locations specified. Optionally (especially in squamous cell carcinomas), 10 sections of bronchi can be blocked.

All lymph nodes should be submitted, and each node should be cut in slices of 3-4 mm and completely embedded. Care should be taken to ensure all intrapulmonary, peribronchial nodes are identified and taken for histologic examination. In cases of more central, bronchial/endobronchial tumours (often squamous cell carcinomas), it is desirable to extensively sample the central, larger bronchi and this may require perpendicular section of the airways in the lung slices to obtain transverse sections of the airways. In such cases, adjacent airways dysplasia and carcinoma in situ should be recorded.

The bronchial and vascular resection margins should be taken for histology, as should blocks of tumour with pleura, as appropriate, to allow complete assessment and staging of the case.

**WEDGE RESECTION (segmentectomy, wedge or similar)** (Radiology diagnosis: (sub)solid lesion greater than or equal to 1.0 cm.)

1. Leave metal staples in specimen on resection line
2. Trim as much tissue as possible from the outer aspect of the suture line – this effectively the surgical resection margin
3. Make a single cut (preferably with a razor blade, skin graft knife or similar) through the centre of the lesion (assuming it is palpable, if not, an estimate of the lesion location should be made), perpendicular to the pleura, beginning opposite the staple line and finishing at the staples in smaller specimens, and beyond the tumour in larger segmentectomies. (Note that some segmentectomies have a recognisable 'hilar' bronchus and may be handled in the same way as a lobectomy, with appropriate provision made for any stapled resections margins). This cut should be in the short axis of the specimen and generally traverse the shortest point between tumour and pleura.
4. Frozen section examination a slice from one cut face of the tumour should be made and this tissue banked as usual. Imprints may be prepared and stored as above if required
5. Random part of uninvolved (no tumour or inflammation) lung tissue should be snap-frozen and banked
6. The specimen should then be inflated with 10% neutral buffered formalin by injection (needle and syringe) until the pleural is flat / maximally stretched
7. After 24 hours, the staple line is trimmed from the specimen as close as possible to the staples, if this was not done ab initio (section 2)
8. The fixed specimen is then sliced at 3-4mm thickness in slices parallel to the initial cut
9. Digital macroscopy photography is recommended for all slices
10. The entire tumour should be blocked up for embedding
11. Several pieces (at least 2) of uninvolved lung should be histologically examined
12. For wedge resections, fixation time should be recorded.

**WEDGE SPECIMEN** (sub) solid lesions equal to or smaller than < 1 cm (probably fewer than 5% of the cases)

1. Optionally some core biopsies of the lesion may be taken using a 16 gauge needle through lesion. These should be examined by frozen section and then stored at -80C. The pathologist should perform this biopsy procedure. This would also apply to impalpable lesions, though needle sampling may thus be impossible.
2. The specimen should then be inflated by injection using 10% neutral buffered formalin.

3. The remainder of the handling and sectioning is as in the preceding section (steps 6-12).
4. The entire specimen should be sectioned and blocked up for histologic examination.

#### **Transthoracic needle biopsy**

Transthoracic needle biopsy is the preferred modality for obtaining tissue for diagnosis of peripheral pulmonary nodules. Available data supports the superiority, in general use, of this method over transthoracic fine needle aspiration cytology, for provision of accurate specific diagnosis. This modality also has the potential to provide tissue for translational research. Diagnosis may be considered at a number of levels. The first is confirming the presence of malignancy. If a malignant tumour is present, it should be classified as far as possible and within the limitations of the tumour sample available, according to the WHO classification of Lung Tumours. Consideration of a diagnosis of malignancy, other than primary lung carcinoma, will depend on histological features in individual cases, together with clinico-pathological correlation. Primary lung carcinomas should be divided into small cell carcinoma and those non-small cell carcinomas (squamous cell, adenocarcinoma, etc). Some cases will demonstrate insufficient histological detail to allow confident sub-classification, particularly in some non-small cell carcinomas. Whilst ancillary histological techniques such as immunohistochemistry may assist in some cases, in others a diagnosis no more specific than 'non-small cell carcinoma, not further specifiable' is appropriate.

In those samples where there is no evidence of malignancy, there are two quite different categories of possible diagnosis. Firstly there are those cases where the histological findings are benign but non-specific, with no features to allow any diagnosis; no explanation apparent for the radiologically detected nodule. In such a case, the biopsy is non-contributory; a malignant nodule is not excluded. Such a situation may arise due to failure to sample the tumour. In some cases, there could be sufficient histological detail to permit diagnosis of a specific benign cause for the radiologically detected nodule (for example, tuberculosis, rheumatoid nodule, amyloidosis etc). Subsequent management of patients in these categories will clearly differ.