Implementing lung cancer CT Screening in the UK: finding an evidence base for practical strategies

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A thesis submitted to University College London for the degree of Doctor of Philosophy

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Declaration

I, Mamta Ruparel confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date: 18.09.2018
Acknowledgements

This programme of work would not have been possible without the guidance of my supervisors, mentors and colleagues - all of whom, I am very grateful to indeed.

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Impact Statement

This thesis addresses issues facing service providers planning the implementation of lung cancer screening (LCS). It focuses particularly on the communication and optimisation of benefits and harms in LCS. The findings can directly inform public health and screening policy in the UK and internationally. In addition, they should enhance the benefit-harm balance to individuals and the population and lead to improved outcomes in lung cancer. The findings will be disseminated in the form of peer-reviewed publications, some of which are currently under review in national and international journals. The research team are engaging with lung cancer expert and advisory groups, public service delivery teams and charity and commercial research collaborators, and are in the process of launching a large-scale academic project that aims to build on research questions from this thesis.

Part A uses qualitative research methods to understand the public’s knowledge and perceptions on lung cancer and screening, to determine their preferences for accessing the relevant information required for informed decision-making, and to explore how best to address smoking cessation. This knowledge informs policy-makers of the public desire and requirements for informed choice in LCS, so that this can be mandated in any on-going LCS projects and used to inform the development of future LCS information materials. This work has already resulted in the development of an information film that was well-received and has been shown in chapter 4 to enhance informed decision-making. The film, (appended to this thesis) is publicly available¹, and the research team have already been contacted for use of the film in external LCS projects. Ideas for further academic work in this area have also been discussed.

Part B evaluates the value of acting on some of the incidental findings in LCS in the UK healthcare context, and these data can inform policy makers about whether or not such findings should be measured and recorded and whether participants and their GPs should be made aware of them. It also highlights where further research can be directed to further determine best practice guidance. Finally, we also demonstrate the feasibility of implementing LDCT screening in a UK ‘real world’ setting and highlight considerations for resources, infrastructure and planning that policy makers can take forward to ensure a high-quality service if and when LCS is implemented.

¹ https://www.roycastle.org/lungcancerscreeningguide
Abstract

Lung Cancer accounts for the greatest number of cancer deaths globally, with poor five-year survival rates of less than 13% in the UK. This is largely due to late stage of diagnosis. Lung cancer screening (LCS) has been shown to significantly reduce lung cancer-specific mortality but various questions on how best to implement LCS in the UK remain. This thesis examines various aspects related to the implementation of LCS and aims to inform on policy as well as future academic work.

Part A used qualitative research methods to determine the information needs of LCS participants, and used this data to develop an information film which was shown to enhance knowledge and reduce decisional conflict without adversely affecting completion rates of low dose computed tomography (LDCT) examination in a randomised study.

Part B used prospective observational data in an LCS demonstration pilot, the Lung Screen Uptake Trial, to evaluate the cancer and non-cancer findings. We determined that 98% of participants had high risk of cardiovascular disease (CVD), suggesting that detecting coronary calcium on LDCT may not add much value as almost all participants qualify for primary prevention strategies by virtue of clinical and demographic risk factors alone. We also discovered a significant burden of ‘undiagnosed’ airflow obstruction and that individuals with LDCT-detected emphysema and airflow limitation commonly have symptoms consistent with Chronic Obstructive Pulmonary Disease (COPD). Longitudinal studies are needed to determine whether this can impact COPD-related outcomes and whether communicating smoking-related incidental findings detected at LCS can impact smoking cessation. Finally, we demonstrated the feasibility of LCS in the UK, and report a higher ratio of cancers to indeterminate nodules than expected from clinical trials in LCS, while maintaining a predominance of early stage disease treated with curative intent. Through this, key areas are identified within policy, resource allocation and infrastructure, targeting of which would help ensure delivery of a high quality LCS service.
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>2WW</td>
<td>Target Two Week Wait Referral</td>
</tr>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Radiologists</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>AUROC</td>
<td>Area Under the Receiver Operating Curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
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<tr>
<td>CAC</td>
<td>Coronary Artery Calcification</td>
</tr>
<tr>
<td>CADe</td>
<td>Computer Aided Detection</td>
</tr>
<tr>
<td>CCG</td>
<td>Care Commissioning Group</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CMS</td>
<td>Center for Medicare and Medicaid Services</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>COSMOS</td>
<td>Continuing Observation of Smoking Subjects</td>
</tr>
<tr>
<td>CRN</td>
<td>Clinical Research Network</td>
</tr>
<tr>
<td>CRUK</td>
<td>Cancer Research United Kingdom</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTDivol</td>
<td>Computed Tomography Dose Index</td>
</tr>
<tr>
<td>Ct-DNA</td>
<td>Circulating tumour Deoxyribonucleic acid</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest X-Ray</td>
</tr>
<tr>
<td>DANTE</td>
<td>Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays</td>
</tr>
<tr>
<td>DCS</td>
<td>Decisional Conflict Score</td>
</tr>
<tr>
<td>DEPISCAN</td>
<td>Pilot Study to Evaluate Low Dose Spiral CT Scanning as a Screening Method for Bronchial Carcinoma</td>
</tr>
<tr>
<td>DLCST</td>
<td>Danish Lung Cancer Screening Project</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DNA</td>
<td>Did Not Attend</td>
</tr>
<tr>
<td>EBUS</td>
<td>Endobronchial Ultrasound</td>
</tr>
<tr>
<td>ECG</td>
<td>Electorcardiography</td>
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<tr>
<td>ELCAP</td>
<td>Early Lung Cancer Action Project</td>
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</table>
E-Nose  Electronic-Nose
FAIMS  Field Asymmetric Ion Mobility Spectrometry
FEV1  Forced Expiratory Volume in 1 second
FOBT  Faecal Occult Blood Test
FVC  Forced Vital Capacity
GC/MS  Gas Chromatography/ Mass Spectrometry
GOLD  Global Initiative Obstructive Lung Diseases
GP  General Practice/ General Practitioner
HBRC  Health Behaviour Research Centre
HDL  High Density Lipoprotein
HUH  Homerton University Hospital
IASLC  International Association Study Lung Cancer
ICS  Inhaled Cortico-Steroid inhaler
IDM  Informed Decision-Making
IDMC  Independent Data Monitoring Committee
IQR  Inter-Quartile Range
I-ELCAP  International Early Lung Cancer Action Project
IG  Information Governance
IHD  Ischaemic Heart Disease
IRAS  Integrated Research Application System
IMD  Index of Multiple Deprivation
INLS  Information Needs of Lung cancer Screening participants
kVp  Peak Kilo-voltage
LABA  Long Acting Beta Agonist Inhaler
LAMA  Long Acting Muscarinic Antagonist Inhaler
LCS  Lung Cancer Screening
LDCT  Low Dose Computed Tomography
LDL  Low Density Lipoprotein
LHC  Lung Health Check
LLP  Liverpool Lung Project
LRTI  Lower Respiratory Tract Infection
LSUT  Lung Screen Uptake Trial
LuCID  Lung Cancer Indicator Detection
LUSI  Lung Cancer Screening Intervention Study
mAS  Milliamp seconds
MDT Multi-Disciplinary Team
MESA Multi-Ethnic Study of Atherosclerosis
MILD Multi-centric Italian Lung Detection Trial
Mi-RNA Micro-RNA
MRC Medical Research Council
mSv Millisieverts
NAEDI National Awareness and Early Diagnosis Initiative
NCCN National Comprehensive Cancer Network
NCSCT National Centre for Smoking Cessation and Training
NELSON Dutch-Belgian Randomised Lung Cancer Screening Trial (Dutch Acronym)
NHS National Health Service
NICE National Institute for Clinical Excellence
NLST National Lung Cancer Screening Trial
NRT Nicotine Replacement Therapy
NSC National Screening Committee
NSCLC Non-small cell lung cancer
NY-ELCAP New York Early Lung Cancer Action Project
OP Occupational Physician
PET-CT Positron Emission Tomography-Computed Tomography
PANCAN Pan-Canadian Early Detection of Lung Cancer Study
PhD Doctor of Philosophy
PLCO Prostate, Lung, Colorectal and Ovarian Study
pGGN Pure Ground Glass Nodule
PPM Parts Per Million
PSN Part Solid Nodule
QALY Quality-Adjusted Life-Year
QOF Quality and Outcomes Framework
RCLCF Roy Castle Lung Cancer Foundation
RCT Randomised Controlled Trial
R&D Research and Development
REC Research Ethics Committee
RR Relative Reduction
SABA Short Acting Beta Agonist
SEP Socioeconomic Position
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
</tr>
<tr>
<td>SN</td>
<td>Solid Nodule</td>
</tr>
<tr>
<td>SSAC</td>
<td>Strategic Screening Advisory Committee</td>
</tr>
<tr>
<td>SSI</td>
<td>Site Specific Information</td>
</tr>
<tr>
<td>SSS</td>
<td>Stop Smoking Service</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UCL</td>
<td>University College London</td>
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<tr>
<td>UCLH</td>
<td>University College London Hospital</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UKLS</td>
<td>United Kingdom Lung Cancer Screening Trial</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USPSTF</td>
<td>United States Preventative Services Task Force</td>
</tr>
<tr>
<td>VDT</td>
<td>Volume Doubling Time</td>
</tr>
<tr>
<td>VOC</td>
<td>Volatile Organic Compound</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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Chapter 1. Introduction

Prognosis from lung cancer remains poor and is largely attributable to late stage of presentation due to the absence of symptoms until the condition becomes more advanced. In the UK, only 12.9% of those diagnosed with lung cancer are alive at five years [1]. Currently 68% of lung cancers are diagnosed at stage III or IV [2] but one-year survival by stage ranges from around 71% for stage I disease to around 14% for stage IV [2]. Early detection, therefore, is imperative to transform outcomes from this condition.

The case for lung cancer screening (LCS) by low dose computed tomography (LDCT) has gained significant momentum over recent years, however, as with any screening programme, potential harms need to be acknowledged and minimised. A number of these harms have been previously discussed [3] and the evidence suggests the harm-benefit ratio may be improved by well-thought-out implementation strategies.

This chapter discusses various aspects of LCS, drawing comparisons to established screening programmes, discussing recent advances in nodule detection and management; and outlines areas where further evidence is required to determine the optimum strategy for implementing LCS. A review paper and a number of editorials on the topic of LCS have been published [4–8] and can be found in appendix 1.

1.1 LCS FROM BEFORE TO NOW

1.1.1 Chest X-ray
Studies in screening for asymptomatic lung cancer began in the 1950s using photofluororograms, and as early as 1959, it was clear that the lung cancer detection rate varied depending on whether medical grounds and risk were used to select the population to be screened [9].

Four randomised controlled trials in chest x-ray (CXR) screening were carried out in the 1970s-80s [10–13]. These reported an increase in long-term survival, but failed to detect a significant mortality benefit. The unequivocal difference in five-year survival between those who had surgical resection compared with those who did not was dismissed and attributed to ‘lead time bias’, i.e. the apparent increase in survival observed due to ‘pre-poning’ the
diagnosis rather than the prolonging of life; ‘lag time bias’, the apparent increase in survival observed due to increased diagnoses of slow growing tumours; and ‘overdiagnosis’, the apparent increase in survival observed due to increased diagnoses of tumours that would have not progressed to cause harm in the patients’ lifetime due to death from another cause. It was noted that these studies failed to utilise a true, null screening control group and instead compared screening with different modalities or at different frequencies. The more robust Prostate, Lung, Colorectal and Ovarian (PLCO) study, which randomised 155,000 ever and never-smokers aged 55-74 to either annual CXR for four years, or to no screen, also reported no effect on lung cancer stage, histology or mortality after 13 years of follow up [14].

1.1.2 LDCT

In the 1990s, the advent of LDCT, a method which reduced the effective radiation dose from 7 to 1.5 mSv revived interest in LCS in the 1990s and a series of randomised and non-randomised studies were undertaken (tables 1.1 & 1.2).

The Mayo Lung Project detected pulmonary nodules in 74% and lung cancer in 4% and again detected increased survival rates but no significant effect on mortality when compared with historical controls subjected to CXR. The study suggested overdiagnosis of indolent early stage cancers was taking place and that due to the risk of complications and expense associated with the frequently occurring false positives, the evidence to support LDCT screening was inconclusive [15,16].

The concept of LDCT screening for lung cancer, therefore, was largely rejected until the Early Lung Cancer Action Project (ELCAP) [25,29]. This study very carefully selected their nodule management algorithm and very promising results were noted. Only 13% of participants were found to have baseline scans positive for pulmonary nodules. 85% of detected lung cancers were stage I, and these patients had an estimated 10-year survival rate of 88%. Only 8% of biopsies revealed benign lesions. The authors compared these results with historical controls and reported improved mortality rates of between 36-64%. This study dramatically transformed prospects for LCS, and it became apparent that deriving benefit from LCS was complex and that even small changes in nodule management protocols could drastically impact the harms and benefits obtained from screening.
<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment Period</th>
<th>Recruitment Criteria</th>
<th>Screening Methods</th>
<th>Sample size (number screened)</th>
<th>Nodule threshold</th>
<th>Mortality Benefit</th>
<th>Cancer Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST [17]</td>
<td>2002-2004</td>
<td>Age 55-74, ≥30PY, quit&lt;15 years ago</td>
<td>Annual LDCT or CXR for 3 years</td>
<td>53454 (26722)</td>
<td>4mm</td>
<td>20% RR* in lung cancer-related mortality; 6.7% RR* in all-cause mortality</td>
<td>1.0%</td>
</tr>
<tr>
<td>MILD [18]</td>
<td>2005-2011</td>
<td>Age&gt;49, ≥20PY, quit&lt;10 years ago, no recent cancer within last 5 years</td>
<td>3 groups- no screen vs. annual LDCT vs. biennial LDCT for 5 years</td>
<td>4099 (2376)</td>
<td>60mm3</td>
<td>No</td>
<td>0.7%</td>
</tr>
<tr>
<td>ITALUNG [19]</td>
<td>2004-2006</td>
<td>Age 55-69, ≥20PY</td>
<td>Annual LDCT for 4 years vs. no screen</td>
<td>3206 (1406)</td>
<td>5mm</td>
<td>No</td>
<td>1.4%</td>
</tr>
<tr>
<td>DANTE [20]</td>
<td>2001-2006</td>
<td>Age 60-75, ≥20PY, quit&lt;10 years ago, male</td>
<td>Annual LDCT for 4 years vs. no screen</td>
<td>2472 (1276)</td>
<td>5mm</td>
<td>No</td>
<td>2.2%</td>
</tr>
<tr>
<td>DEPISCAN [21]</td>
<td>2002-2004</td>
<td>Age 50-75, ≥15PY</td>
<td>Annual LDCT vs. annual CXR for 2 years</td>
<td>765 (336)</td>
<td>5mm</td>
<td>Not reported</td>
<td>2.4%</td>
</tr>
<tr>
<td>DLCST [22]</td>
<td>2004-2006</td>
<td>Age 50-70, ≥20PY, quit&lt;10 years ago, FEV1&gt;30%, able to climb 2 flights of stairs, excluded if recent cancer/ terminal illness</td>
<td>Annual LDCT vs. usual care for 5 years</td>
<td>4104 (2052)</td>
<td>5mm</td>
<td>Not reported</td>
<td>0.8%</td>
</tr>
<tr>
<td>NELSON [23]</td>
<td>2003-2006</td>
<td>Age 50-75, ≥15PY</td>
<td>LDCT screen at 0, 1, 3 &amp; 5.5 years vs. no screen</td>
<td>15822 (7155)</td>
<td>50mm3</td>
<td>Awaited</td>
<td>0.9%</td>
</tr>
<tr>
<td>UKLS [24]</td>
<td>2011-2013</td>
<td>Age 50-75, ≥25% 5 year lung cancer risk as calculated by LLPv2 score</td>
<td>Single LDCT screen vs. no screen</td>
<td>4061 (1994)</td>
<td>≥15mm³/ 3mm: ≥50mm³: 3 month scans</td>
<td>Not reported</td>
<td>2.1%</td>
</tr>
<tr>
<td>Study</td>
<td>Recruitment Period</td>
<td>Recruitment Criteria</td>
<td>Screening Methods</td>
<td>Sample size (number screened)</td>
<td>Nodule threshold</td>
<td>Mortality Benefit</td>
<td>Cancer Detection Rate</td>
</tr>
<tr>
<td>---------------</td>
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<td>-----------------------</td>
</tr>
<tr>
<td>IELCAP [25]</td>
<td>1993-2006</td>
<td>Age&gt;60, ≥10PY</td>
<td>Annual LDCT + CXR for 5 years</td>
<td>31567 (31567)</td>
<td>5mm</td>
<td>Yes (36-64% improved mortality when compared to historical controls)</td>
<td>1.3%</td>
</tr>
<tr>
<td>Mayo LDCT trial [15]</td>
<td>Jan-Dec 1999</td>
<td>Age&gt;50, ≥20PY, quit&lt;10 years ago</td>
<td>Annual LDCT for 5 years</td>
<td>1520 (1520)</td>
<td>4mm</td>
<td>No</td>
<td>1.4%</td>
</tr>
<tr>
<td>PANCAN [26]</td>
<td>2008-2011</td>
<td>Age 50-75, ≥2% 3 year lung cancer risk as calculated by PLCO score</td>
<td>Annual LDCT for 3 years</td>
<td>2537 (1871)</td>
<td>5mm</td>
<td>Not reported</td>
<td>5.5% 5 year rate</td>
</tr>
<tr>
<td>COSMOS [27]</td>
<td>2000-2001</td>
<td>Age&gt;50, ≥20PY</td>
<td>Annual LDCT for 10 years</td>
<td>1035 (1035)</td>
<td>5mm</td>
<td>No</td>
<td>1.2%</td>
</tr>
<tr>
<td>LUSI [28]</td>
<td>2007-2011</td>
<td>Age 50-69, &quot;heavy&quot; smoking history</td>
<td>Annual LDCT + smoking cessation for 5 years vs. smoking cessation alone</td>
<td>4052 (2029)</td>
<td>5mm</td>
<td>Non-statistically significant reduction in mortality</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
The National Lung Screening Trial (NLST) in 2011 reported a 20% and 6.7% relative reduction in lung cancer-specific and all-cause mortality respectively, with a number needed to screen of 320 to save one life from lung cancer after three annual screens and seven years of follow up [17]. In spite of the trial limitations, such as the majority of NLST participants being white, well-educated and affluent, which resulted in under-representation of higher risk individuals, such a highly powered and well-conducted trial had not been carried out in LCS and the results were striking.

Not only were the results from NLST novel, as this was the first randomised study to give evidence in support of LDCT LCS, but the relative reductions in lung cancer-specific and all-cause mortality rivelled those reported in breast and bowel cancer screening. The Cochrane meta-analysis in colorectal faecal occult blood testing reported a 16% reduction of colorectal cancer-specific mortality across four randomised controlled trials after a variable follow up duration of between 8 and 19 years [30] and a similar Cochrane review in mammography screening reported an overall reduction of breast cancer mortality of 25% after 13 years of follow up across seven large randomised trials [31].

Several other trials in LCS in Europe have been carried out (tables 1.1 & 1.2) however all were substantially underpowered and failed to detect a mortality benefit. The exception to this is the Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON) [32], whose mortality results are expected in the next year.

1.1.3 Current LCS Activity

Following the withdrawal of CXR screening by the American Cancer Society in the 1970s, there was no LCS activity worldwide until after NLST when the United States Preventative Services Task Force (USPSTF) [33] recommended screening with LDCT in individuals aged 55-80 who had accrued at least 30 pack years of smoking history and who had given up smoking within the last 15 years.

LDCT screening for lung cancer for insured individuals in the US is now underway though presently there is no national screening programme which allows access to screening for uninsured members of the US population. Arguably, this risks widening the inequalities already acknowledged to exist in lung cancer [34–36]. In an effort to standardise LCS, the American College of Radiology (ACR) runs an accreditation programme outlining basic
standards for performing and evaluating screening scans and advocates use of an LCS-specific nodule management algorithm, the Lung-RADS™ LCS tool [37].

The UK National screening committee (NSC) is supportive of the concept of screening high-risk groups but makes a distinction between this and whole population lung cancer CT screening about which it will make a decision based on the results of the pooled European data [38]. In the meantime, several centres around the UK have initiated ‘high-risk surveillance’ projects and these will contribute to increasing knowledge around the best methods of implementation in the UK [39,40].

| Table 1.3 Summary of BTS guidelines [44] for management of pulmonary nodules detected at baseline screening or incidental scan. VDT= Volume Doubling Time |
|---|---|---|
| **Baseline Scan** | **Solid Nodules** | **Part Solid Nodules** | **Pure Ground Glass Nodules** |
| <5mm or <80mm³ | Discharge | Discharge | |
| 5-6mm | CT at 12 months | | |
| ≥6 - <8mm or 80 - <300mm³ | Interval CT at 3 & 12 months | | |
| >8mm or >300mm³ | 1. PET-CT 2. Assess Herder risk  • If <10%: do CT at 3 & 12 months  • If >10%: consider biopsy or resection or CT surveillance on individual basis  • If >70% favour resection | Interval CT at 3 months | |

<table>
<thead>
<tr>
<th><strong>Interval Scan</strong></th>
<th><strong>2-D</strong></th>
<th><strong>3-D</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stable nodule</strong></td>
<td>1. Discharge after 2 years</td>
<td>If stable or smaller, assess Brock risk at 3 months.  • If risk&lt;10%, continue CT surveillance at 1,2 and 4 years (or until nodule disappears)  • If risk &gt;10% or concerning morphology, consider histological diagnosis &amp; discuss options with patient.  • If growth or altered morphology (especially if solid component growth ≥2mm) favour further work up and definitive management</td>
</tr>
<tr>
<td><strong>Growing</strong></td>
<td>Discharge if stable, and discharge or on-going surveillance if slow growth (VDT&gt;600 days)</td>
<td>N.B. Consider PET if solid component ≥ 8mm</td>
</tr>
<tr>
<td><strong>Stable or slow growth</strong></td>
<td>Further surveillance or biopsy or resection are acceptable, and decision should be based on patient preference</td>
<td></td>
</tr>
<tr>
<td><strong>VDT 400-600 days</strong></td>
<td>Further work up, and consider definitive management</td>
<td></td>
</tr>
<tr>
<td><strong>VDT≤ 400 days</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.1.4 Pulmonary nodules

As described above, LDCT screening has been reported to have a high rate of detection of potentially non-malignant abnormalities, called ‘pulmonary nodules’. Nodules are usually due to scarring, fluid, infection, inflammation or a benign growth, but can rarely be malignant. Various patient characteristics, as well as radiological features of the nodule and its growth, can help predict the likelihood of malignancy [41,42], and various risk scoring calculators that utilise these characteristics [26,43] have been proposed. Adopting a stringent nodule management protocol will help maximise the benefits of screening, and minimise the need for invasive procedures, excessive radiation and the costs incurred.

Until recently, there was a lack of robust evidence to guide the management of pulmonary nodules, so nodule management protocols were cautious and predominantly based on expert opinion [45]. Thanks to evidence from CT screening studies, the first fully comprehensive, evidence based pulmonary nodule guideline was published in 2015 by the British Thoracic Society (BTS) [44]. The BTS were able to recommend a more conservative approach to the management of certain nodules by employing CT surveillance, and advocate a more radical approach for those with increased risk of malignancy (table 1.3). This evidence-based management algorithm should result in reduced radiation exposure to patients, and a reduction in invasive procedures and costs to health services.

1.2 SUCCESSFUL IMPLEMENTATION OF LDCT SCREENING

In 1968 Wilson and Jungner [46] compiled a report commissioned by the World Health Organisation (WHO) and commented that the concept of screening was not without difficulties in terms of optimising benefits and harms. In order to aid the appropriate selection of conditions for which the benefits of screening outweighed the harms, they outlined a set of screening criteria. Table 1.4 lists these criteria and proposes key factors that need to be addressed for successful implementation of a screening programme. These factors are explained in further detail below.

1.2.1 Determining eligibility and frequency of screening

As can be seen in tables 1.1 and 1.2, the baseline lung cancer incidence rates from screening have been highly variable across the LCS studies and this can be largely explained by the heterogeneous eligibility criteria. Individuals with high levels of lung cancer risk
stand to gain the most benefit with less potential harm than those who are low-risk. Indeed, the majority (88%) of screen-prevented deaths in NLST were in participants categorised within the three highest risk quintiles, and the total number of false positive results observed would have been reduced by 36% had only the patients in these three quintiles been screened [47]. This study showed that engaging higher risk participants in screening may also reduce the number needed to screen (in order to prevent one death from lung cancer), the frequency of false positive results, unnecessary invasive procedures and overdiagnosis.

Table 1.4 Wilson and Jungner criteria [46] for a suitable screening programme and where we are with LCS

<table>
<thead>
<tr>
<th>WHO Wilson &amp; Jungner Criteria</th>
<th>Met</th>
<th>Key factors for implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The condition sought should be an important health problem.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2. There should be an accepted treatment for patients with recognized disease.</td>
<td></td>
<td>Resource implications &amp; availability of volumetric assessment</td>
</tr>
<tr>
<td>3. Facilities for diagnosis and treatment should be available.</td>
<td></td>
<td>Overdiagnosis &amp; False positive rates</td>
</tr>
<tr>
<td>4. There should be a recognisable latent or early symptomatic stage.</td>
<td>Yes</td>
<td>Radiation risk</td>
</tr>
<tr>
<td>5. There should be a suitable test or examination.</td>
<td>Yes</td>
<td>Balance of psychological impact &amp; Equitable access, uptake and adherence to screening across the population</td>
</tr>
<tr>
<td>6. The test should be acceptable to the population.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8. There should be an agreed policy on whom to treat as patients.</td>
<td></td>
<td>Optimal eligibility criteria for screening</td>
</tr>
<tr>
<td>9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.</td>
<td>Yes</td>
<td>Co-implementation of smoking cessation, Incidental findings from screening</td>
</tr>
<tr>
<td>10. Case-finding should be a continuing process and not a “once and for all” project.</td>
<td></td>
<td>Interval cancer rate, Regulating CT screening</td>
</tr>
</tbody>
</table>

Several scoring systems to determine lung cancer risk in asymptomatic individuals have been developed with varying predictive performance [48]. The UK Lung Cancer Screening Study (UKLS) utilised the Liverpool Lung Project (LLP) model [49,50] to identify patients with a 5% or greater five year risk of lung cancer with good detection rates of greater than 2% [24]. There is evidence to suggest implementing a risk-score-based strategy to determine
eligibility into screening would be superior [51,52], however, it is unclear what the appropriate risk threshold for eligibility into screening is, and how this interacts with entry and exit age, competing mortality and participant fitness.

Despite this compelling evidence, in the UKLS, the majority of cancers occurred in participants over the age of 59 adding further support to the fact that age and smoking history remain the most weighted of the various predictive factors in the algorithms. It has also been acknowledged [48] that these risk prediction models will need to undergo further refinement and in the future will likely include validated biomarkers that will help to further risk stratify a wider population. A recent review of lung cancer risk prediction scores [48] acknowledges the need for further development of such scores and advocates use of fulfilling either the USPSTF eligibility criteria or high quality risk prediction scores to determine eligibility for screening, as a means to provide further evidence for determining the optimum eligibility criteria for entry into lung cancer LDCT screening.

### 1.2.2 Overdiagnosis

Overdiagnosis is defined as the detection of a cancer that is indolent and would not have progressed within the lifetime of the patient, or a cancer that may have progressed but the affected patient would have died from a competing unrelated cause [53]. It is a well-documented phenomenon that occurs in screening programmes where the objective is to detect early rather than pre-invasive cancers [54–57] and it has been an issue of great controversy in breast screening [58] largely because quantifying overdiagnosis is challenging due to the long duration of follow up that is needed for its accurate estimation. A statement released by the International Agency for Research on Cancer (IARC) estimated overdiagnosis rates with mammography screening of around 6.5% [59]. Other studies have reported estimated numbers of overdiagnosed cancers per breast cancer-specific life saved and this varies from 0.5 [60] to 3 [61] for breast. Overdiagnosis in bowel cancer has not been extensively reported but is also estimated to be around 6-9% [62].

Quantifying overdiagnosis in LCS is particularly challenging due to the paucity of available data to estimate this from. A study by Patz and colleagues, looking at NLST data [63] concluded that each lung cancer detected in NLST had an 18.5% probability of being an overdiagnosed cancer. However, this analysis has been criticised for various reasons [64]. Firstly, it may be difficult to extrapolate the findings from clinical trials, particularly where a
less deprived, and lower-risk population may have been enrolled. Secondly, it is likely that a proportion of the cancers labelled as ‘overdiagnosed’ may indeed become symptomatic after a more prolonged duration of follow up [65]. Thirdly, a more conservative approach to pulmonary nodules than that used in NLST may substantially reduce this figure, as the probability of overdiagnosis was much higher (78.9%) in adenocarcinoma in situ lesions [63]. A study based on mathematical modelling using data from NLST suggested that by altering the entry criteria and frequency of screening the overdiagnosis rate of an ‘efficient’ screening programme could be brought down to between 8.7 and 13.5% of all screen-detected lung cancers [66].

1.2.3 False positive and indeterminate results

As previously described, the proportion of CT scans with pulmonary nodules requiring surveillance has been quite high (around 25% [17,42]), though only ≤10% of these are confirmed to be malignant. The majority of these are ultimately benign and yet, if they are considered ‘false positive’ as in NLST, the false positive rate is indeed very high. The NELSON [42] and UKLS [24] investigators responded to this problem by altering the definition of false positive scans as those nodules that had a baseline appearance or interval growth that supported malignancy. As a result the false positive rate was 3.6% in NELSON, an almost 10-fold difference to the 23.3% observed in NLST.

Aside from painting the figures in a favourable light, there is further justification to this approach. The evidence from screening trials comparing levels of anxiety or distress in screened vs. control patients, suggests any increases in these levels following LCS are mild and short-lived, but may increase with the severity of the result the patient receives [67–69]. Given the frequency at which indeterminate nodules occur, and their low rate of conversion to lung cancer, by differentiating these from ‘positive’ scans, it may be more achievable to reduce LCS-associated anxiety and distress. Effective communication to ensure patients are well informed before screening and when discussing indeterminate nodules is also crucial.

It seems reasonable therefore, to reserve the term ‘positive’ for those patients undergoing tests that are invasive or carry more radiation than an LDCT scan. Nevertheless, extra CT surveillance also still carries harm and cost, and so the frequency of indeterminate nodules
should still be quantified and strategies to maximise efficiency in the management of these nodules should be exercised.

### 1.2.4 Radiation risk

The impact of radiation exposure is difficult to assess. The effect of radiation depends on the dose, the time period and distribution in the body over which it is received and the sensitivity of the individual, which is influenced by age and sex. Smoking is also known to act synergistically with radiation exposure to increase the relative risk of developing cancer [70].

Chronic low dose radiation exposure (in the order of mSv) over days, weeks or years is likely to result in damage after a significant period of latency. However estimating the excess relative risk is difficult given much of what we know about the impact of radiation exposure is based on data from acute exposures to high doses, such as the Hiroshima atomic bomb [71]. In order to estimate the impact of low dose chronic exposures, these data are extrapolated by applying a ‘reduction factor’, which assumes a linear relationship. To make matters more complicated, as stated in the report by Public Health England on the risk of solid tumours following radiation exposure, “there is at present no way of distinguishing the cases caused by radiation exposure from those resulting from other causes” [71].

There is some epidemiologic data on chronic lower dose exposure though the results have been variable and lacking in power, which makes interpretation problematic and hence the atomic bomb studies provide the most reliable data. In a review by Brenner et al it is suggested that the threshold dose for radiation-induced damage occurs at \( \approx 10–50 \) mSv for an acute exposure and \( \approx 50–100 \) mSv for a protracted exposure. The authors also point out that the above mentioned linearity assumption is likely to underestimate the effect of some radiation-induced cancer risks and overestimate the effect of others [72]. Nevertheless, using available data, modelling studies in LCS have estimated the rate of radiation-induced lung cancer deaths to be 24 per 100,000 screened using an NLST-like screening strategy [66].

Over time, the effective radiation dose from thoracic CT imaging has reduced dramatically from 7 mSv to 1.5 mSv. Even when image quality is slightly ‘noisy’ in comparison with conventional CT scanning, many of the post processing techniques allow nodule detection.
for nodules of only a few millimetres in diameter. Recently there have been reports of centres achieving acceptable image quality for detection of pulmonary nodules with “ultra low-dose CT’, exposing patients to effective radiation doses as low as 0.3 mSv [73]. This suggests that the harms from radiation are not insignificant but likely to improve in the future, and individuals should be made aware of them prior to undergoing LCS.

1.2.5 Achieving equitable uptake

Studies for LCS have demonstrated that attendance is adversely affected by demographic factors such as smoking and socioeconomic position (SEP) [74–76]. Data on attendance to LCS is limited to clinical trials, where recruitment has been difficult, with enrolment rates from 0.2%-4.6% of those initially invited [19,77,78]. Typically participation in these trials has favoured ‘low-risk’ candidates that may be younger, less deprived, better educated, and more likely to be former (rather than current) smokers.

Recruitment methods to LCS trials, when reported, have tended to be variable and have utilised advertising, mass mailing and recruitment via primary care [17–24,77,78]. The recruitment process is unavoidably complicated by the need for risk assessment, unlike other screening programmes which invite the whole population within a given age range. In the UKLS pilot study, individuals within the correct age group were invited from electoral registers and mailed questionnaires to enable risk assessment. This resulted in a significant number of ‘non-responders’ and over 250,000 individuals were invited in order to recruit 4000 participants. The French Depiscan [21] study recruited patients via General Practitioners (GP) and Occupational Physicians (OP), but reported great difficulties and high rates of non-attendance to appointments.

The uptake in faecal occult blood test screening for colorectal cancer is approximately 55-60% in the UK [79] and indications from LCS studies point to levels of uptake [75], with the likelihood of a bias against smokers and those from low SEP groups [80]. Factors affecting screening adherence are similar to those affecting uptake, with the added complexity of effects from previous positive and negative results received in previous screening rounds [81].

Engaging the higher-risk group is important to improve the cost-effectiveness and efficacy of screening as described above. However, these individuals are conversely less likely to
attend screening. Reported barriers to participation in those at risk of lung cancer include increased risk perception and fearful, fatalistic and nihilistic beliefs around lung cancer outcomes and low perceived benefit from screening [76,82,83]. Achieving equitable uptake is crucial to prevent further widening of the social inequalities that already exist in lung cancer [84] and so any LCS programme must focus on strategies aimed at attracting individuals from low SEP communities.

1.2.6 Co-implementation of Smoking Cessation
Implementing smoking cessation concurrently with LCS is vitally important as smoking is the sole modifiable risk factor for reducing individuals’ future risk of developing lung cancer. Achieving smoking abstinence in combination with CT screening has been reported to almost double the relative reduction in lung cancer mortality compared with screening alone within the NLST participants [85]. In addition, various studies have stated that the cost-effectiveness of screening may be improved by concurrently delivering smoking cessation interventions [86,87] and so this needs to be central to any LCS programme.

The available evidence suggests LCS may have the potential to motivate quit attempts [88–90]. Several studies have reported an increase in smoking cessation rates in participants of lung screening studies compared with the general population [89,91–93], and in the majority of studies no significant differences in smoking cessation outcomes between the screened and control groups have been noted [90,94,95]. However, participants with successive positive or indeterminate screen results have in some studies been reported to show greater abstinence when compared to those with negative screens [96–98]. Other studies have compared various modalities of delivery of smoking cessation advice in the screened population and found no significant differences [99,100]. Qualitative work has suggested that some LCS participants may perceive an imaging investigation as equally beneficial against lung cancer as smoking cessation [101]. Communicating clearly the message that LCS does not prevent lung cancer while smoking cessation will reduce the risk of developing and dying from lung cancer [85] may help somewhat mitigate these perceptions. Taking advantage of the ‘teachable moment’ that LCS provides is vital for any LCS programme, and we must ensure that we deliver this message together with appropriate support in an effective way.
1.2.7 Incidental findings in LCS

The NLST reported a 6.7% reduction in all-cause mortality by screening, an effect that was most pronounced in Black African-Americans [17,102]. This may be explained by detection of clinical and radiological findings in the process of screening, but also due to the improved access to health care that may prompt intervention for non-lung cancer co-morbidities [6]. Several studies have shown that ungated LDCT scans can accurately predict coronary calcium and subsequent cardiovascular events in a comparable manner to formal coronary calcium scoring [103,104]. The population at risk of lung cancer is also at risk of cardiovascular disease and so, combining risk assessment and screening for both conditions seems sensible, however, further prospective studies are needed.

LDCT scans have also been shown to be useful for detecting emphysema and osteoporosis and may be useful in predicting mortality and lung cancer risk [105,106]. Whilst simultaneous case-finding for these conditions (which occur commonly in life-long smokers) seems worthwhile, the exact impact on disease-related outcomes in this population is not known. Furthermore, discovery of subclinical disease may have implications on participants’ health insurance premiums and be problematic in a health service already under significant resource constraint. Arguably, non-disclosure of such findings may also be considered unethical. Evidenced-based strategies to further understand how best to deal with these findings are imperative.

1.2.8 Biomarkers and exhaled breath testing with LCS

The ultimate goal for any biomarker in the application of LCS would be to either a) act as an initial non-invasive test that could be added to clinical and demographic factors to give a more accurate pre-CT lung cancer risk prediction. The aim of this would be to then enable a wider population including younger and non-smoking individuals to LCS; and/ or b) to be used in conjunction with the LDCT scan to enhance its specificity for pulmonary nodules and reduce the number of surveillance CT scans required, and thereby the associated cost, anxiety and distress to the patient. It is vital for any chosen biomarker test to have a high sensitivity, to be able to detect early, pre-symptomatic disease, not be subject to confounding environmental factors, and to be easy and cheap to carry out [107].

The use of biomarkers in LCS is crucial to its success, and although there are no blood biomarkers that have sufficient evidence for clinical application presently, several are being
researched. The most promising of these are the EarlyCDT autoantibody test and serum and plasma micro RNA (miRNA), all of which have reached phase III prospective validation studies [108]. In addition to these, circulating tumour DNA (ctDNA) may also have promising applications [109,110].

The idea that certain medical conditions have a scent or ‘fetor’ has long been taught in medical school. That dogs can therefore detect cancer seems plausible given their heightened sense of smell. Indeed a patient diagnosed with melanoma was reported to only seek medical attention due her dog’s constant sniffing and attempts to bite off the mole [111]. For several decades, scientists have been developing technology to detect volatile organic compounds (VOCs) in breath, body fluids and faeces. As early as 1985, several VOCs were found to be associated with lung cancer when exhaled breath was analysed using computer-assisted Gas Chromatography/Mass Spectrometry (GC/MS)[112]. The clear advantages of this method of diagnostic testing include its non-invasiveness, speed and potentially low costs, however its application in the lung cancer diagnostic pathway has been limited due to a lack of consensus and poor reproducibility across studies. This is largely explained by the varying populations tested, the effect of confounding factors such as smoking and related comorbidities, small sample sizes and statistical methods used (including over-fitting of models) and the variability in sampling techniques used [113]. Standardisation of these techniques and further studies are needed to help to advance this promising diagnostic tool.

1.2.9 Resource Implications
If the NLST eligibility criteria were to be implemented, an estimated 8.7 million people in the US may be eligible for screening [114]. The size of the UK LCS eligible population is unclear, however, even if assuming uptake levels may be in the region of 40-50%, numbers are likely to be significant. This has considerable resource implications in terms of carrying out baseline and interval CT scans required for nodule follow up and considerable further assessment is needed to understand the optimal operational model, such as the use of mobile CT scanners or dedicated screening centres, for providing LCS in the UK. Scan reading time is also a factor, and research is needed to explore whether feasible options exist that may relieve some of the work from radiologists. Furthermore, exactly what proportion of UK hospitals currently have the technical, radiological and clinical knowhow
to implement volumetric assessment (as recommended by the BTS pulmonary nodule guidelines [44]) has not been determined.

The cost of LCS in the UK has been estimated at £8466 (CI £5,542 - 12,569) per quality-adjusted life-year (QALY) gained [24]. This is well within the £20,000 per QALY threshold deemed acceptable by NICE for cost-effective interventions. This figure suggests LCS is more cost-effective than breast cancer screening (quoted at £20,800 [115]) and comparable to bowel cancer screening (quoted at £6,000-8,000 [116]). Furthermore, this figure can potentially be further improved by refining screening and nodule management protocols.

1.3 INFORMED DECISION-MAKING

It is no longer considered acceptable for medicine to be carried out in a paternalistic manner [117]. In LCS, the importance of ‘shared decision-making’ has been outlined by the American College of Radiology (ACR) [118], although there is little evidence to guide clinicians in how to achieve this. The UK Department of Health has released a statement on the importance of informed consent in screening and urged health services to develop strategies to develop, pilot and evaluate materials to aid this [119]. In addition, the above quoted 1968 Wilson and Jungner [46] principles of screening were modified in 2008 to reflect changes in modern medicine, and now include IDM within the key principles [120].

Informed decision-making (IDM) is considered vital, particularly in decisions where the given intervention is not a required treatment and so choosing whether or not to proceed can vary on an individual basis. Cancer screening is one such example. Here, an otherwise healthy person is subjected to a test, which may or may not lead to potential harms. The benefits of screening are often based on the effects to entire populations and the precise benefit-harm balance to the individual may be less clear and largely dependent on the individual’s beliefs and values. Cancer screening is culturally accepted as a positive intervention, and the public are often unaware that potential harms such as overdiagnosis and false positives exist [117].

IDM occurs when an individual understands the condition being addressed and is aware of the procedure involved, the benefits, risks and limitations of undertaking or not undertaking the test. It is also necessary for the individual to make a decision that is
consistent with his or her own preferences and values, and to participate in decision-making at a level that he or she desires [121].

IDM is particularly pertinent in situations where the benefit is unclear, such as with PSA screening for prostate cancer. Situations where there may be conflicting expert opinion or a lack of sufficient data to make firm conclusions, can lead to increased uncertainty and make IDM more challenging. Providing more information to patients can in fact result in higher levels of decisional conflict, distress and lower decision satisfaction [122]. Even when there is a clear benefit from an intervention, such as with LCS, IDM requires complex processing of information that may be challenging particularly for individuals with low levels of health literacy [123].

The components that make up IDM include knowledge, decisional conflict and satisfaction, values and attitudes. Whilst validated measures exist [124–126] to assess these components, doing so is not without its challenges. Evaluating adequate knowledge is particularly complex as this requires understanding, retention and recall of concepts and statistics, and what threshold signifies ‘adequate’ knowledge is unclear. Ideally all individuals would score 100% in knowledge questions, however, achieving this is not always feasible. It has been shown that knowledge and intentions are not correlated, while values and intention are [127]. Many patients make a decision to take part (or not) that may be based on limited knowledge but is more in line with their values and preconceptions.

In summary, measuring IDM is complex and not without its limitations. Achieving IDM is vital, but challenging. It is important to present the facts in a way that fairly portrays the benefits and harms whilst accurately reflecting the scientific evidence for or against. Decision tools can be a useful adjunct; but should not replace a more personal discussion with a health professional. Exploratory research to improve communication of this information is much needed. This thesis will use qualitative and quantitative research methods to address IDM in individuals considering undergoing LCS.
1.4 AIMS OF THIS THESIS

This thesis evaluates various aspects relevant for the successful implementation of LCS, which are divided into two parts as described below. Part A is made up of two studies and addresses how we should communicate benefits and harms of LCS to individuals considering taking part: Chapter 3 is a qualitative study exploring the information needs of lung cancer participants. The data from this study enabled the development of an information film, which was subsequently tested as a nested randomised study. Chapter 4 presents the results of this nested randomised study. Part B (chapters 5, 6 and 7) addresses important considerations around some of the benefits and harms from LCS and uses clinical and radiological data from the baseline screening round of an LCS demonstration pilot to evaluate specific questions. The specific research questions explored in this thesis are:

Part A: Communicating benefits and harms and enhancing IDM

1. What is the background knowledge and perception of lung cancer amongst LCS-eligible individuals and, what information should be presented and how?
2. Does a novel information film enhance informed decision-making in individuals considering LCS more than a standard information booklet?

Part B: Optimising benefits and harms

3. What is the prevalence and value of coronary calcium and cardiovascular risk in the context of LCS?
4. What is the prevalence and value of Chronic Obstructive Pulmonary Disease (COPD) and emphysema case finding in the context of LCS?
5. Is it feasible to implement low dose CT in the UK?
6. What are the prevalence, stage, histology and treatment outcomes of lung cancers detected after a baseline screen?
Chapter 2. Methods

2.1 THE LUNG SCREEN UPTAKE TRIAL

Chapter 1 describes the importance of carrying out lung cancer screening (LCS) in those at high-risk of lung cancer, in order to improve the risk-benefit balance to the individual, and to improve the cost and efficiency of the programme. The Lung Screen Uptake Trial (LSUT) was the third phase of a programme of work led by Professor Jane Wardle and Professor Sam Janes, and funded by the National Awareness and Early Diagnosis Initiative (NAEDI) & Cancer Research UK (CRUK), entitled: ‘Developing and testing targeted invitation materials to increase uptake of lung cancer screening in communities at high risk of lung cancer’. The initial stages of the work included qualitative [76] and quantitative research [83,128], carried out by Dr Samantha Quaife, aimed at exploring attitudes and barriers to participation in LCS in smokers, in order to develop a novel invitation strategy that was designed to address low uptake in the ‘hard to reach’, i.e. predominantly current smokers from low socioeconomic position (SEP) backgrounds. LSUT was the final part of this work and was a behavioural randomised controlled study aimed to determine if the novel invitation strategy improved uptake to LCS in this group. Individuals were invited to a ‘lung health check’ (LHC) and those meeting the criteria for low dose computed tomography (LDCT), were invited to attend this on the same day. The full protocol is in appendix 2 and has been published (appendix 3 and [129]). A summary of the methods used, and justifications for these choices are presented here.

2.1.1 Study design

LSUT was a randomised study testing a novel invitation strategy against a control, and was primarily aimed to assess differences in uptake to an LHC between the two invitation materials. Participants attending the LHC were invited to be enrolled into the study. Anonymised demographic data and primary care-recorded codes for smoking status were collected for those who did not attend the LHC in order to assess differences between attenders and non-attenders and will be reported elsewhere. A summary of the study design is presented in figure 2.1.
Figure 2.1 Flow chart summary of study

Identify potentially eligible participants from GP records (standardised audit searches by practice administrators)

Individual randomisation (1:1 allocation)
Randomisation list generated at UCL using unique participant IDs

Intervention Arm:
Targeted invitation strategy (n=1000)

Control Arm:
Control invitation strategy (n=1000)

Re-invite once

Attend | Cancel | DNA

Lung Health Check
- Medical and smoking history
- Spirometry
- Determine if scan-eligible
- Smoking cessation intervention and referral

Scan Eligible | Scan Ineligible | Declines or does not attend scan

Low Dose CT Scan

Suspicious lesion
- Letter to GP and patient
- Internal 2WW referral to clinic

Indeterminate nodule
- Letter to GP and patient
- Sensitive patient communication

Incidental finding

Routine patient care pathway
2.1.2 Participants and setting

Participants were identified from primary care health records. General Practice (GP) surgeries from 3 London boroughs surrounding University College London Hospital (UCLH) and Homerton University Hospital (HUH) were invited to participate in the study. In order to engage practices, we enlisted the lead GP for cancer within each Clinical Commissioning Group (CCG) to act as a champion for the study, and placed advertisements in CCG newsletters and presented the study to GPs at CCG forum meetings.

With assistance from the research team, administrators from participating practices identified potentially eligible participants by carrying out a GP database search aiming to identify smokers and recent former smokers (i.e. recorded as a current smoker within the preceding 5-7 years), aged between 60 and 75. Exclusion criteria included any active lung cancer diagnosis, cancer metastasis, palliative care treatment and lack of capacity to consent. In order to avoid contamination of the groups, where applicable, where more than one individual was identified from the same household, one, selected at random, was excluded from the study. The remaining participants were randomised into two groups (control and invitation strategy), and invited by a letter from their GP to a pre-allocated ‘lung health check’ (LHC) appointment. The LHCs took place at UCLH or HUH between November 2015 and July 2017. Those who failed to attend the first appointment (and had not contacted the study team to decline the appointment), were given a second pre-allocated ‘reminder appointment’. Those who attended were invited to be enrolled into LSUT.

2.1.3 Eligibility to LDCT

Individuals who were enrolled, were invited to LDCT on the same day if meeting any of the following three criteria:

- Those who were currently smoking or who had given up within the preceding 15 years and who met a 30 pack year smoking history (as per the United States Preventative Services Task Force recommendation (USPSTF) [33]
- Those meeting a lung cancer risk of 1.51% or higher as per the Prostate, Lung, Colorectal and Ovarian trial cohort developed (PLCOm2012) lung cancer risk prediction model (adapted for use in the UK)[130]
- Those meeting a lung cancer risk of 2.5% or higher as per the Liverpool Lung Project (LLP) lung cancer risk prediction model [131]
Participants were excluded from the LDCT if they did not have capacity to give consent, their weight exceeded restrictions for scanner (>200Kg), they were unable to lie flat, had poor physical fitness such that radical treatment would be contra-indicated, or had had a CT scan of their chest within the previous 12 months. A summary flow chart of the study design is presented in figure 2.1.

2.1.4 Intervention

Both strategies included a pre-invitation letter to ‘prime’ the individual about the new service, followed by either an invitation letter plus detailed information booklet that contained information on the benefits and harms of LCS (control), or an invitation letter plus a targeted, low burden leaflet, which was more focussed on the LHC than LCS, used more pictures and simpler language and did not mention smoking (intervention).

2.1.5 Lung health check training

Study practitioners, comprised of research nurses and clinical trials practitioners, were trained to carry out the LHC appointments. An intensive training programme, comprised of education about LCS, the study protocol and aims, the consent procedure, data collection, measuring and interpreting spirometry and other clinical parameters and biological sampling was carried out. Study practitioners were given multiple resources, including advice on calculating smoking pack-years, alcohol intake, naming inhaled treatments, calculating predicted values for spirometry and eligibility and referral to LDCT. Study practitioners were also provided with a ‘script’ to act as a reminder of all the points to be covered during the appointment and the process of consent to LDCT. This included welcoming the participant and informing them that they had been invited to a new service that was part of a research study. Participation in the study was not compulsory, and decliners would get a focussed LHC with no data collection. Enrolment in the study was necessary to qualify for an LDCT. The full script can be found in appendix 4.

2.1.6 Informed consent

Participants were given written information on the study (in the participant information sheet (PIS), appendix 5), and the lung health check and LDCT (in the control information booklet, appendix 6). Initial consent to be enrolled into the study and collect data was
taken at the start of the appointment. Further consent for the LDCT and biological sampling were taken at the end of the appointment, following a discussion by the study practitioner regarding potential benefits and harms of LCS. A checklist of points to be covered for ensuring informed consent to LDCT was provided (figure 2.2). The consent form can be found in appendix 7.

**Consent checklist**

- If appropriate- tell them they have a higher than average risk of lung cancer due to their age, smoking and other history and that they are eligible to be offered a CT scan
- CT scan is a 3d x-ray test, not painful, like a big doughnut.
- Takes about 10 minutes with perhaps a little waiting before hand
- Important to hold their breath for a short time but they will be instructed.
- But before they decide whether to go ahead, they should be aware of the pros and cons and make their own mind up whether its right for them to go ahead.

**Pros:**

- Currently lung cancer is often **diagnosed late** due to symptoms occurring late. With screening we aim to **detect lung cancer earlier** which offers a **higher chance of cure**.
- A US study showed we **might save 20% of lives** that could have been lost from lung cancer if we screen high-risk individuals

**Cons:**

- **Radiation**- the amount of radiation in 1 scan is about the same as what you’d get from the environment in a year, and isn’t too harmful. However many scans over a lifetime especially when young, can cause harm.
- **Indeterminate results**- about a quarter of all patients undergoing screening will have a “spot”. This will mean the need for further tests to check for growth. This can cause anxiety. If this does happen to you, try not to worry as about 90% of those with spots, will turn out not to have cancer. I.e. only 2 in every 100 screened will have cancer.
- **Overdiagnosis**- The screening test may pick up slow growing cancers that you may end up having tests or treatments, when they may be so slow growing that without the screening tests you may have gone on another 15-20 years without knowing there was cancer, and it may not cause symptoms.
- Very rarely, the test may **miss small cancers**

**Figure 2.2 Checklist for informed consent of LDCT for study practitioners**

2.1.7 Smoking cessation

Very brief smoking cessation advice (a standardised intervention from the UK National Centre for Smoking Cessation and Training [132]), was given to all current smokers at the LHC. Currently smoking participants were also randomised to receive details of their local NHS smoking cessation service or be proactively referred to the smoking cessation service.
2.1.8 Data collection

Data were prospectively collected by a study practitioner at the LHC and included self-reported demographic data, smoking and medical history and family history (table 2.1). Participants were also asked about symptomatic help-seeking, and to give feedback on the information materials. Hand-held spirometry, height, weight and blood pressure were recorded. 20 ml venous blood for plasma and serum and exhaled breath samples were taken, processed and frozen in a biobank at -80 degrees. For a sub-population, exhaled breath samples were also taken and analysed for biomarker research in collaboration with Owlstone Medical Inc. Participants were also asked to complete a psychological and quality of life assessment at the end of the appointment. There were two further questionnaires administered on the morning after the LHC and 3 months after the LHC.

During the LHC, data were entered by the study practitioner directly into the electronic study database. Radiology data were entered directly into the electronic database by the radiologists. Questionnaire data were inputted following the receipt of completed forms. Follow up clinical data were entered by myself or another respiratory clinical research fellow, Dr Sophie Tisi.

<table>
<thead>
<tr>
<th>Table 2.1 Data collected during LHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age, gender, ethnicity, education level, marital status, employment status, IMD score and rank</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Current smoking status, age started and stopped, years smoked and quit, average and maximum smoking intensity, pack years, tobacco products used, quitting aids and attempts, nicotine dependence and willingness to quit</td>
</tr>
<tr>
<td>Symptoms &amp; help seeking</td>
</tr>
<tr>
<td>History (current or within the past 12 months) of cough, dyspnoea, chest or shoulder pain, hoarse voice, weight loss, loss of appetite, haemoptysis, fatigue, lower respiratory tract infection, barriers to help seeking, number of GP visits in the past 12 months, participation in bowel breast and cervical cancer screening</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>COPD, asthma, pulmonary fibrosis, TB, lung cancer, asbestos exposure, Coronary heart disease, atrial fibrillation, hypertension, hypercholesterolaemia and statin use, diabetes mellitus, risk factors present in the Q2RISK, inhaler use, alcohol intake</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Heart disease, lung cancer, gastrointestinal caner, breast cancer, ovarian cancer, prostate cancer</td>
</tr>
</tbody>
</table>
2.1.9 LDCT referral and acquisition

The study practitioner carried out the lung cancer risk assessment and determined whether the participants met any of the three criteria for LDCT. If any of these were met, the participant was informed about the harms and benefits and counselled to make a shared decision of whether or not to go ahead with the LDCT. If they chose to go ahead, they would sign the second page of the consent (appendix 7) and be able to have the LDCT the same day. In some cases participants preferred to come back on another day, and they were given an appointment to do so. The referral to the LDCT at UCLH was transmitted electronically to the Research Imaging Department. At HUH, a paper based referral was given to the participant to take to the radiology department. At both sites the referral was protocol driven. In the event that a participant who was due to attend their CT, did not, the clinical research fellow would flag the non-attendance to the study practitioner who would contact the participant. A minimum of three attempts to contact the participant were made, after which they would be sent a letter telling them their appointment had been cancelled, and that if they wished to have the LDCT, they should get in touch with a member of the research team. Those wishing to reschedule were able to do so.

Participants undertook the examination via a sixteen channel or higher multi-detector, non-ECG-voltage-gated CT without the administration of intravenous contrast. Imaging was performed during suspended maximal inspiration. The lung parenchyma (lung apices to bases) was 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. Thin detector collimation (0.5 mm) was used. Images were reconstructed at 0.5 -1.0 mm section thickness using standard soft tissue and lung algorithms. Radiation exposures were as low as possible whilst maintaining good image quality. The tube potential and tube current-time product varied according to participant body habitus and were between 80-120 kVp and 20-80 mAs respectively.

2.1.10 LDCT results and follow up process

Once the LDCT had been performed, they would be added to an automatic work list for the radiologists to review. Additionally, the clinical research fellow sent lists to the reporting radiologists once a week, of all participants who been scanned, to ensure none were
missed. The target was for results to be received by the participant within 2 weeks of undertaking the LDCT.

The patient and GP would receive a letter and a copy of the CT report would also go to the GP. Example letters are in appendix 8. Those with normal CT results, or with non-urgent incidental findings were discharged. Where necessary the patient would be asked to see the GP for further assessment, treatment or for referral to secondary care, and the GP would be given tailored advice on any further action required. The clinical research fellow would refer participants with certain thoracic incidental findings (such as an endobronchial lesion requiring fibre-optic bronchoscopy, or interstitial lung disease requiring formal lung function testing and specialist clinical assessment) to an appropriate thoracic physician. Those with indeterminate nodules or suspicious lesions would be automatically booked into a thoracic clinic within six weeks, or two weeks if concern of malignancy (2WW). For those with suspicious non-thoracic lesions, the clinical research fellow would make an automatic 2WW referral to the appropriate specialist clinic (figure 2.3).

Five percent of scans were randomly chosen for second-reading by a radiologist from the opposite site as part of a quality assurance process. Any discrepancies, as well as any missed findings, were reviewed and arbitrated by an independent third radiologist who had not previously seen the scans. The arbitration process is currently still on-going.

2.1.11 Ethical approvals and study registration

Ethical approvals (and any ensuing amendments) were granted by the City Road and Hampstead NHS Research Ethics Committee (REC; reference: 15/LO/1186) (appendix 9). Site specific and local R&D approvals were granted by each participating hospital site. The study was sponsored by University College London (UCL) and was adopted by the National Institute for Health Research clinical research network portfolio.

The study has also been registered by clinicaltrials.gov (NCT02558101) and with the International Standard Registered Clinical/social study Number (ISRCTN21774741). The study was registered on the Data Protection Register (Z6364106/2015/10/34).
Figure 2.3. Flow chart of management and referral pathways following baseline LDCT. (2WW= 2 week wait urgent pathway; MDT= Multidisciplinary team)
2.1.12 Trial oversight
LSUT had a Trial Management Group (TMG) made up of researchers, clinicians and study practitioners involved in the planning and delivery of the study. The Trial Steering Committee (TSC) included core members of the TMG, and independent members with expertise in lung cancer, clinical trials and medical statistics and included a lay patient representative. An Independent Data Monitoring Committee (IDMC) made up of an independent medical statistician, and independent clinical and academic members, was also assembled. They reviewed the interim data, and also contributed to the trial oversight. The groups met regularly (in person or virtually) during the planning and active phases of the study, to review and approve any amendments to the protocol, and to review progress and accrual.

2.1.13 Statistical analysis
The sample size for LSUT was determined on the basis of the primary research question, and the expected attendance rate. Based on studies in bowel cancer screening and psychoeducational materials, this was estimated to be 35% in the control group and be 7% higher in the intervention group. It was estimated that a 1000 patients per group would provide 90% power to detect a significant difference of 35% vs. 42%, with 5% significance level and two-sided testing. Other analyses were planned as detailed in the relevant chapters in this thesis.

2.2 DETERMINING THE INFORMATION NEEDS OF LUNG SCREENING PARTICIPANTS
Communicating all the harms and benefits of LCS to participants in order to enhance informed decision-making (IDM) is crucial to the successful implementation of LCS. Ensuring IDM occurs is usually challenging, and this is particularly so in LCS, where the demographic being targeted are those from low SEP backgrounds who are likely to have lower levels of literacy and numeracy [133]. It is known that written materials are often not read and poorly understood [134], and that graphics, illustrations and animation can improve understanding [135–137]. In order to tackle this, we put together a research proposal aimed at tackling this issue, and we were awarded a project grant from the Roy Castle Lung Cancer Foundation to carry out the below programme of work which make up chapters 3 and 4 of this thesis.
When complex information is communicated in written form, the high information burden and the perceived effort required to read the materials may act as barriers. Indeed, it has been reported that patients often do not read written materials [138]. Furthermore, individuals of varying demographic backgrounds have different preferences in how this information should be presented in terms of content and graphics [139]. It therefore seems worthwhile to consider other formats for delivering the information and to ascertain their suitability for the target audience.

The proposal was a three phase programme of work (figure 2.4), where phase 1 was exploratory qualitative work aimed to determine the information needs of LCS participants and used focus groups and interviews. The methods and findings from this are presented in chapter 3. The second phase was the development of an information film described in detail below. The third and final phase was a nested randomised study that compared IDM outcomes between individuals exposed to the information film and written information booklet against the written booklet alone in a sub-sample of participants from LSUT. The plan for integrating this into LSUT is detailed below and the methods and findings for this are described in chapter 4.

Figure 2.4 Flow diagram illustrating the three phases of the informed decision-making study

- Qualitative Study
  - To explore the information needs of LCS participants
  - Focus groups with LCS-eligible individuals
  - Interviews with GPs, Lung cancer nurse specialists, public health consultants and respiratory physicians

- Development of information-film
  - Use of data from the exploratory phase to make a 5.5 minute information film targeted to the LCS-eligible population aimed at improving informed decision making

- Quantitative study
  - A nested randomised study in a sub-sample of participants from LSUT (n=229) evaluating informed decision making with exposure to the information film + booklet against the booklet alone
2.2.1 Developing the film

The full protocol of the qualitative study can be found in appendix 10. Ethical approvals for this study were granted by the East of England - Cambridge East Research Ethics Committee (16/EE/0089) and can be found in appendix 11. Following the first round of focus groups in the exploratory qualitative work, a summary of findings relating to the content, tone and format of the information was collated. This allowed the team to draft ideas for the film in the form of storyboards, which we could use to get feedback on before putting together the final film (figure 2.5). The aim was to produce a five-minute film that provided an overview of the same facts contained in the written information booklet. It was required to be easily understood for individuals of all educational backgrounds, though it was anticipated some individuals may want more detailed information.

In addition to the themes described in chapter 3, from the focus groups and interviews it was clear that the film should be clear and simple, with use of simple graphics, presented without unnecessary motion or complexity. The use of appropriate language without jargon was preferred. Participants’ appetite for statistical information varied, but most considered it reasonable to provide a basic level of statistical information, best presented in the form of icon arrays such as the one in figure 2.6 (taken from our control information booklet), with the option for obtaining further detailed statistics from the study practitioner if necessary. Some participants preferred a light hearted and entertaining tone, while many others felt that to be trivialising, and so a neutral tone was planned. The use of analogies was favoured by many, but some cautioned against analogies sometimes overcomplicating the message. Participants expressed a desire to hear the positive effects of LCS, as well as be made aware of the harms, and many were in favour of a lung cancer patient’s view. Conversely, participants had mixed opinions on the appearance of a ‘medical expert’ appearing on the film. Participants were also keen to be shown what the CT scan would entail, and preferred for the message to be relevant to the local population (for example a dislike of the use of clips featuring American accents was expressed).
Focus groups with lung cancer LDCT screening eligible individuals identified in primary care

Interviews with clinicians with experience of lung cancer patients

Development of ideas, story boards and script for the film

Feedback from the same groups regarding content and script of proposed film

Written feedback on developed ideas

Information film produced

Figure 2.5 Flow chart describing the stages for development of the film

Out of 100 people scanned...

73 normal scans

25 repeat scans

2 cancers
(usually diagnosed after further scans or tests)

Based on numbers from a UK lung cancer screening study

Figure 2.6 Icon array featured in LSUT control information booklet
In view of the fact that it would be challenging to address everyone’s diverse preferences, particularly within the five-minute timeframe, so the aim was to produce a film that would be palatable to all, and where individuals could seek more information if needed. It was clear we would not be able to address all the requirements of a ‘decision-aid’ as stipulated by the International Patient Decision Aids Standards (IPDAS) Collaboration [140] in a five-minute film, and anything longer would be less likely to hold the viewer’s attention, so the plan was for the film to be used to support and facilitate the study practitioner discussion around informed consent for the LDCT rather than as a decision-aid per se.

A brief of our aims and a draft script containing everything to be included in the film were given to a creative script writing and film production team. From the qualitative data and the team’s experience in LCS, we suggested some possible options of how to present this information, though we were very keen to give them freedom of creativity. The production team drafted some storyboards (figure 2.7), and organised regular meetings and discussions with us to refine the ideas. About half (n=18) of the focus group participants re-attended for feedback focus groups following the development of storyboards. Based on this feedback, any necessary changes could be made prior to finalising the script, planned animation and live filming. The clinicians interviewed were also invited to give written feedback on the storyboards.

The film was reviewed by members of the LSUT TMG and TSC, including our lay patient representative prior to approval of the final cut. The final film can be accessed via the Roy Castle Lung Cancer Foundation website\(^2\) and has been appended to this thesis in the form of a DVD.

### 2.2.2 Integrating the sub study into LSUT

The target sample size (described in detail in chapter 4) for the nested study was 210. A substantial amendment to the original protocol was submitted to allow the sub-sample of LSUT participants to undergo the extra activities required for the film study. The protocol, PIS and consent form in the appendix include these amendments.

\(^2\) [https://www.roycastle.org/lungcancerscreeningguide](https://www.roycastle.org/lungcancerscreeningguide)
Figure 2.7 An example page from the storyboard sent to participants for feedback
### 2.3 TIMELINE OF WORK

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<thead>
<tr>
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<td>Feedback and further focus groups</td>
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<td>GP searches</td>
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<td>Analysis and write up</td>
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**Figure 2.8** Gantt chart detailing the timeline of activities relating to this thesis
2.4 CONTRIBUTIONS TO THE WORK REPORTED IN THIS THESIS

The design of LSUT was led by Professor Jane Wardle and Professor Sam Janes. My role, in collaboration with Dr Samantha Quaife was in planning and executing the study. We were responsible for delivering the protocol, study documents, development of referral pathways, ethics and local approvals and ensuring the study was compliant with information and data governance regulations. I organised relevant contracts and data sharing agreements for the study and the locations for the LHC and LDCT to take place, any equipment needed for the LHC and the process of referring for LDCT.

I led the process of recruiting GP practices and attended GP practices to oversee the identification of participants for the study. I was responsible for the drafting of the case record forms and the electronic study database, the software for which was developed by a specialist company, Sealed Envelope. I organised the study registrations and the TMG, TSC and IDMC meetings and updates. I was responsible for compiling and updating the Trial Master File.

I carried the study mobile phone, upon which participants called to cancel and reschedule appointments and for any other queries. I carried out several of the first 100 LHC appointments and devised and carried out the study practitioner training. A number of study practitioners carried out the LHC at both hospital sites for the duration of the study. I was responsible for feeding back any participants who had not attended the scans to the study practitioners, so they could be contacted, and for checking the LDCT results and generating result letters and referrals as required. These tasks were covered by Dr Jennifer Dickson when I was away on maternity leave.

I was responsible for carrying out much of the follow up data collection, together with the help from Dr Sophie Tisi, Dr Carolyn Horst and Dr Helen Hall. Dr Bhagbhatti Ghimire and Professor Stephen Duffy have assisted and guided me with the statistical analysis in chapter 4. Interpretation of data in chapter 5 has also included intellectual contributions from Professor Aroon Hingorani, Dr Riyaz Patel, Dr Reecha Sofat and Dr Emma O’Dowd.
Dr Samantha Quaife led on designing and creating the study information booklet and invitation strategy and materials for LSUT, the behavioural and smoking cessation related aspects of the study, together with Professor Jane Wardle, Dr Jo Waller and myself.

Professor David Baldwin first suggested the need for an information film. With Professor Jane Wardle as the applicant and supervisor, and with Dr Samantha Quaife’s and Professor Sam Janes’ help, I applied for the project grant to the Roy Castle Lung Cancer Foundation. Dr Samantha Quaife and Dr Jo Waller have also helped with the data analysis and coding of the qualitative data. Dr Brintha Selvarajah did the voice over for the film.

I have had much guidance and advice at all stages, from my senior supervisors and mentors, mentioned in the acknowledgement section of this thesis.
PART A

Communicating benefits and harms and enhancing informed decision-making
Chapter 3. Explores the information-needs of lung cancer screening participants - a qualitative study

3.1 INTRODUCTION

Lung cancer screening (LCS) by low dose computed tomography (LDCT) is the only intervention for lung cancer other than smoking cessation that has been shown to dramatically reduce lung cancer-specific mortality. The US National Lung Screening Trial (NLST) showed annual LDCT of high-risk adults for three years, reduced lung cancer-specific mortality by 20% compared with chest radiograph [17].

LDCT screening does however, also pose risk through overdiagnosis, false positive findings, clinical investigations, radiation exposure and psychological burden. Even if the ratio of harms to benefit is low, individuals need to be made aware of the risks in order to make an informed decision to participate. A participant-centred approach may not only promote informed decision-making, but could reduce the psychological burden of harms [141]. The US Center for Medicare and Medicaid services mandates a ‘shared decision-making’ process for individuals undergoing LCS, thereby re-enforcing the importance of informing individuals [142].

Communicating complex medical statistics and risks (such as overdiagnosis in mammography [143]) is challenging, but there is strong evidence to suggest individuals wish to be informed about these risks [144,145]. Optimising communication is particularly pertinent in lung cancer, where those from lower socio-economic backgrounds, who often have lower levels of literacy and numeracy [146] make up a large proportion of the at-risk population [147]. Decision tools therefore need to be effective in communicating this information and address the preferences of this target population.

The ultimate aim of this study was to produce an information film to help people make an informed decision about whether or not to have a LDCT to screen for lung cancer. We found limited evidence about what to include, how best to present the information and how to approach the issue of smoking cessation for the target audience [148,149]. Furthermore, preferences and definitions of ‘informed choice’ can differ between lay people and policy makers [150]. Therefore, we carried out an in-depth qualitative study...
with the lung cancer ‘at-risk’ population and Health Care Professionals (HCP) to address the below research questions.

### 3.1.1 Aims
What do (i) LCS-naïve individuals who are likely to be eligible for screening, and (ii) healthcare professionals involved in lung cancer and public health believe LCS participants:
a) know and perceive about lung cancer treatment; b) know, perceive and want to know about LCS (including harms and benefits); c) feel about smoking cessation advice and the how it should be approached in the context of LCS.

### 3.2 METHODS
The full protocol can be found in appendix 10 and is summarised below.

#### 3.2.1 Participants

**Focus groups**
Participants were purposively recruited from six general practices in an ethnically diverse area of London, where LCS was not being carried out. Practice administrators carried out an electronic record search to identify patients aged 60 to 75 who had been recorded as current smokers within the past 15 years, in order to identify those likely to be eligible for LCS. This strategy mimicked the search strategy in LSUT. An invitation letter addressed from the individual’s general practitioner (GP) that included information about the study, and an option to opt out of being contacted by the research team was sent to those identified. A member of the research team phoned those who had not opted out, and collected data on smoking history (status, years smoked and average cigarette consumption per day) and demographic details (age, sex, education level, ethnicity, religion), which enabled individuals who agreed to participate to be allocated to a focus group based on smoking status and educational level. Sample size was determined on the attainment of data saturation, with scope for a further phase of recruitment if required.

**Interviews**
We recruited a variety of healthcare professionals to obtain a wide range of perspectives. Participants from four disciplines (GPs, lung Cancer Nurse Specialists (CNS), respiratory physicians (RP) and public health (PH) consultants), were recruited using snowballing. The
target sample size was attained when three or more participants from each discipline were recruited and when data saturation was achieved.

3.2.2 Data Collection

Focus groups
The focus groups were carried out in May 2016 in a local library and lasted 90 minutes each. Written consent was obtained prior to starting the groups. The sessions were run by two facilitators (one to facilitate the discussion and one to observe), and were audio-recorded.

“Research in the US has shown that if we carry out a CT scan (a detailed sort of X-ray) once a year on people who have a higher risk of lung cancer due to the amount they have smoked in the past, we may save 20% of lives by detecting the cancer early and giving a higher chance of cure. There are more trials underway, and depending on the results of those, we may start doing lung cancer screening in the UK in a few years. As with the other screening programmes we have discussed, there are pros and cons to screening for lung cancer. Here are some leaflets on lung cancer screening. I will give you some time to read through them and then, if it’s ok, I’ll ask you for your thoughts on them.”

Figure 3.1 What focus group participants were told about LCS during the discussion.

Open discussion between participants was encouraged and facilitated, with more narrow questions where needed to address the research questions as described in the discussion guide (appendix 12). The facilitator provided some verbal (figure 3.1) and written information on LCS. Participants could ask questions and were encouraged to give feedback and opinions on lung cancer and screening, LCS harms and benefits, the written information materials and the issue of smoking cessation in the context of LCS.

Interviews
Telephone interviews were carried out to enable busy professionals from different parts of the country (in rural and urban practice) to participate and were conducted from April to June 2016. Participants were sent information about the study and a consent form by email. Interviews lasted between 25 and 50 minutes and were audio-recorded.

The interview schedule (appendix 12) followed a similar structure to the focus group discussion guide. Participants were asked about their views on patients’ perceptions of lung
cancer, the harms and benefits of screening, their experiences of communicating complex facts or statistics and smoking cessation.

3.2.3 Analysis
Focus groups and interviews were transcribed verbatim. MR coded the data inductively and SQ second-coded >10% of focus group transcripts using the same coding framework. The codes were collated, organised into themes, and analysed using the matrix-based framework method [151,152], with themes in the columns and participants in the rows. This allowed examination of focus group data by educational background and smoking status. The framework was discussed with co-authors SQ and JW (both behavioural scientists) and the transcripts were re-reviewed following the group discussion. Analysis continued into the write-up phase. Coding was carried out using NVivo v11.

3.2.4 Ethical approvals
The study was granted approvals by the Cambridge East NHS Research Ethics Committee (ref: 16/EE/89) and the Health Research Authority (ref: 192823), which can be found in appendix 11.

3.3 FINDINGS
Of the 1690 individuals identified and invited from 6 GP practices, 280 individuals were contacted by phone and 74 agreed to take part in the study. Of the 61 individuals allocated and invited to a focus group, 35 individuals participated in 7 focus groups (figure 3.2). The demographic and smoking related characteristics of participants are described in table 3.1.

Of the 18 HCP participants, seven were GPs (some of whom had a special interest in cancer), four were lung Cancer Nurse Specialists (CNS), four were respiratory physicians and three were public health consultants.
<table>
<thead>
<tr>
<th>Table 3.1 Focus group participant characteristics (% totals may not sum up due to rounding)</th>
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<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Age, median (IQR)</strong></td>
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<td>Age, years</td>
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<td><strong>Ethnicity, n (%)</strong></td>
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<td>British Indian</td>
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<td>Kurdish</td>
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<td>Somali</td>
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<tr>
<td>Prefers not to say</td>
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<tr>
<td>Jewish</td>
</tr>
<tr>
<td>Muslim</td>
</tr>
<tr>
<td>Hindu</td>
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<tr>
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<tr>
<td>Completed CSEs, O-levels or equivalent</td>
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<tr>
<td>Completed A-levels of equivalent</td>
</tr>
<tr>
<td>Completed further education but not a degree</td>
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<tr>
<td>Completed a Bachelor's degree</td>
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<tr>
<td>Completed a further degree (e.g. Masters/ PhD)</td>
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<td><strong>Smoking status, n (%)</strong></td>
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<td>Former smoker</td>
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<td><strong>Smoking- current smoker groups, median (IQR)</strong></td>
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<td>Years smoked</td>
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<td>Average smoked per day, cigarettes/day</td>
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<td>Smoking pack-years</td>
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<td><strong>Smoking- former smoker groups, median (IQR)</strong></td>
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<td>Years smoked</td>
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<td>Average smoked per day, cigarettes/day</td>
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<td>Smoking pack-years</td>
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</table>
1690 potentially eligible for LCS individuals identified from 6 GP practices and invited to participate with option to opt out of study

Due to geographic proximity – we attempted to recruit from 3 practices. n=946

165 opted out

Attempted to contact 781 patients by phone

Unable to reach 501 individuals

206 declined

74 agreed

13 not invited to focus groups

61 invited to focus groups

8 cancelled

18 did not attend

7 focus groups with 35 participants

Current smoker, education > O-level n=5 & n=6

Current smoker, education ≤ O-level n=4 & n=2

Former smoker, education > O-level n=8 & n=5

Former smoker, education ≤ O-level n=5

Figure 3.2 Process of recruitment for the focus groups
Figure 3.3 Thematic structure
3.3.1 Themes

Three general themes were interpreted to address the research questions for both the focus group and interview data, each with a number of subthemes (figure 3.3). Below are descriptions of each subtheme with illustrative extracts from the data (also tables 3.2-3.4).

3.3.2 Theme 1: Appetite for balanced information

I. Fatalism and perception of lung cancer as incurable

Many participants described lung cancer with terms such as “death sentence” (INT54_CNS) or “death knell” (M6, FG64_FS_ED+). Focus group participants, most commonly smokers, expressed views that it had poor prognosis, worse than other cancers and this was echoed by the HCPs. One smoker stated that they were “wary” (F2, FG63_CS_ED+) of LCS given the poor prognosis of lung cancer.

Many participants were unaware of curative treatment options. Some had encountered surgery, but still associated this with negative outcomes, such as cancer recurrence. A few recounted stories of positive surgery outcomes, but cited that this was unusual.

The HCPs also described a lack of public awareness of curative treatments and talked about smokers being “extremely worried about lung cancer” (INT38_GP) describing a “degree of fatalism and denial about cancer and perhaps more so with smokers” (INT57_PH).

II. Belief in screening

Although some participants were cautious about screening, many described it as “a precaution” (F5, FG65_FS_ED+) or that “prevention is better than cure” (M6, FG63_CS_ED+), suggesting it “makes sense” (F1, FG68_CS_ED-). Many participants recognised the benefits of early detection of cancers, and recognised screening as an ‘opportunity’, stating it was “silly” to not “take advantage” (F2, FG64_FS_ED+). Participants also described screening as “worthwhile” due to its ability to “save lives” (F1, FG68_CS_ED-).

Footnote:
3 Focus group participants (FG) are denoted by gender (M/F), smoking status (CS, current smoker /FS, former smoker) and education descriptor (ED+, education >O-level / ED-, education ≤O-level). The interview participants (INT) are denoted by their professional role (GP (general practitioner) / RP (respiratory physician)/ CNS (lung cancer nurse specialist) / PH (Public health consultant).
This belief in screening, which was more frequently expressed by those with less education, appeared to be associated with a trust in medicine. Participants described attending screening because it was “recommended” (M4, FG65_FS_ED+), or because “my doctor told me to do it” (M2, FG67_FS_ED-). This phenomenon was reiterated by the HCPs.

Some participants seemed reluctant to acknowledge the harms of screening. The rationalisations included that harms were “so rare” (F1, FG68_CS_ED-), that “nothing is 100%” (F1, FG64_FS_ED+); and that “there’s also human error in all this” (F7, FG64_FS_ED+). HCPs described a need to dissuade people from tests at times, where the harms outweighed the benefits.

III. Right to an informed-decision

Many focus group participants expressed the “human right” (F1, FG63_CS_ED+) to be informed and to make an “individual choice” (M4, FG65_FS_ED+) about participating. Participants, particularly current smokers and those with higher education, expressed a desire for information in order “to make an informed decision” (M6, FG63_CS_ED+), and be better prepared for screening outcomes. Others were in favour of the decision being made on a population level, to avoid varying practices of different HCPs.

HCPs also acknowledged the ‘right’ to decide, and that people “want to know the facts and figures” (INT49_CNS) but that individual preferences varied. Some reported that balancing harms and benefits could be challenging particularly for “the group in the middle” (INT38_GP) with whom it was most necessary for clinicians to spend time “not make the decision for people but trying to explain how to make that decision” (INT38_GP).

IV. Too much information

In contrast to the previous subtheme, a number of participants, most commonly current smokers, also expressed that at times “too much information” (F8, FG64_FS_ED+) can be “too scary” (F4, FG63_CS_ED+), or paralysing: “you can’t make any decision” (M2, FG65_FS_ED+). Some participants referenced medical leaflets or information on the internet as a means to “frighten yourself to death” (F1, FG68_CS_ED-) and some advocated placing “more emphasis on the positives” (M6, FG63_CS_ED+) to mitigate this. Many participants, particularly those in the more educated groups expressed scepticism that statistics “can be played with” (M6, FG64_FS_ED+) and are often manipulated citing the phrase “lies, damn lies and statistics” (M2, FG65_FS_ED+). HCPs similarly highlighted that
written information materials don’t always get read, and often resulted in “information overload” (INT58_CNS), and suggested it was necessary to moderate the information given.

3.3.3 Theme 2: Reactions to the harms of LCS

I. Anxiety associated with indeterminate nodules

There were mixed views on indeterminate nodules. Many participants, particularly current smokers, stated that being called back for repeated CT scanning could be “a worry” (M8, FG63_CS_ED+) or “a concern” (M6, FG63_CS_ED+). Some felt that “walking into hospital” was “bad enough” (F3, FG68_CS_ED-), or that the anxiety caused “in itself is bad for your health” (M2, FG_70_CS_ED+). Others suggested, “how you tell people” (M2, FG65_FS_ED+) was important, and that being told the risk of cancer following an indeterminate result was low, could “make me feel a bit more confident and less worried” (M4, FG68_CS_ED-).

Some HCPs described circumstances where patients were “more worried than they need to be” (INT40_GP) and the challenge in communicating that the “rate of that nodule being malignant is actually pretty low” (INT51_RP), but that doing so was part of the role of the medical professional. Other HCPs felt it wasn’t a “big problem for patients” (INT45_RP) and that CT surveillance was a reassuring process for many.

II. False positives and negatives

A number of participants acknowledged the potentially “serious sequelae” that may result from “interventions which might harm” (M3, FG_70_CS_ED+) and some expressed concern that some people “wouldn’t be able to cope” (M2, FG65_FS_ED+). Importantly, participants who had actually experienced false positives spoke of the “terrible fright” (F1, FG68_CS_ED-) caused.

On the other hand, others suggested that they would find additional tests reassuring, as though “somebody’s looking after me” (F4, FG63_CS_ED+). A number of participants felt false negatives were a far bigger worry “than the other way round” (F4, FG67_FS_ED-), due to the fact that further tests for false positives could resolve the problem, while nothing could be done for missed cancers.
III. Overdiagnosis

Most focus group participants needed detailed explanation of the term ‘overdiagnosis’, though one participant who had a history of prostate cancer described the ‘tiger’ and the ‘sleepy’ cancers, and said “But if you get the tiger ... you’re in trouble” (M4, FG68_CS_ED-). This fear of cancer, perhaps accounted for why many felt “probably, it wouldn’t stop me being screened” (M6, FG65_FS_ED+). Some participants were concerned about being “happy, smiley... and suddenly ... get told, you’ve got cancer” (M6, FG64_FS_ED+). Despite this, many felt they would rather know about the cancer and have the option not to treat it. When it was suggested that it may not always be possible to determine prognosis, participants felt “you can’t take that risk” (F3, FG68_CS_ED-) of not treating. HCPs also acknowledged that patients often “don’t necessarily want to just say oh leave it to be” (INT51_RP). One RP felt overdiagnosis was a “fallacy” (INT72_RP) and supported the idea that expectant management of some ‘ground glass’ pulmonary nodules would reduce overdiagnosis.

IV. Radiation exposure

The issue of radiation exposure generated some debate as it was acknowledged that “there’s no conclusion to be drawn from it because no one knows” (M4, FG68_CS_ED-) because the exact harms from cumulative, medical doses were speculative. Some acknowledged that they knew very little about “x or radio, whatever it’s called” (F2, FG64_FS_ED+), though overall most people felt it didn’t “worry me at all” (F1, FG65_FS_ED+) or that “it’s a necessary thing unfortunately ... And it’s not that bad” (M8, FG63_CS_ED+), or that “the equipment nowadays is... much safer” (M2, FG65_FS_ED+). Some did express some “concerns” (F5, FG65_FS_ED+) due to having to go for repeat scans, while others felt it would not stop you having the test, “but it would be nice to know” (M4, FG68_CS_ED-). HCPs placed different levels of importance upon this harm. Some were concerned radiation was often ignored or caused much anxiety due to poor understanding, while others felt it was “doctors that are more concerned about that than the patients” (INT45_RP).
3.3.4 Theme 3: Attitudes and preferences for smoking cessation

I. Smokers’ perceptions of smoking

It was widely expressed, particularly amongst smokers, that smoking is “one of the strongest addictions” (F3, FG63_CS_ED+), that overcoming it was very challenging and removing the option to smoke altogether by making it “too expensive for people to buy” (M6, FG63_CS_ED+), to “stop producing it” (F2, FG63_CS_ED+) or to go somewhere to be “incarcerated for a certain amount of time” (F5, FG7_CS_ED+) might be helpful. Participants illustrated their dependence by describing how cutting down made them “jump down people’s throats” (F1, FG69_CS_ED-), or their inability to stop smoking despite no longer getting “enjoyment” (M2, FG68_CS_ED-) or having had cancer, including self-blame “I’m an idiot … I mean, it’s ridiculous” (F5, FG70_CS_ED+).

Participants felt that non-smokers couldn’t “get how difficult, how addictive it is” (F1, FG68_CS_ED-), though HCPs recognised that “trying to get [older smokers] off nicotine is quite difficult” (INT61_GP) and advocated openly acknowledging this difficulty and that “quitting is a cycle” (INT46_PH) to smokers participating in LCS.

Many focus group participants were aware that smoking causes lung cancer. Nevertheless, smokers, most commonly those with higher levels of education, downplayed the harms. The views varied on a spectrum from total rejection of smoking as harmful: “it’s something else give you cancer, not the smoke” (M5, FG63_CS_ED+); through to accepting that smoking causes harm, but that other exposures such as “pollution” (M4, FG65_FS_ED+), “processed foods” (F3, FG63_CS_ED+) and “genetic foods” (M5, FG63_CS_ED+) were equally or more responsible for causing cancer; to the notion that smoking affected their health indirectly, by putting “extra weight on” (F1, FG69_CS_ED-).

Some used examples, such as a healthy “93 year-old lady puffing away” (F5, FG65_FS_ED+) to demonstrate that smoking is not always bad for your health. Others used anecdotal evidence of lifelong non-smokers who had run “six London marathons” (M2, FG70_CS_ED+) or led an “exemplary lifestyle” (F3, FG63_CS_ED+) but who subsequently developed lung cancer, to undermine the strong link between smoking and lung cancer.
II. Helpful and unhelpful motivators for cessation

Many participants, particularly current smokers, described how being “preached at” (F4, FG63_CS_ED+) and having smoking cessation advice “ramming ... in your face” (F1, FG67_CS_ED+) was “patronising” (F1, FG68_CS_ED-). Smokers stated that they “know” (F4, FG63_CS_ED+) that smoking is bad for them. HCPs were also aware of the aversion to “being lectured to by health professionals” (INT50_GP) and knew that doing so could “put them off coming back” (INT53_GP).

Using “scare tactics” (M4, FG68_CS_ED-) as a method of encouraging people to stop smoking was also commonly felt to be unhelpful, particularly by current smokers. One participant talked about televised advertisements that used fear, saying that “all it does is make you change the television” (F4, FG67_CS_ED+). Other participants talked about the messages on cigarette packets suggesting it “doesn’t mean a thing” (M3, FG67_CS_ED+). Interestingly some HCPs had more favourable views on the use of fear to motivate behaviour change, and felt that this may be a good way to “bring it home to people” (INT50_GP), and that they worked “to some extent” (INT72_RP).

Many participants, particularly the former smokers, talked about success with smoking cessation often being motivated by life events such as pregnancy, ill health or relatives with cancer. One participant talked about seeing the “lung that was removed from my sister [who had lung cancer]” (F1, FG64_FS_ED+). One HCP also recognised that health scares “not necessarily cancer but maybe an MI” can be “the trigger to stopping” (INT50_GP).

Several participants talked about positive experiences with smoking cessation aids, stating that “The only thing that helped me was an e-cigarette” (F5, FG63_CS_ED+) and “the patches worked for me” (F1, FG63_CS_ED+). While many others dismissed their usefulness “I’ve tried patches, I’ve tried hypnotherapy, I’ve been to cessation sessions. (F5, FG70_CS_ED+) or complained of their side effects “They [tablets] make me ill actually” (M2, FG69_CS_ED-). One of the participants complained of the expense of them, and expressed surprise at the ‘free help’ available “Can you really? ... I didn’t know that” (F1, FG68_CS_ED-) suggesting a need to inform smokers of the extent of NHS support available.

HCPs also expressed that “signposting people to where they can get that support and help and advice” (INT38_GP) was worthwhile because there was “no point discussing smoking cessation unless you have some pathway of offering them something” (INT49_CNS).
Empowerment

Many smokers expressed preference for emphasis on the positive impact of smoking cessation such as the possibility to “save money” (F1, FG69_CS_ED-) or other health benefits including the more immediate, such as emphasising symptom relief. Some smokers however, expressed a lack of perceived benefit from smoking cessation in older age. One participant said “at my age ... what’s the point?... I won’t reach those benefits” (M4, FG68_CS_ED-).

HCPs also often cited the need to emphasise the “positive effect of stopping smoking at any stage” (INT40_GP) and the benefit for the “whole of your body” (INT44_CNS). Others advocated encouraging messages such as the impact on heart disease, and to empower individuals even when they had had unsuccessful quit attempts: “not quitting is not failure, it’s part of your journey towards quitting” (INT46_PH). Another GP talked about “helping people not to feel helpless... doing it in a positive way that helps them feel empowered” (INT40_GP).
Table 3.2 Quotes illustrating the theme 'Appetite for balanced information'

<table>
<thead>
<tr>
<th>Theme 1: Appetite for balanced information’</th>
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<tbody>
<tr>
<td><strong>Fatalism and perception of lung cancer as incurable</strong></td>
</tr>
<tr>
<td>“My father had [lung cancer], but really in the ‘70s so it was… quite new, it wasn’t a new cancer but it was… to survive it, and he survived it” F4, FG67_FS_ED-</td>
</tr>
<tr>
<td>“they were 99.9% certain they’d got rid of all the cancer … but three weeks later it was back” F5, FG67_FS_ED-</td>
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<tr>
<td>“I don’t know much. I had a friend that got it and he died but they kept him going for quite some time somehow … they told him he was going to die within six months and he got probably about three years” M4, FG68_CS_ED-</td>
</tr>
<tr>
<td>“Well if you hear that someone’s got lung cancer, you know, you do feel that it’s not a good prognosis. Put it that way” F8, FG64_FS_ED+</td>
</tr>
<tr>
<td>“it’s the big C word to the general populous, isn’t it? … and the minute you mention that word, everything is invasive and almost terminal. … it’s the worst possible scenario for most people to hear they’ve got cancer” F5, FG70_CS_ED+</td>
</tr>
<tr>
<td>“As treatments have got better again there will be a certain amount of day to day experience of knowing people who have had it for longer … but… there probably is the perception that it’s quite a bad one to get” INT57_PH</td>
</tr>
<tr>
<td>“I think [for patients] cancer equals, you know death, chemotherapy, suffering all those, all those bad things” INT50_GP</td>
</tr>
<tr>
<td>“I think probably a lot of their knowledge comes from people they already know who have had lung cancer and because of its frequent terminal course, they’re very frightened of the diagnosis of lung cancer” INT55_GP</td>
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<tr>
<td><strong>Belief in screening</strong></td>
</tr>
<tr>
<td>“I mean people who throw it [bowel screening kit] away I don’t understand, quite frankly, for the effort it takes. Any prevention is better than cure” M6, FG63_CS_ED+</td>
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<tr>
<td>“any screening that’s ever offered, I think anybody that doesn’t take it must be completely bonkers. I mean why wouldn’t you? If it’s offered. You need to know. And as early as possible” F7, FG64_FS_ED+</td>
</tr>
<tr>
<td>“I did believe in having the screening because if cancer’s caught early enough … you can battle” F5, FG67_FS_ED-</td>
</tr>
<tr>
<td>“I trust the consultant … why would he put me through this if he thinks it’s a waste of time and a waste of National Health money” F4, FG63_CS_ED+</td>
</tr>
<tr>
<td>“generally people want the test and it’s you saying to them, well actually you need to understand that we’ve got to have a good reason to do it because we might pick up things that are not helpful” INT38_GP</td>
</tr>
<tr>
<td>“most of the patients … they’re happy to do whatever the doctor thinks is right and actually it doesn’t really matter what you say to them, you could tell them there’s a 99% risk of death but if you recommended it to them they’d still want to have it done” INT45_RP</td>
</tr>
<tr>
<td>“I think that patients had … cancer screening programme fully explained to them I, I suspect they might still have an exaggerated view of those benefits because people want to believe that the screening is good for you” INT52_PH</td>
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</table>
“Well yeah, I mean I know that some people say that they’ve got mistaken results ... and it’s caused them great distress. But, you know, I think that must be the minority of what happens and as such I can’t see it to be a reason for not doing it”  
“But all the tests you can make are not infallible ... mistakes can be made”  
“If it was very common it might change my mind but I think you only hear about the ones that are false negatives or false positives rather than the thousands and millions of tests where they get it right ... So it wouldn’t put me off”  
“I think if there’s a large amount, that if it was common, they would, they would find what was going wrong ... And put it right”

The right to an informed decision

“you want to make a decision that’s an informed one ... Not one where you say afterwards, oh, I didn’t know that ... I just want to be told the full facts”  
“I would like to know exactly what’s going on, all the test and the results and everything and then I make my own conclusion”  
“I tend to probably express it... there are further consequences and, but actually if you really are at risk, or you want to know the result, then this is the next step, and you need to be aware that this is what could be coming next”  
“[we] would wish patients to be given a totally impartial degree of information so ... they did understand that ... you get interval cancers ... sometimes things do go wrong”  
“I think now this is a concept in general practice of giving people the facts in a way that they can understand so that they can make that shared decision”

Too much information

“When I had my babies I didn’t even think about a miscarriage or percentages or this, that and the other. But now they scare them, they scare the mothers to death and other people, because they give out too much information”  
“There’s also an argument that says, do you really want to ... access the information, because sometimes the information can be more scary [than the disease]”  
“the egg crisis, the beef crisis, didn’t stop me. ... If you look at them, it’s all, this is bad for you, that’s bad for you, I mean, now I mean, they’re, they’re, they’re on about sugar... I’m very cynical in a lot of things because I don’t trust what a lot of people say”  
“Oh, they manipulate everything these days to suit themselves ... Because, because everybody from the Government, all the way down, massage things to suit whatever they’re doing at that time”  
“I think trying to read a black and white document is very difficult... it’s just such a lot of information that I think people do struggle”  
“So it’s not trying to undermine the risks but ... you’re not scaring them as well”
### Table 3.3 Quotes illustrating the theme 'Reactions to the harms of LCS'

<table>
<thead>
<tr>
<th>Theme 2: ‘Reactions to the harms of LCS’</th>
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<tbody>
<tr>
<td><strong>Anxiety associated with indeterminate results</strong></td>
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<tr>
<td>“It wasn’t saying that there was a problem. It was just saying inconclusive. But even so, you think, oh, yeah”</td>
<td>F5, FG70_CS_ED+</td>
</tr>
<tr>
<td>“whatever you’re told you still worry. I’m, you know, a terrible worrier. But I keep saying to myself, don’t worry about things until you’ve got something to worry about. But, you know, you can’t help it.”</td>
<td>M6, FG64_FS_ED+</td>
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<tr>
<td>“if it can be resolved quickly then I suppose it’s not pleasant but it’s less of a worry, but if … that could be a prolonged period of time that people could be quite distressed”</td>
<td>INT38_GP</td>
</tr>
<tr>
<td>“They would say things like I’m glad it, I’m glad this nodule hasn’t changed and I have been a bit worried about it but at least it was found and at least somebody’s looking after it”</td>
<td>INT45_RP</td>
</tr>
<tr>
<td>“[indeterminate results] can cause a lot of anxiety and that’s where the clinicians role is, to reassure them and that can take some time”</td>
<td>INT72_RP</td>
</tr>
<tr>
<td><strong>False positives and negatives</strong></td>
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<tr>
<td>“I’m thinking I’d rather be one of those thirty false positives out of the thousand and they do something”</td>
<td>F5, FG64_FS_ED+</td>
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<tr>
<td>“I was told … it’s just a polyp … And it wasn’t a polyp … it was a tumour … he … could have said … well I think it’s a tumour. Not, not, oh don’t worry about it, it’s just a polyp”</td>
<td>M6, FG64_FS_ED+</td>
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<tr>
<td>“I think the biggest problem is when they do a test and they say, oh, yes, you’re fine, and in actual fact, it didn’t pick up the problem … a false positive is probably OK because they … they’ll have a, probably a backup test … or they’ll do the test again”</td>
<td>M3, FG65_FS_ED+</td>
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<tr>
<td>“I’ve actually known that happen to someone where they got a letter through the post saying everything was OK and six weeks later they were dead”</td>
<td>M4, FG68_CS_ED-</td>
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<tr>
<td>“I certainly think that anybody who is flagged as suspicious and requires a further intervention, I think that is a much greater harm than the others, and partly psychological but they also undergo that physical harm as well”</td>
<td>INT46_PH</td>
</tr>
<tr>
<td>“False negatives I would think would be a concern. False positives are a concern but as long as it’s presented to patients in a way that … it isn’t normal but it might not be anything and … it’s dealt with in a timely fashion then I guess people probably would cope with it reasonably well”</td>
<td>INT38_GP</td>
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<tr>
<td>Overdiagnosis</td>
<td>F1, FG64_FS_ED+</td>
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<td>“somebody giving me a sound sort of prognosis... like saying, well you could actually live with this for X number of years ... or they will say, well look we think this is serious and it could spread and so on”</td>
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<tr>
<td>“But at that stage would they give you the choice then whether to, to do something or not? ... there’s the other side of it ... where things aren’t done ... And weren’t acted upon quickly enough”</td>
<td>F3, FG68_CS_ED-</td>
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<tr>
<td>“Well, I think he [my father] took to it [watching and waiting] OK. I think the rest of the family were going, so he’s saying he’s got cancer and he doesn’t want to do anything about it. ... has my father not been assertive enough? Has the doctor just said, go away, we’re not bothered?”</td>
<td>M2, FG70_CS_ED+</td>
</tr>
<tr>
<td>“I still think I’d go the whole hog just so that I could still be alive and say, OK, so it wasn’t that necessary but... you should because I’m still here”</td>
<td>F1, FG68_CS_ED-</td>
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<table>
<thead>
<tr>
<th>Radiation exposure</th>
<th>INT46_PH</th>
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<tbody>
<tr>
<td>“I think radiation is particularly difficult because people are, either just ignore it because they don’t understand it or they become very, very anxious about it because they don’t understand it”</td>
<td></td>
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<tr>
<td>“You don’t very often hear patients worrying about radiation doses”</td>
<td>INT38_GP</td>
</tr>
<tr>
<td>“I think across the board that [radiation] is the least worry thing, worrisome thing for them”</td>
<td>INT72_RP</td>
</tr>
<tr>
<td>“I wonder if they’ve overplayed the radiation risk sometimes”</td>
<td>INT75_RP</td>
</tr>
<tr>
<td>“I think most people’s perception of radiation is oh well, I’ll trust you doc, it’s a low dose, it’s worth the risk”</td>
<td>INT61_GP</td>
</tr>
<tr>
<td>“Some people are aware of radiation but others, now with scanning ... so frequent nowadays, you go in and you have a CT scan for goodness knows what, it seems to be part and parcel of it ... I’m not sure whether or not people A) can understand or B) how one gets that across to people in a way that they can understand and make that decision”</td>
<td>INT61_GP</td>
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</tbody>
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**Table 3.4 Quotes illustrating the theme 'Attitudes and preferences for smoking cessation'**

<table>
<thead>
<tr>
<th>Smokers perceptions on smoking</th>
<th>Battling with smoking addiction</th>
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<tbody>
<tr>
<td><strong>Smokers perceptions on smoking</strong></td>
<td></td>
</tr>
<tr>
<td>Battling with smoking addiction</td>
<td></td>
</tr>
<tr>
<td>“Smoking is an addiction ... Stop them making cigarettes”</td>
<td>F8, FG63_CS_ED+</td>
</tr>
<tr>
<td>“So I started smoking as a temporary thing. Now I know I’m addicted. But it isn’t just a question of willpower. You’ve got to want to stop”</td>
<td>F4, FG63_CS_ED+</td>
</tr>
<tr>
<td>“I was a drug addict many years ago ... And smoking is the most difficult [addiction], I, I can’t crack it, well I’ve not cracked it as yet”</td>
<td>M4, FG68_CS_ED-</td>
</tr>
<tr>
<td>“It’s extremely difficult to change deeply embedded habits, whether they’re as a result of physical addiction or other factors”</td>
<td>M3, FG70_CS_ED+</td>
</tr>
<tr>
<td>“[the] no smoking pack help thing... it’ll have bits and bobs in and, and a tension ball, I mean for heaven’s sake, you know, give me strength”</td>
<td>F1, FG68_CS_ED-</td>
</tr>
<tr>
<td>“life is that little bit more chaotic that they often regress back to the norm again... They felt paralysed, that they were hooked for life”</td>
<td>INT61_GP</td>
</tr>
</tbody>
</table>

| Reduced perceived relative risk of smoking |
| “So apart from the smoking I just try to do what my body tells me to do, which means lots of movement, decent food made from scratch. No processed food. Stuff like that” | F3, FG63_CS_ED+ |
| “all the emissions in the air are worse than two ... cigarettes a day” | F4, FG63_CS_ED+ |
| “he had a [electricity] pylon virtually outside the house and he got stomach cancer and she’s convinced it was from the pylon” | F4, FG63_CS_ED+ |
| “who should we screen? Well, maybe ex smokers or smokers and ex smokers and so on, yeah, but if you look at sort of current research, and so on, anybody who lives in a big city. ... with the air pollution that’s around like that” | M2, FG65_FS_ED+ |
| “[smoking] It’s been mentioned but I’ve still got an open mind on that. ... the amount of rubbish these, these cars and buses are sputtering out ... You look at processed food now” | M2, FG69_CS_ED- |
| “Because, because everybody from the Government, all the way down, massage things to suit whatever they’re doing at that time ... because they think maybe there’s too many people using the National Health who are smokers. I don’t know” | F4, FG63_CS_ED+ |
| “do you think smokers are in denial? ... on some level we are defensive, I think, you see, about the whole, a bit, aren’t we? Because we self inflicted this” | M4, FG70_CS_ED+ |
| “my nan died of lung cancer, right? ... And they said, said that she was smoking, I think it was about 50 or 60 fags a day ... She never smoked in her life” | M2, FG69_CS_ED- |
| “I know quite a few people whose, members of whose families have died from lung cancer who have never smoked, have always exercised, have had a healthy lifestyle, have always been in a smoke free home...” | F5, FG70_CS_ED+ |
“I know people who have had an exemplary lifestyle, they got it age 45, 50. It’s, seems to be, hit and miss and that is not, I’m not saying this in order to defend smoking, far from it. But it crops up in all sorts”

“I’ve thought about this, and I know people quite old who are still smoking. Young people who have smoked that have stopped, who have now got lung cancer, so how do you determine this? How do you predict it?”

Helpful and unhelpful motivators for cessation

Preaching message

“I think I’d already know... I don’t think anyone needs to tell me. It’s quite obvious isn’t it?”

“I’ve tried the whole, been very stern, you mustn’t smoke and what’s the point in us doing all of this while you’re still smoking type thing and that doesn’t work very well”

“if you’re just hitting a closed door then you could know where to give up and know that you’ve got to come back to that another time”

“I’m very blunt. ...Every single person who comes back to me says I’ve stopped smoking, but I sometimes take it with a pinch of salt”

“You can give them all the advice but if they perceive it as if you’re telling them what to do well then they won’t do it, which is the nature of the beast”

Fear as a motivator

“And advertising packaging on the thing, that’s scare tactics, isn’t it? ... Well it doesn’t work if you’re a smoker, no, that’s for sure”

“What I find extremely unhelpful are, are graphic detail or images showing you how much harm smoking does to you ... because that causes me anxiety ... And if you’re anxious, your willpower is impaired”

“one of the things I use is there was a television advert a while ago that had the, a child with all this smoke coming out of its nose... we did have a couple of patients... said it shouldn’t be allowed to be shown... but that’s the point”

“If it’s non malignant then we say things like, well it’s lucky it isn’t malignant, isn’t it, but if you keep on smoking next time it probably will be. So we use those things”

Personal experiences

“my sister never got to see her grandchildren and I decided I wanted to get to know my grandchildren”

“I actually gave up smoking because ... I got pneumonia in India and I was quite poorly. ... So maybe having a personal experience of, of what cigarettes can do, I’ve no doubt, it was the cigarettes, obviously, that made me ill”

“the only thing that made me ... gave up was when I was at the park with my son and I got out of breath, and my little one sat on my lap and said, Dad, I don’t want you to die”
Smoking cessation aids

“Well I’ll tell you one thing that I tried and it stopped me for six months and nothing else has ever done that before, I tried one of those like vaping pens”

“If you come along to one of our stop smoking cessation clinic ... you’re four times more likely to stop smoking”

Empowerment

“I don’t get bronchitis or chest infections so often now I, I used to get them ... I’m not out of breath so much”

“I read the, the statistics said that ten years after ... lots of the effects of smoking has sort of been dissipated... not completely but, but almost”

“But I would also like to get some positive message about what I can do for myself and what the enormous difference is if I either cut down, get physically active or do anything to counter it and maybe slowly come off”

“there is a relative quickness of a benefit if you managed to quit. ... [the risk of] heart disease halved within a year and was pretty well back to normal within ten years”

“To give solid examples that it is doable. It’s not easy, but it is doable”

“The best successes I’ve had is when you’ve actually literally really empowered people to make that choice ... when they realised that they didn’t have to be hooked for life, they had it within their power to do it, then it was successful.

“reiterating the message that stopping at any time is ... that it’s never too late to see the benefits of stopping”
3.4 DISCUSSION

This study was the first step towards developing a decision-support information film for people considering LCS. We used qualitative methods to investigate the opinions of LCS-eligible individuals and HCPs involved in the care of patients with lung cancer, focusing on the key features of lung screening, with a focus on benefits and harms. This allows the development of information materials that can be targeted to address the concerns highlighted in a way that is likely to be understood. We found people at risk of lung cancer generally perceived it as an incurable and frightening condition, and smokers were particularly fatalistic. Despite this we found a persistent ‘belief in screening’, an appetite for information, with many participants expressing a ‘right’ to be fully informed, but others cautioning against too much information. False positives and false negatives were the harms that generated the most concern, but most participants were not deterred from screening. Although participants were aware of the harms of smoking, many current smokers perceived other factors as more detrimental to their health. We found that participants preferred the benefits of quitting to be emphasised, and for advice to be delivered in a positive and empowering manner.

Our finding that participants were generally unaware of curative treatment and thought it to be an incurable condition, is supported by previous studies that have shown fear, worry and fatalism about lung cancer [76,153,154] as well as poor perceived benefit from LCS particularly amongst current smokers [76,80]. A few participants were aware of positive outcomes in lung cancer, which may increase as more patients undergo curative treatment, but this finding demonstrates the need to provide information about curative treatment following LCS.

Our finding that participants and HCPs held a belief in screening as something that saves lives and expressed trust in medicine are supported in the literature [155–157]. Thornton et al [156], reported that medical imaging is perceived as highly beneficial, though some contrasting studies have reported a variety of levels of trust of medical systems [158,159]. In the face of this overriding trust in screening, we found a degree of disregard of the harms as either uncommon or insignificant, thus suggesting that providing information about the harms is unlikely to deter most individuals from LCS. Similar findings were reported in a study which demonstrated that individuals placed greater importance on LCS benefits than harms, particularly with respect to decision-making [160].
Participants had varying information preferences, with many feeling they had a ‘right’ to know and to make an informed decision, a finding that is supported by previous studies [141,145,161]. Generally, it was accepted that policy makers should decide who screening should be offered to, and that the decision to participate should ideally be made by individuals with support from a medical professional if required. Other studies have similarly reported that autonomous decision-making with expert guidance is preferable [162,163]. On the other hand, some participants were cynical or overwhelmed by ‘too much information’ and this variability in preferences makes designing decision literature and aids challenging. People have been shown to prefer personalised decision aids [141], and the limitations in literacy found in the at-risk population will make this even more important. For the core information materials we therefore propose that it be not overly burdensome, with signposting to more detailed information.

Our finding that participants wanted to know about the potential harms of screening, even though these would be unlikely to deter them from participating, emphasises the importance of including these in information materials. False negatives appeared to be of greater concern than false positives (in contrast to one other study [164]) and some people found additional investigations reassuring. Those who had encountered false positives and negatives were generally more concerned, suggesting that the hypothetical scenarios presented may understate people’s true reactions. These findings are very useful to inform the emphasis placed on the content of information; with the caveat that individuals do not feel reliant on further testing for reassurance when this is not advised clinically.

Awareness of overdiagnosis was low and the concept challenging to explain. However, most did not find this worrisome, either because they valued cancer treatment in spite of this issue or because they could opt for expectant management. Similar findings have been reported with respect to overdiagnosis in mammography screening [145]. Radiation risk was poorly understood, although not a major deterrent. This is supported by a study investigating patients’ views on tests with ionising radiation, where many wanted to be made aware of the potential harms, however uncertain, while others found the uncertainty disconcerting and unhelpful [156].

Anxiety with indeterminate results, such as pulmonary nodules, was a concern for some participants which is supported by previous studies suggesting uncertainty associated with indeterminate nodules can weigh heavily on patients [165]. Many participants were less
worried by the prospect of interval scanning and felt that the psychological distress could
be reduced by education around the low subsequent risk of developing cancer in the
context of indeterminate pulmonary nodules. Studies have found individual differences in
tolerance of uncertainty, that can affect how people weigh up benefits and risks, and that
better communication that prepares patients for this likelihood, may mitigate poor
tolerance of uncertainty [166] and distress associated with pulmonary nodules [167,168].

Maximising support for smoking cessation in the context of LCS is imperative. Our findings
suggest acknowledging the difficulties of overcoming tobacco addiction, highlighting the
positive messages around the benefits of stopping at any age, and doing so in an
empowering manner. Smokers were generally aware of the harms of smoking and disliked
a ‘preaching’ tone, though many expressed concerns that other environmental harms or
side effects such as weight gain caused by smoking cessation, may pose a greater threat to
their overall health (also previously reported [154,169]) than smoking. Experiences of non-
smokers with lung cancer or smokers who remained free of cancer, further fostered these
beliefs. This could be a response to the cognitive dissonance smokers experience as a
means to reduce the importance of the role their smoking behaviour may play on their risk
of developing cancer [153,170]. Personal experiences such as lung cancer in a relative or
personal ill health were cited as triggers for successfully motivating quitting, as were
smoking cessation aids. Some smokers were unaware of the free help available within the
health service or of how to access this, suggesting information on exactly how to quit is just
as important as why. Acknowledging these findings in the design of any LCS literature may
help reduce the burden of future smoking related disease in this population and enhance
the efficacy and cost-effectiveness of LCS.

3.4.1 Strengths and limitations
Selection bias is possible despite our attempts to mitigate this by purposive sampling of
varying educational backgrounds. Despite this, it is likely that certain viewpoints may have
been missed or under- or over-represented. One focus group only had two participants due
to low turnout, but contrasting viewpoints were still expressed. HCPs were also included in
the study design to provide insights that may have been missed by selection bias, and their
data have significantly contributed to the structure and relative importance of the themes.
Focus group participants discussed screening in the hypothetical sense, and the fact that
screening intentions are recognised to potentially differ from actual screening behaviours
[171] should be considered in the overall interpretation. The HCP interviews were carried out by telephone, which aided recruitment to the study but may have reduced implicit and non-verbal communication from the participants. Finally, the interviewer, who has a background in LCS and is an HCP, may have unintentionally biased the elicited data despite attempts to circumvent this (such as not disclosing her background, knowledge or any personal bias to the participants).

The strengths of the study include the wide range of ethnic, age and educational backgrounds of participants. They were invited by a primary care database search in a similar way to what might occur in the setting of national LCS implementation in the UK, and almost all the participants would qualify for LCS if offered according to the US Preventative Services Task Force recommendations. We believe our findings are likely generalisable to the non-UK population, though another recent US study with similar aims reported themes more focussed on cost and eligibility criteria for screening, highlighting how certain differences in healthcare structure between the US and UK may also be necessary to consider when developing information materials in those contexts [172]. Furthermore, the lack of availability and public knowledge in the UK for LCS has enabled recruitment of a group of individuals with no prior knowledge of LCS and pre-existing external biases.

3.4.2 Conclusions

Addressing the information needs of the whole screening-eligible population in a way that meets diverse information preferences is challenging. Policy makers need to ensure LCS information materials are effective in helping individuals comprehend complex risks and benefits in a way that addresses the concerns and preferences found here. In particular, our findings suggest that decision tools are best presented simply, and should direct participants to more detailed information if preferred, and not replace the support of an HCP. Supporting smoking cessation is vital to enhance the efficacy of LCS, and it should be done in an empowering manner, that highlights the benefits of stopping in older age, and signposts individuals to stop smoking services and support. Future work could be carried out to further explore how we might effectively support individuals with high nicotine dependence to stop smoking, and to test the impact of targeted decision tools on informed decision-making.
Chapter 4. Impact of an information film on informed decision-making in lung cancer screening participants- a nested randomised study

4.1 INTRODUCTION

From the study in the previous chapter and other available literature, we know that people want to be made aware of the harms of lung cancer screening (LCS), and value the ‘right’ to an informed decision [141,173]. We also know that these harms and benefits are poorly understood [141,173] and that failure to communicate information to those with lower health literacy may disengage individuals and adversely affect participation [133]. Techniques to aid the decision-making process are urgently needed. Considering only 1.9% of those eligible for LCS in the US are estimated to have received a low dose computed tomography (LDCT) screen [174], measures to promote understanding whilst empowering individuals to make an informed decision are urgently needed.

Studies have shown that using illustrative materials, such as pictograms and icon arrays have been associated with improving understanding and knowledge around risk perception [135]. The use of graphics and animation have also been noted to enhance knowledge and recall of facts related to the specific health care interventions [136,137]. Several randomised studies evaluating the use of ‘educational videos’ in different health care settings have found this to be an effective medium for enhancing knowledge and understanding without worsening anxiety and conflict [175–179]. Interestingly, one randomised study by Frosch and colleagues in prostate screening compared usual care (i.e. no specific decision tools) with a health care professional (HCP) discussion alone, an educational video alone, and a combination of the video and HCP discussion. The HCP discussion, video and HCP discussion + video groups scored means of 3.9, 3.4 and 3.8 respectively while the usual care group scored a mean of 1.6, suggesting that both the film and HCP discussion more than doubled knowledge [180].

Although a shared decision-making process is mandated for re-imbursement by the US Centers for Medicare and Medicaid Services [142], in the relatively young field of LCS by low dose computed tomography (LDCT), very few studies evaluating decision tools exist. Lau et al, in 2015, tested the impact of a web based interactive decision tool on informed
decision-making (IDM) in a group of smokers and former smokers considering participation in LCS [181]. The authors reported a significant improvement in knowledge and reduction in decisional conflict, though they also acknowledged that access to such a tool may not be equitable in all screening-eligible participants.

Two studies in LCS have evaluated the impact of video on IDM, a medium that may better transcend varying socio-demographic groups [182,183]. Volk et al., developed a film and tested it in 52 participants of a tobacco treatment programme, and noted high acceptability of the film, significant improvement of knowledge scores from baseline to post intervention, and a high level of interest in LCS, though patient demographics and screening attendance data were not described in this brief report [182]. More recently, Reuland and colleagues evaluated their film, also in a single group of 50 participants, many of whom had lower levels of education, and again reported an improvement in knowledge from baseline to post intervention [183]. Interestingly, of 36 participants for whom screening intention and behaviour was collected, 18 intended to participate, and 6 completed an LDCT examination.

The studies with LCS information materials to date, have been limited by small sample sizes and single group designs. We have identified the need for information materials that enhance IDM and that are accessible, engaging and comprehensible to individuals from a variety of demographic and educational backgrounds. No studies exist which evaluate the impact of such information materials on IDM and on uptake to LDCT when compared with a control. Furthermore, validation of such materials, could endorse their use in LCS.

4.1.1 Aims
In this nested randomised study we aimed to evaluate the impact of an information film\(^4\) compared with the information booklet alone, on IDM in individuals considering undergoing an LDCT as part of LCS. The aim of the information materials was to provide some basic, standardised information on LCS and its harms and benefits which could later be supplemented with an HCP discussion to provide an opportunity for the participant to ask questions and obtain further information, a better understanding and assistance with the IDM process if required. The analysis of the qualitative data preceding the development

\(^4\) appended as a DVD to this thesis and also available from: https://www.roycastle.org/lungcancerscreeningguide
of the film is presented in chapter 3, and the development of the film is described in chapter 2.

We hypothesised that the film plus information booklet would enhance objective and subjective knowledge more than the booklet alone. We also aimed to evaluate any additional impact on decisional conflict and attendance to LDCT, and to assess the acceptability of both the booklet and film.

4.2 METHODS

4.2.1 Participants and setting
The present study was a nested randomised study within the Lung Screen Uptake Trial (LSUT), which has been described in chapter 2. Briefly, LSUT invited smokers and former smokers to a ‘lung health check’ appointment (LHC) using one of two sets of invitation materials, which were randomly allocated. The control invitation materials included an information booklet that contained information on the benefits and harms of LCS and which also served as the control intervention in the present study. Those who attended the LHC were invited to be enrolled in LSUT. Between August 2016 and February 2017, LSUT attendees were also invited to participate in the information film study. Individuals who were enrolled, were invited to LDCT if meeting the required risk thresholds for eligibility to LDCT as described in chapter 2.

4.2.2 Study design & interventions
Following obtaining informed consent, participants underwent simple parallel randomisation with a 1:1 individual allocation to each group. A study practitioner, who was restricted to the assignment schedule, carried out the randomisation.

Those allocated to the booklet group were given an information booklet containing information on the LHC, LCS and the LDCT including potential harms. They were allocated 10 minutes to read the booklet, in the presence of a study practitioner. Those allocated to the film + booklet group were similarly given 10 minutes to watch the film on a computer and read the booklet if they wished.
4.2.3 Outcome measures

The primary endpoint was a 10-point objective investigator-designed knowledge assessment (table 4.1) that assessed facts contained in both sets of information materials. Secondary endpoints included a 5-point subjective investigator-designed knowledge assessment (table 4.1), adapted measures from the low literacy decisional conflict scale (DCS) \cite{124} (table 4.1), LDCT completion and feedback on the information materials. Subjective and objective knowledge assessments were carried out at baseline and immediately post intervention for both groups, and other secondary outcomes were assessed at the end of the consultation with the HCP. Demographic and medical history data were also collected as detailed in chapter 2.

4.2.4 Sample size

A sample size of 210 participants was calculated to confer more than 90% power to detect as significant a mean difference of 0.6 between the knowledge scores of the groups, with a standard deviation (sd) of 1.9 (2-sided testing at 5% significance level), as per the power calculation below.

\[
\text{n} = \frac{(Z_{\alpha/2} + Z_b)^2 \times 2 \times (sd)^2}{d^2}
\]

where:

\( n \) = sample size

\( Z_{\alpha/2} \) = critical value of normal distribution for 95% confidence interval and \( p=0.05= 1.96 \)

\( Z_b \) = critical value of normal distribution for power of 90%\( = 1.28 \)

\( sd \) = estimated standard deviation

\( d \) = difference between means of two groups

Based on previous similar studies and a dependant outcome on a continuous scale from 0 to 10, we estimated the effect size to be 0.6, and the sd to be 1.9:

\[
\text{n} = \frac{(1.96 + 1.28)^2 \times 2 \times (1.9^2/0.6^2)}{0.6^2}
\]

\[
\text{n} = 10.5 \times 2 \times 10
\]

\[
\text{n} = 210
\]
Table 4.1 Outcome measures for objective and subjective knowledge items and adapted low literacy decisional conflict scale

**Objective Knowledge questions:**
- Everyone in the population has the same risk of lung cancer
- Lung cancer screening is only for people with symptoms
- All lung cancers found by screening will eventually cause illness and death if they are not treated
- When lung cancer is picked up at screening, the chances of cure are higher than without screening
- Lung cancer screening will pick up every lung cancer
- If there is an unclear result at screening, the chance of having lung cancer is greater than 50%
- The amount of radiation from a screening CT scan is low and is similar to a year’s worth of radiation from the natural environment
- All people with suspected lung cancer on the screening CT scan, who go on to have tests, will have lung cancer
- Research has shown CT screening for lung cancer may save 20% more lives from lung cancer than chest x-rays
- If 100 smokers were screened for lung cancer, how many do you think would be found to have lung cancer? (please write number)

**Subjective Knowledge questions:**
- Do you understand who could benefit from lung cancer screening?
- Do you know your level of risk for lung cancer?
- Do you understand what the aims of lung cancer screening are?
- Do you understand what the risks of lung cancer screening are?
- Do you understand how often the risks of lung cancer screening occur?

**Adapted decisional conflict scale questions:**
- Do you know the benefits of lung cancer screening?
- Do you know the risks and side effects of lung cancer screening?
- Are you clear about which benefits matter most to you?
- Are you clear about which risks and side effects matter most to you?
- Do you have enough support from others to make a choice about whether or not to be screened for lung cancer?
- Are you choosing without pressure from others?
- Do you have enough advice to make a choice about whether or not to be screened for lung cancer?
- Are you clear about whether being screened for lung cancer is the best choice for you?
- Do you feel sure about choosing whether to be screened or not?

4.2.5 Statistical analysis

Descriptive statistics were used to evaluate the demographic characteristics of both groups and the acceptability data. Univariate analyses using the Wilcoxon signed rank test were used to compare knowledge scores pre- and post-intervention. Observations with missing
values were excluded from the analysis. Multivariate analyses, using multiple linear regression and logistic regression, and adjusting for baseline scores, educational level, ethnicity, index of multiple deprivation (IMD) score and smoking duration (as these were factors with clinical and/or statistical relevance), were used to assess between trial-arm differences in overall knowledge scores and individual items for knowledge, DCS and uptake to LDCT between the groups. Data analyses were carried out using STATA v13 & v14.

4.2.6 Ethical approvals

The above study is part of the Lung Screen Uptake Trial (LSUT), which has had ethical approvals granted by the City Road and Hampstead NHS Research Ethics Committee. Further details on approvals and registration can be found in chapter 2.

![Consort diagram for study participants](image-url)
4.3 RESULTS

Table 4.2 Participant characteristics by group (% totals may not sum up due to rounding, or missing data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups N (%) or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention, n=120 (Film + Booklet)</td>
</tr>
<tr>
<td>Age (in years)</td>
<td></td>
</tr>
<tr>
<td>60 - 63</td>
<td>40 (33.33)</td>
</tr>
<tr>
<td>64 - 67</td>
<td>33 (27.50)</td>
</tr>
<tr>
<td>68 - 71</td>
<td>33 (27.50)</td>
</tr>
<tr>
<td>72 - 76</td>
<td>14 (11.67)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65 (54.17)</td>
</tr>
<tr>
<td>Male</td>
<td>54 (45.83)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>98 (81.67)</td>
</tr>
<tr>
<td>Black/ African/ Caribbean</td>
<td>13 (10.83)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2.50)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5.00)</td>
</tr>
<tr>
<td>Level of Education</td>
<td></td>
</tr>
<tr>
<td>At or before 15</td>
<td>61 (50.83)</td>
</tr>
<tr>
<td>CSEs, O-levels or equivalent</td>
<td>12 (10.00)</td>
</tr>
<tr>
<td>A-levels or equivalent</td>
<td>20 (16.67)</td>
</tr>
<tr>
<td>Further education</td>
<td>6 (5.00)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>12 (10.00)</td>
</tr>
<tr>
<td>Further higher degree</td>
<td>8 (6.67)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.83)</td>
</tr>
<tr>
<td>Index of Multiple Deprivation (IMD) quintile</td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>69 (57.50)</td>
</tr>
<tr>
<td>2</td>
<td>35 (29.17)</td>
</tr>
<tr>
<td>3</td>
<td>3 (2.50)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>80 (66.7)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>40 (33.3.)</td>
</tr>
<tr>
<td>Average cig smoking (cig/day), median</td>
<td>16 (10,20)</td>
</tr>
<tr>
<td>Number of pack-years, median</td>
<td>38 (21,50)</td>
</tr>
<tr>
<td>Years smoked, median</td>
<td>47 (43,52)</td>
</tr>
<tr>
<td>Research Site</td>
<td></td>
</tr>
<tr>
<td>University College Hospital London</td>
<td>45 (37.5)</td>
</tr>
<tr>
<td>Homerton University Hospital</td>
<td>75 (62.5)</td>
</tr>
<tr>
<td>Invitation group (from primary randomisation in LSUT)</td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>52 (43.33)</td>
</tr>
<tr>
<td>Group B</td>
<td>68 (56.67)</td>
</tr>
</tbody>
</table>
252 LSUT participants were invited to take part in the present sub-study. 246 participants agreed to participate and were randomised. 17 participants had incomplete baseline data and so 229 participants were included in the final analysis (figure 4.1). The demographics of the study participants are reported in table 4.2.

There was an increase in objective knowledge scores in both groups, with a change in median scores from 5/10 to 8/10, and 5/10 to 7/10 in the film + booklet and booklet alone groups respectively (both \( p<0.001 \)). There was also an increase in subjective knowledge scores in both groups (change in median scores from 4/5 to 5/5 in both groups, \( p<0.001 \)) (figure 4.2). The changes in mean scores are presented as they demonstrate the group differences, but should be interpreted with caution given the discrete rather than continuous nature of the scores. Mean objective knowledge scores increased by 2.16 (s.d. 1.8) and 1.84 (s.d. 1.9) in the film + booklet and booklet alone groups respectively. Mean subjective knowledge increased by 0.92 (s.d. 1.0) and 0.55 (s.d. 1.1) in the film + booklet and booklet alone groups respectively.

In a multivariate analysis adjusted for age, education, ethnicity, years smoked and index of multiple deprivation (IMD) score, the information film group showed a greater increase in post-intervention objective (\( p=0.007 \)) and subjective (\( p=0.019 \)) knowledge scores (figure 4.2 and table 4.3).

Of all the individual items in the subjective and objective knowledge questionnaires, only two items from the objective knowledge questions showed any statistically significant difference between the two groups. These two items reflected a greater improvement in response in the film + booklet group compared with the booklet alone group and referred to understanding the concept that an ‘unclear’ result at screening (i.e. an indeterminate pulmonary nodule) did not mean a high risk of cancer, and that the amount of radiation in an LDCT scan is equivalent to one year of background radiation in the UK (table 4.4).
Figure 4.2 Knowledge scores by intervention group: a) objective knowledge at baseline; b) objective knowledge post-intervention; c) subjective knowledge at baseline; d) subjective knowledge post-intervention
Table 4.3 Multivariate analysis table for objective and subjective knowledge. Values expressed as P-value and confidence interval (CI) of regression coefficient. [* p<0.05]

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression of post-intervention objective score with different variables n= 196 P (confidence interval of regression coefficient)</th>
<th>Regression of post-intervention subjective score with different variables n= 196 P (confidence interval of regression coefficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intervention score</td>
<td>0.000* (0.434-0.688)</td>
<td>0.000* (0.324 – 0.562)</td>
</tr>
<tr>
<td>Intervention group (film vs. booklet)</td>
<td>0.007* (0.172 – (1.076)</td>
<td>0.018* (0.054 – 0.578)</td>
</tr>
<tr>
<td>Age</td>
<td>0.107 (-0.100 – 0.010)</td>
<td>0.551 (-0.041 – 0.022)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.001* (-0.117 – -0.012)</td>
<td>0.785 (-0.033 – 0.025)</td>
</tr>
<tr>
<td>Educational level</td>
<td>0.114 (0.087 – 0.357)</td>
<td>0.871 (-0.071 – 0.083)</td>
</tr>
<tr>
<td>Years smoked</td>
<td>0.073 (-0.052 – 0.006)</td>
<td>0.955 (-0.017 – 0.016)</td>
</tr>
<tr>
<td>Index of multiple deprivation index</td>
<td>0.000* (-0.044 – 0.002)</td>
<td>0.016* (-0.030 –0.003)</td>
</tr>
</tbody>
</table>
Table 4.4 Logistic regression for difference between groups in individual objective and subjective knowledge items. [* p<0.05]

<table>
<thead>
<tr>
<th>Item question</th>
<th>95% confidence intervals for odds ratio (booklet alone group as reference)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Everyone in the population has the same risk of lung cancer</td>
<td>-1.68- 0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>2. Lung cancer screening is only for people with symptoms</td>
<td>-0.44- 0.88</td>
<td>0.5</td>
</tr>
<tr>
<td>3. All lung cancers found by screening will eventually cause illness and death if they are not treated</td>
<td>-0.40- 0.86</td>
<td>0.47</td>
</tr>
<tr>
<td>4. When lung cancer is picked up at screening, the chances of cure are higher than without screening</td>
<td>-0.86- 1.19</td>
<td>0.75</td>
</tr>
<tr>
<td>5. Lung cancer screening will pick up every lung cancer</td>
<td>-0.24- 0.85</td>
<td>0.25</td>
</tr>
<tr>
<td>6. If there is an unclear result at screening, the chance of having lung cancer is greater than 50%</td>
<td>0.12- 1.21</td>
<td>0.016*</td>
</tr>
<tr>
<td>7. The amount of radiation from a screening CT scan is low and is similar to a year’s worth of radiation from the natural environment</td>
<td>0.05- 1.18</td>
<td>0.031*</td>
</tr>
<tr>
<td>8. All people with suspected lung cancer on the screening CT scan, who go on to have tests, will have lung cancer</td>
<td>-0.54- 0.66</td>
<td>0.84</td>
</tr>
<tr>
<td>9. Research has shown CT screening for lung cancer may save 20% more lives from lung cancer than chest x-rays</td>
<td>-0.32- 1.07</td>
<td>0.29</td>
</tr>
<tr>
<td>10. If 100 smokers are screened for lung cancer, how many do you think would be found to have lung cancer?</td>
<td>-0.61- 0.46</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Subjective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Do you understand who could benefit from lung cancer screening?</td>
<td>-0.40- 2.79</td>
<td>0.14</td>
</tr>
<tr>
<td>2. Do you know your level of risk for lung cancer?</td>
<td>-0.55- 0.79</td>
<td>0.34</td>
</tr>
<tr>
<td>3. Do you understand what the aims of lung cancer screening are?</td>
<td>-0.39- 1.53</td>
<td>0.24</td>
</tr>
<tr>
<td>4. Do you understand what the risks of lung cancer screening are?</td>
<td>-0.19- 1.00</td>
<td>0.18</td>
</tr>
<tr>
<td>5. Do you understand how often the risks of lung cancer screening occur?</td>
<td>-0.26- 0.84</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Figure 4.3 The frequency histograms of the adapted DCS by group
Figure 4.4 Acceptability of film and information booklet
Because the study was nested within LSUT, half the participants in both groups (randomly allocated) would have seen the control booklet prior to arriving at the LHC. A sensitivity analysis was therefore carried out by repeating the multivariate analysis, adjusting for exposure to the control booklet prior to the LHC. This revealed that prior exposure to the information booklet did not have significant impact on knowledge scores of the group, objective (p=0.33) and subjective (p=0.11).

The adapted low literacy DCS score was high (reflecting low decisional conflict) in both groups with a median of 9/9 (IQR 9,9) and mean of 8.5 (s.d. 1.25) in the film + booklet group; and a median of 9/9 (IQR 8,9) and mean of 8.24 (s.d. 1.49) in the booklet alone group (figure 4.3). (Again, the mean scores need to be interpreted with caution given the discrete, rather than continuous nature of the scores.) The film + booklet group had higher adapted DCS than the booklet alone group in the adjusted multivariate analysis (p=0.007) reflecting greater decision certainty in the film + booklet group. A Cronbach’s test for internal validity of the adapted scale showed acceptable internal consistency (α=0.78). A logistic regression showed no significant group differences in LDCT completion by intervention group (p=0.66).

The film and information booklet were both well accepted and felt to be useful, comprehensible and contain the correct level of information, though more participants watched all the film than read all the booklet (100% vs. 62%, p<0.001), and more understood all or most of the film than booklet (96.5% vs. 85.9%, p<0.001). Additionally, participants generally felt the film to be memorable, fairly balanced and helpful, and 79.4% would have watched the film if it had been available to them before the LHC (figure 4.4).

### 4.4 DISCUSSION

We report the findings of, what is to our knowledge, the first randomised study evaluating the impact of a novel decision tool on IDM in LCS. In this nested study of 229 participants from a larger cohort of individuals invited to a LHC in the UK by their GP, an information film plus supporting information booklet improved objective and subjective knowledge, and decisional conflict scores more than the booklet alone, with no significant impact on numbers of individuals completing a LDCT examination; both decision tools were well received.
Our findings that baseline objective knowledge was poor (median 5/10) is in keeping with other studies [141,183], while subjective knowledge was better (median 3/5) suggesting that individuals perceptions of their knowledge about LCS may be optimistic. Both groups significantly improved their knowledge scores after exposure to the decision tools, which demonstrates that use of such tools enhances understanding of LCS, consistent with other single group studies of decision tools in LCS [182–185]. Our findings support the use of the film, which contained graphics and animation as an engaging and effective means to enhance understanding. The film was designed to be used as an adjunct to an HCP consultation, whose role in shared decision-making is vital. Most conventional LCS information materials are written, but reliance on written communication materials have been noted to be problematic [133,134]. Web-based tools can be effective and personalized to the individuals’ needs, but may be less accessible to older or lower SES populations who are the target for LCS. This study has shown a significant impact of the information film over the booklet alone on knowledge and decisional conflict, in a population that was eligible for LDCT screening in a non-hypothetical scenario, making the results directly generalisable for the target population.

The film had a greater impact than the booklet, on two aspects of specific knowledge: the significance of radiation exposure from LDCT and the fact that an ‘unclear’ result (signifying an indeterminate pulmonary nodule) carries a low overall risk of malignancy. This is of value, as better understanding of these concepts may in turn have an impact on the psychological responses to LCS and indeterminate (termed false positives in NLST) results [186,187]. Certainly, improved communication has been reported to be associated with improved adherence to CT surveillance, and reduced distress in the context of non-LCS-detected pulmonary nodules [167] and it is imperative that we translate these findings into any developed information materials in LCS.

LCS has been proven to be an effective intervention that reduced lung cancer-specific mortality by 20% [17] and has been recommended by the USPSTF in 2013 [33]. Despite this, uptake to LDCT in the US has been low with 1.9% of the 7.6 million eligible smokers having undergone a LDCT examination as part of LCS according to a recent report from data from the American College of Radiology LCS registry [174]. Whilst the likely barriers to uptake are multifactorial and complex [76], it is vital that we are able to communicate information on the benefits and harms of LCS in a manner that is palatable to those of varying educational backgrounds, and without overstating the harms or benefits. Indeed,
participants in our qualitative work advocated emphasis on the benefits of LCS (chapter 3). Individuals have been noted to have a desire to hear an ‘expert opinion’ [162] or ‘clinician guidance’ [163] when making medical and screening related decisions and it is important that information materials take notice of this evidence.

The data from our study shows that the film was well received, and generally participants found it to be helpful and balanced, although a small proportion found it to be biased towards screening and unhelpful for decision-making. We did not collect further data to understand why people felt this way, but the high DCS scores (median 9/9 in both groups) suggest people were ultimately happy with the decision they made. The decision of whether or not to be screened and the DCS questionnaire both took place after the HCP discussion at the end of the consultation, and so were likely to have been influenced by the HCP discussion. The low decisional conflict observed suggest participants were ultimately happy with their decision, and re-enforces that the film should not replace the HCP discussion, as some participants may desire more detailed information or help relating the information to their values. The ultimate aim for IDM is for the individual to possess the relevant information on harms, benefits and the options available to them, and then to be able to process that information to make a decision that is in line with their personal beliefs and values [117]. The film can aid this process and the HCP can further help individuals arrive at an informed decision where required.

### 4.4.1 Strengths and limitations

The information film is not a decision aid as it does not meet all the criteria on the International Patient Decision Aid Standards (IPDAS) checklist which is a detailed list of specifications that we were unable to comprehensively address in a short film [140]. Our intention was for the film to be used to facilitate the HCP in their discussion, and not to replace it. Secondly, we used an adapted version of the low literacy DCS scale [124], which has not been validated but showed acceptable internal validity. The likely impact of the information materials is likely to be understated, as a ceiling effect was observed with both the DCS and the subjective knowledge scores. Thirdly, both the interventions were delivered in the presence of a nurse and so did not imitate a real-world setting where there may be variability in the amount of decision tool watched or read. We wanted to ensure consistency between groups and so opted for this study design. The study is strengthened by the likely generalisability of the results to the target population, given the demographics
of the study participants and their method of invitation. This was similar to several small scale UK LCS pilots, where people are invited by their GP to a LHC or similar and invited to LDCT using similar eligibility criteria [39,40].

Future work could involve development of the tool to have a ‘values clarification’ element, which could help individuals further with IDM, and to assess longer-term knowledge and decisional conflict and satisfaction. Making the film available to people prior to attendance to LHC, and re-evaluating its impact on IDM and uptake to LDCT would also be worthwhile. The research team have been approached by a number of centres in the UK and US for use in their local LCS projects, and the strength of this medium is that it can be easily adapted for local needs and preferences.

4.4.2 Conclusions

This nested randomised study has demonstrated that the developed information film has positively impacted IDM more than the booklet alone without impacting uptake to LDCT. We propose that use of the film as an adjunct to the HCP role in shared decision-making, standardises and enhances knowledge about LCS benefits and harms, and improves decisional conflict.
PART B

Optimising benefits and harms
Chapter 5. Is lung cancer screening an opportunity to reduce cardiovascular mortality?

5.1 INTRODUCTION

In Part A we focussed on the importance of communicating the benefits and harms to individuals considering taking part in LCS. In Part B we will address important considerations around some of the benefits and harms from LCS.

In the National Lung Screening Trial (NLST), lung cancer screening (LCS) by low dose computed tomography (LDCT), improved lung cancer-specific mortality by 20% and all-cause mortality by 6.7% [17]. Unsurprisingly, following the reduction in lung cancer death in the LDCT arm, and given the age and smoking history of the cohort, Coronary Heart Disease (CHD) was responsible for the majority of deaths in the LDCT arm [17]. In the UK, CHD accounts for the greatest number of deaths annually [188], and given both lung cancer and CHD risk are associated with increasing age and smoking history, the LCS population is at a disproportionately high risk of CHD-related morbidity and mortality.

Currently, primary prevention of CHD is recommended in terms of adequate control of any diabetes and hypertension and the use of statins, even in the presence of normal serum cholesterol levels. Various algorithms for predicting cardiovascular disease (CVD) risk exist. The most commonly used are the Framingham [189] and QRISK2 scores [190] (see table 5.1), and the latter is recommended for use in the UK. The National Institute for Health and Care Excellence (NICE) guidelines for primary prevention of cardiovascular disease state that those who have a ≥10% CVD risk as calculated by the QRISK2, should be commenced on atorvastatin 20mg per day [191].

A non-invasive means of detecting CHD is by quantification of CT coronary calcium. Coronary calcium is a marker of atherosclerosis, with almost no false positives although one drawback is that its presence is not always associated with luminal stenosis or obstruction [192]. The Coronary Artery Calcium (CAC) score or Agatston score, on electrocardiography (ECG)-gated CT has been noted to correlate with the volume of plaque seen at post mortem, though non-calcified plaques, (most commonly present in younger patients) can rupture, and are not always detected by coronary CT angiography [192]. Nevertheless, a
CAC score of 0 has been reported to reliably predict a very low risk of events, while increasing CAC scores have been noted to be associated with a stepwise increase in risk of cardiac events [192–195].

**Table 5.1 Cardiovascular risk assessment tools: QRISK2 and Framingham risk. (HDL= high density lipoprotein, LDL= low density lipoprotein)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>QRISK2</th>
<th>Framingham risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gender</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Townsend score</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cholesterol/ HDL ratio</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH of angina/ MI in 1st degree relative aged &lt;60</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease stage IV or V</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>On blood pressure treatment</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Formal CAC scoring is a complex and time-consuming addition to the radiology reporting workload in the context of potential LCS programmes. However, numerous studies have shown that CAC assessments on ungated LDCT scans are comparable to formal ECG-gated CAC measurements [104,196–198]. A systematic review of studies comparing conventional CAC scoring to ungated LDCT CAC assessments, suggested accuracies are comparable, with good agreement between the methods. Direct comparison between these methods has demonstrated a variation of false-negative rates with ungated scans from 2.3 to 14%, and underestimation of high CAC in 0 to 23.4% of cases [199]. However, these discrepancies may not be of clinical significance if undetected CAC in this group is not translated into cardiovascular events, and the high-risk individuals are appropriately managed.

Further studies evaluating either formal Agatston scoring or a visual CAC score in the LCS cohort have been carried out, and have shown CAC on LDCT to be a reliable predictor of cardiovascular events. Importantly, very low event rates have been reported in the CAC=0 group, suggesting there may be a utility for reporting a visual absence of CAC in the LCS population; although the definitions of “event” and median follow-up durations of these studies were variable [103,200–204] (table 5.2).
<table>
<thead>
<tr>
<th>Study</th>
<th>Cardiovascular endpoint</th>
<th>Follow up duration</th>
<th>Assessment method of CAC</th>
<th>CAC cut offs</th>
<th>Event rate, n (%)</th>
<th>Adjusted HR (CI)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shemesh et al, 2010[200]</td>
<td>Cardiovascular death (n=193)</td>
<td>72.3 months (=6 years)</td>
<td>Non-gated LDCT scan 3 categories of CAC visually assessed CAC</td>
<td>CAC 0 CAC 1-3 CAC 4-12</td>
<td>43/3573 (1.2) 66/3569 (1.8) 84/1640 (5.1)</td>
<td>1.0 (0.7-1.5) 2.1 (1.4-3.1)</td>
<td>IELCAP LCS study</td>
</tr>
<tr>
<td>Sverzellati et al, 2012[201]</td>
<td>Fatal and non-fatal cardiovascular event (n=33)</td>
<td>36 months (=3 years)</td>
<td>Non gated LDCT Formal Agatston scoring</td>
<td>CAC &lt;400 CAC &gt;400</td>
<td>26/1079 (2.4) 7/80 (8.8)</td>
<td>1.0 (0.7-1.5) 2.1 (1.4-3.1)</td>
<td>Multi-centrist Italian Lung Detection (MILD) LCS study</td>
</tr>
<tr>
<td>Jacobs et al, 2012[202]</td>
<td>Fatal and non-fatal cardiovascular event (n=127)</td>
<td>9.5 months (&lt;1 year)</td>
<td>Non-gated LDCT Formal Agatston scoring</td>
<td>CAC 0 CAC 1-100 CAC 101-1000 CAC &gt; 1000</td>
<td>10/1814 (0.6) 27/2191 (1.2) 32/2267 (1.4) 58/1285 (4.5)</td>
<td>1.8 (0.8-3.9) 1.9 (0.9-4.2) 5.3 (2.5-11.6)</td>
<td>NELSON LCS study</td>
</tr>
<tr>
<td>Takx et al, 2014[203]</td>
<td>Fatal and non-fatal cardiovascular event (n=186)</td>
<td>2.9 years</td>
<td>Non-gated LDCT Formal Agatston scoring</td>
<td>CAC 0 CAC 1-10 CAC 11-100 CAC 101-400 CAC &gt; 400</td>
<td>CAC=0: Age adjusted 3 year CV event rate of 6.1/1000 Other categories: NR</td>
<td>3.39 (1.2-9.59) 6.52 (2.73-15.6) 6.58 (2.75-15.78) 12.58 (5.42-29.16)</td>
<td>NELSON LCS study</td>
</tr>
<tr>
<td>Rasmussen et al, 2015[204]</td>
<td>Cardiovascular death (n=19)</td>
<td>85 months (=7 years)</td>
<td>Non-gated LDCT Formal Agatston scoring</td>
<td>CAC 0 CAC 1-400 CAC&gt;400</td>
<td>5/1035 (0.48) 9/778 (1.2) 5/132 (3.8)</td>
<td>1.6 (0.5-4.9) 3.8 (1.0-15)</td>
<td>Danish LCS study</td>
</tr>
<tr>
<td>Chiles et al, 2015[103]</td>
<td>CHD death (n=171)</td>
<td>5-7 years</td>
<td>Non gated CT, 4 categories of visually assessed CAC</td>
<td>CAC none CAC mild CAC medium CAC heavy</td>
<td>18/387 (4.7) 64/628 (10.1) 40/229 (17.5) 49/198 (24.7)</td>
<td>2.09 (1.3-4.16) 3.86 (2.02-8.2) 6.95 (3.73-15.67)</td>
<td>NLST LCS study</td>
</tr>
</tbody>
</table>
There may be an opportunity to combine cardiovascular risk assessment with lung cancer risk assessment in order to improve the cost-effectiveness of LCS programmes and further improve the all-cause mortality benefit from screening. It is currently unclear whether there is a need for further cardiovascular risk assessment within the LCS-eligible population and whether the grading of visual CAC on LDCT would add any value to existing primary prevention measures.

5.1.1 Aims
In the present study we aimed to determine the prevalence and importance of coronary calcium and cardiovascular risk in asymptomatic LCS participants. In particular, we aimed to determine: a) the prevalence and extent of coronary calcium in LCS participants using a quantification system considered to be an acceptable alternative to Agatston scoring; b) participant risk estimates using QRISK2 and how this is distributed across CAC scores and finally c) the proportion of statin use and non-use among those with both high and low risk estimates.

5.2 METHODS

5.2.1 Study design, participants and setting
This prospective observational cohort study is embedded within the Lung Screen Uptake Trial (LSUT), the methods for which are described in chapter 2 and previously [129]. Briefly, individuals at high-risk of lung cancer were invited by their general practitioner (GP) for a ‘lung health check’ (LHC) at one of two London hospitals between November 2015 and July 2017. Individuals attending the LHC were invited to participate in the study, and those meeting the required lung cancer risk threshold (as described in chapter 2) were invited to have an LDCT on the same day.

Very brief smoking cessation advice was given to the participant if they were still smoking at the LHC, and participants were randomised to receive details of their local smoking cessation clinic or be proactively referred to the smoking cessation clinic. Participants were given written information on the potential benefits and harms of LCS and following a discussion with the study practitioner, were asked to give informed consent to have an LDCT as part of LCS.
5.2.3 Data collection

Data were prospectively collected by a study practitioner at the LHC. Self-reported history of demographic and smoking variables (as described in chapter 2), cardiovascular and lung cancer risk factors (including all those contained in the QRISK2), history of CHD, and number of GP attendances in the past year were recorded. Hand-held spirometry, height, weight, blood pressure and MRC were also recorded at the LHC.

5.2.4 LDCT acquisition

Participants undertook the examination via a sixteen channel or higher multi-detector, non-ECG-voltage-gated CT without the administration of intravenous contrast. Thin detector collimation (0.5 mm) was used. Images were reconstructed at 0.5 -1.0 mm section thickness using standard soft tissue and lung algorithms. Radiation exposures were as low as possible whilst maintaining good image quality. For further details see section 2.1.9.

5.2.5 Outcome measures

QRISK2 scores were calculated by ClinRisk Ltd using their QRISK2-2017 Java batch processor. These are estimated QRISK2 scores, as we did not have serum cholesterol values for participants as part of the study, and the batch processor substitutes an age-sex-ethnicity estimate of cholesterol/HDL ratio when this is presented as missing. Three patients had missing systolic blood pressure values hence the batch processor substituted an age-sex-ethnicity estimate of systolic blood pressure for these participants. Self-reported use of statins and history of chronic kidney disease (without specifying the stage of disease) was recorded.

The LDCT scans were single-read by a team of radiologists with expertise in thoracic CT reporting, and experience ranging from 5 to 28 years. Reports included recording of a visual grading of coronary calcium as defined by Chiles et al [103]. The grades of none, mild, medium or heavy that were used, have demonstrated good correlation with formal Agatston scores at cut offs of 0, 1-100, 100-300 and >300.

5.2.6 Sample size & statistical analysis

Sample size was based on the primary behavioural research question and has been discussed in chapter 2 [129]. Patients without an LDCT, with known IHD or missing QRISK2
scores were excluded from the analysis. Individuals were categorised by QRISK2 scores into categories of low (0-10%), moderate (10-20%) and high risk (20%) of CVD.

Descriptive statistics were used to determine the demographic and clinical characteristics of individuals in each QRISK2 category. The distribution of QRISK2 scores by CAC grade, and prevalence of CAC by grade in each QRISK2 category was summarized and compared. Associations between QRISK2 score and CAC grade were assessed using chi square and unadjusted multivariate ordinal logistic regression analyses. Next, the prevalence of self-reported statin use was compared by QRISK2 category and bivariate associations between statin use and various clinical and demographic variables were assessed using chi square analysis. A multivariate logic regression model was used to assess independence in these associations, adjusting for age, Index of Multiple Deprivation (IMD), Body Mass Index (BMI), history of hypertension, history of diabetes and family history of CHD. Missing values were excluded from the analyses (and were present for only one variable, IMD). Likelihood ratio testing was used for tests of significance.

5.2.7 Study registration, funding and ethical approvals

The above study is part of the Lung Screen Uptake Trial (LSUT), which has had ethical approvals granted by the City Road and Hampstead NHS Research Ethics Committee. Further details on approvals and registration can be found in chapter 2.
5.3 RESULTS

From 2012 potentially eligible individuals identified in the primary care records of 16 GP practices, 1005 attended for an LHC and were recruited into the study. Of those, 770 underwent a baseline LDCT examination, though a further 85 participants were excluded due to a history of self reported CHD and 5 due to missing QRISK2 score data, leaving a total of 680 participants in the final analysis (Figure 5.1). Participant characteristics by QRISK2 category are as described in table 5.3.

Figure 5.1 Flow diagram for study participants
Table 5.3 Participant characteristics by QRISK2 category (% totals may not sum up due to rounding)

<table>
<thead>
<tr>
<th>Variables</th>
<th>QRISK2 Score category: n(#) or median (IQR)*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10% n=12</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>10-20% n=192</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20% n=476</td>
<td></td>
</tr>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 – 63</td>
<td>10 (83.3)</td>
<td>225</td>
</tr>
<tr>
<td>64 – 67</td>
<td>2 (16.7)</td>
<td>224</td>
</tr>
<tr>
<td>68 – 71</td>
<td>0 (0)</td>
<td>147</td>
</tr>
<tr>
<td>72 – 76</td>
<td>0 (0)</td>
<td>84</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (100)</td>
<td>261</td>
</tr>
<tr>
<td>Male</td>
<td>0 (0)</td>
<td>419</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (91.7)</td>
<td>560</td>
</tr>
<tr>
<td>Black/ African/ Caribbean</td>
<td>0 (0)</td>
<td>73</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>1 (8.3)</td>
<td>41</td>
</tr>
<tr>
<td>Level of Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At or before 15</td>
<td>5 (41.7)</td>
<td>357</td>
</tr>
<tr>
<td>CSes, O-levels or equivalent</td>
<td>2 (16.7)</td>
<td>65</td>
</tr>
<tr>
<td>A-levels or equivalent</td>
<td>1 (8.3)</td>
<td>67</td>
</tr>
<tr>
<td>Further education</td>
<td>0 (0)</td>
<td>33</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>3 (25.0)</td>
<td>81</td>
</tr>
<tr>
<td>Further higher degree</td>
<td>1 (8.3)</td>
<td>64</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>13</td>
</tr>
<tr>
<td>Index of Multiple Deprivation (IMD) quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>5 (41.7)</td>
<td>369</td>
</tr>
<tr>
<td>2</td>
<td>5 (41.7)</td>
<td>230</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>missing</td>
<td>12 (16.7)</td>
<td>64</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>2 (16.7)</td>
<td>490</td>
</tr>
<tr>
<td>Former smoker</td>
<td>10 (83.3)</td>
<td>190</td>
</tr>
<tr>
<td>Years smoked (years)</td>
<td>45 (42-27)</td>
<td>49</td>
</tr>
<tr>
<td>Average smoking intensity (cigs/day)</td>
<td>10 (7-18)</td>
<td>20</td>
</tr>
<tr>
<td>Pack years</td>
<td>25 (15, 37)</td>
<td>41</td>
</tr>
<tr>
<td>Lung cancer risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLCO (% 6 year risk)</td>
<td>1.2 (0.5, 1.8)</td>
<td>4.4</td>
</tr>
<tr>
<td>LLP (% 5 year risk)</td>
<td>3.1 (2.5, 4.9)</td>
<td>6.0</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (l/min)</td>
<td>2.0 (1.89, 2.33)</td>
<td>2.02</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>89 (78.5, 106)</td>
<td>81</td>
</tr>
<tr>
<td>FEV/FVC (%)</td>
<td>66 (62, 77)</td>
<td>67</td>
</tr>
</tbody>
</table>
Table 5.3 (continued) Participant characteristics by QRISK2 category (% totals may not sum up due to rounding)

<table>
<thead>
<tr>
<th>Variables</th>
<th>QRISK2 Score category: n(%) or median (IQR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10% n=12</td>
</tr>
<tr>
<td><strong>Other cardiovascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>On hypertensive treatment</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Family History of heart disease</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>0 (0)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.9 (19.8, 30.2)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>114 (100, 121)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73 (70, 75)</td>
</tr>
</tbody>
</table>

Figure 5.2 QRISK2 score distribution for each visually determined CAC grade on LDCT. The horizontal dotted line represents the threshold for initiation of statin therapy for primary prevention (10%)
The range of QRISK2 scores within each CAC group was wide (figure 5.2), with a trend to median QRISK2 score increasing with CAC grade. This association was supported by increasing odds ratios for each increasing QRISK2 category (table 5.4).

Based on QRISK2 alone, 98% of individuals had a QRISK2 of ≥10%, and were therefore eligible for statin primary prevention (table 5.5), although more than half (54.7%) the participants with a QRISK2 score of 10-20%, had a no CAC visible. Of those that did qualify for a statin based on their QRISK2 score, 56.8% did not self-report a history of statin use, with this number being even higher (76.6%) in the 10-20% QRISK2 category (table 5.6). 90% of participants who did not report statin use, reported they had seen their GP ≥1 times in the past year. In the multivariate analysis, statin use was independently associated with age, history of hypertension, diabetes, and BMI (table 5.7). Several variables including gender, smoking status, years smoked, years quit, pack-years, systolic BP, number of GP visits in the past year and education level were not found to be associated with statin use in the univariate analysis or after adjusting for other variables.

Table 5.4 Unadjusted ordinal logistic regression for association between LDCT CAC grade and QRISK2 category

<table>
<thead>
<tr>
<th>QRISK2 category</th>
<th>OR (CI) (unadjusted)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>10-20%</td>
<td>4.29 (0.93-19.88)</td>
<td>0.062</td>
</tr>
<tr>
<td>&gt;=20%</td>
<td>12.29 (2.69-56.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 5.5 Prevalence of CAC on LDCT by QRISK2 score category

<table>
<thead>
<tr>
<th>QRISK2 risk category</th>
<th>None</th>
<th>Visual CAC grade, n(%)</th>
<th>Heavy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>10 (83.3)</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td>12 (1.8)</td>
</tr>
<tr>
<td>10-20%</td>
<td>105 (54.7)</td>
<td>58 (30.2)</td>
<td>24 (12.5)</td>
<td>192 (28.2)</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>144 (30.3)</td>
<td>167 (35.1)</td>
<td>121 (25.4)</td>
<td>476 (70.0)</td>
</tr>
<tr>
<td>Total</td>
<td>259</td>
<td>227</td>
<td>145</td>
<td>49</td>
</tr>
</tbody>
</table>
Table 5.6 Number of individuals qualifying for a statin based on QRISK2 alone compared with self-reported history of statin use, and with self-reported number of GP attendances in the past year.

<table>
<thead>
<tr>
<th>QRISK2 score category, n (% of row)</th>
<th>On statin</th>
<th>Not on statin</th>
<th>Not on statin, when indicated by QRISK2 score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>0 (0)</td>
<td>12 (100)</td>
<td>0</td>
</tr>
<tr>
<td>10-20%</td>
<td>45 (23.4)</td>
<td>147 (76.6)</td>
<td>76.6</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>237 (49.8)</td>
<td>239 (50.2)</td>
<td>50.2</td>
</tr>
<tr>
<td>Total</td>
<td>282</td>
<td>386</td>
<td>56.8</td>
</tr>
</tbody>
</table>

Number of GP attendances in past year, n (% of column)

<table>
<thead>
<tr>
<th>Number of GP attendances in past year</th>
<th>0</th>
<th>1-5</th>
<th>&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 (3.6)</td>
<td>47 (11.8)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>211 (74.8)</td>
<td>285 (71.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>61 (21.6)</td>
<td>66 (16.4)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.7 Univariable and multivariable logistic regression model for history of self-reported statin use

<table>
<thead>
<tr>
<th></th>
<th>OR (CI) (unadjusted)</th>
<th>P value</th>
<th>OR (CI) (adjusted)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-63</td>
<td>1</td>
<td></td>
<td>1.29 (0.88- 1.90)</td>
<td>0.0010</td>
</tr>
<tr>
<td>64-67</td>
<td>2.08 (1.36- 3.18)</td>
<td></td>
<td>2.08 (1.36- 3.18)</td>
<td></td>
</tr>
<tr>
<td>68-71</td>
<td>2.20 (1.32- 3.66)</td>
<td></td>
<td>2.20 (1.32- 3.66)</td>
<td></td>
</tr>
<tr>
<td>72-76</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>0.76 (0.54-1.06)</td>
<td>0.1113</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.19 (0.87- 1.61)</td>
<td></td>
<td>1.19 (0.87- 1.61)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1</td>
<td></td>
<td>1.31 (0.93- 1.87)</td>
<td>0.1217</td>
</tr>
<tr>
<td>Current</td>
<td>0.76 (0.54-1.06)</td>
<td></td>
<td>0.76 (0.54-1.06)</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.26 (3.03-5.96)</td>
<td>&lt;0.001</td>
<td>4.26 (3.03-5.96)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13.55 (6.85- 26.8)</td>
<td>&lt;0.001</td>
<td>13.55 (6.85- 26.8)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>0.91 (0.27-3.02)</td>
<td>&lt;0.001</td>
<td>0.91 (0.27-3.02)</td>
<td></td>
</tr>
<tr>
<td>18.5-25</td>
<td>1.64 (1.14- 2.36)</td>
<td></td>
<td>1.64 (1.14- 2.36)</td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
5.4 DISCUSSION

In this prospective observational study in a cohort of individuals undergoing an LDCT examination for LCS, we have found that more than 98% of LCS-eligible individuals meet the ≥10% 10-year CVD risk threshold required for statin primary prevention of CV events in the UK. Despite this overwhelming majority, more than half of these individuals did not report a history of statin use, which suggests that assessment of this population during LCS provides an opportunity for CVD risk reduction. Statin use was associated with factors related to increasing cardiovascular risk, but not number of GP visits within the past year. Overall, increasing QRISK2 was associated with increasing CAC grade on LDCT, but more than half of participants in the moderate (10-20%) CVD-risk group had no visible CAC.

It is striking that almost all participants met the required CVD risk threshold for statin therapy for primary prevention of cardiovascular events. This proportion may be higher than expected, based on results from other LCS screening studies, however, those cohorts have typically been slightly younger and have included fewer current smokers [17,22,205,206]. Independent of the variability between cohorts, LCS-eligible individuals are disproportionately likely to develop CHD. A recent study reporting 10-year outcomes in a sub-cohort of participants who met the USPSTF criteria [207] for LCS from the Multi-Ethnic Study of Atherosclerosis (MESA) noted an almost three-fold increase in the cardiovascular event rate (20.8%) in this group [208] than the 10-year event rate reported in the overall MESA cohort (7.8%) (table 5.8) [209]. This suggests that the vast majority of LCS-eligible individuals may benefit from statins, and routine assessment of CVD risk and initiation of a statin where appropriate should be carried out alongside LCS. This intervention also highlights LCS as a ‘teachable moment’ for multiple behaviour change; an opportunity for encouraging improved diet and physical activity levels, optimisation of blood pressure, and importantly, smoking cessation. Together, these interventions have the potential to improve cardiovascular (and perhaps all-cause) mortality and morbidity and may enhance the cost-effectiveness of LCS when measured against cost per quality-adjusted life year gained.
Table 5.8 Summary of long-term outcomes from MESA cohort and sub-cohorts

<table>
<thead>
<tr>
<th>Sub-cohort</th>
<th>Sub-cohort characteristics</th>
<th>Events</th>
<th>CAC cut offs</th>
<th>Adjusted HR (CI)</th>
<th>Event rate in CAC=0 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budoff et al, 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole MESA cohort</td>
<td>Included 50% never smokers, ages 45-84</td>
<td>500/6814 (7.4%) overall</td>
<td>CAC 0</td>
<td>3.78-7.14%</td>
<td>3.78-7.14%</td>
</tr>
<tr>
<td>Leigh et al, 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MESA ever smokers</td>
<td>Younger, less smoking history</td>
<td>445/3356 (13.4)</td>
<td>CAC 0: CAC&gt;0: CAC 1-100: CAC 1-300: CAC&gt;300</td>
<td>1.8 (1.08-3.17) 1.65 (0.96-2.94) 2.39 (1.26-4.61)</td>
<td>6.7%</td>
</tr>
<tr>
<td>MESA-USPSTF-eligible</td>
<td>more likely to: be on statins, have DM, be current smokers, have &gt;10-year CVD risk score &amp; high CAC.</td>
<td>100/481 (20.8)</td>
<td>CAC 0: CAC&gt;0: CAC 1-100: CAC 1-300: CAC&gt;300</td>
<td>1.93 (1.51-2.47) 1.66 (0.99-2.88) 5.62 (4.35-7.28)</td>
<td>14.2%</td>
</tr>
</tbody>
</table>
Our analysis found that the rate of uptake to a statin is low (approximately 50% who qualify, reported statin use, falling to 23% in the 10-20% QRISK2 category). This result is consistent with other UK and US studies, who have reported 46.0% and 49.7% statin use in their eligible cohorts, respectively. [210]. In the UK, individuals aged between 40 and 74 are invited to NHS health checks in order to carry out CVD risk assessment, though uptake to this has been low at only 30% in 2012 [211]. These findings re-enforce the argument that LCS could offer an opportunity to initiate primary prevention of CVD through appropriate risk stratification and subsequent statin prescription.

Studies have noted that CAC score is associated with clinical and demographic predictors of coronary risk and is an independent marker for the risk of coronary events, after adjustment for conventional risk factors [212]. Our findings of a positive association between CAC grade and QRISK2 are in keeping with this, though the odds ratios in the logistic regression are noted to be wide for the >20% group. It has also been shown that combining clinical and demographic predictors with the CAC score can enhance predictive accuracy, particularly in the intermediate risk group [213]. Our finding that CAC grade on LDCT is associated with CVD risk is supported by several studies reporting an association between CAC grade and CVD events [103,200–204] (table 5.2). However, this may not offer any clinical benefit, as most participants qualify for a statin by virtue of their CVD risk alone. Nevertheless, reporting CAC using the visual grading method used in the present study is quick and may be motivational in initiating statin prevention and adherence to therapy as well as other lifestyle prevention behaviours [214]. In the UK NHS health checks, initiation of statin treatment only occurs in 20% of NHS health check attendees with ≥20% CVD risk [211], suggesting there is a need to boost uptake to this highly efficacious and cost-effective strategy for preventing CVD events. Most participants with heavy CAC grade in this study had a QRISK2 score greater than 20%, suggesting that reporting this back to participants may be of value. Furthermore, as novel preventative therapies emerge, the uniformly high CVD risk in this group (65.7% with ≥20% 10-year risk) may warrant more discerning risk stratification strategies.

The large number (54.7%) of participants in the moderate QRISK2 category (10-20%) with CAC=0 is also noteworthy, and it was suggested from the LCS cohorts that many of these will not have a CVD event (table 5.2) [103,200–204]. However, many of these studies only
looked at fatal CHD events, or had limited follow-up duration. More recent data from the USPSTF-eligible cohort in MESA discussed above [208], demonstrated the 10-year CVD event rate to be 14.2% in this group, suggesting that the true long term (fatal and non-fatal) event rate is not low enough to negate the use of statins for primary prevention in this high CVD-risk group (table 5.8). Interestingly, the wide range of QRISK2 scores in those with CAC=0 observed in this study, imply caution should be taken with interpretation of either QRISK2 or CAC in isolation, and that the two together may enable more accurate CVD risk prediction in this group.

5.4.1 Strengths and limitations

The current study is limited by the lack of cardiovascular event data, and future studies that assess the predictive power of clinical, demographic and CAC related factors in prospective LCS cohorts are needed. The population in the present study is likely to have a particularly high-risk of lung cancer, as the primary research question targeted socioeconomically deprived smokers (22). Nevertheless, the findings are likely to be generalisable, particularly given emerging evidence advocating the selection of LCS-eligible individuals to be based on lung cancer risk [47,215]. Secondly, we did not collect data on NHS health check attendance, or on reasons for the lack of statin use. A large body of research [216] implicates patient-related, behavioural barriers in non-adherence to statins (e.g. concerns about side effects, misconceptions about causality and symptoms, low perceived benefit), and has shown that behavioural interventions targeting these barriers are effective [217]. Awareness of the presence of CAC may have a positive effect on statin use in this group, particularly if barriers among those who previously declined treatment could be identified and addressed. We did not measure serum cholesterol and so our QRISK2 score used a substitute value, which may make the scores less accurate. Measuring serum cholesterol may not add a great deal of value given the high-risk of participants due to other (smoking and age) risk factors, and adds expense and time. Further studies could evaluate the predictive power of the risk scores with and without serum cholesterol values and measure the cost-effectiveness of both strategies. Finally though the visual CAC grades are clearly defined in terms of appearance on LDCT, there may have been a degree of subjectivity in the assessment, and we did not specifically measure inter-observer variation with respect to CAC grade. Despite these limitations, this novel study was carried out in a practical and pragmatic manner with high uptake rates making the findings generalisable to a population rather than a biased volunteer group.
5.4.2 Conclusions
This study noted almost universally high estimated CVD risk and significant underutilisation of statin therapy for primary prevention of cardiovascular events among LCS participants. We propose that all individuals invited to LCS should have a CVD primary prevention review. Reporting of CAC may not add a great deal of benefit in terms of risk assessment and treatment, however, it may help to improve adherence to lifestyle and pharmacological interventions for the prevention of CVD. Future studies are needed to further understand the relationship of clinical, demographic and CAC score predictors to long term CVD events; and to evaluate the impact on initiation and adherence to primary preventative strategies following the reporting of CAC results to individuals.
Chapter 6. Is lung cancer screening an opportunity for active case finding of chronic obstructive pulmonary disease and emphysema?

6.1 INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the third biggest killer globally, after Coronary Heart Disease (CHD) and stroke [218]. The presence of emphysema, airflow limitation, increasing COPD severity and exacerbation frequency have been shown to be associated with a greater risk of lung cancer [219,220], though this effect is dissipated after adjustment for smoking history and other confounders [221]. Biologically, this may be explained by a combination of chronic inflammation, impaired mucociliary action, DNA damage and repair and genetic susceptibility [222,223].

Lung cancer screening (LCS) has been shown to reduce lung cancer-specific and all-cause mortality by 20% and 6.7% respectively in the National Lung Screening Trial (NLST) [17]. Evidence suggests that cohorts at higher-risk for lung cancer may benefit more from LCS than those with lower-risk [47,51]. A secondary analysis of data from NLST confirmed a two-fold increase in lung cancer prevalence amongst participants with pre-bronchodilator spirometry consistent with COPD [224]. The authors also reported a greater stage shift and reduced overdiagnosis, in terms of lower lung cancer incidence and no bronchoalveolar cell carcinoma (which is the typical histology in overdiagnosed cases), amongst those with airflow limitation compared to those without [224]. These findings, which are supported by an earlier pilot study [225] suggest LCS in individuals with COPD may result in greater lung cancer-specific mortality reduction than those without, though the severity of COPD, which could impact morbidity and mortality from competing causes, must also be considered.

Age and smoking history are the strongest predictors in the development of lung cancer and COPD, enabling a common population in which to carry out ‘case-finding’ for the two conditions. Several studies have demonstrated a significant burden of undiagnosed COPD within primary care populations [226–229], though currently ‘screening’ for asymptomatic COPD is not recommended by the United States Preventative Services Task Force (USPSTF) [230], as it has not been shown to impact COPD-related endpoints, including exacerbations, hospitalisation or mortality. The revised 2017 GOLD criteria place increasing importance on
symptom burden and exacerbation frequency over and above spirometry values as key in guiding treatment decisions [231]. This change follows evidence that symptoms, exacerbation frequency and comorbidities are more important determinants of prognosis than spirometry [231,232]. Furthermore, comorbidities such as CHD, heart failure, cardiac arrhythmias, hypertension, hypercholesterolaemia, osteoporosis and diabetes are frequent in COPD and may be undertreated [231,233] and optimisation of these conditions may positively impact COPD outcomes.

The LCS-eligible population is therefore likely to be enriched with COPD, with previously reported prevalence rates of 38% [234], almost four-fold higher than rates reported in the general population [227]. The GOLD 2017 report has recommended active case finding for those with symptoms and/or risk factors [231], but whether detecting emphysema on low dose computed tomography (LDCT) carried out in LCS provides any additional benefit to spirometry is inconclusive.

In this study we aimed to determine: a) the burden of symptoms, comorbidities and inhaler use in LCS participants with spirometry consistent with COPD; and b) the burden of COPD symptoms and radiological emphysema in current and former smoking participants with ‘undiagnosed’ COPD (i.e. participants without a self-reported history of COPD, but with spirometry consistent with COPD).

6.2 METHODS

6.2.1 Study design, participants and setting
This prospective observational cohort study is nested within the Lung Screen Uptake Trial (LSUT), the methods for which have been described previously [129] and in chapter 2. Briefly, individuals aged between 60 and 75, who had been recorded in their GP record as current smokers within the past 5 to 7 years, were invited by their primary care physician for a ‘lung health check’ (LHC) at one of two London hospitals between November 2015 and July 2017. Individuals attending the LHC were invited to participate in the study and those meeting the required threshold for lung cancer risk were invited to have an LDCT the same day (as detailed in chapter 2).
Very brief smoking cessation advice (standardised intervention from the UK’s National Centre for Smoking Cessation and Training [132] was given to all current smokers at the LHC, and participants were also randomised to receive details of their local NHS smoking cessation service or be proactively referred to the smoking cessation service.

6.2.2 Data collection
Data were prospectively collected by a study practitioner at the LHC. Self-reported demographics (age, sex, ethnicity, education level, Index of Multiple Deprivation (IMD) score and rank), smoking, family and medical history were recorded (as detailed in chapter 2). Hand-held spirometry, height, weight and blood pressure were recorded.

6.2.3 Outcome measures
Symptoms: Participants were asked about current or recent (within the past 12 months) history of dyspnoea, cough and lower respiratory tract infection (LRTI). Those without a self-reported current history of cough or dyspnoea were categorised as ‘asymptomatic’. Medical Research Council dyspnoea (MRC) score was also assessed and recorded by the study practitioner.

Comorbidities: Participants were specifically asked about a known history of COPD, asthma, previous pneumonia, coronary heart disease, hypertension (including those with normal blood pressure on antihypertensives), atrial fibrillation, hypercholesterolaemia, diabetes mellitus, osteoporosis and previous non-thoracic malignancy. Participants were labelled as ‘undiagnosed’ COPD if answered no to the question: do you have a prior history of COPD, bronchitis or emphysema? Participants were also specifically asked about inhaled therapy use, and were given the names of different classes of inhalers and some commonly used examples, e.g. a short acting beta agonist inhaler such as salbutamol, terbutaline, with pictures available to act as a prompt.

Spirometry: Pre-bronchodilator spirometry was measured in all participants using a vitalograph® micro handheld spirometer during the LHC in accordance with the joint European Respiratory Society and American Thoracic Society [235] and the British Thoracic Society recommendations [236]. Participant ethnicity, age and height were used to calculate predicted values, enabling absolute and percentage predicted values to be recorded. A participant was defined as having COPD if FEV1/FVC was <70%. Participants
with COPD with FEV1 >80%, <80% but ≥50%, <50% but ≥30% or <30% were classified as GOLD class I, II, III or IV respectively. The 2014 GOLD report was the basis for COPD diagnosis and management at the start of the study, hence data were collected in accordance with GOLD classes I-IV [237].

Emphysema: The LDCT scans were single-read by a team of radiologists with expertise in thoracic CT reporting, and experience ranging from 5 to 28 years. Reports included recording of emphysema grade, which was subjectively determined on a visual scale of none, mild, moderate or severe. 5% of all LDCT scans were second-read by a radiologist from the opposite participating site for quality assurance purposes.

6.2.4 Sample size & statistical analysis
The sample size of the LSUT cohort was based on the primary behavioural research question and has been described in chapter 2 and in the published protocol [129]. Participants who had never smoked or who had missing spirometry data were excluded from the analysis. Descriptive statistics were used to determine the demographic and clinical characteristics of individuals grouped by presence or absence of COPD. Univariate associations between symptoms, comorbidities and inhaler use and GOLD grade were explored using chi square and fisher’s exact tests. A final sub-analysis was carried out in those with ‘undiagnosed’ COPD, to explore the presence and association of symptoms between known and ‘undiagnosed’ COPD, and emphysema with and without airflow limitation, using chi square and fisher’s exact tests. Associations between presence and grade of emphysema and GOLD class for those who undertook an LDCT scan were also explored. Missing values were excluded from the analyses (and were present for only one variable, IMD rank).
6.3 RESULTS

Figure 6.1 shows the flow diagram of the study participants. Of 1005 participants recruited to LSUT, 986 participants were included in the present analysis, of which 560 (56.8%) had spirometry consistent with COPD. The demographic characteristics of participants are detailed in table 6.1. Of the entire cohort, 756 participants had no self-reported history of COPD and were included in a further sub-analysis, of which 579 undertook LDCT.
Table 6.1 Participant characteristics by group (% totals may not sum up due to rounding, or missing data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD based on pre-bronchodilator spirometry at lung health check appointment pre-LDCT</th>
<th>No COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) or median (IQR*)</td>
<td>n=426</td>
<td>n=560</td>
</tr>
<tr>
<td></td>
<td>(43.2% of cohort)</td>
<td>(56.8% of cohort)</td>
<td></td>
</tr>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 – 63</td>
<td></td>
<td>176 (41.3)</td>
<td>160 (28.5)</td>
</tr>
<tr>
<td>64 – 67</td>
<td></td>
<td>131 (30.8)</td>
<td>188 (33.6)</td>
</tr>
<tr>
<td>68 – 71</td>
<td></td>
<td>74 (17.4)</td>
<td>140 (25.0)</td>
</tr>
<tr>
<td>72 – 76</td>
<td></td>
<td>45 (10.6)</td>
<td>72 (12.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>213 (50.0)</td>
<td>325 (58.0)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>213 (50.0)</td>
<td>235 (42.0)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>324 (76.1)</td>
<td>491 (87.7)</td>
</tr>
<tr>
<td>Black/ African/ Caribbean</td>
<td></td>
<td>62 (14.5)</td>
<td>38 (6.8)</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>12 (2.8)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>7 (1.6)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>21 (4.9)</td>
<td>16 (2.9)</td>
</tr>
<tr>
<td>Highest Level of Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left school at or before age 15</td>
<td></td>
<td>207 (48.6)</td>
<td>308 (55.0)</td>
</tr>
<tr>
<td>CSEs, O-levels or equivalent</td>
<td></td>
<td>45 (10.6)</td>
<td>59 (10.5)</td>
</tr>
<tr>
<td>A-levels or equivalent</td>
<td></td>
<td>44 (10.3)</td>
<td>52 (9.25)</td>
</tr>
<tr>
<td>Further education</td>
<td></td>
<td>23 (5.4)</td>
<td>24 (4.3)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td></td>
<td>51 (12.0)</td>
<td>68 (12.1)</td>
</tr>
<tr>
<td>Further higher degree</td>
<td></td>
<td>46 (10.8)</td>
<td>40 (7.1)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>9 (2.1)</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>1 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Index of Multiple Deprivation (IMD) quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td></td>
<td>239 (56.1)</td>
<td>298 (53.2)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>136 (31.9)</td>
<td>201 (35.9)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>12 (2.8)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1 (0.23)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>38 (8.9)</td>
<td>52 (9.3)</td>
</tr>
<tr>
<td>Smoking History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>288 (67.6)</td>
<td>410 (73.2)</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td>138 (32.3)</td>
<td>150 (26.8)</td>
</tr>
<tr>
<td>Years smoked (years)</td>
<td></td>
<td>46 (41, 50)</td>
<td>48 (44, 52)</td>
</tr>
<tr>
<td>Years quit (years)</td>
<td></td>
<td>0 (0, 1)</td>
<td>0 (0,0)</td>
</tr>
<tr>
<td>Average smoking intensity (cigs/day)</td>
<td></td>
<td>15 (10, 20)</td>
<td>20 (10, 20)</td>
</tr>
<tr>
<td>Pack years</td>
<td></td>
<td>33 (18, 47)</td>
<td>39 (25, 54)</td>
</tr>
</tbody>
</table>
Table 6.1 (continued) Participant characteristics by group (% totals may not sum up due to rounding, or missing data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>COPD based on pre-bronchodilator spirometry at lung health check appointment pre-LDCT n (%) or median (IQR*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No COPD n=426 (43.2% of cohort)</td>
</tr>
<tr>
<td></td>
<td>COPD n=560 (56.8% of cohort)</td>
</tr>
<tr>
<td>Lung cancer risk</td>
<td></td>
</tr>
<tr>
<td>PLCO (% 6 year risk)</td>
<td>2.8 (1.0, 5.1)</td>
</tr>
<tr>
<td>LLP (% 5 year risk)</td>
<td>4.6 (2.7, 6.5)</td>
</tr>
<tr>
<td>FEV1 (l/min)</td>
<td>2.29 (1.86, 2.72)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>91 (79.0, 102.5)</td>
</tr>
<tr>
<td>FVC (l/min)</td>
<td>2.97 (2.39, 3.56)</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>94 (81.0, 107.0)</td>
</tr>
<tr>
<td>FEV/FVC (%)</td>
<td>76.5 (73.0, 80.0)</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.8 (23.6, 30.1)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134 (122, 147)</td>
</tr>
<tr>
<td>MRC dyspnoea score</td>
<td></td>
</tr>
<tr>
<td>0- breathless on strenuous exercise only</td>
<td>310 (72.6)</td>
</tr>
<tr>
<td>1- slightly breathless e.g. up hills</td>
<td>104 (24.4)</td>
</tr>
<tr>
<td>2- slower than contemporaries</td>
<td>11 (2.6)</td>
</tr>
<tr>
<td>3- 100m exercise tolerance</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>4- Housebound</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>LDCT</td>
<td></td>
</tr>
<tr>
<td>LDCT performed</td>
<td>317 (74.4)</td>
</tr>
<tr>
<td>Not eligible due to low smoking history or lung cancer risk</td>
<td>57 (13.4)</td>
</tr>
<tr>
<td>Other reason LDCT not performed (e.g. declined, DNA, previous CT in past year)</td>
<td>52 (12.2)</td>
</tr>
<tr>
<td>Follow up duration since LDCT (days)</td>
<td>627 (481, 783)</td>
</tr>
</tbody>
</table>

Of the 560 participants who met spirometry criteria for COPD, 86.3% of them had pre-bronchodilator spirometry consistent with GOLD class I or II; and 38.5% of participants in GOLD class I had symptoms compared with 87.5% in class IV (p<0.001) (table 6.2). Dyspnoea and cough were present currently in 34.5% and 28.2% of participants with spirometry consistent with COPD, while 18.4% had both, and 45.5% of participants had either. 29.9% of participants with spirometry consistent with COPD had a history of a lower respiratory tract infection (LRTI) in the past year. All symptoms were more frequent with increasing GOLD class (p<0.001, table 6.2).

A prior self-reported diagnosis of COPD was absent in 67.3% of participants with spirometry consistent with COPD, though this varied by GOLD class (p<0.001). In GOLD class I, only 21%
of those with pre-bronchodilator spirometry consistent with COPD reported a history of COPD, compared with 87.5% in class IV (p<0.001) (table 6.3). 16.3% of participants across all GOLD classes had a self-reported history of asthma. Previous pneumonia was also more common with increasing GOLD class, (14.5% in class I vs. 33.3% in class III, p=0.001). Non-respiratory comorbidities were frequent, with no association with GOLD class. Hypertension and hypercholesterolaemia were the most commonly occurring in 35.7% and 45.7% of participants respectively. 11.1% participants reported a history of CHD, 10.5% of diabetes, and 4.6% of atrial fibrillation. Of non-cardiovascular comorbidities, 10.7% reported a history of osteoporosis and 7.7% of prior extra-thoracic malignancy.

Table 6.2 Symptoms suggestive of COPD in participants with spirometry consistent with COPD by GOLD class (LRTI= lower respiratory tract infection)

<table>
<thead>
<tr>
<th>n (%) in participants with spirometry consistent with COPD</th>
<th>No COPD</th>
<th>GOLD 1: Mild, FEV1 ≥ 80%</th>
<th>GOLD 2: Mod, FEV1 50-80%</th>
<th>GOLD 3: Severe, FEV1 30-50%</th>
<th>GOLD 4: V Severe, FEV1 &lt; 30%</th>
<th>All GOLD classes</th>
<th>Fishers exact test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n=426</td>
<td>234</td>
<td>249</td>
<td>69</td>
<td>6</td>
<td>8</td>
<td>560</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**CURRENT SYMPTOMS**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No symptoms</th>
<th>Dyspnoea</th>
<th>Cough</th>
<th>Cough + dyspnoea</th>
<th>Cough or dyspnoea</th>
<th>LRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>285 (66.9)</td>
<td>90 (21.1)</td>
<td>79 (18.5)</td>
<td>31 (7.28)</td>
<td>138 (32.4)</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>144 (61.5)</td>
<td>56 (23.3)</td>
<td>55 (23.5)</td>
<td>24 (10.3)</td>
<td>87 (37.1)</td>
<td>15 (6.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>124 (49.7)</td>
<td>91 (36.6)</td>
<td>69 (27.7)</td>
<td>41 (16.5)</td>
<td>119 (47.8)</td>
<td>17 (6.8)</td>
</tr>
<tr>
<td>Cough + dyspnoea</td>
<td>27 (39.1)</td>
<td>40 (58.0)</td>
<td>29 (42.0)</td>
<td>27 (39.1)</td>
<td>42 (60.9)</td>
<td>8 (11.6)</td>
</tr>
<tr>
<td>Cough or dyspnoea</td>
<td>1 (12.5)</td>
<td>6 (75.0)</td>
<td>6 (62.5)</td>
<td>4 (50.0)</td>
<td>7 (87.5)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>LRTI</td>
<td>296 (52.9)</td>
<td>193 (34.5)</td>
<td>158 (28.2)</td>
<td>96 (17.1)</td>
<td>255 (45.5)</td>
<td>296 (52.9)</td>
</tr>
</tbody>
</table>

**SYMPTOMS WITHIN THE LAST YEAR**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No symptoms</th>
<th>Dyspnoea</th>
<th>Cough</th>
<th>Cough + dyspnoea</th>
<th>Cough or dyspnoea</th>
<th>LRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>217 (50.9)</td>
<td>125 (29.3)</td>
<td>118 (27.7)</td>
<td>53 (12.4)</td>
<td>190 (44.6)</td>
<td>65 (15.3)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>102 (43.6)</td>
<td>79 (33.8)</td>
<td>85 (36.3)</td>
<td>43 (18.4)</td>
<td>121 (51.7)</td>
<td>50 (21.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>78 (31.3)</td>
<td>124 (49.8)</td>
<td>107 (43.0)</td>
<td>70 (28.1)</td>
<td>161 (64.7)</td>
<td>74 (29.7)</td>
</tr>
<tr>
<td>Cough + dyspnoea</td>
<td>11 (15.9)</td>
<td>50 (72.5)</td>
<td>43 (62.3)</td>
<td>37 (53.6)</td>
<td>56 (81.2)</td>
<td>33 (47.8)</td>
</tr>
<tr>
<td>Cough or dyspnoea</td>
<td>1 (12.5)</td>
<td>6 (75.0)</td>
<td>6 (62.5)</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>LRTI</td>
<td>192 (34.3)</td>
<td>259 (46.3)</td>
<td>241 (43.0)</td>
<td>155 (27.7)</td>
<td>345 (61.6)</td>
<td>163 (29.1)</td>
</tr>
</tbody>
</table>

<0.001
### Table 6.3 Comorbidities in participants with spirometry consistent with COPD by GOLD class

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>No COPD</th>
<th>GOLD 1: Mild, FEV1 ≥ 80%</th>
<th>GOLD 2: Mod, FEV1 50-80%</th>
<th>GOLD 3: Severe, FEV1 30-50%</th>
<th>GOLD 4: V Severe, FEV1 &lt; 30%</th>
<th>All GOLD classes</th>
<th>Fishers exact test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=426</td>
<td>n=234</td>
<td>n=249</td>
<td>n=69</td>
<td>n=8</td>
<td>n=560</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>47 (11.0)</td>
<td>49 (21.0)</td>
<td>92 (37.0)</td>
<td>35 (50.7)</td>
<td>7 (87.5)</td>
<td>183 (32.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>44 (10.3)</td>
<td>31 (13.3)</td>
<td>46 (18.5)</td>
<td>13 (18.8)</td>
<td>1 (12.5)</td>
<td>91 (16.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>Previous pneumonia</td>
<td>56 (13.2)</td>
<td>34 (14.5)</td>
<td>48 (19.3)</td>
<td>23 (33.3)</td>
<td>2 (25)</td>
<td>107 (19.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>46 (10.8)</td>
<td>23 (9.8)</td>
<td>32 (12.9)</td>
<td>7 (10.1)</td>
<td>0 (0)</td>
<td>62 (11.1)</td>
<td>0.806</td>
</tr>
<tr>
<td>Hypertension on anti-hypertensives</td>
<td>162 (38.0)</td>
<td>71 (30.3)</td>
<td>96 (38.6)</td>
<td>30 (43.5)</td>
<td>3 (37.5)</td>
<td>200 (35.7)</td>
<td>0.175</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19 (4.5)</td>
<td>11 (4.7)</td>
<td>7 (2.8)</td>
<td>6 (8.7)</td>
<td>2 (25)</td>
<td>26 (4.6)</td>
<td>0.035</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>202 (47.4)</td>
<td>98 (41.9)</td>
<td>118 (47.4)</td>
<td>38 (55.1)</td>
<td>2 (25)</td>
<td>256 (45.7)</td>
<td>0.225</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>78 (18.3)</td>
<td>18 (7.7)</td>
<td>33 (13.3)</td>
<td>8 (11.6)</td>
<td>0 (0)</td>
<td>59 (10.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>44 (10.3)</td>
<td>23 (9.8)</td>
<td>33 (13.3)</td>
<td>4 (5.8)</td>
<td>0 (0)</td>
<td>60 (10.7)</td>
<td>0.407</td>
</tr>
<tr>
<td>Previous extra-thoracic malignancy</td>
<td>36 (8.5)</td>
<td>13 (5.6)</td>
<td>24 (9.6)</td>
<td>4 (5.8)</td>
<td>2 (25)</td>
<td>43 (7.7)</td>
<td>0.152</td>
</tr>
</tbody>
</table>

### Table 6.4 Self-reported inhaled treatment use by GOLD class (SABA= short acting beta agonist, LABA= long acting beta agonist, LAMA= long acting muscarinic antagonist, ICS= inhaled corticosteroid)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No COPD</th>
<th>GOLD 1: Mild, FEV1 ≥ 80%</th>
<th>GOLD 2: Mod, FEV1 50-80%</th>
<th>GOLD 3: Severe, FEV1 30-50%</th>
<th>GOLD 4: V Severe, FEV1 &lt; 30%</th>
<th>All GOLD classes</th>
<th>Fishers exact test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=426</td>
<td>n=234</td>
<td>n=249</td>
<td>n=69</td>
<td>n=8</td>
<td>n=560</td>
<td></td>
</tr>
<tr>
<td>SABA</td>
<td>42 (9.9)</td>
<td>42 (17.9)</td>
<td>81 (32.5)</td>
<td>41 (59.4)</td>
<td>6 (75.0)</td>
<td>170 (30.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LABA</td>
<td>4 (0.9)</td>
<td>4 (1.7)</td>
<td>10 (4.0)</td>
<td>9 (13.0)</td>
<td>2 (25.0)</td>
<td>25 (4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAMA</td>
<td>12 (2.8)</td>
<td>6 (2.6)</td>
<td>23 (9.2)</td>
<td>15 (21.7)</td>
<td>3 (37.5)</td>
<td>47 (8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LABA +ICS</td>
<td>14 (3.2)</td>
<td>17 (7.3)</td>
<td>38 (15.2)</td>
<td>20 (28.9)</td>
<td>3 (37.5)</td>
<td>78 (13.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 6.2 The burden of symptoms in (a) participants with known vs. undiagnosed COPD and (b) emphysema with airflow obstruction vs. without airflow obstruction in participants with undiagnosed COPD
Of those not meeting spirometry criteria for COPD, 9.9% were on inhaled short acting beta agonists (SABA) (table 6.4), and just under half of them reported a history of asthma. Use of other inhaled therapy was fairly low ranging from 4.5% to 13.9% across all GOLD classes, with a trend to increasing use by increasing GOLD severity (p<0.001).

Of the 377 participants with ‘undiagnosed’ COPD, 90.7% of them had pre-bronchodilator spirometry consistent with GOLD class I or II. 36.9% had dyspnoea, cough and/or LRTI within the preceding 12 months, and 74.8 were current smokers. There was a statistically significant difference in symptom prevalence between those with known COPD and ‘undiagnosed’ COPD (figure 6.2a). 68.0% of participants with undiagnosed COPD had emphysema on LDCT while 48.9% of those with preserved spirometry and without a self-reported history of COPD, had emphysema on LDCT (table 6.5). Of those with emphysema, 265 (77.9%) were current smokers. Those with undiagnosed COPD, emphysema and airflow limitation had greater dyspnoea than those without airflow limitation, while all other symptoms were similar in both these groups (figure 6.2b).

### 6.4 DISCUSSION

In this observational cohort study of 986 individuals attending an LHC, 56.8% met spirometry criteria for COPD and had a significant proportion of them had respiratory symptoms and these increased by GOLD severity. Comorbidities, particularly those related to cardiovascular disease were also common. Some inhaled treatment under-use was
apparent, though use of inhalers increased by GOLD class. There was a significant burden of ‘undiagnosed’ COPD, and 90.7% of these individuals had pre-bronchodilator spirometry consistent with GOLD class I or II. A significant proportion of these individuals had symptoms and/ or emphysema on LDCT and the majority were still smoking. Symptom burden was greater in those with known COPD than those with ‘undiagnosed’ COPD, and in those with emphysema with airflow limitation than those without.

The proportion of participants with spirometry consistent with COPD observed in the present study (56.8%) is higher than that reported in a previous secondary analysis of a sub-population of NLST (34.4%) [224], though the majority were in GOLD class I or II (86.3%) and were asymptomatic (52.9%). This high prevalence may be explained by the population recruited to the present study which, due to the primary research question, were largely current smokers from low socioeconomic position (SEP) backgrounds; and also because of the ‘real-world’ nature of the present study, as participants were invited for an NHS ‘lung health check’ and not to participate in a clinical trial. Conversely, NLST participants were typically younger, more affluent and educated, and less likely to be currently smoking [17].

Another important observation is that a significant number of the participants with airflow limitation were symptomatic, suggesting many participants may have clinically significant COPD and may be more likely to experience COPD-related and worse lung cancer outcomes (due to reduced lung function and increased complication rates with invasive investigations and treatments). The proportion of participants receiving inhaled treatment however, was relatively low, with only between 4.5 and 13.9% of participants with spirometry consistent with COPD reporting use of inhaler classes other than SABA. The data presented here were collected prior to the publication of the newer 2017 GOLD report which recommends symptoms and exacerbation frequency and not spirometry to determine treatment decisions [231] and as we did not have data on exacerbation frequency, we were unable to determine who would qualify for treatment according to the newer guidelines. Nevertheless, the data reported here suggest there may be some under-treatment when compared to GOLD 2016 guidance [238]. This is likely to be due to the burden of ‘undiagnosed’ COPD rather than under-treatment in those with known COPD, as 67.3% of those with airflow obstruction consistent with COPD did not report a history of COPD. Consideration should be paid to the possibility of some participants underreporting a diagnosis of COPD, misreporting COPD as asthma or having COPD-asthma overlap.
syndrome. Reassuringly though, very few participants (approximately 5%) reported inhaler use without a history of COPD or asthma, suggesting that under-reporting of COPD diagnosis was uncommon.

Comorbidities are gaining increased importance in the context of COPD, and cardiovascular risk factors and disease may be the most important determinants of prognosis in COPD [233]. The population studied here did indeed have high rates of these conditions, with almost half of all participants reporting a history of hypercholesterolaemia, and over a third reporting hypertension. The prevalence of high cardiovascular disease risk in this population is reported in chapter 5 and supports the need for placing value upon these comorbidities. Another noteworthy finding is that of osteoporosis, which was present in >10% of participants. Osteoporosis is another important comorbidity in COPD, due to its increase in prevalence with age, smoking and steroid use as well as other factors related to COPD [17,31], and it is likely that the burden of osteoporosis in this cohort is higher than reported, given the association between osteoporosis and worsening emphysema observed in LCS participants previously [240].

The significance of LDCT-detected emphysema in the context of preserved spirometry is another important debate. 58.7% of individuals with ‘undiagnosed COPD’ who had an LDCT in our cohort had some LDCT-detected emphysema. Although in the majority this was mild, this prevalence is much higher than that reported in other cohorts [241]. CT emphysema has been reported to predict COPD in the LCS setting with a sensitivity of 63% and specificity of 88% [234]. However, the majority of the participants in the ‘undiagnosed’ group (60.4% of those with emphysema and airflow obstruction) were asymptomatic, and currently only lifestyle modifications such as smoking cessation are recommended in such individuals [231]. In our cohort, 77.9% of participants with ‘undiagnosed’ COPD and LDCT-detected emphysema were current smokers, suggesting LCS may offer an opportunity for a ‘teachable moment’ for participants with asymptomatic subclinical emphysema. Studies are needed to understand whether informing individuals of early changes of smoking-related lung disease and delivery of more intense smoking cessation interventions in this population can successfully enhance smoking cessation rates.

Almost 40% of the ‘undiagnosed’ COPD participants with emphysema and airflow limitation also had symptoms suggestive of COPD, suggesting they would benefit from COPD assessments, for example, by a general practitioner (GP), but whether reporting this
information back to GPs and patients impacts outcomes such as future COPD exacerbation frequency and hospitalisations is not known. Those with emphysema and no airflow obstruction, were significantly less likely to report symptoms and case-finding of asymptomatic COPD is currently not recommended [230]. Studies have reported increased exacerbation frequency and reduced activity levels [227,228] in smokers without airflow obstruction but with symptoms, and not in those without airflow limitation or symptoms. Associations between radiological findings consistent with COPD and exacerbation frequency have been previously been reported [242], but whether these participants had airflow limitation and symptoms was not stated. In contrast, a recent study in China found an improvement in forced expiratory volume (FEV1), exacerbation frequency and quality of life with tiotropium compared with placebo in those with mild COPD with few or no symptoms [243] but this finding is yet to be reproduced in other populations. Collecting longitudinal data on COPD symptoms and diagnoses, exacerbation frequency and hospitalisations in these different groups is required to understand the relevant importance of CT-detected emphysema in those with and without airflow limitation and symptoms. For now, other than smoking cessation, no specific interventions can be recommended for those with asymptomatic COPD or emphysema detected at LCS, though future studies using tiotropium may be of value. LCS policy makers need to be mindful of the wider implications of reporting LDCT findings with no evidence to support specific interventions, including risk of medication overuse and impact on insurance eligibility.

Another noteworthy point is that individuals with early COPD (including those with ‘undiagnosed’ COPD with mild or no symptoms, and typically in GOLD class I and II), stand to gain the most benefit from LCS. An analysis looking at a sub-cohort of participants from NLST, demonstrated a 40% relative reduction in lung cancer-specific mortality (double that seen in NLST [17]) in those with spirometry consistent with GOLD classes I or II [244]. This mortality reduction was still impressive at 32% in those with undiagnosed COPD of any GOLD class, but there was no reduction in mortality in those with GOLD stage III or IV. This can be explained by the more common competing risks of death [245] and reduced surgical resection rates in individuals with more advanced COPD. The majority of the participants in the LSUT cohort had GOLD stage I or II (86.3% in the whole cohort and 90.7% in the ‘undiagnosed’ sub-group) and so were in the target group that stands to gain the most benefit from LCS. Nevertheless, a small proportion of individuals attending for an LHC, had more advanced COPD, and 81% opted to have an LDCT. Denying individuals the opportunity
to take part in LCS on the basis of available evidence is controversial, and has complex implications on the shared decision-making conversation required in such cases. Further work is needed to determine whether techniques such as stereotactic ablative radiotherapy, and video-assisted sub-lobar resections, which are increasingly popular, may offer more favourable outcomes in those with reduced fitness and lung function, and around communicating the complex harm-benefit balance in this group of participants [246].

Early detection of COPD in symptomatic individuals with airflow limitation in the LCS setting could provide an opportunity for greater motivation to stop smoking, increased rates of vaccination against respiratory infection, and other self-education measures (including attention to diet and activity and symptom awareness) as well as appropriate pharmacotherapy. Whether this might in turn prevent further lung function decline, and improve future symptoms, exercise capacity and performance status needs to be ascertained in prospective randomised studies. In those with screen-detected lung cancers, earlier COPD diagnosis and optimisation might impact downstream curative and surgical treatment rates and complications. This, together with the capacity for greater mortality benefit in those with early COPD could impact the efficacy and cost-effectiveness of LCS.

6.4.1 Strengths and Limitations
This study may have been limited by selection bias, as people with symptoms may have been more likely to attend an LHC appointment. Due to the primary research question targeting socioeconomically deprived smokers [129], the cohort were predominantly current smokers and may have slightly higher rates of COPD and lung cancer than the wider LCS-eligible population. Nevertheless, similar lung cancer prevalence and demographics have been described in reports of other UK based pilots [39,40] suggesting the results observed here may be fairly close to what may be seen in the context of LCS in the UK. Given emerging evidence advocating selection of LCS-eligible individuals based on lung cancer risk [47,215], the findings reported here are generalisable to the desired LCS-eligible population. Secondly, many of the outcome measures were dependant on self-reported history and it is possible that true rates of diagnoses and inhaler use may have been underreported, and that some participants may have confused COPD with asthma. Conversely, some of our participants with airflow obstruction may have had asthma rather than COPD, though this is likely to be uncommon given the age and smoking history of the
participants. Thirdly, pre-bronchodilator spirometry was used to classify COPD, though the strict definition for COPD uses post-bronchodilator values. Several other studies including NLST [224] have used pre-bronchodilator spirometry as a metric, and it may be a more pragmatic approach to COPD case-finding in the context of LCS. Finally, emphysema was graded visually, and may be subject to inter-observer bias, though the quality assurance carried out suggested generally good agreement. A Fleischner society statement recommends a mixture of visual and quantitative assessment of CT emphysema, though this may be too onerous for reporting in the context of LCS [247] and an ideal, less subjective manner in which to grade and report emphysema in LCS is needed.

6.4.2 Conclusions
This study has demonstrated the significant burden of COPD, respiratory symptoms and comorbidities in a cohort of individuals attending a LHC. The large number of participants with ‘undiagnosed’ symptomatic, and asymptomatic COPD and emphysema, was also high, and these individuals may stand to gain more benefit from LCS. In addition, many of these participants were current smokers, and although the benefit of CT-detected emphysema over spirometric and symptomatic assessment seems modest, it may lead to the identification of a greater proportion of participants who may benefit from targeted smoking cessation interventions and may be at risk of clinically significant COPD in the future. Nevertheless, detection of COPD and emphysema in LCS could be used as a ‘teachable moment’ for smoking cessation and provide an opportunity for other lifestyle and pharmacological interventions that may improve COPD related morbidity in the future, particularly in those with symptoms and/or airflow limitation. Further prospective studies are needed to evaluate impact on smoking cessation and COPD exacerbation and hospitalisation rates in LCS participants.
Chapter 7. Results from a prevalence round of LDCT screening for lung cancer in the Lung Screen Uptake Trial

7.1 INTRODUCTION

Many questions about lung cancer screening (LCS) have been evaluated using data from the National Lung Screening Trial (NLST) and other LCS studies [17,248–251], however, how these data translate to a ‘real-world’, non clinical-trial setting is not clear. The NLST typically enrolled a younger, more educated, and former rather than currently smoking population compared to the population that might be targeted for LCS, particularly when considering the evidence that has shown that screening the highest risk quintiles can optimise the benefit-harm ratio to individuals while making LCS more efficient and cost-effective [47,252]. The UK Lung Cancer Screening Study (UKLS) used a risk-based approach to screening, which yielded a higher baseline lung cancer prevalence, but demonstrated the challenge of collecting the necessary information to calculate participants’ lung cancer risk and eligibility to LCS without deterring them from participating [75]. In fact, all the LCS trials, which have used a variety of strategies for inviting and risk profiling potential participants [77,253], have had a very low rate of uptake compared with numbers initially approached (table 7.1). The risk profile of the population enrolled determines subsequent factors such as the prevalence and stage of lung cancers, the false positive rate, the treatment rates and the overall mortality benefit [66].

Evidence suggests that using risk stratification (as opposed to basic age and smoking criteria as proposed in the 2015 recommendation for LCS by the US Preventative Services Task Force [USPSTF]) to determine eligibility into LCS, is the best strategy for enrolling the highest risk [51]. Several mathematical models have been proposed to predict risk of lung cancer, and perform with varying accuracy as indicated by the area under the receiver operating curve (AUROC) scores [48]. One model, the Prostate Lung Colorectal Ovarian (PLCO_m2012), was applied to the NLST dataset by Tammemagi and colleagues. It was noted that application of a 1.51% 6-year risk of lung cancer as predicted by this model in comparison with the NLST criteria would have deemed 8.8% less people as eligible for screening and a 12.4% higher proportion of cancers would have been detected, thus improving the false positive rate and positive predictive value of the screening test [51].
<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment Period</th>
<th>Recruitment Criteria</th>
<th>Participants</th>
<th>Method of Recruitment</th>
<th>Uptake/Enrolment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSLT</td>
<td>2002-2004</td>
<td>Age 55-74, ≥30PY, quit&lt;15 years ago</td>
<td>53,454</td>
<td>Mixed methods including media, mailing, community groups</td>
<td>3.7% enrolment rate</td>
</tr>
<tr>
<td>MILD</td>
<td>2005-2011</td>
<td>Age&gt;49, ≥20PY, quit&lt;10 years ago, no recent cancer within last 5 years</td>
<td>4,099</td>
<td>Media based</td>
<td>Not reported</td>
</tr>
<tr>
<td>ITALUNG</td>
<td>2004-2006</td>
<td>Age 55-69, ≥20PY</td>
<td>3,206</td>
<td>Mail</td>
<td>3206 randomised from 71,232 letters sent (enrolment efficacy 4.5%)</td>
</tr>
<tr>
<td>DANTE</td>
<td>2001-2006</td>
<td>Age 60-75, ≥20PY, quit&lt;10 years ago, male</td>
<td>2,472</td>
<td>Mail/ media/ via GP</td>
<td>Not reported</td>
</tr>
<tr>
<td>DEPISCAN</td>
<td>2002-2004</td>
<td>Age 50-75, ≥15PY</td>
<td>765</td>
<td>Via 232 GP/ occupational physicians</td>
<td>Very challenging recruitment, exact numbers recruited from approached unclear</td>
</tr>
<tr>
<td>DLCST</td>
<td>2004-2006</td>
<td>Age 50-70, ≥20PY, quit&lt;10 years ago, FEV1&gt;30%</td>
<td>4,104</td>
<td>Media based</td>
<td>Not reported</td>
</tr>
<tr>
<td>NELSON</td>
<td>2003-2006</td>
<td>Age 50-75, ≥15PY</td>
<td>15,822</td>
<td>Population/media based</td>
<td>Approximately 32% of approached returned questionnaire of which 26% were current smokers. In total of 335,441 patients approached to recruit 15,822 (4.7%)</td>
</tr>
<tr>
<td>UKLS</td>
<td>2011-ongoing</td>
<td>Age 50-75, ≥5% 5 year lung cancer risk as calculated by LLPv2 score</td>
<td>4,061</td>
<td>Population based</td>
<td>3.5% of 247,354 approached returned questionnaire and fulfilled eligibility criteria</td>
</tr>
<tr>
<td>IELCAP</td>
<td>1993-2006</td>
<td>Age&gt;60, ≥10PY</td>
<td>31,567</td>
<td>Unclear</td>
<td>Not reported</td>
</tr>
<tr>
<td>PANCAN</td>
<td>2008-2011</td>
<td>Age 50-75, ≥22% 3 year lung cancer risk as calculated by PLCO score</td>
<td>2,537</td>
<td>Media based</td>
<td>Not reported</td>
</tr>
<tr>
<td>COSMOS</td>
<td>2000-2001</td>
<td>Age&gt;50, ≥20PY</td>
<td>1,035</td>
<td>Media</td>
<td>Not reported</td>
</tr>
<tr>
<td>LUSI</td>
<td>2007-2011</td>
<td>Age 50-69, &quot;heavy&quot; smoking history</td>
<td>4,052</td>
<td>Population based</td>
<td>1.7% of 292,440 approached returned questionnaire and fulfilled eligibility criteria</td>
</tr>
</tbody>
</table>
The Liverpool Lung Project (LLP) model has also been previously used in UKLS at a threshold of 5% which was shown to be an effective strategy in terms of higher baseline lung cancer prevalence and cost-effectiveness whilst retaining the presumed benefits of early stage detection [24]. However, where exactly the optimum threshold for entry into screening is placed will be a trade-off between the positives (e.g. number of lives saved, lung cancers detected) and negatives (false positives, overdiagnosis, radiation, cost) [254]. No prior studies have prospectively compared the PLCO and the LLP models to the USPSTF criteria.

In addition, the feasibility of running an LCS programme in a National Health Service (NHS) setting is not known. In the US, it has been estimated there may be over 8 million individuals eligible for LCS, although less than 2% have been reported to have undertaken a LDCT as part of LCS [174]. While strategies to enhance uptake and minimise socioeconomic inequalities are needed and are being examined in the Lung Screen Uptake Trial [129] and in other screening pilots [40,255], what burden LCS would put on UK resources is not clearly known. Policy makers and service providers will need data on the expected numbers of individuals attending, being screened and with positive findings, and to understand any other potential barriers to implementation, in order to estimate workforce and costs and to put in place a high-quality service and LCS infrastructure.

### 7.1.1 Aims

The aims of the present study were to: a) assess the feasibility of implementing LDCT in an NHS setting in terms of achievability of low radiation dose, reading time capacity and volumetric nodule analysis; b) determine the number of individuals that may be eligible for LCS via primary care, and what proportion of those attending may be eligible for and complete an LDCT examination; and c) determine the nodule and lung cancer outcomes from the baseline LDCT in a non-clinical trial LCS setting.

### 7.2 METHODS

#### 7.2.1 Participants, setting and study design

This prospective observational cohort study evaluates the lung cancer and implementation related outcomes from the Lung Screen Uptake Trial (LSUT), the methods for which have been described previously [129] and in chapter 2. Briefly, individuals aged between 60 and
75, who had been recorded in their GP record as current smokers within the past 5 to 7 years, were invited by their primary care physician for a ‘lung health check’ (LHC) at one of two London hospitals between November 2015 and July 2017. Individuals were excluded if they had an active lung cancer diagnosis, cancer metastasis, were on palliative care treatment or had a lack of capacity to consent. Individuals attending the LHC were invited to participate in the study.

Those meeting the US Preventative Services Task Force (USPSTF) criteria for LCS (i.e. ≥30 pack-years and quit ≤15 years ago) [207], or a lung cancer risk of 1.51% as determined by the Prostate Lung Colorectal Ovarian study (PLCOm2012) model [130] or 2.5% as determined by the Liverpool Lung Project (LLP) model [49], were offered a LDCT scan on the same day to screen for lung cancer.

7.2.2 Data collection
Data were prospectively collected by a study practitioner at the LHC. Self-reported demographics (age, sex, ethnicity, education level, Index of Multiple Deprivation (IMD) score and rank), smoking, family and medical history were recorded (as detailed in chapter 2). Hand-held spirometry, height, weight and blood pressure were recorded. Radiological data was recorded by the radiologist at the time of reporting the LDCT and clinical and pathological outcomes were recorded by a thoracic clinical research fellow. Data reported in this chapter are based on outcomes recorded until 11 months after the last participant recruited.

7.2.3 Outcome measures
PLCO and LLP scores
The publicly available algorithms for both of these risk prediction tools [49,256] were programmed into the study electronic database. The PLCO model was adapted for UK use. The ethnicity categories ‘white’, ‘black’ and ‘other’, used the coefficients from the PLCO model for ‘white’, ‘black’ and ‘Asian’ respectively. The education categories were also translated to match the UK education system with the same number of categories matching to a similar age or qualification.
**LDCT**

LDCT scans were carried out in the acute scanner at each hospital site and were single-read by a team of radiologists with expertise in thoracic CT reporting, and experience ranging from 5 to 28 years. Radiologists recorded details on up to two nodules, the total number of nodules seen, and any incidental findings. Data on radiation dose was entered by a clinical research fellow, from the dose-report capture within the image series.

LDCT results were categorised into five categories as described in chapter 2. In this study, we report the outcomes relating to LDCT scans with a radiologist-designated category of ‘indeterminate pulmonary nodule’ or ‘suspicious of lung cancer’. Other outcomes from LDCT included scans with a pulmonary or non-pulmonary incidental findings that may have required further assessment or treatment, or no significant findings, which were categorised separately as described in chapter 2 (see also appendix 8). For the purpose of this analysis, we have grouped these 3 into a single category of ‘negative’ scans. Indeterminate pulmonary nodules included those typically under 8mm or 300mm³ that generally required a repeat scan at three or twelve months, and were managed according to the British Thoracic Society (BTS) guidelines for pulmonary nodules [44] (though radiologists’ discretion was also permitted). ‘Positive’ findings were referred to the local thoracic oncology multi-disciplinary team (MDT) for further assessment and were managed according to the BTS guidelines for pulmonary nodules [44] and the National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of lung cancer [257].

**Lung cancer**

Due to the small sample size, we have included all subtypes of invasive and non-invasive lung cancer within our definition of lung cancer. These included neuroendocrine tumours including small cell and carcinoid; adenocarcinoma, including minimally invasive adenocarcinoma (MIA), and adenocarcinoma in situ (AIS); and other non-small cell lung cancers, including squamous cell, adeno-squamous and large cell carcinomas. Staging was carried out according to the 7th edition TNM classification system as this was the edition in use in participating thoracic oncology MDT meetings for the majority of the study.
7.2.4 Sample size & statistical analysis

The sample size for LSUT was based on the primary behavioural research question and is described in chapter 2. For the present analysis, all study participants with complete smoking and lung cancer risk data were included. Participants were divided into three groups: those who did not have an LDCT, those who had an LDCT without lung cancer and those who had an LDCT who had a lung cancer diagnosed at some point during the follow up period. The follow up duration for participants in this chapter varied by date of enrolment into the study, but was a minimum of 11 months from the last participant recruited. Descriptive statistics were used to present the data required to address the research questions above.

7.3 RESULTS

Figure 7.1 shows the flow chart of participants in this study. The demographic characteristics of the 995 participants that were included in the present analysis are presented in table 7.2. A total of 31 lung cancers (4%) were diagnosed at a median follow up duration of 652 days (1.8 years).

![Flow chart of participants in the study]

Figure 7.1 Flow chart of participants in the study
Table 7.2 Participant characteristics by group (% totals may not sum up due to rounding, or missing data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>LDCT not performed n=227 median (IQR) or n (%)</th>
<th>No lung cancer n= 737 median (IQR) or n (%)</th>
<th>Lung cancers n=31 median (IQR) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (in years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 – 63</td>
<td>86 (37.9)</td>
<td>241 (32.7)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>64 – 67</td>
<td>72 (31.7)</td>
<td>240 (32.6)</td>
<td>9 (29.0)</td>
</tr>
<tr>
<td>68 – 72</td>
<td>47 (20.7)</td>
<td>161 (21.9)</td>
<td>10 (32.2)</td>
</tr>
<tr>
<td>73 – 76</td>
<td>22 (9.7)</td>
<td>95 (12.9)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>109 (52.0)</td>
<td>321 (43.6)</td>
<td>19 (61.3)</td>
</tr>
<tr>
<td>Male</td>
<td>118 (48.0)</td>
<td>416 (56.5)</td>
<td>12 (38.7)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>182 (80.2)</td>
<td>612 (83.0)</td>
<td>29 (93.6)</td>
</tr>
<tr>
<td>Black/ African/ Caribbean</td>
<td>23 (10.1)</td>
<td>77 (10.5)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (5.3)</td>
<td>7 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (1.3)</td>
<td>7 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (3.1)</td>
<td>31 (4.2)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Prefers not to say</td>
<td>0 (0)</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Highest Level of Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left school at or before age 15</td>
<td>105 (46.3)</td>
<td>399 (54.1)</td>
<td>16 (51.6)</td>
</tr>
<tr>
<td>CSEs, O-levels or equivalent</td>
<td>26 (11.5)</td>
<td>76 (10.3)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>A-levels or equivalent</td>
<td>24 (10.6)</td>
<td>70 (9.5)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Further education</td>
<td>14 (6.2)</td>
<td>31 (4.2)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>34 (15.0)</td>
<td>84 (11.4)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Further higher degree</td>
<td>19 (8.4)</td>
<td>64 (8.7)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.2)</td>
<td>13 (1.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Index of Multiple Deprivation (IMD) quintile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>117 (51.6)</td>
<td>404 (54.8)</td>
<td>17 (54.8)</td>
</tr>
<tr>
<td>2</td>
<td>86 (37.9)</td>
<td>248 (33.7)</td>
<td>9 (29.0)</td>
</tr>
<tr>
<td>3</td>
<td>3 (1.3)</td>
<td>17 (2.3)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>21 (9.3)</td>
<td>66 (9.0)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td><strong>Smoking History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>148 (65.2)</td>
<td>529 (71.8)</td>
<td>29 (93.6)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>79 (34.8)</td>
<td>208 (28.2)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Years smoked (years)</td>
<td>42 (32, 51)</td>
<td>47 (44, 51)</td>
<td>51 (47, 54)</td>
</tr>
<tr>
<td>Years quit (years)</td>
<td>0 (0, 3)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Average smoking intensity (cigs/day)</td>
<td>14 (8, 20)</td>
<td>20 (10, 20)</td>
<td>20 (10, 21)</td>
</tr>
<tr>
<td>Pack years</td>
<td>23 (10, 41)</td>
<td>38 (26, 51)</td>
<td>50 (26, 65)</td>
</tr>
</tbody>
</table>
### Table 7.2 (continued) Participant characteristics by group (% totals may not sum up due to rounding, or missing data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>LDCT not performed n=227</th>
<th>No lung cancer n=737</th>
<th>Lung cancers n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (IQR)</td>
<td>median (IQR) or n (%)</td>
<td>median (IQR) or n (%)</td>
</tr>
<tr>
<td><strong>Lung cancer risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLCO (% 6 year risk)</td>
<td>1.4 (0.39, 5.51)</td>
<td>3.74 (1.79, 7.15)</td>
<td>5.19 (2.94, 9.19)</td>
</tr>
<tr>
<td>LLP (% 5 year risk)</td>
<td>2.99 (1.55, 7.16)</td>
<td>5.57 (3.79, 8.75)</td>
<td>5.8 (4.56, 10.4)</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (l/min)</td>
<td>2.12 (1.68, 2.57)</td>
<td>2.06 (1.64, 2.55)</td>
<td>1.74 (1.12, 2.2)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>85 (69, 98)</td>
<td>82 (66, 96)</td>
<td>73 (53, 87)</td>
</tr>
<tr>
<td>FEV/FVC (%)</td>
<td>70 (63, 77)</td>
<td>69 (61, 75)</td>
<td>62 (54, 69)</td>
</tr>
<tr>
<td><strong>Other physical measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.8 (22.8, 29.1)</td>
<td>26.2 (23, 29.4)</td>
<td>23.5 (22.6, 26)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 (120, 148)</td>
<td>135 (124, 147)</td>
<td>133 (123, 152)</td>
</tr>
<tr>
<td><strong>WHO Performance Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0- Asymptomatic</td>
<td>202 (89.0)</td>
<td>665 (90.2)</td>
<td>23 (74.2)</td>
</tr>
<tr>
<td>1- Completely ambulatory</td>
<td>23 (10.1)</td>
<td>64 (8.7)</td>
<td>8 (25.8)</td>
</tr>
<tr>
<td>2- &lt;50% of day in chair/ bed</td>
<td>1 (0.4)</td>
<td>8 (1.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3- &gt;50% of day in chair/ bed</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4- Bedbound</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>LDCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up duration since LDCT (days)</td>
<td>N/a</td>
<td>651 (495, 785)</td>
<td>683 (580, 817)</td>
</tr>
</tbody>
</table>

### Table 7.3 CT acquisition and reporting parameters

<table>
<thead>
<tr>
<th></th>
<th>Median / n</th>
<th>IQR / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time taken to report each scan (mins)</td>
<td>10</td>
<td>5, 15</td>
</tr>
<tr>
<td>Time taken for CT report (days)</td>
<td>13</td>
<td>4, 24</td>
</tr>
<tr>
<td>Number of solid nodules with volume measured</td>
<td>46</td>
<td>53.5%</td>
</tr>
<tr>
<td>Effective radiation dose (1st 50 patients Homerton) (mSv)</td>
<td>1.7</td>
<td>1.1, 2.1</td>
</tr>
<tr>
<td>Effective radiation dose (cohort not including 1st 50 patients Homerton) (mSv)</td>
<td>1.2</td>
<td>0.9, 1.6</td>
</tr>
</tbody>
</table>
Table 7.4 Data from GP searches (extending smoking history to 15 years to be more consistent with a likely screening programme). *Some patients excluded due to exclusion criteria described in methods section above

<table>
<thead>
<tr>
<th>GP</th>
<th>Number of registered patients</th>
<th>Patients aged 60-75 as % of total registered</th>
<th>Smoking data complete (%)</th>
<th>Recorded as a current smoker in last 15 years (% of total registered aged 60-75)</th>
<th>Patients included from total aged 60-75* (%)</th>
<th>Final number as % of registered patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9571</td>
<td>3</td>
<td>99</td>
<td>35</td>
<td>28</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>4555</td>
<td>9</td>
<td>99</td>
<td>31</td>
<td>22</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>10982</td>
<td>8</td>
<td>99</td>
<td>35</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>4</td>
<td>12679</td>
<td>9</td>
<td>99</td>
<td>35</td>
<td>26</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>14101</td>
<td>8</td>
<td>99</td>
<td>37</td>
<td>29</td>
<td>2.3</td>
</tr>
<tr>
<td>6</td>
<td>6857</td>
<td>7</td>
<td>99</td>
<td>39</td>
<td>34</td>
<td>2.4</td>
</tr>
<tr>
<td>7</td>
<td>6018</td>
<td>7</td>
<td>100</td>
<td>32</td>
<td>24</td>
<td>1.6</td>
</tr>
<tr>
<td>8</td>
<td>5405</td>
<td>13</td>
<td>98</td>
<td>32</td>
<td>29</td>
<td>3.7</td>
</tr>
<tr>
<td>9</td>
<td>12024</td>
<td>6</td>
<td>99</td>
<td>33</td>
<td>28</td>
<td>1.8</td>
</tr>
<tr>
<td>10</td>
<td>7398</td>
<td>13</td>
<td>99</td>
<td>32</td>
<td>29</td>
<td>4.0</td>
</tr>
<tr>
<td>11</td>
<td>12784</td>
<td>9</td>
<td>99</td>
<td>32</td>
<td>23</td>
<td>2.0</td>
</tr>
<tr>
<td>12</td>
<td>12952</td>
<td>11</td>
<td>99</td>
<td>32</td>
<td>28</td>
<td>2.9</td>
</tr>
<tr>
<td>13</td>
<td>7528</td>
<td>5</td>
<td>98</td>
<td>26</td>
<td>17</td>
<td>0.9</td>
</tr>
<tr>
<td>14</td>
<td>8525</td>
<td>8</td>
<td>98</td>
<td>30</td>
<td>22</td>
<td>1.7</td>
</tr>
<tr>
<td>15</td>
<td>13473</td>
<td>9</td>
<td>99</td>
<td>31</td>
<td>26</td>
<td>2.2</td>
</tr>
<tr>
<td>16</td>
<td>11175</td>
<td>11</td>
<td>99</td>
<td>24</td>
<td>21</td>
<td>2.2</td>
</tr>
<tr>
<td>Mean</td>
<td>9752</td>
<td>8.5</td>
<td>98.9</td>
<td>32.3</td>
<td>25</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Table 7.3 shows that the median time taken to report a scan in the study was 10 minutes, and reports were generated within a median of 13 days. Just over half of solid nodules had volumetry recorded. The effective radiation dose\(^5\) was generally good (median= 1.2mSv), except for the first 20-50 scans at one participating site which had a CT scanner which was over seven years old, and for which the acquisition protocols had to be adapted to achieve the low dose.

Table 7.4 shows the data extracted at the time of carrying out the search of the GP databases. Smoking data was very well recorded (with 98.9% completeness), and a mean of 32.3% of participants aged 60-75 had been recorded as a current smoker within the preceding fifteen years. A number of individuals were excluded from the search

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\(^5\) The radiation dose data entry was not complete at the time of writing this thesis, and the data presented exclude 31 participants with missing data of 770 LDCT performed.
for reasons such as dementia or a history of metastatic cancer, as described in chapter 2. A mean of 2.2% of registered patients per practice would have been eligible for invitation to LCS6.

A total of 895 (89.9%) of participants were eligible by one or more of the three eligibility criteria, and 85.7% of them completed an LDCT (table 7.5). The PLCO model selected 73.3% of participants for LDCT, and 90.3% of all lung cancers were in this group. Conversely the USPSTF criteria selected fewer individuals for screening (61.5%) and detected fewer lung cancers (71%) while the LLP model at a threshold of 2.5% was the most permissive model allowing 83.4% of individuals to be eligible for an LDCT scan, and 93.5% of all cancers were present in this group.

Table 7.5 Eligibility to LDCT. *includes 1 participant who had a scan due to incorrect entry of gender into risk score calculator, which when corrected was below the required threshold

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting any 3 criteria</td>
<td>895</td>
<td>89.9</td>
</tr>
<tr>
<td>Completed LDCT *</td>
<td>768</td>
<td>85.7</td>
</tr>
<tr>
<td>Lung cancers in whole cohort</td>
<td>31</td>
<td>100.0</td>
</tr>
<tr>
<td>LLP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants meeting 2.5 threshold</td>
<td>830</td>
<td>83.4</td>
</tr>
<tr>
<td>Completed LDCT</td>
<td>708</td>
<td>85.3</td>
</tr>
<tr>
<td>Lung cancers in this group</td>
<td>29</td>
<td>93.5</td>
</tr>
<tr>
<td>PLCO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants meeting 1.51% threshold</td>
<td>731</td>
<td>73.5</td>
</tr>
<tr>
<td>Completed LDCT</td>
<td>622</td>
<td>85.1</td>
</tr>
<tr>
<td>Lung cancers in this group</td>
<td>28</td>
<td>90.3</td>
</tr>
<tr>
<td>USPSTF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants meeting USPSTF threshold</td>
<td>612</td>
<td>61.5</td>
</tr>
<tr>
<td>Completed LDCT</td>
<td>524</td>
<td>85.6</td>
</tr>
<tr>
<td>Lung cancers in this group</td>
<td>22</td>
<td>71.0</td>
</tr>
</tbody>
</table>

N.B. the data from the GP searches presented here differ from the search carried out in LSUT, which specifically targeted current smokers and therefore invited individuals recorded as a current smoker within the previous 5-7 years. Here we present the search for those recorded as a current smoker within the past 15 years as these data may be more relevant to a LCS programme if it were implemented nationally.
Table 7.6 LDCT scan completion rates, and reasons for non-completion

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
<th>% of total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had CT</td>
<td>768</td>
<td>77.2</td>
</tr>
<tr>
<td>Declined</td>
<td>67</td>
<td>6.7</td>
</tr>
<tr>
<td>Did not attend</td>
<td>24</td>
<td>2.4</td>
</tr>
<tr>
<td>Not eligible</td>
<td>136</td>
<td>13.7</td>
</tr>
<tr>
<td>Insufficient smoking history</td>
<td>99</td>
<td>10.0</td>
</tr>
<tr>
<td>Previous CT thorax in past year</td>
<td>35</td>
<td>3.5</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 7.7 Outcome from baseline scan. *1 participant had a radiological diagnosis of lung cancer and an extra-thoracic cancer. Extra-thoracic cancers include 2 bowel cancers, 1 head and neck cancer and 1 sarcoma (leg)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal scan</td>
<td>615</td>
<td>80.1</td>
</tr>
<tr>
<td>Indeterminate pulmonary nodule</td>
<td>119</td>
<td>15.5</td>
</tr>
<tr>
<td>No cancer</td>
<td>105</td>
<td>88.2</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>12</td>
<td>10.1</td>
</tr>
<tr>
<td>Multiple or mixed histology (small cell + non-small cell)</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Referred to MDT</td>
<td>34</td>
<td>4.4</td>
</tr>
<tr>
<td>No cancer</td>
<td>14</td>
<td>41.2</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>11</td>
<td>32.4</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Multiple or mixed histology (small cell + non-small cell)</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Radiological diagnosis</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Benign resection</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Extra-thoracic cancers*</td>
<td>3</td>
<td>8.8</td>
</tr>
</tbody>
</table>

The rate of conversion from the LHC to LDCT was 77.2%, and of those who did not undergo an LDCT, 10% had a smoking history or lung cancer risk too low to be eligible for LDCT (table 7.6). The remainder declined, failed to attend or were ineligible by other reasons.

80% of participants had a negative scan, 15.5% had an indeterminate pulmonary nodule for surveillance and 4.4% of participants had a ‘positive’ result and were referred to the thoracic oncology MDT (table 7.7). 19 lung cancers were diagnosed directly from the baseline scan, and a further 14 cancers were diagnosed from surveillance of the
indeterminate pulmonary nodules. In addition, four extra-thoracic cancers were detected in the study (one head and neck, one sarcoma of the leg and two bowel cancers⁷). There were two false positives where participants had benign resections. The majority of nodules and cancers were solid nodules on the baseline scan (56.7%), and almost a quarter were in the right upper lobe (table 7.8). Of those with pure ground glass lesions classed as lung cancer in this analysis, one was AIS, one was a radiological diagnosis, and two were invasive adenocarcinoma. Figure 7.2 shows the CT images of one participant with an indeterminate nodule that was subsequently a resected squamous cell carcinoma.

45 participants underwent a positron emission tomography (PET) scan, while 9 had endobronchial ultrasound and 18 participants had surgical resection without prior histological confirmation of malignancy, though some had undergone diagnostic staging examinations (Table 7.8). 2 of 33 (9.5%) lung resections were subsequently found to be benign.

71% of lung cancers were stage I or II and 23% were non-small cell lung cancer (table 7.9). Of those with non-small cell lung cancer, 75.9% had curative-intent treatment (including sub-lobar resection, lobectomy and stereotactic ablative radiotherapy [SABR]). Of the two participants with small cell lung cancer, both had concurrent chemo-radiation. 29% of participants had advanced stage (III or IV) disease, and as a result 13.8% had palliative chemotherapy or radiotherapy only. A detailed table of all the lung cancers is presented in table 7.10.

---

⁷ One bowel cancer was detected from a non-pulmonary incidental finding of a liver lesion from the baseline scan, and so was not diagnosed from the thoracic oncology MDT.
Table 7.8 Characteristics of the indeterminate pulmonary nodules detected in the study

<table>
<thead>
<tr>
<th>Nodule type</th>
<th>Cancers n=31</th>
<th>Non-cancers n=122</th>
<th>Total n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid nodule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>67.7%</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Part solid nodule</td>
<td>1</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Pure ground glass nodule</td>
<td>4</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>9</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>3</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>10</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>5</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>25</td>
<td>28</td>
</tr>
</tbody>
</table>

Figure 7.2 Serial radiology images of enlarging solid nodule confirmed to be Squamous cell carcinoma, T1bN0M0, treated with lobectomy- pT1bN0MxPL0R0.
Table 7.9 The stage and histology distribution and investigation and treatment rates from the baseline LDCT scan

<table>
<thead>
<tr>
<th>Diagnostic or staging investigations</th>
<th>Number</th>
<th>% of total lung cancers unless *otherwise specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron Emission Tomography (PET)</td>
<td>45</td>
<td>145</td>
</tr>
<tr>
<td>Percutaneous non-lung biopsy</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Other percutaneous biopsy</td>
<td>4</td>
<td>12.9</td>
</tr>
<tr>
<td>Cervical lymph node FNA</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Fibre-optic bronchoscopy</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Endobronchial ultrasound</td>
<td>9</td>
<td>29.0</td>
</tr>
<tr>
<td>Endoscopic ultrasound</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>1st histology at video-assisted or open surgical procedure</td>
<td>18</td>
<td>58.0</td>
</tr>
<tr>
<td>Lung resection</td>
<td>21</td>
<td>67.8</td>
</tr>
<tr>
<td>Benign lung resection (*% is of total lung resections)</td>
<td>2</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>23</td>
<td>74.2</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Multiple or mixed histology (small cell + non-small cell)</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Radiological diagnosis</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Stage (TNM 7th edition)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I &amp; II</td>
<td>22</td>
<td>71.0</td>
</tr>
<tr>
<td>Ia</td>
<td>18</td>
<td>58.1</td>
</tr>
<tr>
<td>Ib</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIA</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>IIB</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>IIIa</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>IIIb</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Treatments (NSCLC) (*% are of total NSCLC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative intent</td>
<td>22</td>
<td>75.9</td>
</tr>
<tr>
<td>Sub-lobar resection</td>
<td>8</td>
<td>27.6</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>13</td>
<td>44.8</td>
</tr>
<tr>
<td>SABR</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>Concurrent chemo-radiation</td>
<td>2</td>
<td>6.9</td>
</tr>
<tr>
<td>Palliative chemo-radiation</td>
<td>4</td>
<td>13.8</td>
</tr>
<tr>
<td>Surveillance</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Treatments (SCLC) (*% are of total SCLC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent chemo-radiation</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 7.10 All 31 cancers as recorded at the beginning of July 2018

<table>
<thead>
<tr>
<th>Route of diagnosis</th>
<th>Diagnosis</th>
<th>Histology</th>
<th>Primary treatment</th>
<th>Clinical TNM stage (pre-treatment)</th>
<th>Final clinical stage I-IV</th>
<th>Final TNM stage</th>
<th>Final pathological stage I-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PLO R0</td>
</tr>
<tr>
<td>2</td>
<td>Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PLO R0</td>
</tr>
<tr>
<td>3</td>
<td>Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Sub-lobar resection</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PLO R1</td>
</tr>
<tr>
<td>4</td>
<td>Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Adeno-squamous cell carcinoma</td>
<td>Lobectomy</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PLO R0</td>
</tr>
<tr>
<td>5</td>
<td>Nodule surveillance</td>
<td>Adenocarcinoma in situ</td>
<td>Adenocarcinoma in situ</td>
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</tr>
<tr>
<td>6</td>
<td>Baseline scan to MDT</td>
<td>Carcinoid</td>
<td>Carcinoid</td>
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<td>Stage 1A</td>
<td>pT1aN0M0 PLO R0</td>
</tr>
<tr>
<td>7</td>
<td>Baseline scan to MDT</td>
<td>Mixed/ multiple histology lung cancer</td>
<td>3 separate primaries: 2 contralateral invasive adenocarcinoma and 1 small cell</td>
<td>Sub-lobar resection</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PLO R1</td>
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<tr>
<td>8</td>
<td>Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>Sub-lobar resection</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>N/a</td>
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<td>9</td>
<td>Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T1aN0M0</td>
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</tr>
<tr>
<td>10</td>
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<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PLO R0</td>
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Table 7.10 (continued) All 31 cancers as recorded at the beginning of July 2018

<table>
<thead>
<tr>
<th>Route of diagnosis</th>
<th>Diagnosis</th>
<th>Histology</th>
<th>Primary treatment</th>
<th>Clinical TNM stage (pre-treatment)</th>
<th>Final clinical stage I-IV</th>
<th>Final TNM stage</th>
<th>Final pathological stage I-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Undifferentiated or poorly differentiated carcinoma</td>
<td>Lobectomy</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PL0 R0</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>12 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Undifferentiated or poorly differentiated carcinoma</td>
<td>Sub-lobar resection</td>
<td>T1aN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PL0 R1</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>13 Baseline scan to MDT</td>
<td>Small cell lung cancer</td>
<td>Small cell lung cancer</td>
<td>Concurrent chemoradiation</td>
<td>T1aN1M0</td>
<td>Stage 2A</td>
<td>pT1aN0M0 PL0 R0</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>14 Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>Lobectomy</td>
<td>T1bN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PL0 R0</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>15 Baseline scan to MDT</td>
<td>Radiological diagnosis of lung cancer</td>
<td>N/a</td>
<td>SABR</td>
<td>T1bN0M0</td>
<td>Stage 1A</td>
<td>pT1aN0M0 PL0 R0</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>16 Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Sub-lobar resection</td>
<td>T1bN0M0</td>
<td>Stage 1A</td>
<td>N/a</td>
<td>N/a</td>
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<tr>
<td>17 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>Lobectomy</td>
<td>T1bN1M0</td>
<td>Stage 2A</td>
<td>pT4N1M0 PL2 R1</td>
<td>Stage 3A</td>
</tr>
<tr>
<td>18 Baseline scan to MDT</td>
<td>Radiological diagnosis of lung cancer</td>
<td>N/a</td>
<td>No treatment</td>
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<td>Stage 1B</td>
<td>pT2aN1M0 PL0 R0</td>
<td>Stage 2A</td>
</tr>
<tr>
<td>19 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T2aN1M0</td>
<td>Stage 2A</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>20 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T2bN0M0</td>
<td>Stage 2A</td>
<td>pT1bN1M0 PL0 R0</td>
<td>Stage 2A</td>
</tr>
<tr>
<td>21 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Concurrent chemoradiation</td>
<td>T1aN2M0</td>
<td>Stage 3A</td>
<td>pT1aN0M0 PL1 R0</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>22 Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Sub-lobar resection</td>
<td>T1bN0M0</td>
<td>Stage 1A</td>
<td>N/a</td>
<td>N/a</td>
</tr>
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</table>
Table 7.10 (continued) All 31 cancers as recorded at the beginning of July 2018

<table>
<thead>
<tr>
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<th>Final TNM stage</th>
<th>Final pathological stage I-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Concurrent chemo-radiation</td>
<td>T2aN2M0</td>
<td>Stage 3A</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>24 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Lobectomy</td>
<td>T2aN2M0</td>
<td>Stage 3A</td>
<td>pT2aN2M0 R0 PL0</td>
<td>Stage 3A</td>
</tr>
<tr>
<td>25 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Squamous cell carcinoma</td>
<td>Palliative radiotherapy</td>
<td>T2bN2M0</td>
<td>Stage 3A</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>26 Nodule surveillance</td>
<td>Mixed/ multiple histology lung cancer</td>
<td>Mixed adenocarcinoma + large cell</td>
<td>Lobectomy</td>
<td>T3N0M0</td>
<td>Stage 2B</td>
<td>N/a</td>
<td>N/a</td>
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<tr>
<td>27 Nodule surveillance</td>
<td>Non-small cell lung cancer</td>
<td>Large cell carcinoma</td>
<td>Lobectomy</td>
<td>T3N1M0</td>
<td>Stage 3A</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>28 Baseline scan to MDT</td>
<td>Small cell lung cancer</td>
<td>Small cell lung cancer</td>
<td>Concurrent chemo-radiation</td>
<td>T4N2M0</td>
<td>Stage 3B</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>29 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Palliative chemotherapy</td>
<td>T1aN2M1b</td>
<td>Stage 4</td>
<td>N/a</td>
<td>N/a</td>
</tr>
<tr>
<td>30 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Palliative chemotherapy</td>
<td>T4N3M1b</td>
<td>Stage 4</td>
<td>pT1bN0M0 PL0 R0</td>
<td>Stage 1A</td>
</tr>
<tr>
<td>31 Baseline scan to MDT</td>
<td>Non-small cell lung cancer</td>
<td>Invasive adenocarcinoma</td>
<td>Palliative chemotherapy</td>
<td>T4N3M1b</td>
<td>Stage 4</td>
<td>pending</td>
<td>pending</td>
</tr>
</tbody>
</table>
7.4 DISCUSSION

This observational cohort study demonstrated that approximately 2% of patients registered to a London GP practice may be considered high enough risk to be assessed for eligibility for LCS. Of 2012 individuals invited, about half underwent an LHC, and 77% of those completed an LDCT examination, while for about 10% of participants, their lung cancer risk or smoking history was too low to be eligible for an LDCT scan. The LLP and PLCO risk models allowed greater numbers of individuals to be scanned, and detected more lung cancers than the USPSTF criteria. Indeterminate pulmonary nodules were diagnosed in 15.5% of participants, and the majority of these were solid nodules. Lung cancer was detected in 4%. 71% of participants with non-small cell lung cancer were early stage, and 76% had treatment with curative intent.

That smoking data was so well recorded in primary care is reassuring, and suggests using primary care databases may be a viable strategy for inviting participants to LCS. While alternative strategies may also be viable and warrant appraisal, these would require a pre-LHC assessment of smoking history. Prior studies have utilised such a two-phased approach with disappointing results. In NELSON, more than two thirds of individuals failed to return an initial risk assessment questionnaire, and less than 5% of those initially approached were finally recruited to the study [78]. What is not clear from the data presented here, however, is how many eligible participants have been missed by this strategy, perhaps due to incorrect coding at the practice, and how many potential cancers may have been missed. Further studies are needed to evaluate this in more detail.

The high attendance rate is revelatory and contradictory to evidence on uptake to prior LCS studies [17,18,22,75,78]. The specific reasons for this are likely to be multifactorial and will be addressed in a detailed analysis relating to the primary research question of LSUT. We believe that the stepped invitation strategy, the invitation letter that was addressed from patients’ GP and the pre-allocated appointments may have all been contributing factors [258]. Further analysis is required to fully determine which factors enhance engagement and uptake, and implementing these measures will be crucial to the successful implementation of LCS.
Again, supporting the feasibility of inviting participants via primary care, is the high conversion rate to LDCT. Participants had very little knowledge of LCS prior to attending, and were being invited to an LHC. That only 10% did not meet the eligibility criteria, and 9% chose not to attend the LDCT (despite having to wait for an appointment for an acute scanner), resulted in an efficient programme. Even after participants were given the opportunity to make an informed choice about whether to participate, the majority opted to do so, suggesting there is an appetite for LCS amongst individuals in London.

The conversion rate to LDCT is dependent on what criteria are used to determine eligibility to LDCT. The data presented here represent the first prospective comparison of the USPSTF criteria with the LLP and PLCO models. The LLP model at a threshold of 2.5% was most permissive risk model, and unsurprisingly therefore, detected the most cancers (94%). The USPSTF criteria alone, on the other hand, deemed almost 40% less participants eligible for LDCT than performed in this study, but would have missed almost a third of the cancers. The PLCO model detected 90% of cancers (one less than the LLP model) and required over a quarter fewer LDCTs than performed in this study. These data need to be interpreted with caution due to the low numbers of cancers, and the sample has insufficient power to detect a true difference in performance between these models; nevertheless this data supports findings from studies demonstrating that risk based entry into screening is superior to age and smoking history alone [47,259,260]. A previous retrospective study has suggested the PLCO model may be superior to other models [52] and future larger prospective studies are needed to confirm this finding. The appropriate threshold for entry into screening needs to carefully weigh up the harmful effects of more LDCT scans (such as cost, radiation and indeterminate pulmonary nodules) with the positive effects of detecting and curing more lung cancers. Emerging evidence also suggests that those at very high risk of lung cancer are also at risk of death from competing causes, other than lung cancer, and LCS in these individuals may not have as high a magnitude of benefit as that reported in the NLST [244–246,261]. However, conflicting data [262] suggests that when the lowest-risk group are excluded, competing risk of death is similar between the groups selected by risk based or NLST-like criteria. It is therefore unclear whether a ceiling of entry to LCS due to comorbidities should be implemented and further work is needed to better define the group to whom the mortality benefit seen in NLST may not apply [246]. In addition, introduction of a ceiling of entry to LCS is ethically challenging and it would be important to communicate these complex issues to participants, which is also challenging.
Low radiation dose for the CT was achieved in this study, despite initial difficulties due to the age of the CT scanner at one site. However, whilst the images were acceptable, some images were slightly granular, and optimisation of these images would be preferable. Almost half of participants with solid nodules did not have volume recorded. This was likely due to the fact that volumetry was not readily available at one of our participating sites, and so obtaining volumetric measurements added too much time to the reporting time and was not feasible during the study. The median time taken to read a scan was 10 minutes and the average number of days to generate a report was 13 days. While the latter is an acceptable number, it was higher than we had anticipated, with greater delays at times of understaffing in the radiology department. As scanners and imaging information technology in the NHS are updated, some of these problems will dissipate, however this data highlights the need for a dedicated LCS infrastructure and workforce if LCS is to be implemented.

The rate of indeterminate pulmonary nodules was much lower than in NLST [17] and NELSON [23] and is in keeping with another UK based LCS pilot in Manchester [40]. This may have been due to implementation of the 2015 BTS pulmonary nodule guidelines which enables a more conservative approach to nodules smaller than 5mm [44]. Despite this, a high rate (4%) of lung cancer was detected, which was unexpected, given the majority of large LCS trials have detected cancers in the range 1-2% [17,42,249]. Notably other LCS cohorts, including one where individuals were selected by virtue of spirometry consistent with COPD, have demonstrated a similar lung cancer prevalence to that seen here [40,263]. In addition, 71% were diagnosed with early stage disease and 76% received treatment with curative intent. This is slightly lower than the 86% and 83% of stage I and II disease and surgical resection rates observed in UKLS [249], which again may reflect the population screened [75] as 29% of participants with confirmed cancer had stage III or IV disease. The incidence of early stage lung cancer would be likely to improve if further annual or biennial screening were taking place. Similar surgical resection rates have been observed in the other LCS pilots [40,264], suggesting it is feasible to uphold a high standard outside of a large clinical trial setting. These similarities likely reflect the ‘real-world’ populations recruited (who were more commonly from low socio-economic position backgrounds), the risk-based approach to determining eligibility to LDCT, and the BTS-based nodule management algorithms adopted by both programmes. It is possible that the greater lung cancer to indeterminate pulmonary nodule ratio observed in these pilots will result in a
greater balance of benefit to harms than that seen in NLST, and may result in an even greater mortality benefit with the above caveat relating to risk of competing mortality.

7.4.1 Strengths and limitations
As this study was intended to be a pilot study, it was limited by the small sample size and low number of cancers. Despite this, a great amount of data and experience has been generated and can be utilised in the planning of further LCS projects in the UK. LSUT was a charity-funded behavioural research study, and so did not have the necessary funding for putting in place the optimal LCS infrastructure, but it has highlighted where such funding would be most required to deliver an efficient and high-quality LCS programme.

7.4.2 Conclusions
In this observational cohort study we have demonstrated that it is feasible to carry out LCS by LDCT. The study has highlighted areas where resources are required in order to scale up the service. We have also demonstrated that invitation via primary care is a viable strategy resulting in good uptake to the LHC and conversion to LDCT, and the data presented here support that a risk-based strategy to determine eligibility into screening is superior to the USPSTF criteria. Of those screened, the rate of indeterminate pulmonary nodules was lower and the rate of lung cancer was higher than expected, suggesting that LCS in a ‘real-world’ setting may result in less harms and be more efficient and cost-effective than estimated from the larger LCS studies.
Chapter 8. Discussion

Outcomes from lung cancer remain poor globally, with late stage of presentation and thus limited options for curative treatment [1,2]. Chapter 1 described how lung cancer screening (LCS) has evolved over time, and that using low dose CT (LDCT) can reduce lung cancerspecific and all-cause mortality [17]. Also discussed was the evidence base around LCS, which is large and continually growing. Despite this, a number of questions around LCS implementation remain. When determining key decisions such as who screening should be offered to, and how the findings from LCS should be managed, considerations need to be made to the balance of harms and benefits to the patient, the benefit to the population, and cost and resource implications. As well as relying on the existing evidence base, data from ‘real world’ pilot studies such as that described in this thesis will aid policy makers to plan LCS service and infrastructure. The specific findings from each chapter are summarised below with the relevant implications of these findings, and areas for further research.

8.1 PART A: COMMUNICATING BENEFITS AND HARMS AND ENHANCING INFORMED DECISION-MAKING

8.1.1 What is the background knowledge and perception of lung cancer amongst LCS-eligible individuals, and what information should be presented and how?

Chapter 3 used qualitative data from smokers and former smokers from within the relevant age bracket for LCS, and HCPs who have been involved in public health and the care of patients with lung cancer, to understand better how best to meet their needs and to enhance informed decision-making (IDM). This chapter highlighted the importance of educating individuals about LCS as many people expressed fatalistic views, a poor understanding of the benefits and harms, and expressed a desire for the opportunity to make an informed choice. The findings suggest that providing an avenue for IDM is unlikely to unduly deter individuals from screening; in fact, the qualitative analysis showed that people generally perceived screening as beneficial and individuals did not express a great deal of concern about the risks of overdiagnosis and radiation exposure. Ultimately, it emerged that it is important not to overburden people with too much complex information,
and to emphasise the benefits as much as the harms in order to empower people to taking positive steps towards their health.

As well as highlighting the poor awareness and understanding of many of the harms of screening, this study demonstrated the relative value of these harms to individuals. False negatives and false positives were of most concern, suggesting that LCS governance and quality assurance processes need to be firmly in place in order to reduce the frequency of these events. Indeterminate pulmonary nodules, overdiagnosis and radiation exposure can also be minimised by on-going refinement of nodule management protocols, and by adopting a more conservative approach where the evidence supports this [265,266]. We believe this research can directly impact LCS policy, which should consider participants’ views on these harms when designing protocols for the management of screen-detected findings. In addition, information materials should incorporate these principles in order to successfully educate individuals and help minimise the uncertainty often associated with these harms [166]. Future work could be directed at determining whether these strategies may reduce some of the psychological harms associated with LCS and explore factors affecting decision certainty.

Smoking cessation should be a central component of any LCS programme, though how best to do so is not clearly known [267], and a large collaboration aimed at addressing many issues within the field of smoking cessation in LCS is underway [267]. In this study we found that participants often battled with the addiction of smoking, and although some displayed cognitive dissonance towards these harms, most were aware of them, and responded poorly to preaching or fear-inducing messages. Life experiences such as relatives with cancer and ill health were reported to have positively impacted motivations to quit, suggesting a possible role for LCS and perhaps the use of smoking-related incidental findings to provide a ‘teachable moment’ in order to enhance abstinence rates. From these data we propose that the message for smoking cessation should be an empowering one, that highlights the benefits of stopping smoking and gives people the means to do so. Future work could further explore the feasibility of using smoking-related incidental findings in LCS to promote smoking cessation and further evaluate barriers to smoking cessation in this population, and whether use of the techniques suggested here can impact outcomes in smoking cessation.
8.1.2 Does a novel information film enhance informed decision-making in individuals considering LCS, more than a standard information booklet?

Based on the findings in chapter 3, a novel information film that aimed to improve knowledge in an educationally diverse population was developed. Chapter 4 described a study that used a randomised design to validate the use of the information film to enhance components of IDM. It demonstrated that this tool could be used to educate people about the harms and benefits of LCS, and was more effective at doing so than a written booklet alone. The film was well received, and more people watched all of it than read all the booklet, and more people understood all or most of the film than those who understood all or most of the booklet. Overall the film plus booklet improved subjective and objective knowledge and reduced decisional conflict more than the booklet alone, and had no impact on numbers of participants completing an LDCT. This study was strengthened by its high-risk population, who were invited to an LHC by their GP and faced with the decision of whether or not to undergo an LDCT. In addition, the medium of film lends itself to be easily adapted for local preferences such as replacing the voice-over with local accents. The film could be shown on a loop in an LHC centre so participants waiting for an LHC could have standardised information in an engaging format, that has been proven to enhance components of IDM more than a written booklet alone, while waiting for the HCP discussion and LDCT consent process.

Participants could also have the information film made available to them prior to attending, so that they would be better informed on arrival. The lack of adverse impact on LDCT completion in the study is encouraging, though caution must be taken as this was in a group of individuals already attending and engaged in the screening process. Future work could be carried out to determine the impact of the film on uptake to LCS if it were watched prior to attending the LHC. Nevertheless, the film was not felt to be balanced against screening, suggesting that individuals open to LCS may not be unduly deterred by the film. Other future work could evaluate longer-term knowledge retention and decision satisfaction, and could involve expansion of the film to include interactive and/or ‘values clarification’ elements (intended to align the decision with the participant’s values) that may further aid the decision-making process.
8.2 PART B: OPTIMISING BENEFITS AND HARMS

8.2.1 What is the prevalence and value of coronary calcium and cardiovascular risk in the context of LCS?

Chapter 5 evaluated prospectively collected data from the Lung Screen Uptake Trial (LSUT) to assess the value of cardiovascular disease (CVD) risk assessment and grading of coronary artery calcification (CAC) on LDCT. The most striking finding was that 98% of participants who had an LDCT and who were without a prior history of CVD, had an estimated 10-year CVD risk of ≥10%, but more than half of these individuals did not report a history of statin use despite 90% of them having seen their GP in the past year. This suggests there may be an opportunity to improve cardiovascular health and outcomes by instituting lifestyle modification advice and primary prevention with statin therapy in almost all individuals undergoing LCS. Although there was an association between increasing CAC severity and increasing QRISK2 score, there was no clear evidence of benefit from reporting CAC grade to participants or GPs when the necessary interventions were already indicated in the majority of individuals by virtue of their QRISK2 alone. Roughly half the participants with a moderate CVD risk (10-20%) had no visible CAC on LDCT, though the utility for this is also somewhat limited, as the relatively high cardiovascular event rate in the USPSTF-eligible sub-cohort from the Multi-Ethnic Study of Atherosclerosis (MESA) study suggests statins are still worthwhile in this group despite an absence of CAC, due to their high CVD risk [208].

It was unclear from our data whether the lack of statin use in our cohort was because participants had not had prior CVD risk assessment, or they had declined statin use. Further studies are needed to evaluate prior CVD risk assessment, attendance to NHS health checks and reasons for statin non-use in individuals attending for LCS. Nevertheless, given the previously reported low rates of statin use in those who qualify for statins following an NHS cardiovascular health check [211], it is possible that reporting of CAC on LDCT could act as a motivating factor for initiating statins. Future work could be carried out to determine the impact of reporting LDCT-detected CAC to participants on initiation and adherence to statin primary prevention and other lifestyle modifications such as smoking cessation.
We did not measure serum cholesterol values in this cohort, as this would add time and cost to the LHC. This is an issue that would remain problematic if LCS were scaled to national implementation, and therefore there is a need to determine whether measured serum cholesterol values are needed in this context and whether they are needed for acceptable accuracy of the estimated CVD risk. This could be established in longitudinal studies that evaluate the long term fatal and non-fatal cardiovascular event rates to further understand the value of CAC and serum cholesterol in predicting cardiovascular events, relative to other well established clinical and demographic predictors. The cost-effectiveness of strategies with and without measurement of serum cholesterol and CAC could also be modelled.

8.2.2 What is the prevalence and value of Chronic Obstructive Pulmonary Disease and emphysema case finding in the context of LCS?

Chapter 6 used data from LSUT to evaluate the intersection between spirometry, emphysema, comorbidities and Chronic Obstructive Pulmonary Disease (COPD) symptoms in LCS participants. The study demonstrated that airflow obstruction consistent with COPD is common (56.8%) in LCS individuals attending an LHC. A significant number of participants with spirometry consistent with COPD also reported respiratory symptoms, and unsurprisingly this increased with GOLD severity. Recent evidence suggests comorbidities are important in the assessment and prognosis of COPD [232] and these occurred in a significant proportion, thus supporting the findings from chapter 5 of the need for instituting lifestyle modifications (e.g. for reducing cardiovascular risk) in this cohort. The data presented also suggest possible underuse of inhalers, though this may be mostly explained by under-diagnosis of COPD and needs further assessment in future work in the context of exacerbation frequency and Medical Research Council (MRC) dyspnoea score, which are important in determining treatment decisions in the newer Global Initiative for Obstructive Lung Disease (GOLD) guidelines [231].

There was a significant burden of undiagnosed COPD (67% of all those with spirometric COPD), and 91% of these individuals had spirometry consistent with GOLD I or II. Recent reports suggest this is the group that stands to gain the most benefit from LCS, with double the relative reduction of lung cancer-specific mortality than that reported in NLST [244]. Symptoms were more common in those with known COPD compared with those with
‘undiagnosed’ COPD. Nevertheless, almost 40% of the ‘undiagnosed’ COPD participants with emphysema and airflow limitation also had symptoms suggestive of COPD, suggesting many would benefit from COPD assessments, e.g. by their general practitioner (GP). Associations between asymptomatic COPD and emphysema, and endpoints such as lung function decline, exacerbation frequency and hospitalisation, are less well established than in those with symptoms [227,228], however exciting new data suggests there may be a role for therapeutic agents such as tiotropium, which has been shown to result in reduced lung function decline and exacerbation frequency in patients with asymptomatic, mild COPD [243]. Emphysema was fairly common, though often not associated with airflow limitation, while a combination of emphysema with airflow limitation was significantly associated with the prevalence of dyspnoea, and likely represents clinically significant disease.

These data together with the available evidence base [228,231,232] suggest that case finding and early detection of emphysema may be worthwhile in those with airflow limitation particularly in the presence of symptoms suggestive of COPD, and can result in important interventions such as symptom awareness education, vaccination against respiratory infection and appropriate inhaled therapies. For now, smoking cessation remains the only indicated intervention in those with asymptomatic COPD or emphysema without airflow obstruction, though emerging data may suggest new targets to improve prognosis in these individuals in the future. Nevertheless, the value of LDCT-detected emphysema may be less than gained from spirometry and symptom assessment. While many of these participants may develop clinically significant COPD in the future and may benefit from monitoring, it remains unclear whether case finding of COPD is cost-effective and whether it reduces exacerbations and hospitalisations. Longitudinal cohort studies collecting data on future COPD symptoms and diagnoses, exacerbation frequency and hospitalisations in LCS participants with and without symptoms, airflow limitation and LDCT-detected emphysema are needed.

The caveat to this is that smoking cessation is the one intervention that is indicated in all currently smoking participants. Informing participants about the prevalence of clinically insignificant smoking related changes such as emphysema may trigger quit attempts and sustained smoking abstinence, and future work is needed to further explore whether such findings may be exploited to motivate smoking cessation.
8.2.3 Is it feasible to implement low dose CT in the UK?

Chapter 7 presented data from LSUT and demonstrated that implementation of LDCT screening in a UK setting was feasible. LSUT revealed many aspects that worked well, and highlighted areas where further resource, infrastructure or planning are required.

LSUT utilised GP surgeries to identify potentially-eligible LCS participants and typically invited approximately 2% of individuals registered to a practice. We found smoking data was well-recorded in primary care though approximately 10% of participants had inaccurate data recorded and when further assessed at the LHC, had insufficient smoking history or lung cancer risk to qualify for an LDCT. Furthermore, we do not know how many registered patients may have qualified for an LDCT that we did not invite, perhaps due to inaccurate coding of smoking data in those patients. Future work could use modelling to determine how best to use GP databases to invite individuals to LCS in terms of numbers identified that would be eligible and would be missed by various strategies, and try to determine the most efficient strategy. More sophisticated approaches using primary care data to develop novel predictive algorithms for identifying those at high risk of developing lung cancer are now underway and if successful may be embedded into GP software to enable selection of individuals to be invited for LCS. Important learning points from LSUT’s invitation strategy include use of GP endorsement and the stepped and low burden approach on the invitation materials [129]. These factors have been proven to enhance uptake in other cancer screening studies [258,268] and all ensure that the invitation process is not too onerous on individuals, and may help to address existing inequalities in uptake to LCS [75,253].

As well as the 10% of LSUT participants who were subsequently excluded from the LDCT due to low smoking history or lung cancer risk, another 4% were excluded for other reasons (e.g. CT thorax in past year). Overall a good conversion rate to LDCT (77%) was demonstrated with 9% declining the LDCT or failing to attend. This resulted in an efficient search, invitation and recruitment strategy, while demonstrating that participants were able to make an informed choice. Altering the criteria for the initial search and identification of potentially eligible participants or for eligibility to LDCT would impact this efficiency and needs to be monitored in any on-going LCS projects to determine the most efficient strategy.
Low radiation dose was achievable but challenging at times, and this study highlighted the need for adequate scanning capacity and protocols, and to ensure stringent quality assurance processes around radiation dose are in place. The LDCT scans took a median of 10 minutes per scan to be reported, and reports were generated within a median of 13 days. However, LSUT was a low-intensity project with typically less than 10 scans per site per week, and no additional radiology staff employed for the project. In order to perform and read the necessary volume of scans and to do so in a timely fashion on a larger scale, adequate workforce and resource is needed. In addition, due to lack of the necessary software, nodule volume was not recorded in half of patients with solid nodules. Use of volume measurements reduces the necessary period of surveillance of stable solid nodules from two years to one year and enhances the sensitivity and specificity of the nodule management algorithms [44,269]. Volumetric software packages need to be in place and nodule management protocols need to be followed, audited and continually updated with emerging evidence in order to improve LCS efficacy, reduce harms and ensure high quality results from LCS.

8.2.4 What are the prevalence, stage, histology and treatment outcomes of lung cancers detected after a baseline screen?

Chapter 7 also described the lung cancer outcomes from LSUT. The prospectively collected data presented support the predominantly retrospective evidence base [47,52,260] in favour of the use of risk based determination of eligibility for LDCT rather than the use of the US Preventative Services Task Force (USPSTF) criteria of age and smoking alone, though caution should be paid to the low numbers in this study. In this cohort the USPSTF criteria missed almost a third of the total numbers of cancers detected. It is likely this selection strategy for LDCT and the high-risk cohort recruited largely accounted for the higher than expected 4% lung cancer prevalence. The low prevalence of indeterminate nodules likely reflects the nodule management protocol, and resulted in a more favourable nodule to cancer ratio than expected from the larger LCS studies. This suggests the benefit-harm balance from LCS in a real world setting could be greater than that seen in the trials. Despite the high-risk population, we demonstrated high levels of early stage detection (71%) and resection rates (76%) for non-small cell lung cancer. In order to reproduce these results, robust quality assurance processes are required. In addition, sufficient thoracic,
radiology, oncology and surgical workforce required needs to be in place to ensure cancers are identified and treated promptly.

Quality assurance processes should monitor a variety of metrics including false positives and negatives, interval cancer rates, indeterminate pulmonary nodules, invasive procedure rates, curative and surgical treatment rates. Caution should be paid to the use of metrics such as stage shift, and survival due to lead and length time bias and overdiagnosis. Protocols and policies must be frequently audited and refined as new evidence emerges. In order to facilitate these processes, information technology links between primary and secondary care data and registry data need to be put in place, as well as to ensure prompt and timely communication between primary, secondary and tertiary care providers.

8.3 CONCLUSIONS

The research methods utilised in this thesis have provided a broad overview of many issues facing successful and high-quality implementation of LCS and address many of the key principles outlined in the modified Wilson and Jungner criteria [120]. LSUT was a small-scale demonstration pilot that has provided ‘real world’ UK data that can be used to inform further large scale projects and policy. We have identified key messages that should be incorporated into LCS materials and designed and tested a successful information film that promotes IDM. We have evaluated incidental findings such as COPD and coronary calcium in a UK setting where the approach to health care is different to the US and some countries in Europe. Indeed there may be some merit in combining CVD health checks with lung health checks in smokers in the desired age range for LCS, and using this as a route to LDCT. Our data suggest it may be worthwhile to assess cardiovascular risk in this population and initiate statin therapy as well as to report a combination of airflow limitation with symptoms suggestive of COPD to GPs. Using non-cancer findings at the LHC and LDCT may enhance positive health interventions such as smoking cessation and other lifestyle and primary prevention interventions, and the impact of this needs to be further researched. However, ultimately these potential benefits need to be balanced with the risks of hindering LCS implementation due to problems with cost and overburdening GP workload.
We have also identified key areas where resource, planning and infrastructure for LCS are required, and highlighted the need for stringent quality assurance processes and audit. Although national implementation of LCS is not imminently proposed in the UK or Europe currently [270], a number of projects are underway [40,255], and there is an urgent need to standardise the way LCS is carried out. The findings presented in this thesis can inform policy and protocols in terms of management of screen-detected findings, use of information materials and ensuring we are striving for IDM in all projects. Failing to maintain high standards may prevent confirmation of the efficacy seen in the high-quality LCS studies, and restrict implementation. This thesis has demonstrated that it is feasible to detect and treat lung cancer successfully in the UK health care setting, and highlighted opportunities for enhancing all-cause mortality in an LCS-eligible population. Nevertheless, high-quality detection and treatment of lung cancer and smoking cessation interventions should remain the primary focus of an LCS programme, with a view to incorporating supplementary beneficial interventions if confirmed to impact morbidity, mortality and quality of life.
Chapter 9. References


7 Ruparel M, Navani N. Reply. *Am J Respir Crit Care Med* 2015;**192**.


Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential
doi:10.1136/thoraxjnl-2015-207140

doi:10.1056/NEJMoa060476

doi:10.1056/NEJMc1312411


doi:10.1097/JTO.0000000000000530

doi:10.1016/S0140-6736(99)06093-6

doi:10.1002/14651858.CD001216.pub2

doi:10.1002/14651858.CD001877.pub5

doi:10.1097/JTO.0000000000000488


45 MacMahon H, John M Austin BH, Gamsu G, et al. Guidelines for Management of


van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, *et al.* Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J*


van der Aalst CM, van den Bergh KAM, Willemsen MC, et al. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised


100 Clark MM, Cox LS, Jett JR, *et al.* Effectiveness of smoking cessation self-help


110 Eric A. Klein, Earl Hubbell, Tara Maddala, Alex Aravanis, John F. Beausang, Darya Filippova, Samuel Gross, Arash Jamshidi, Kathryn Kurtzman, Ling Shen, Anton Valouev, Oliver Venn, Nan Zhang, David A. Smith, Timothy Joseph Yeatman, Robert Tibshirani, Richa M. Development of a comprehensive cell-free DNA (cfDNA) assay for early detection of multiple tumor types: The Circulating Cell-free Genome Atlas


participating in colorectal cancer screening: The role of information processing. 

134 Özhan MÖ, Süzer MA, Çomak I, *et al.* Do the patients read the informed consent? 


136 Schnellinger M, Finkelstein M, Thygeson M V., *et al.* Animated Video vs Pamphlet: 
Comparing the Success of Educating Parents About Proper Antibiotic Use. 

137 Leiner M, Handal G, Williams D. Patient communication: a multidisciplinary 
approach using animated cartoons. 


139 Chan ECY, Haynes MC, O’Donnell FT, *et al.* Cultural sensitivity and informed decision 
making about prostate cancer screening. 


A Survey and Focus Group Study. 


143 Ghanouni A, Meisel SF, Renzi C, *et al.* Survey of public definitions of the term ‘overdiagnosis’ in the UK. 


Cardiovascular disease: risk assessment and reduction, including lipid modification | 4-Other-information | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/cg181/chapter/4-Other-information (accessed 24 Apr 2016).


doi:10.1136/BMJ.E3953


Çolak Y, Afzal S, Nordestgaard BG, et al. Prognosis of asymptomatic and


238 Global Strategy for Diagnosis, Management, and Prevention of COPD - 2016 - Global Initiative for Chronic Obstructive Lung Disease - GOLD. https://goldcopd.org/global-


244  Young RP, Hopkins RJ. Chronic obstructive pulmonary disease (COPD) and lung cancer screening. *Transl Lung Cancer Res* 2018;7:347–60. doi:10.21037/tlcr.2018.05.04


249 Field JK, Duffy SW, Baldwin DR, *et al.* UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2015;**71**:161–70. doi:10.1136/thoraxjnl-2015-207140


Pulmonary nodules and CT screening: the past, present and future

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ABSTRACT
Lung cancer screening has come a long way since the early studies with chest X-ray. Advancing technology and progress in the processing of images have enabled low dose CT to be tried and tested, and evidence suggests its use can result in a significant mortality benefit. There are several issues that need refining in order to successfully implement screening in the UK and elsewhere. Some countries have started patchy implementation of screening and there is increased recognition that the appropriate management of pulmonary nodules is crucial to optimise benefits of early detection, while reducing harms caused by inappropriate medical intervention. This review summarises and differentiates the many recent guidelines on pulmonary nodule management, discusses screening activity in other countries and exposes the present barriers to implementation in the UK.

INTRODUCTION
Individuals diagnosed with lung cancer generally have a poor prognosis, largely attributable to delayed diagnosis due to the absence of discriminant symptoms at the early stages of the disease. In the UK, it was recently estimated for the period 2010–2012 that the net 5-year survival rate of lung cancer patients was 12.7%—a reflection on the 67.6% of lung cancers that are diagnosed at stage III or IV. One-year survival ranges from 14% for patients who present with stage IV disease to 71% for patients with stage I disease. Early detection has the potential to transform lung cancer outcomes and the case for screening with low radiation dose CT (LDCT) has recently gained significant momentum. However, there is a need to ensure cost-effectiveness and minimisation of harms are considered in the face of a considerable healthcare burden that has arisen from these LDCT studies; namely the management of the pulmonary nodule. In this review, we briefly discuss the pedestrian history of lung cancer screening through to the rapid evolution of the present, and highlight potential important differences in the management of the pulmonary nodule between recent guidelines.

THE HISTORY OF LUNG CANCER SCREENING
Studies in screening for asymptomatic lung cancer began in the 1950s using fluoroscopy. As early as 1959, it was clear that the lung cancer detection rate varied depending on whether medical risk was used to select the population to be screened.

Early studies using chest X-ray
Unfortunately, the trials for chest X-ray (CXR) screening for lung cancer failed spectacularly. Four large randomised controlled trials in the 1970s–1980s failed to detect a significant mortality benefit from CXR screening. Sadly, none of these studies used a true, null screening control group and rather compared screening with different modalities or at different frequencies. Both the Johns Hopkins and Memorial Sloan Kettering projects compared CXR with or without spumon cytology. Likely due to the trial designs and the short period of follow-up, no statistically significant differences in lung cancer-specific mortality were detected. However, an increase in early detection and a threefold increase in long-term survival were reported in both arms of the Memorial and Hopkins studies, when compared with the National Cancer Institutes’ Surveillance Epidemiology and End Results for unscreened cancers data. At the time, this was attributed to lead time bias (ie, the apparent increase in survival observed due to ‘preparing’ the diagnosis rather than the prolonging of life). Of particular note however, was an unequivocal difference in 5-year survival of early-stage detected cancers between those who had surgical resection (70%) and those who did not (10%) due to either refusal or medical contraindication, suggesting a successful early diagnosis strategy should save lives.

Despite the overall negativity following these early trials, more robust studies were carried out including the Prostate, Lung, Colorectal and Ovarian (PLCO) study which started in 1993. 155 000 smokers and non-smokers aged 55–74 were randomised to have either annual CXR for 4 years or no screening. Diagnostically, the authors reported no effect on lung cancer diagnosis, stage, histology or mortality after 13 years of follow-up. A subanalysis of the efficacy of yearly CXR screening in those at high risk also demonstrated no effect on lung cancer incidence or mortality.

Computed tomography
The Mayo Lung Project, a North American single-arm, LDCT screening pilot carried out in 1999, detected pulmonary nodules in 74% and lung cancer in 4% of those screened. The authors concluded that LDCT could detect early-stage lung cancers but had no significant effect on mortality when compared with subjects screened by CXR in the earlier Mayo Clinic Study. They suggested that LDCT screening had led to overdiagnosis of
indolent early-stage cancers and that due to the high false positive rate, the risk of complications and expense incurred in the work-up of false positive lesions, the evidence to support LDCT screening was inconclusive.

Therefore, the concept of LDCT screening for lung cancer was largely rejected until the Early Lung Cancer Action Project. This study increased the threshold for nodule positivity to a diameter of 5 mm and consequently only 13% of participants had baseline scans positive for pulmonary nodules. The prevalence lung cancer detection rate was 1.2% of all those screened and 9.7% of positive baseline scans. The majority (85%) of detected lung cancers were stage I, and these patients had an estimated 10-year survival rate of 88%. Only 8% of biopsies revealed benign lesions. These findings dramatically transformed prospects for lung cancer screening and it became apparent that deriving benefit may be possible, but further evidence from well-powered randomised studies was required. Furthermore, this study emphasized the importance of optimizing protocols to manage positive screens.

This leads us to the pivotal North American, National Lung Screening Trial (NLST). This was the first well-powered randomised study that compared LDCT screening with CXR in smokers and former smokers aged 55–74. A 20% and 6.7% relative reduction in lung cancer-specific and all-cause mortality, respectively, was observed across the two groups; with a needed screen of 1.20 to save one life from lung cancer after three annual screens and seven years of follow-up. The use of CXR as a control has provoked controversy, as some argue the lack of mortality benefit observed by screening smokers and former smokers in the PLCO trial justifies CXR as equivalent to null screening, while others have argued otherwise. Another limitation of this study is that the majority of NLST participants were younger, white, well-educated and affluent, while higher risk individuals were under-represented. This brings us to two important observations. First, the failure to engage those most at risk of lung cancer in screening in the NLST study may have led to an underestimation of the potential benefit of screening. Second, this study importantly highlights the difficulties faced in undertaking a cost-effective screening approach across society.

NLST radically changed prospects for LDCT screening, but can these data be extrapolated to the UK and Europe? One of the aims of the UK Lung Cancer Screening Trial (UKLS) was to address this and to evaluate costs within the UK National Health Service (NHS). Several other trials in Europe have also been recruited, but those that reported on mortality were substantially underpowered and failed to detect a benefit. Combining the populations within these studies together with the Dutch-Belgian lung cancer screening trial (NELSON), the Danish Lung Cancer Screening Trial and UKLS will amount to a total of approximately 36,000 participants; although, with varying nodule management algorithms and criteria for eligibility. The pooled results are eagerly awaited by physicians and health providers alike, and should mature in 2016.

**LDCT: MANAGEMENT OF PULMONARY NODULES**

The studies discussed have clarified the CT features of nodules and growth rates that support benign or malignant diagnoses. Several predictive models taking into account clinical and demographic factors, as well as CT and positron emission tomography (PET) features of nodules have been proposed and validated, enabling quantification of risk of malignancy for a given nodule. As a result, we can adopt a more conservative approach to certain nodules by employing CT surveillance, reserving the more invasive procedures for higher risk nodules.

In 2005, in response to the growing problem of small CT-detected nodules, the Fleischner Society published a management algorithm. The strategy adopted was a conservative one that mandated that all small nodules should be followed-up in high-risk people (essentially smokers or former smokers). More recent guidelines, published by the American College of Chest Physicians (ACCP), generally mirror the Fleischner guidelines with little change to follow-up recommendations (table 1). The Fleischner Society have recently responded to the problem of the subside nodule by publishing a further statement on their management. For those who are at high risk as per the US Preventative Services Task Force (USPSTF) criteria, the Lung CT Screening Reporting and Data System (Lung-RADS) has been specifically created. However, there is emerging evidence that implementation of the ACCP guidelines in the US has been suboptimal and that performance of Lung-RADS may not be as accurate as an approach using the Brock University nodule risk prediction model. Tables 1–3 show the comparison between these various nodule management strategies, which vary considerably.

The British Thoracic Society (BTS) published new guidelines on the investigation and management of pulmonary nodules in July 2015 following a comprehensive review of the evidence, with a third of the references cited from 2012 or later. Importantly, recommendations differ substantially from the earlier guidelines, especially for very small nodules, and recommend higher nodule follow-up thresholds, the use of risk prediction calculators and automated volumetric assessment to clarify follow-up requirements and growth rates (table 4). The inclusion of volumetric measurement will be challenging to implement across the UK but this will be offset by a substantial reduction in follow-up scans compared with previous guidelines. The Brock University risk prediction tool, which was developed from the Pan-Canadian screening cohort and the Herder model, where PET-CT results are available, are recommended to more accurately define risk of malignancy. The role of further imaging, minimally invasive investigations and therapy is reviewed and recommendations made. This guideline also includes a service delivery model.

**CURRENT CT SCREENING ACTIVITY INSIDE AND OUTSIDE THE UK**

Lung cancer screening by CXR was advocated by the American Cancer Society in the 1970s, however this recommendation was withdrawn following evidence from the trials in the 1980s. Following the publication of the NLST results, the USPSTF recommended screening with LDCT of individuals aged 55–80 who have accrued at least a 30 pack-year smoking history and are current or former smokers who have given up for ≥ 15 years. The ACCP/American Thoracic Society, American College of Radiology (ACR) and National Comprehensive Cancer Network have all also released statements or guidelines for screening.

In February 2015, the US insurers, the Center for Medicare and Medicaid Services agreed to fund screening of asymptomatic insured individuals aged 55–77 who meet the USPSTF smoking criteria. The newly instated ‘Obamacare’ enables some 30% of the uninsured population to access LDCT screening; however, once a nodule is detected it is classified as surveillance rather than screening, and perverse funds are insufficient to cover this crucial aspect of the screening process. Furthermore, a significant proportion of the US population do not qualify for screening at all through lack of insurance coverage. What is really required, therefore, is a national screening programme that is accessible to individuals from all communities such as the US National Breast Cancer Foundation (NBCF).
and Cervical Cancer Early Detection Program. Nonetheless, LDCT screening for insured individuals is now underway in the US. The ACR runs an accreditation programme outlining basic standards for performing and evaluating screening scans using the above-mentioned Lung-RADS. At the time of writing, there were 1220 accredited centres for LDCT screening in the US, 43 of which had been awarded ‘diagnostic imaging centre of excellence’. The ACR has constructed a lung cancer screening registry, to record outcomes from screening and the first feedback was expected in autumn 2015.

Screening has not yet been initiated in Canada, and the European Society of Radiology and European Respiratory Society recommend that screening should be performed in ‘comprehensive, quality-controlled longitudinal programmes’. In China, several lung cancer screening programmes have been initiated, particularly in areas with high lung cancer incidence, funded by central or local government.

The UK National Screening Committee (NSC) is due to make a decision on lung cancer LDCT screening in the UK pending the results of the pooled European data. In the meantime, several centres around the UK have initiated early diagnosis campaigns or pilot screening projects and these will contribute increasing knowledge around the best methods of implementation in the UK.

**PRESENT BARRIERS TO SUCCESSFUL IMPLEMENTATION OF LDCT SCREENING**

With these advances in CT technology and pulmonary nodule management, are we now in a position to recommend screening? In 1968, Wilson and Jargner compiled a report commissioned by the WHO highlighting that while the concept of screening was admirable, it was not without difficulties in terms of optimising benefits and harms. In order to aid the appropriate selection of conditions for which the benefits of screening outweigh the harms, they outlined 10 screening principles for appraising the viability, effectiveness and appropriateness of a screening programme, which form the basis for the criteria outlined by the UK NSC. Table 5 lists these 10 principles, and

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**Table 1** Comparison of Fleischer, Lung-RADS and ACCP guideline management of SN detected within or outside of screening

<table>
<thead>
<tr>
<th>Location</th>
<th>Fleischer</th>
<th>Lung-RADS</th>
<th>ACCP</th>
<th>Low risk</th>
<th>High risk</th>
<th>Low risk</th>
<th>High risk</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>No follow-up</td>
<td>No follow-up</td>
<td>Not specified</td>
<td>Category 1 (negative) return to annual screening at 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mm</td>
<td>Interval CT at 12 months</td>
<td>Interval CT at 12 months then discharge if stable</td>
<td>Category 2 (benign) return to annual screening at 12 months</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4-6 mm</td>
<td>Interval CT at 12 months</td>
<td>Interval CT at 12 months then discharge if stable</td>
<td>Interval CT at 6-12 and 18-24 months and discharge at 24 months if stable</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>6-8 mm</td>
<td>Interval CT at 6-12 and 18-24 months</td>
<td>Interval CT at 6-12 and 18-24 months and discharge at 24 months if stable</td>
<td>Interval CT at 6-12 and 18-24 months and discharge at 24 months if stable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8 mm</td>
<td>Interval CT at 3, 6, 12 months, dynamic CT chest, PET-CT/cholangiography</td>
<td>Risk:5% perform PET-CT interval CT at 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>&lt;6 mm (new)</td>
<td>Discharge if resolved at 12 months if no growth</td>
<td>If there is clear evidence of growth (VDT-100 days is suggestive of malignancy), direct surgical resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4-6 mm (new)</td>
<td>Discharge if resolved at 1 year if no growth</td>
<td>If there is clear evidence of growth (VDT-100 days is suggestive of malignancy), direct surgical resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mm (new/growing)</td>
<td>Discharge if resolved at 24 months if no growth</td>
<td>Discharge if resolved at 12 months if no growth</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;8 mm (new/growing)</td>
<td>Perform PET-CT/cholangiography</td>
<td>Discharge if resolved at 24 months if no growth</td>
<td></td>
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</tbody>
</table>

N.B. Lung-RADS is for CT screening scans only.

ACCP, American College of Chest Physicians; PET, positron emission tomography; RADS, Reporting and Data System; SN, solid nodules.
### Table 2
Comparison of Fleischer, Lung-RADS and ACCP guideline management of PSN detected at baseline screening or incidental scans

<table>
<thead>
<tr>
<th></th>
<th>Fleischer</th>
<th>ACCP</th>
<th>Lung-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline scan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No nodules or nodules with benign features</td>
<td>Internal CT at 3 months</td>
<td>If &lt;8 mm: internal CT at 3 and 12 months and then annually for 3-5 years. If multiple, consider each nodule separately</td>
<td>Category 1 (negative): internal CT at 12 months</td>
</tr>
<tr>
<td>≥5 mm component &lt;6 mm</td>
<td>Internal CT at 3 months</td>
<td>If &gt;8 mm: internal CT at 12 months</td>
<td>Category 2 (benign): internal CT at 12 months</td>
</tr>
<tr>
<td>≥5 mm with solid component ≥6-8 mm</td>
<td>Internal CT at 3 months+PET if solid component ≥8 mm</td>
<td>Category 3 (probably benign): internal CT at 6 months</td>
<td>Category 4A (suspicious): internal CT at 3 months; PET-CT if solid component ≥8 mm</td>
</tr>
<tr>
<td>≥5 mm with solid component ≥8 mm</td>
<td>Internal CT at 3 months+PET if solid component ≥8 mm</td>
<td>N.B. If &gt;15 mm, consider PET+biopsy reaction at baseline</td>
<td>Category 4B (suspicious): standard CT with or without contrast; PET-CT if solid component ≥8 mm; histology</td>
</tr>
</tbody>
</table>

**Internal scan**

<table>
<thead>
<tr>
<th></th>
<th>Fleischer</th>
<th>ACCP</th>
<th>Lung-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 mm nodule</td>
<td>Persistent nodules with solid component &lt;5 mm: perform annual CT for minimum 3 years</td>
<td>Annual CT for 3-5 years. Any growth or development of solid component should prompt further investigation/resection</td>
<td>&lt;5 mm nodule: category 2 (benign): internal CT at 12 months</td>
</tr>
<tr>
<td>≥5 mm with smaller solid component</td>
<td>Annual CT for minimum 3 years</td>
<td>≥5 mm nodule solid component &lt;6 mm for new nodule</td>
<td>≥5 mm nodule solid component &lt;6 mm for new nodule; internal CT: category 3 (probably benign) internal CT at 6 months</td>
</tr>
<tr>
<td>≥5 mm with larger solid component</td>
<td>Persistent solitary nodule or multiple nodules with one dominant nodule with solid component ≥5 mm: favour biopsy/resection (PET-CT if nodule &gt;10 mm)</td>
<td>≥5 mm nodule with solid component 6-8 mm or new nodule ≥4 mm: category 4A (suspicious): internal CT at 3 months</td>
<td>≥5 mm with solid component ≥6 mm or new nodule ≥4 mm: category 4B (suspicious): standard CT with or without contrast; PET-CT; histology depending on risk</td>
</tr>
</tbody>
</table>

**Note:** Lung-RADS is for CT screening scans only.

ACCP, American College of Chest Physicians; PET, positron emission tomography; PSN, part-solid nodules; RADS, Reporting and Data System.

### Table 3
Comparison of Fleischer, Lung-RADS and ACCP guideline management of pGGN detected at baseline screening or incidental scans

<table>
<thead>
<tr>
<th></th>
<th>Fleischer</th>
<th>ACCP</th>
<th>Lung-RADS</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline scan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>No follow-up if solitary, but if multiple, perform annual CT at 2 and 4 years</td>
<td>No follow-up</td>
<td>See below</td>
</tr>
<tr>
<td>≥5 mm</td>
<td>Interval CT at 3 months, then annual for minimum 3 years (for solitary and multiple nodules)</td>
<td>Annual CT surveillance for minimum 3 years; follow-up at 3 months if &gt;10 mm</td>
<td>Category 2 (benign): internal CT at 12 months</td>
</tr>
<tr>
<td>&lt;20 mm</td>
<td>As above</td>
<td>Annual CT surveillance for minimum 3 years; follow-up at 3 months if &gt;10 mm</td>
<td>Category 3 (probably benign): internal CT at 6 months</td>
</tr>
<tr>
<td>≥20 mm</td>
<td>As above</td>
<td>Annual CT surveillance for minimum 3 years; follow-up at 3 months if &gt;10 mm</td>
<td>Category 4A (suspicious): internal CT at 3 months</td>
</tr>
</tbody>
</table>

**Internal scan**

<table>
<thead>
<tr>
<th></th>
<th>Fleischer</th>
<th>ACCP</th>
<th>Lung-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>New nodule</td>
<td>As for baseline scan</td>
<td>Annual CT surveillance for a minimum of 3 years</td>
<td>Category 2 (benign): internal CT at 12 months</td>
</tr>
<tr>
<td>≥20 mm and stable or slow growth</td>
<td>As for baseline scan</td>
<td>≥10 mm and persistent or growing linear reaction</td>
<td>Category 3 (probably benign): internal CT at 6 months</td>
</tr>
<tr>
<td>Persistent nodule</td>
<td>As for baseline scan</td>
<td>≥20 mm and stable or slowly growing</td>
<td>Category 4 (suspicious): standard CT with or without contrast; PET-CT; histology depending on risk</td>
</tr>
</tbody>
</table>

**Note:** Lung-RADS is for CT screening scans only.

ACCP, American College of Chest Physicians; pGGN, pure ground glass nodules; RADS, Reporting and Data System.
Table 4: Summary of BTS guidelines for management of pulmonary nodules detected at baseline screening or incidental scans

<table>
<thead>
<tr>
<th>Baseline scan</th>
<th>Solid nodules</th>
<th>Part solid nodules</th>
<th>Pure ground glass nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 mm or &lt;80 mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Discharge</td>
<td>Discharge</td>
<td></td>
</tr>
<tr>
<td>5–6 mm</td>
<td>CT at 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 to &lt;8 mm or 80 to &lt;300 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Interval CT at 3 and 12 months</td>
<td></td>
<td>Interval CT at 3 months</td>
</tr>
<tr>
<td>&gt;8 mm or &gt;300 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1. PET-CT 2. Assess-Need risk  ▶ if &lt;10% do CT at 3 and 12 months  ▶ if &gt;10% consider biopsy or resection or CT surveillance on individual basis  ▶ if &gt;70% linear resection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interval scan

2D
- Stable nodule: Discharge after 2 years
- Growing: PET-CT and Needler score

3D
- Stable or slow growth: Discharge if stable and discharge or ongoing surveillance if slow growth (VDT>600 days)
- VDT ≥600 days: Further surveillance or biopsy or resection acceptable and decision should be based on patient preference
- VDT ≤600 days: Further work up and consider definitive management

BTS: British Thoracic Society; PET, positron emission tomography; 2D, two-dimensional; 3D, three-dimensional.

proposes key factors that need to be addressed for successful implementation of a lung cancer screening programme. These factors are discussed below.

Radiation risk

Advances in CT scanning technology have improved nodule detection and characterisation while reducing radiation dose. Techniques such as iterative reconstruction (which reduces the extent of noise and artefact associated with images at lower radiation doses), altering tube voltage, current and gantry rotation speed are valuable in reducing effective radiation doses. Further reduction to overall radiation exposure over time will follow implementation of the more conservative approaches to managing positive findings, suggested in the more recent guidelines. Nevertheless, radiation risk will remain a problem and always needs to be considered when balancing risks and benefits.

Overdiagnosis and false positives

Overdiagnosis is the detection and characterisation of disease that would not otherwise cause harm. It may be minimised in LDCT screening by taking into account morphological features that denote more indolent cancers that may be managed with a more conservative approach less likely to cause harm. False positives are benign lesions that undergo investigation and may therefore result in harm, both physical and psychological. Pure ground glass nodules and solid and subsolid nodules with longer volume doubling times are more likely to be indolent or benign. The recent BTS guidelines support a more conservative management of volumetrically assessed, potentially indolent or benign lesions, thus reducing the rate of overdiagnosis and benign histological diagnoses.

Optimal eligibility criteria for screening

It is clear that overdiagnosis rates, false positive rates, the number needed to be screened to save one life from lung cancer and cost of screening can all be reduced by selecting the higher risk population. However, what the appropriate threshold for risk is, and how this interacts with entry and exit age, competing mortality and fitness are complex. Randomised trials of LDCT screening have adopted a number of different approaches in determining who to invite to screening. The UKLS sent out questionnaires which enabled determination of the Liverpool Lung Project lung cancer risk prediction algorithm and had a relatively high lung cancer detection rate (2.1%), while the NLST used just age and smoking status. Which risk assessment tool most appropriately balances simplicity and predictive accuracy still needs to be determined. Furthermore, based on the results from the NELSON study, screening interval may also need to be varied by risk. They showed that interval cancers occur at a low rate (1%) and this occurrence was associated with age but not smoking status. Further research into other factors predictive of interval cancers is needed. With ongoing research into potential biomarkers, LDCT screening may one day be offered to a wider demographic and include non-smokers with a positive biomarker test.

Balance of psychological impact

The psychological burden of screening remains to be determined, and for the individual, may in large part depend on the severity...
of the screening result and psychosocial characteristics. To date, most studies of trial participants undergoing lung screening have shown that the anxiety and distress associated with false positive screens are minimal and short-lived. Clinically, meaningful changes in health-related quality of life were observed one month after the detection of an indeterminate pulmonary nodule, but returned to prescreening levels after two years, suggesting no long-lasting effects. However, this is yet to be studied in the community context and there is evidence from other screening programmes for long-term psychological distress. Furthermore, given a significant proportion of screening participants will at one time receive a false positive or indeterminate result, further research is needed to monitor the psychological impact of the surveillance process, examine individual differences in response and develop strategies which minimise harm. Qualitative evidence suggests effective communication about indeterminate nodules by health professionals could be one such strategy and ensuring patients are well-informed about the screening process and possible results will be essential. In addition, there is concern that an ‘all clear result’ could be falsely interpreted to mean low future risk of developing lung cancer, and a lower susceptibility to the effects of smoking. This issue of over- reassure is has been studied for other cancer types, with evidence that it may compromise future symptom appraisal and delay symptomatic help-seeking. Care must therefore be taken to tailor individual communication, so as to minimise adverse psychological responses to screening and any negative impact on future health behaviours.

Incidental findings from screening

Incidental findings are often viewed as a negative aspect of CT screening, but their detection may also provide an opportunity to rectify other conditions that threaten quality of life or survival. The NLST reported a 6.7% reduction in all-cause mortality, an effect most pronounced in Black African-Americans. This may be explained by detection of clinical and radiological findings in the process of screening, and due to the improved access to healthcare brought about by screening that may prompt intervention for non-lung cancer co-morbidities. Several studies have shown that unaged LDCT scans can accurately predict coronary calcium and subsequent cardiovascular events comparable to formal coronary calcium scoring. Those at high risk of lung cancer are also at higher risk of cardiovascular disease, and combining risk assessment and screening provides opportunity to improve outcomes for both conditions. However, further prospective studies are needed. LDCT scans have also been shown to be useful for detecting emphysema, which is a recognised risk factor for lung cancer, and osteoporosis which was associated with all-cause mortality in the NELSON cohort.

Co-implementation of smoking cessation

Achieving smoking abstinence in combination with LDCT screening has been reported to almost double the reduction in lung cancer mortality compared with screening alone within the NLST participants, but the impact of screening on smoking cessation is unclear. Several studies have reported increased smoking cessation in trial participants compared with the background population. However, no significant differences in outcomes between the screened and control groups have been noted, suggesting that trial participants may be more motivated groups. Few studies have noted an increase in the number of participants abstaining from smoking with successive positive or indeterminate screen results compared with those with negative screens. The optimal method of promoting smoking cessation in screening participants has not been determined. Further studies of patients, rather than trial participants, in the real-life screening context are needed to further explore this.

Resource implications and availability of volumetric assessment

Several studies, based primarily on US data, have reported varying Incremental Cost Effectiveness Ratios per quality of life.
adjusted life year (QALY) gained, ranging from US$28 000 to over US$100 000.86 The cost of lung cancer screening in the UK is not known, but has been estimated to be around £9000 per QALY gained,7 well below the threshold of £30 000 deemed acceptable by the National Institute for Health and Care Excellence. If NLST eligibility criteria were to be implemented, an estimated 8.7 million people in the US may be eligible for screening.87 The size of the UK lung cancer screening eligible population is unclear, however, even assuming uptake levels may be low (in the region of 50%), numbers are likely to be significant. This has considerable resource implications in terms of carrying out the baseline and interval CT scans required for nodule follow-up.

Most hospitals now have the technology to perform LDCT scans and take advantage of many of the other CT advances such as Maximum Intensity Projections (which allow enhanced visualisation of high attenuating structures such as nodules) and Multi-Planar Reconstruction (where images are reconstructed in customised planes). Automated estimation of the volume of nodules, calculated by mapping the CT attenuation values, is also possible with modern volumetric nodule assessment packages. These packages also auto calculate volume doubling times, which can more accurately quantify growth of a nodule than conventional two-dimensional measurements.60 However, exactly what proportion of UK hospitals currently has access to the technical, radiological and clinical know-how to implement volumetric assessment needs to be determined.

Various strategies as outlined above including appropriate selection criteria for screening and improved management of pulmonary nodules will help reduce the cost of screening. The cost of various methodologies that can be used in the screening process, such as the use of mobile CT scanners versus dedicated screening centres, also needs to be evaluated. Scan reading time is also a factor, and research is needed to explore whether there are feasible options that will relieve some of the work from radiologists.

Equitable access, uptake and adherence to screening across the population

Participation in national screening programmes for breast and colorectal cancer is around 70% and 60%, respectively, but there is evidence to suggest this will be lower in future lung cancer screening programmes. In the NELSON trial, 32% of the approached persons (aged 50–75 years) in the general population responded to an initial questionnaire on general health, lifestyle and smoking history (which did not mention the NELSON trial) similar to the response rate for the UKLS pilot randomised control trial.62 In NELSON, 19% (45% overall) of these were at high risk and half gave informed consent and were recruited. In UKLS, only 11.3% met the risk threshold for trial entry (higher than for NELSON) and a similar proportion were recruited. Although participation in a trial might be less than in a screening programme, in both of these well-conducted studies the participation rate of higher risk people was low enough to be of concern for implementation. UKLS also showed that current smoking and low socioeconomic status (SES) were associated with lower uptake, a problem observed across European and US trials63,64 and for other cancer screening programmes more widely.65 Lung cancer prevalence is higher in lower SES communities, where life expectancy is lower and obesity is more widespread.66 Indeed, over 40% of the lung cancers detected in UKLS were in people from the most deprived quintile. Reported barriers to participation among smokers include concern about risk of lung cancer, a lower perceived benefit of early detection, perceived blame and stigma and fearful, fatalistic and nihilistic beliefs around lung cancer outcomes.67–70

In addition, methods of recruitment, which demand significant correspondence from potential participants (as required by most trials), are likely to increase attrition among lower SES groups. A UK study has begun recruitment to a trial examining a tailored invitation method designed to overcome these barriers and reduce inequalities in participation (Quaife et al, manuscript in preparation).

Factors affecting screening adherence may be similar to those affecting uptake, with the added complexity of psychological responses to positive and negative results received in previous screening rounds.71 Given that the ratio of screening benefit to risk increases with lung cancer risk, promoting engagement of the higher risk and hard-to-reach groups aims to reduce lung cancer inequalities and improve the cost-effectiveness and efficacy of screening.

Regulating CT screening

Any screening programme needs to have stringent audit and quality control to ensure compliance with best practice. Availability of adequate resources to successfully implement and deliver such a programme to a high standard is vital. Controls also need to be in place to ensure uniformity, so radiation doses are used, scans are read to an adequate level of accuracy and that nodules and other findings are appropriately managed. A database to record outcomes is crucial to enable measurement of screening outcomes and further develop and improve the protocols used for all aspects of screening.

CONCLUSION

LDCT screening is undoubtedly a promising method to improve lung cancer outcomes. If lung cancer screening is to be initiated in the UK, adequate provision of resources is essential, with employment of stringent screening protocols and regulatory processes to ensure benefits outweigh harms and costs are minimised. Although it is acknowledged that the UK NHS is under considerable resource pressure, lung cancer is a condition that has not seen the improved outcomes observed in other cancers. With an overall 5-year survival for lung cancer in the UK <13%72 and the limited efficacy of available treatments for late-stage disease, there seems to be no alternative but to proceed with screening to improve rates of early detection and curative treatment.

Author note

We are sad to announce that Professor Jane Wardle passed away whilst this paper was in preparation. Jane had a phenomenal wealth of experience, knowledge and understanding of cancer screening and was an academic she was an inspiration to all who knew her. She is deeply missed by all of her co-authors and colleagues.

Contributors

MR, SQ, NN, AW, SM, DRB were responsible for the conception, drafting and final approval of the article.

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Competing interests

None declared.

Provenance and peer review

Not commissioned; externally peer reviewed.
Review

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both clinical variables and biologic markers may provide a more comprehensive classification of patients with ARDS that may ultimately lead to clinical trials that could more specifically target the degree of lung endothelial or epithelial injury as well as the inflammatory pathways in acute lung injury.

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

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Fulfilling the Dream
Toward Reducing Inequalities in Lung Cancer Screening

Martin Luther King, Jr, once said, "We may have all come on different ships, but we're in the same boat now." However, more than 50 years on, inequalities still exist in health care, and cancer outcomes vary greatly between different racial and socioeconomic groups (1). This is largely because of late presentation, leading to less radical treatment in these groups (2). In the United States, individuals from African American populations are less likely to have medical insurance or a regular primary care physician (3, 4). Lung cancer low-dose computed tomography (LDCT) screening in the National Lung Cancer Screening Trial (NLST) (5) had a clinically and statistically significant effect on lung cancer-specific and all-cause mortality when compared with chest radiograph (CXR) alone. However, whether LDCT screening has the same effect in all racial groups had not yet been evaluated.

Lung cancer LDCT screening aims to detect lung cancers earlier to improve radical treatment rates and, in turn, improve long-term survival and quality of life. However, individuals from nonwhite racial groups have been shown to have a reduced likelihood of undergoing curative surgery even after racial segregation and insurance coverage are accounted for (6). It is likely, therefore, that in addition to tobacco use and socioeconomic status (SES), factors such as health beliefs, trust in health care, and difficult access to health care may contribute to delayed presentation.

In this issue of the Journal, Tanner and colleagues (pp. 200-208) have shown that the reduction in lung cancer-specific mortality caused by LDCT screening was more pronounced in black individuals than white individuals (hazard ratio, 0.61 in black individuals vs. 0.86 in white individuals), although the risk of death from lung cancer was almost doubled in black compared with white current smokers (hazard ratio 4.10 vs. 2.25) (7). This improved benefit was seen despite the fact that black NLST
participants had more features associated with socioeconomic deprivation, such as lower education and unmarried status, although SES as a variable was not reported. They also show that when stratifying by race, all-cause mortality was significantly reduced by LDCT compared with CXR in black individuals, but not white individuals.

The authors propose this to be primarily a result of the improved access to health care brought about by screening in this group (and hence was more pronounced in the LDCT group than the CXR group, as LDCT was more sensitive in picking up findings that would result in regular health care consultations). In fact, they note that death from infections and coronary disease was also reduced in the LDCT screening group compared with the CXR group. It is not clear whether this effect is related to particular strategies or protocols held by the different screening centers, and further evaluation of this would be of utmost interest.

This study has obvious strengths in that it evaluates the effect of screening in different racial groups in a very powerful data set, and to date, NLST has the richest set of data in the field. However, the authors acknowledge that approximately 90% of NLST participants were white, which is clearly not representative of the US population as a whole. Certainly, the 2010 U.S. national census data report an excess of 12% of the U.S. population to be black or African American, which is three times the proportion within NLST participants (8). It is also difficult to separate the deprivation effect from the race effect. The present study reports significantly increased correlates of deprivation within the black study participants compared with the white participants, suggesting most black individuals in the study were from low-SES groups, whereas most white individuals were not. Therefore, the differences in outcomes in the two groups may be subject to confounding from SES. A study comparing the effect of outcomes in different racial groups after adjusting for SES is needed to distinguish such effects. Nonetheless, a study in lung cancer LDCT screening with these numbers of black participants has not been done to date, and with these limitations in mind, much can be inferred from this study.

NLST used age and smoking criteria to determine eligibility for screening, although many risk prediction tools now exist that allow more sophisticated methods of selection of high-risk participants, and many of these place great value on race as a predictor of lung cancer risk (9). Certainly, the modified risk prediction model, derived from the prostate, lung, colorectal, and ovarian (PLCO) participants (PLCO), gives varying risk scores, depending on race. For example, a white 60-year-old male high school graduate with emphysema who smoked 20 cigarettes a day for 30 years until 10 years ago would have a lung cancer probability of 0.014. A black man with the same risk factors would score 0.029 and would meet the risk entry criteria for screening, whereas the white patient would not. Use of such scores may help reduce inequalities by acknowledging the higher risk found in some racial groups.

Selection is only one part of the problem, and improving uptake and adherence to screening is also of great importance. Certainly black individuals and current smokers are acknowledged to have lower risk perception of lung cancer (10), and smokers and individuals from low-SES groups have shown poor participation in lung cancer screening studies (11). Nonadherence to lung cancer screening has been shown to be associated with African American race, less than high school education, and false-positive screening results (12). Studies in prostate and bowel screening modalities have also shown an association between nonadherence and current smokers and individuals with chronic bronchitis (13).

Recruitment methods in NLST were highly variable across the different screening centers, particularly with respect to attempts to recruit participants from socioeconomically deprived communities by community outreach programs (14). Success with such programs was poor, with 53 of 79 of such programs failing to recruit or recruiting badly. Six centers implemented programs to specifically target African American minorities in a variety of ways, and although success rate by ethnicity is not currently reported, it is acknowledged that some institutions used community outreach programs to increase their recruitment of minority groups. However, 17 of the 23 community outreach programs within these six institutions failed to recruit or recruited badly, implying that limited success was achieved in minority groups. Furthermore, it was noted that outreach programs were very expensive, at a median cost per recruit of $4, compared with mass media ($79 per recruit) and direct mail ($101 per recruit). Of these programs, television advertising has been reported to most significantly increase the cost of recruitment (15).

Tanner and colleagues are to be commended on their study, which demonstrates that black NLST participants benefited more from LDCT screening in terms of lung cancer-specific and all-cause mortality than white participants. The association between African American participants and probable increased socioeconomic deprivation highlights the importance of good access to health care in low-SES groups. The use of risk prediction scores and recruitment strategies that value racial origin are likely to gain increasing importance. By increasing our understanding of racial differences in the recruitment, adherence, and efficacy of screening, we can not only improve the cost-effectiveness of lung cancer screening but also improve access to health care in individuals from minority groups. III

Author disclosures are available with the text of this article at www.airjcc.org.

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References
3. Schiller JS, Ward BWG. Early release of selected estimates based on data from the national health interview survey; usual place to go for medical care. Hyattsville, MD: National Center for Health Statistics;


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Reply

From the Editorialists:

We thank Hopkins and colleagues for their interest in our editorial (1). We acknowledge the important studies cited, which suggest that African Americans have an increased susceptibility to cigarette smoke and are therefore at higher risk of developing chronic obstructive pulmonary disease (COPD) and lung cancer than matched white individuals (even after considering the impact of other related factors).

We would, however, like to highlight the difference between lung cancer detection rate and reduction in mortality. Although both are related to lung cancer risk and incidence, the latter also addresses factors affecting competing mortality. The article by Tanner and colleagues that we referred to reported a more pronounced mortality benefit with low-dose computed tomography (LDCT) screening compared with chest X-ray in African American compared with non-African American National Lung Screening Trial (NLST) participants (2). This suggests an observed effect of LDCT screening in African American participants over and above that explained by the increase in risk and incidence alone in this ethnic group.

As well as ethnicity, other factors appear to influence lung cancer susceptibility. Sex is another important demographic that influences lung cancer risk, and certainly it has been suggested that the cost-effectiveness of lung cancer screening is far higher in women than in men (incremental cost-effectiveness ratio, $46,000 vs. $147,000 [3]). Furthermore, as well as COPD, other comorbidities also increase susceptibility to lung cancer through varying mechanisms. Certainly, HIV and idiopathic pulmonary fibrosis have also been associated with a higher risk of lung cancer even after accounting for smoking history (4, 5).

Another interesting observation is that interval cancers in the NLSON (Dutch–Belgian randomized lung cancer screening trial) study were associated with increased age, though not smoking status (6). Apart from this study, little is known about the relative importance of other factors influencing interval cancer incidence with LDCT screening and whether such occurrences may be predicted by evaluating risk in screened individuals. If this were so, screening intervals could be tailored individually by risk.

The relationship between individual lung cancer risk, lung cancer detection, survival benefit of the screened population, and cost-effectiveness of lung cancer screening is complex. The current U.S. Preventive Services Task Force criteria (7) for screening eligibility are reasonable at this time but are likely to be adapted in the future, given the growing evidence base that will in due course inform the medical communities on how best to optimize the harms and benefits of lung cancer screening in individuals with varying risk profiles. Screening may be appropriate at alternative age and risk thresholds or at more or less frequent intervals in certain groups. Lung cancer risk and detection rate both need to be balanced with competing mortality to maintain or exceed the sensitivity and mortality benefit with screening seen in NLST.

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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**References**


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**Excess Risk of Cancer from Computed Tomography Scan Is Small but Not So Low as to Be Incalculable**

**To the Editor**

We read with interest the study by Rosenow and colleagues related to quantification of cystic fibrosis (CF) using computed tomography (CT) scan (1). We congratulate the authors for their important work on the subject. However, we would also like to comment on the conclusion of the study, assuming that the excess relative risk (ERR) of cancer related to CT scan exposure at two time points
Appendix 2- Lung Screen Uptake Trial (LSUT) Protocol

Study protocol: Lung Screen Uptake Trial v4 27.06.2016

Study Protocol v4

Study Title (Long):
RANDOMISED CONTROLLED TRIAL TO TEST NOVEL INVITATION METHODS AND MATERIALS TARGETED TO INCREASE INFORMED UPTAKE OF LUNG CANCER SCREENING IN INDIVIDUALS AT HIGH RISK OF LUNG CANCER

Study Title (Short):
LUNG SCREEN UPTAKE TRIAL

Funded by: NAEDI Initiative & CRUK
Sponsor & Monitor: UCL
IRAS Number: 15/0204
NIHR CRN Number: 19480
CSP/ R&D Number: 166426
Clinicaltrials.gov Number: NCT02558101
ISRCTN Number: ISRCTN21774741
Data Protection Number: Z6364106/2015/10/34
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<td>Professor Sam Janes</td>
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<td>Dr Asia Ahmed</td>
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<td>Dr Anand Devraj</td>
<td>Professor Paul Dolan</td>
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Study protocol: Lung Screen Uptake Trial v4 27.06.2016

Professor Stephen Duffy

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Study protocol: Lung Screen Uptake Trial v4 27.06.2016

## Signatures

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<tr>
<td><strong>Name:</strong> Professor Samuel Janes</td>
<td><strong>Role:</strong> Principle Investigator</td>
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<tr>
<td><strong>Signature:</strong></td>
<td><strong>Date:</strong> 17/06/2016</td>
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List of Abbreviations & Definitions

2WW  Target 2 Week Wait Referral
ACCP  American College of Chest Physicians
ATS   American Thoracic Society
BTS   British Thoracic Society
CADe  Computer Aided Detection
COPD  Chronic Obstructive Pulmonary Disease
COSMOS Continuing Observation of Smoking Subjects
CRN   Clinical Research Network
CT    Computed Tomography
CXR   Chest X-Ray
DANTE Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays
DEPISCAN Pilot Study to Evaluate Low Dose Spiral CT Scanning as a Screening Method for Bronchial Carcinoma
DLCST Danish Lung Cancer Screening Project
DMC   Data Monitoring Committee
ELCAP Early Lung Cancer Action Project
FEV₁ Forced Expiratory Volume in 1 second
FVC   Forced Vital Capacity
GOLD Global Initiative Obstructive Lung Diseases
GP    General Practice/ General Practitioner
HUH   Homerton University Hospital
I-ELCAP International Early Lung Cancer Action Project
IASCN International Association Study Lung Cancer
IG    Information Governance
INLS  Information Needs of Lung Screening Participants
IRAS  Integrated Research Application System
IMD   Index of Multiple Deprivation
LDCT  Low Dose Computed Tomography
LLP   Liverpool Lung Project
LLPv2 Liverpool Lung Project – Lung Risk Tool (version 2)
LUSI  Lung Cancer Screening Intervention Study
MILD  Multi-centric Italian Lung Detection Trial
MDT   Multi-Disciplinary Team Meeting
MREC Main Research Ethics Committee
NADD National Awareness and Early Diagnosis Initiative
NCNN National Comprehensive Cancer Network
NCSCST National Centre for Smoking Cessation and Training
NELSON Dutch-Belgian Randomised Lung Cancer Screening Trial (Dutch Acronym)
NLST  National Lung Cancer Screening Trial
NRT   Nicotine Replacement Therapy
NSCLC Non-small cell lung cancer
NY-ELCAP New York Early Lung Cancer Action Project
OP    Occupational Physician
PANCAN Pan-Canadian Early Detection of Lung Cancer Study
pGGN  Pure Ground Glass Nodule
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>PPM</td>
<td>Parts Per Million</td>
</tr>
<tr>
<td>PSN</td>
<td>Part Solid Nodule</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-Adjusted Life-Year</td>
</tr>
<tr>
<td>QOF</td>
<td>Quality and Outcomes Framework</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>SES</td>
<td>Socioeconomic Status</td>
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<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
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<tr>
<td>SN</td>
<td>Solid Nodule</td>
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<tr>
<td>SSI</td>
<td>Site Specific Information</td>
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<tr>
<td>SSAC</td>
<td>Strategic Screening Advisory Committee</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UCL</td>
<td>University College London</td>
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<tr>
<td>UCLH</td>
<td>University College London Hospital</td>
</tr>
<tr>
<td>UKLS</td>
<td>United Kingdom Lung Cancer Screening Trial</td>
</tr>
<tr>
<td>USPSTF</td>
<td>United States Preventative Services Task Force</td>
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<tr>
<td>VDT</td>
<td>Volume Doubling Time</td>
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Summary of study

**Background:** Implementation of lung cancer screening is being considered in the UK, but first, practically feasible strategies are needed which successfully engage the at-risk community. Individuals at high risk of lung cancer are overrepresented in socioeconomically deprived groups because the prevalence of smoking increases with deprivation. However, evidence shows that smokers from low socioeconomic status backgrounds are least likely to attend for lung cancer screening. This study constitutes the final stage of a programme of work which has investigated the factors explaining low uptake of low dose computed tomography (LDCT) screening by heavy smokers from socioeconomically deprived communities, and designed an invitation strategy which aims to achieve equitable participation across high risk groups.

**Design:** This is a randomised controlled trial to test whether tailored invitation materials are effective at increasing participation in lung cancer screening by the high-risk target group, and if primary care is a viable route for patient identification. Potential participants will be identified from General Practice (GP) patient records, in practices which serve a higher proportion of socioeconomically deprived neighbourhoods. Each patient will be sent a letter inviting them to a pre-arranged ‘lung health check’ appointment at University College London Hospital (UCLH) or Homerton University Hospital (HUH). Those randomised to the intervention arm, will also be sent targeted information materials designed to address misconceptions and reduce barriers to screening. The primary outcome is screening attendance and will compared in the group receiving the targeted screening invitation materials (intervention group) versus the group receiving more conventional invitation materials (control group). We will also collect data on the following: demographic and smoking characteristics of all those invited to explore any bias in uptake, smoking cessation rates, clinical outcomes and high risk markers.

At each appointment, a research nurse will obtain informed consent and collect data on the participant’s medical and smoking history to determine their eligibility for an LDCT scan (the lung cancer screening test). They will assess participant’s lung function using spirometry and advise smokers on the benefits of combined behavioural support and nicotine replacement therapy (NRT) for stopping smoking. At this point, patients from both groups will be re-randomised into a control (information giving only) arm and an opt-out smoking cessation referral intervention to determine the impact of a simultaneous smoking cessation intervention if it were implemented alongside a screening programme.

Eligible patients will then be offered an LDCT scan and this will be followed up with repeat CT scans or further investigations as indicated by the trial protocol and current national guidelines. Data will also be collected around the reading and findings on the CT scans, cost-effectiveness, longer term patient outcomes and the impact on NHS services during the implementation of a pilot lung cancer screening scheme to determine the feasibility of such a programme if it were a national screening initiative.
Figure 1: Study Flow Chart

Identify and recruit GP practices on a rolling basis

Identify potentially eligible participants from GP records (audit searches by practice administrators)

Individual randomisation
Randomisation list generated at UCL using unique participant IDs

Intervention Arm:
Targeted invitation strategy (n=1000)

Control Arm:
Control invitation strategy (n=1000)

Attend Cancel DNA

Re-invite once

Lung Health Check
- Medical and smoking history; Spirometry
- Determine if scan-eligible
- Smoking cessation intervention and referral
- Film intervention on sub-sample (n=210)

Scan Eligible Scan Ineligible

Low Dose CT Scan
- Double read
- Volumetric analysis
- Nodule risk assessment

High risk Low risk

Letter to GP and patient Internal 2WW referral to clinic

Letter to GP and patient Sensitive patient communication

Routine patient care pathway
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1.0 Background and rationale

Why screen for lung cancer?
Lung cancer kills more people than any other cancer; ~1.8 million globally in 2012\(^1\). This is partly because it is diagnosed late when prognosis is poor. Close to 70% of patients present with incurable advanced disease\(^2\) and ~40% as emergencies\(^3\), while early disease is typically diagnosed incidentally\(^4\). Five year survival for lung cancer is under 10%\(^5\) in the UK and 30% of patients die within 90 days of being diagnosed\(^6\). Part of the problem is that lung cancer is a difficult disease to diagnose early. In the early stage patients often experience no symptoms and when symptoms do develop they are often non-specific and misinterpreted as non-serious illness or the consequences of smoking. Screening high-risk individuals for early stage disease using low-dose computed tomography (LDCT) is one promising means by which to improve earlier detection of lung cancer and therefore survival.

Review of evidence from screening trials
The National Lung Screening Trial (NLST)\(^7\) was the first large randomised control trial of LDCT. Over 53,000 participants, aged 55 to 74 years of age with a smoking history of at least 30 pack-years, were randomised to receive three annual screens by either chest x-ray (CXR) or LDCT. LDCT resulted in a 20% and a 6.7% relative risk reduction in lung cancer related and all-cause mortality respectively. The number needed to screen (NNS) to save one death from lung cancer was 320. Based on this evidence, screening is recommended by the United States Preventive Services Task Force (USPSTF)\(^8\) and covered by US government insurers, the Center for Medicare and Medicaid Services. Numerous oncology and respiratory organisations have released various guidelines for screening including the National Comprehensive Cancer Network (NCCN)\(^9\), American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP)\(^\text{10}\), the American College of Radiology (ACR)\(^\text{11}\) and the International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC)\(^\text{12}\). Implementation of CT screening is being considered in the UK, but strategies are needed to achieve adequate uptake and minimise inequalities.

A number of other smaller trials of LDCT screening have been carried out around the world and are summarised in table 1 below\(^7\)-\(^\text{19-23}\). The Early Lung Cancer Action Project (ELCAP) group compared 7995 patients from their study with historical controls and reported improved mortality rates of between 36-64%. To date, European studies have not been sufficiently powered to show mortality benefit on their own, but the combined mortality results of the Danish Lung Cancer Screening Trial (DLCST) and the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) are the exception to this and results are expected by 2016.

One large-scale study has been carried out here in the UK. The UK Lung Cancer Screening Trial (UKLS) recruited participants aged 50-75 who achieved a Liverpool Lung Project risk (LLPv2) score of ≥5%. This score signifies an individual’s risk of developing lung cancer in the next five years based on numerous risk factors discussed in more detail below. Their current lung cancer detection rate is in the order of 2.1% (awaiting publication). This was a feasibility study and therefore was not designed to detect mortality benefit, however the study has suggested that LDCT screening was a cost-effective intervention in the UK. The estimated cost of screening per quality-adjusted life-year (QALY) gained was £3,100 (CI £5,721-12,978) (awaiting publication). This figure has potential to be enhanced by successfully engaging the high-risk constituency and extending the screening interval. This is a very complex analysis as calculations are based on not only potential mortality benefits but also taking into account lead-time bias, overdiagnosis and additional costs incurred from investigation and management of screen detected findings. Only with further time will such a figure be more accurately determined and the present study will hope to provide descriptive data to better understand the cost of local implementation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment Period</th>
<th>Recruitment Criteria</th>
<th>Screening Methods</th>
<th>Number of Participants</th>
<th>Number of Cancers Detected at Baseline Round Screening</th>
<th>Nodule cut off for surveillance</th>
<th>Mortality Benefit</th>
<th>Cancer Detection Rate</th>
<th>Method of Recruitment</th>
<th>Uptake/Enrolment Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST</td>
<td>2002-2004</td>
<td>age 55-74, ≥20PY, quit&lt;15 years ago</td>
<td>Annual LDCT or CXR for 3 years</td>
<td>53,454</td>
<td>26,722</td>
<td>270</td>
<td>4mm</td>
<td>20% RR* in lung cancer related mortality: 6.7% RR* in all cause mortality</td>
<td>1.0%</td>
<td>mixed methods including media, mailing, community groups</td>
</tr>
<tr>
<td>MILD</td>
<td>2005-2011</td>
<td>age=49, ≥20PY, quit&lt;10 years ago, no recent cancer within last 5 years</td>
<td>3 groups: no screen vs annual LDCT vs biennial LDCT for 5 years</td>
<td>4,099</td>
<td>2376</td>
<td>17</td>
<td>60mm3</td>
<td>no</td>
<td>0.7%</td>
<td>medbased</td>
</tr>
<tr>
<td>ITALLUNG</td>
<td>2004-2006</td>
<td>age 55-69, ≥20PY</td>
<td>Annual LDCT for 4 years vs no screen</td>
<td>3,206</td>
<td>1406</td>
<td>20</td>
<td>5mm</td>
<td>no</td>
<td>1.4%</td>
<td>mail</td>
</tr>
<tr>
<td>DANTE</td>
<td>2001-2006</td>
<td>age 60-74, ≥20PY, quit≥10 years ago, male</td>
<td>Annual LDCT for 4 years vs no screen</td>
<td>2,472</td>
<td>1276</td>
<td>28</td>
<td>5mm</td>
<td>no</td>
<td>2.2%</td>
<td>mail/ media/ via GP</td>
</tr>
<tr>
<td>DEPSCAN</td>
<td>2002-2004</td>
<td>age 50-75, ≥15PY</td>
<td>Annual LDCT or annual CXR for 2 years</td>
<td>765</td>
<td>336</td>
<td>8</td>
<td>5mm</td>
<td>not reported</td>
<td>2.4%</td>
<td>vis 231 GP/ occupational physicians</td>
</tr>
<tr>
<td>DILCST</td>
<td>2004-2006</td>
<td>age 50-70, ≥20PY, quit≥10 years ago, FEV1≥30%, able to climb 2 flights of stairs without pausing, excluded if recent cancer, other terminal illness</td>
<td>Annual LDCT vs usual care for 5 years</td>
<td>4,104</td>
<td>3052</td>
<td>17</td>
<td>5mm</td>
<td>not reported</td>
<td>0.8%</td>
<td>medbased</td>
</tr>
<tr>
<td>NEILSON</td>
<td>2003-2006</td>
<td>age 50-75, ≥15PY</td>
<td>Annual LDCT for 4 years vs no screen</td>
<td>15,822</td>
<td>7155</td>
<td>62</td>
<td>50mm3</td>
<td>not reported</td>
<td>0.9%</td>
<td>population/ med based</td>
</tr>
</tbody>
</table>
### Table 2. Summary of Lung Cancer Screening Studies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment Period</th>
<th>Recruitment Criteria</th>
<th>Screening Methods</th>
<th>Participants</th>
<th>Number Screened</th>
<th>Number of Cancers Detected at Baseline Round Screening</th>
<th>Nodule cut off for surveillance</th>
<th>Mortality Benefit</th>
<th>Cancer Detection Rate</th>
<th>Method of Recruitment</th>
<th>Uptake/Enrolment rate</th>
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<tbody>
<tr>
<td>RCT (cont)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>UKLS</td>
<td>2011-ongoing</td>
<td>age 50-75, ≥1% 5 year lung cancer risk as calculated by LLP2 score</td>
<td>2 bi-annual LDCT screening rounds vs no screen</td>
<td>4,061</td>
<td>1994</td>
<td>41</td>
<td>≥15mm/3/3mm had 12 month interval scan &amp; ≥50mm/3 for 3 month interval scan</td>
<td>not reported</td>
<td>2.1%</td>
<td>population based</td>
<td>3.5% of 247,354 approached returned questionnaire and fulfilled eligibility criteria</td>
</tr>
<tr>
<td>Non-RCT</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ELCAP</td>
<td>1993-2006</td>
<td>age ≥60, ≥10PY</td>
<td>Annual LDCT + CRR for 5 years</td>
<td>31,567</td>
<td>31,567</td>
<td>405</td>
<td>5mm</td>
<td>yes (36-64% improved mortality when compared to historical controls)</td>
<td>1.3%</td>
<td>unclear</td>
<td>not reported</td>
</tr>
<tr>
<td>Mayo LDCT Trial</td>
<td>Jan-Dec 1995</td>
<td>age ≥50, ≥30PY, quit&lt;50 years ago</td>
<td>Annual LDCT for 5 years</td>
<td>1,520</td>
<td>1520</td>
<td>21</td>
<td>4mm</td>
<td>no</td>
<td>1.4%</td>
<td>media based</td>
<td>not reported</td>
</tr>
<tr>
<td>PANCAN</td>
<td>2008-2011</td>
<td>age 50-75, ≥2% 3 year lung cancer risk as calculated by PLCO score</td>
<td>Annual LDCT for 5 years</td>
<td>2,537</td>
<td>1871</td>
<td>baseline rate not reported</td>
<td>5mm</td>
<td>not reported</td>
<td>5.5% per year</td>
<td>media based</td>
<td>not reported</td>
</tr>
<tr>
<td>COSMODS</td>
<td>2000-2001</td>
<td>age ≥50, ≥30PY</td>
<td>Annual LDCT for 10 years</td>
<td>1,035</td>
<td>1035</td>
<td>12</td>
<td>5mm</td>
<td>no</td>
<td>1.2%</td>
<td>media</td>
<td>not reported</td>
</tr>
<tr>
<td>LLGI</td>
<td>2007-2011</td>
<td>age 50-69, &quot;heavy&quot; smoking history</td>
<td>Annual LDCT + smoking cessation for 5 years vs smoking cessation alone</td>
<td>4,052</td>
<td>2020</td>
<td>22</td>
<td>5mm</td>
<td>non-statistically significant reduction in mortality</td>
<td>1.1%</td>
<td>population based</td>
<td>1.7% of 292,440 approached returned questionnaire and fulfilled eligibility criteria</td>
</tr>
</tbody>
</table>
Lung cancer detection rates from screening have been highly variable across the studies and this can be largely explained by the heterogeneous eligibility criteria. The rational for selection of eligibility criteria for screening and other methodology in our study are based on a review of the available literature and are further detailed below.

**Optimum management of pulmonary nodules and reading protocol**

As well as established lung cancer, LDCT screening for lung cancer will pick up abnormalities, called “pulmonary nodules”. A pulmonary nodule is defined as an area of increased opacification that is roughly spherical and can be of varying density. Such nodules can be an early cancer, but they may also occur due to scarring, fluid, infection, inflammation or a benign growth. Clinical features of the nodule can help to predict the underlying aetiology of the abnormality at baseline in addition to the presence and rate of growth of the nodule as determined by repeat interval CT scans. It is important that nodules are handled appropriately to maximise the benefits of screening, and minimise the need for invasive procedures and excessive radiation. The recommended period of follow up for screen-detected nodules varies between one and four years depending on the density of the nodule (BTS guidelines 2015).

Various algorithms for how best to manage screen detected nodules have been proposed and a new national guideline that advises on surveillance frequency and duration is currently awaiting publication by the British Thoracic Society (BTS). Our screening protocol will be based upon these guidelines to ensure that the screening algorithm and nodule size cut-off optimises the balance of cancer detection and risk of overdiagnosis.

Approximately a quarter of baseline LDCTs are likely show one or more pulmonary nodule(s). Previous guidelines have been based on diameter of nodule alone whilst recent advances in CT reading software has enabled more accurate size quantification by way of calculation of nodule volume. Furthermore, detecting a change in volume on consecutive scans further increases the risk of malignancy for any given lesion, whilst minimising overdiagnosis and false positive lesions. Volume doubling times (VDT) have been recommended for risk stratification. Additionally, the risk of malignancy can be further stratified by other characteristics and various risk scoring calculators have been proposed. The BTS advocate the use of such risk calculators when planning nodule management.

In recent years, there have been large advances in radiology reading software. Whilst there is still need for further technological development, current computer aided detection (CADe) software packages have reached a standard whereby automated detection and reading for lung nodules can take place. Studies have shown that use of CADe can enhance reader sensitivity without overly compromising speed of reading. The major drawback and area for further development with CADe is the high rate of false positive readings and the increased CT scan reading time. The CADe systems still have less sophistication than is required to differentiate benign from suspicious nodules and in some small, irregular nodules or ground glass nodules, it may not be possible to accurately determine growth of nodules. A trained Radiologist or Radiographer is therefore required to improve specificity and accuracy. Another important finding from the literature is that the same version of software and segmentation algorithms should be used when assessing nodule growth.

The UKLS and NELSON studies had a rigorous nodule reading protocol with two Radiologist readers reading each scan and a third opinion by an additional Radiologist to resolve discrepancies. This reading process is very labour and time intensive for highly qualified specialists and evidence suggests the involvement of two readers does not add significant benefit. Furthermore, there is concern that such
process is unrealistic for already overburdened healthcare services. UKLS additionally tested the sensitivities and specificities of Radiographers and whilst overall these were lower than the Radiologists, the best Radiographer outperformed the worst Radiologist (awaiting publication). There could, therefore be a role for Radiographers in the reading of screening scans; however this may represent a lost opportunity for detecting non-nodule incidental findings.

Further recommendations that have been noted whilst constructing this study protocol include those by the ATS/ ACCP pertaining to image acquisition, image interpretation and nodule algorithms, components required for a lung screening facility and multidisciplinary team, patient and provider education, data collection and smoking cessation.

The optimum protocol for management of screen detected nodules, as well as the methods adopted for quality control of the reading of screening LDCT scans that remains feasible in an NHS setting, will be subject to appraisal in this study and is among the secondary outcomes of the study.

**Incidental findings and the potential for earlier diagnosis of chronic diseases**

Screening may pick up incidental findings\(^5^6\) that are not suspicious for lung cancer but may be of clinical significance for the patient. This may enable the early diagnosis of conditions such as osteoporosis\(^5^6\) and emphysema\(^5^7\), which can be treated and managed to prevent or slow deterioration. CT calcium scoring, a tool that is used to screen for possible coronary artery disease, can also be carried out on ungated LDCT scans and has been reported to correlate well with cardiac risk in screening participants with these incidental findings\(^5^8-5^9\), however it is a complex addition as images need to reconstructed and read by specifically trained Radiologists. Although this may be a worthwhile intervention, in a population who are at increased risk of cardiac disease due to their smoking history, it is possible that the extra resources required to enable such findings do not translate into lives saved. Indeed, the NELSON investigators published a study that suggested screening scans for incidental findings was not worthwhile in terms of improved mortality related outcomes although this study was underpowered to detect such an effect\(^6^0\). The present study will evaluate differences between CT reading personnel on screening outcomes and the diagnosis of incidental findings.

**Lung cancer risk: eligibility for screening and the harm-benefit ratio**

Increasing the risk profile of screening participants has potential to improve the harm-benefit ratio of screening by improving the likelihood of survival benefit and the lung cancer detection rate. For example, in the NLST, the majority (88%) of screen-prevented deaths were for participants categorised within the three highest risk quintiles\(^6^0\). Engaging higher risk participants in screening may also reduce the number needed to screen (in order to save one life), the frequency of false positive results, unnecessary invasive procedures and overdiagnosis. Overdiagnosis is defined as the detection of a cancer that is indolent and would not have progressed within the lifetime of the patient, or a cancer that is malignant but the affected patient would have died from a competing unrelated cause\(^7^0\). It is a well-documented phenomenon that occurs in screening programmes where the objective is to detect early rather than pre-invasive cancers\(^7^1-7^4\).

The overdiagnosis rate is not well defined in lung cancer screening. A study looking at NLST data\(^7^5\) concluded that each lung cancer detected in NLST had an 18.5% probability of being an overdiagnosed cancer. Of those, the probability of overdiagnosis was increased to 22.5% in non-small cell lung cancer (NSCLC) and 78.9% in adenocarcinoma in situ. The number of overdiagnosed cancers in the 320 people screened to achieve one life saved for screening was 1.38.
Study protocol: Lung Screen Uptake Trial v4 27.06.2016

One proposed solution to further improve the risk-balance ratio of screening is to target the most at risk sub-population and several scoring systems to determine this risk have been developed with varying predictive performance. UKLS utilised the LLPv2 scoring system \(^{75,76}\) to identify patients with a 5% or greater five year risk of lung cancer with good detection rates of greater than 2% (awaiting publication). The PLCO\(_{2012}\) (Prostate, Lung, Colorectal and Ovarian 2012 model) scoring system, has also been well validated\(^{76}\). This model was also applied to the NLST dataset by Tammemagi and colleagues. It was noted that application of a 1.5% 6 year risk of lung cancer as predicted by this model would have deemed 8.8% less people as eligible for screening and a 12.4% higher proportion of cancers would have been detected, thus improving the false positive rate and positive predictive value of the screening test\(^{79}\). The risk factors that are entered into both of these models are noted in table 2.

Table 2. Liverpool lung Project versions 2 (LLPv2) and Prostate, Lung, Colorectal and Ovarian (PLCO) Lung Cancer Risk Tool

<table>
<thead>
<tr>
<th>LLPv2</th>
<th>PLCO score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age (years)</td>
</tr>
<tr>
<td>Smoking duration (years)</td>
<td>Education (1-6)</td>
</tr>
<tr>
<td>Previous pneumonia/ COPD/ emphysema/ bronchitis/ TB</td>
<td>BMI</td>
</tr>
<tr>
<td>Occupational asbestos exposure</td>
<td>COPD/ chronic bronchitis/ emphysema</td>
</tr>
<tr>
<td>Previous history of malignancy</td>
<td>Personal history of lung cancer</td>
</tr>
<tr>
<td>Previous family history of lung cancer (and relative’s age at onset)</td>
<td>Family history of lung cancer</td>
</tr>
<tr>
<td>Race (White, Black, Hispanic, Asian, Native American, Native Hawaiian)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Average number of cigarettes smoked per day</td>
<td></td>
</tr>
<tr>
<td>Duration smoked (years)</td>
<td></td>
</tr>
<tr>
<td>Years ago quit smoking</td>
<td></td>
</tr>
</tbody>
</table>

Despite this compelling evidence, in the UKLS, the majority of cancers occurred in participants over the age of 69. It has also been acknowledged\(^{76}\) that these risk prediction models will need to undergo further refinement and in the future will likely include validated biomarkers that will help to further risk stratify a wider population. A recent review of lung cancer risk prediction scores\(^{78}\) acknowledges the need for further development of such scores and advocates use of fulfilling either the USPSTF eligibility criteria or high quality risk prediction scores to determine eligibility for screening. This data will provide further evidence for optimum eligibility criteria into lung cancer LDCT screening.

Other scoring systems, such as the Q-Cancer score that have been created and validated to predict risk for a number of cancers\(^{80,81}\). The Q-Cancer score has recently been added to some GP software in the UK to enable GPs to collect information on this readily. The Q-Cancer score algorithm uses age, gender, body mass index, chronic pancreatitis, chronic obstructive pulmonary disease, diabetes, family history, alcohol, smoking, deprivation, 23 symptoms, anaemia and venous thrombo-embolism to calculate risk.

The present study offers an opportunity to collect data on this score as well as the ones mentioned above. Samples of blood, exhaled breath, sputum and buccal swabs will also be collected in this high risk cohort.
which will also provide further useful biological markers that may help in understanding the relative role of future biomarkers in predicting lung cancer risk.

Psychological impact of screening
Potential psychological harms from screening include distress, anxiety, depression and other adverse effects on quality of life. There is potential for patients to experience psychological harm at every stage of the lung cancer screening process, including the lead up to the screening test, the time spent waiting for the results, the receipt of an abnormal or positive result, monitoring of suspicious findings, diagnostic tests, diagnosis and treatment. However, the psychological burden of lung cancer screening specifically is unclear. Preliminary evidence suggests any adverse effect on levels of anxiety or distress following lung cancer screening may be mild and short-lived, but may increase with the severity of the result the patient receives. A study comparing the psychological impact of screening in 1000 patients from NLST with either incidental findings, negative, false positive or true positive results reported similar levels of distress in all groups at six months except those with true positive results, who were understandably more distressed. Other studies have found that patients with indeterminate nodules (i.e. are suspicious but following observation most often turn out to be non-serious) have increased levels of distress throughout the surveillance period, though it is unclear how long these effects continue. In addition, reports on overdiagnosis in non-lung cancer screening suggest distress and anxiety are associated with the labelling attached to a diagnosis which would otherwise not have been made.

Communicating results appropriately to patients and the expectations for follow-up procedures may also be important for minimising psychological distress. A qualitative study by Wiener et al demonstrated that patients undergoing CT scans had a poor understanding of the implications of pulmonary nodules and suggested this could be improved by the delivery of more effective communication by physicians. The careful communication of results to patients will be prioritised within this study in an attempt to minimise distress.

Emerging evidence suggests that certain patient sub-groups may be more vulnerable to adverse psychological reactions to screening. A study by the NELSON group assessed affective risk perception in patients one day prior to undergoing screening and found that this predicted higher levels of distress six months after screening. Other studies have associated guilt about smoking and fear of lung cancer with heightened distress among patients screened for lung cancer, and stigma has been shown to predict poorer psychological adjustment among patients with lung cancer. Furthermore, data suggest that patient sub-groups most vulnerable to adverse psychological effects from screening have been underrepresented in studies to date due to a bias in participation. Compared with a similar population sample, DLCST participants had fewer negative psychological characteristics at baseline, independent of demographic factors. This suggests it is important to assess psychological burden in a sample of screening participants who better represent those who might undergo screening offered by the National Health Service. This study will further explore the psychological impact of screening among a sample of screening participants which is intended to better represent those participating in any future health service (due to its targeted invitation approach).

A teachable moment for smoking cessation
Various studies have stated that the cost effectiveness of screening is improved by concurrently delivering smoking cessation interventions. The available evidence suggests lung cancer screening has potential to motivate quit attempts, and this will be an integral component of the present lung cancer screening trial.
Study protocol: Lung Screen Uptake Trial v4 27.06.2016

To date, evidence for the impact of lung cancer screening on smoking cessation is inconclusive. Several studies have reported an increase in smoking cessation rates in participants of lung screening studies compared with the general population. Among those that compare outcomes between groups, several report no significant differences in outcomes between the screened and control groups suggesting that involvement in the trial rather than screening per se is a factor. However, some studies have noted an increase in the number of participants abstaining from smoking with successive positive or indeterminate screen results when compared to those with negative screens. Other studies have compared various modalities of delivery of smoking cessation advice in the screened population and found no significant differences.

Factors that have been found to be associated with increased success of smoking cessation include older age, worsening lung function or symptoms and lower nicotine dependence. Some studies report an improvement in willingness, readiness and motivation to quit in participants of screening trials, however research shows that this does not always translate into actual abstinence.

The extent to which screening for lung cancer acts as a “teachable moment” for delivering other health promoting messages such as smoking cessation remains to be determined. A “teachable moment”, becomes such, due to a given event provoking an increased perception of personal risk, an increased emotional response to this risk and redefinition of one’s own concept or social role. Unfortunately, this emotional response can promote either engagement with or avoidance of screening and other protective health behaviours. Other reported barriers include cognitive dissonance, fatalism, nihilism, avoidance and excess fear and worry. Therefore whilst smoking cessation outcomes may be improved in screened participants, the challenge lies in encouraging disengaged individuals to screening in the first place and then applying the optimal methods of promoting other health behaviours. This study is therefore crucial in furthering our understanding in how to best achieve this and how to gain additional benefit on an individual and population level by supplementing screening with other health promoting interventions.

We explored the acceptability of offering stop smoking support at lung cancer screening appointments during an interview study (n=21) of smokers and ex-smokers of lower SES backgrounds. Participants warned that mentioning smoking cessation within the invitation materials could deter uptake among smokers, and was unnecessary because the provision of smoking cessation advice at the appointment would be expected by those attending. Some participants emphasised that advice should be delivered sensitively so as not to implicate blame.

Problems with uptake

Recruitment to lung screening trials has been difficult, with enrolment rates from 0.2%-4.6% of those initially invited. Participation is also skewed toward ‘low-risk’ candidates. NLST participants were younger, better educated, and more likely to be former (than current) smokers than a cohort of eligible US counterparts. In the UKLS trial, both socioeconomic deprivation and smoking status were independently associated with response to the first trial invitation letter. Affluent former smokers were the most likely to respond positively (37.3%) while just 18% of current smokers from the three most deprived quintiles in England (Index of Multiple Deprivation, IMD) were positive responders; fewer still attended for screening. Indeed, lower socio-economic status (SES) groups tend to have lower uptake of all types of cancer screening, as do smokers. Paradoxically then, the very two factors associated with low uptake, also predict high lung cancer risk and therefore a greater likelihood of benefit from screening.

Trial recruitment methods have been heterogeneous; often involving mass mailing and substantial correspondence to determine eligibility (see table 1). For example, both NELSON and UKLS
identified individuals within the correct age group from electoral registers and mailed questionnaires, which included information about smoking history, in order to determine eligibility. High numbers of invitations were needed in order to recruit patients. Some trials have involved primary care but none have issued screening invitations directly to individuals identified in primary care. The French Depiscan study recruited patients via General Practitioners (GP) and Occupational Physicians (OP), but reported great difficulties and high rates of non-attendance of appointments.

We are not aware of attempts to design and test invitation materials for lower SES groups. This is a constituency that had a higher level of attrition at every stage of correspondence during the UKLS trial. Therefore, invitation strategies need also to minimise and simplify correspondence with patients. The success of any future lung cancer screening programme hinges on developing an invitation strategy which successfully engages high risk candidates, and is practically feasible for a national programme.

**Overcoming socioeconomic and smoking-related biases in screening uptake: targeted screening invitation materials**

Socioeconomically deprived communities are an important target group for screening because rates of smoking are high and lung cancer survival is poor. Recent data confirm that a greater number of low SES individuals achieve a high lung cancer risk score. Previous studies indicate that smokers perceive fewer benefits to cancer screening than non-smokers, but few examine attitudes towards lung cancer screening specifically. In a US survey, smokers who recognised their increased risk of the disease remained less likely to say they would consider lung CT screening, and a UK study found that those declining trial participation (n=24) believed they would not benefit, held fatalistic perceptions or were too worried to attend.

To better understand the attitudes of smokers from socioeconomically deprived communities we carried out a proactive, mixed-methods, community-focused phase of research to explore the factors which might promote or deter lung cancer screening participation in heavy smoking, socioeconomically deprived communities. All participants completed a questionnaire (n=175) on attitudes towards lung cancer screening, and a smaller sub-sample of smokers and ex-smokers (n=21; age 47-73) took part in semi-structured interviews to explore their views in-depth. Our main findings suggest that lower SES smokers report high perceived risk and worry about lung cancer, and are more pessimistic about lung cancer outcomes and the likelihood of personal screening benefit than their non-smoking counterparts. While most interviewees were supportive of lung cancer screening in principle; discussions gave insight into fearful, avoidant and fatalistic beliefs which could deter uptake. Lung cancer was perceived as an uncontrollable disease with regards to perceived risk, ineffective treatment and poor survival, and the perception that lungs are not a treatable organ appeared to be implicated here. The belief that it is too late to benefit from lung cancer screening due to age and smoking history was commonly cited. These findings suggest that the communication of a screening offer needs to be designed carefully and sensitively if low SES smokers are to be engaged in considering the offer. Detailed information on the approach, rationale and design of the targeted invitation strategy is given in section 6.

**Conclusion**

This study aims to improve uptake of lung cancer screening in those at highest risk of lung cancer but least likely to attend screening. It is this subpopulation, in whom the optimum risk benefit ratio can be obtained and lung cancer screening is most worthwhile and cost-effective. Outcomes from this study relating to invitation and uptake as well as appraisal of various practical aspects and stages of the screening process in association with the NHS, will provide a valuable evidence base for implementation of a national screening programme should this go ahead in the future.
2.0 Study objectives and design

Goal:
- To secure the best yield for any future investment in lung cancer screening by increasing informed uptake in high-risk individuals

Primary objective:
- To test whether targeted screening information materials increase informed uptake of low-dose computed tomography (LDCT) screening in those at greatest risk of lung cancer

Secondary objectives:
- To explore demographic and smoking-related biases in participation
- To examine the proportion of attendees who are eligible for a CT scan
- To explore the feasibility of enrolling patients for lung cancer screening through primary care, and in doing so, gather important procedural information for any future lung-screening programme
- To collect detailed data on lung cancer risk, and use risk prediction tools to explore how many of those attending can be classified as high risk according to more specific risk criteria
- To explore the extent to which participants make an informed decision to take part in lung cancer screening in order to i) ensure the effectiveness of information-giving at the appointment and ii) ensure the approach of the targeted invitation strategy supports decision-making at the appointment
- To explore the effect of an opt-out smoking cessation referral on smoking outcomes in participants, compared with local quit rates
- To collect biological samples to inform the research and development of potential biomarkers for lung cancer
- To collect and analyse data pertaining to clinical outcomes e.g. detected cancers, comorbidities, all-cause and lung cancer related mortality and nodule reading protocols
- To examine whether the accuracy of CT reporting of pulmonary nodules by Radiographer + CADe combinations are comparable to local Radiologists’ accuracy of reading LDCT screening scans
- To compare the effects of different CT reading personnel on lung cancer risk prediction scores, further management plans, clinical outcomes and detected incidental findings
- To determine healthcare costs associated with screening and impact on local services in terms of numbers of investigations and referrals for further follow up/ specialty input
- To explore the psychological burden of undergoing lung cancer screening

Design:
A blind two-arm, individually randomised controlled demonstration pilot comparing screening attendance in patients who receive a targeted screening invitation strategy vs. patients receiving a ‘control’ screening invitation strategy mimicking that of existing screening programmes. The unit of randomisation is the patient.
3.0 Study outcome measures

Primary outcome measure:
- Attendance at the screening appointment

Secondary outcome measures:
- Demographic data on all patients invited – age, sex, ethnicity, smoking status, and Index of Multiple Deprivation (IMD) score and rank
- Additional smoking data on all attenders including quit confidence and tobacco dependence
- Uptake of CT scans (among those who are eligible) and willingness to be screened (among those who are ineligible)
- Proportion attending that are eligible for a CT scan (in terms of pack-year smoking history)
- Individual risk score data (retrospectively - according to different individual risk calculation models)
- Psychological burden of screening (cancer worry, anxiety and depression)
- Informed decision-making and decision satisfaction (short and longer term)
- Smoking cessation outcomes following an opt-out referral intervention, including acceptability, clinic attendance, quit dates set and 4 week quit rates
- Number of detected nodules, cancers and other incidental findings with 1 year survival and follow up data
- Data relating to prevalence of biomarkers in screened participants from biological samples from buccal mucosa, sputum, blood and exhaled breath
- Investigations and treatments generated by screening
- Local healthcare costs, number of referrals for further follow up/ specialty input
- Relative accuracy, generated clinical management plans and detected incidental findings of local Radiologist and Radiographer + CADe readers of LDCT screening scans
- Adverse events from screening process and subsequent investigations
4.0 Subject selection and recruitment

4.1 Inclusion criteria
- Aged 60 to 75 years
- Recorded as a current smoker during the year 2010 or in subsequent years since then. (This will identify a group of predominantly current smokers, and a smaller percentage of recent ex-smokers. These individuals are those most likely to have accrued a 30 pack-year smoking history which would qualify them for a CT scan, and are also the most difficult to attract to lung cancer screening).

4.2 Exclusion criteria
- Active diagnosis of lung cancer or metastases
- CT thorax within the past year
- Inability to consent to study
- Palliative care register
- GPs alert to co-morbidity that contraindicates screening or treatment for lung cancer

4.3 Subject selection and recruitment
GP practices across Camden, Islington and Hackney and City CCGs have been approached to participate in the study and to date (at June 2015), 22 have agreed to take part. The letter inviting GPs to participate and information booklet are included within the submission for ethical approval.

A member of the research team will carry out site visits with each GP practice at the time of patient identification to offer support with the process and to ensure the protocol is adhered to. GPs and other practice staff will be provided with information including a list of frequently asked questions about the study, should their patients contact them with questions. At the initial site visit, the researcher will talk to the practice staff about the study and explain how the research team can be contacted for advice. An administrator from the practice will then run a standardised search to identify eligible patients as outlined above, and run a report against this search to extract patient name, address, postcode, age, sex, ethnicity and smoking status. These searches have been tested and prepared and will be imported by administrative staff for ease and consistency of patient identification. Once a list of potentially eligible patients has been extracted, the researcher will convert postcodes into deprivation scores (IMD scores and ranks, and Townsend score). Other fields will be hidden so that only postcode data is visible to the researcher. GPs will then have a week to screen this list and exclude patients they deem to be inappropriate for inclusion. Following GP screening, names, addresses and postcodes will be removed from this list, which will then be pseudonymised (using a unique identifier) and exported to the research team for randomisation and appointment allocation. At this point this data will be entered by the research team into the study database. The randomisation and appointment list will then be sent back to the practice. The practice administrator will repopulate patient names and addresses back into the list and send to DocMail (compliant with data protection and governance) to mail the invitation materials on their behalf. DocMail will send each GP administrator a sample letter prior to commencing each mail out. The researcher will support the administrator with this process during a second site visit.
5.0 Randomisation and consent

5.1 Randomisation
Randomisation, with blocking by practice, will be carried out without using patient identifiable data and using a web-based randomisation programme.

5.2 Consent
Prior to consent and randomisation, age, gender, ethnicity, smoking status, IMD score and rank and Townsend score will be collected on invited participants. This data will be anonymised and no identifiable data will be collected. It is important for us to collect this data in order to evaluate secondary factors affecting uptake in both the intervention and control invitation groups, particularly in those who chose not to attend as this relates to the primary outcome of the study. We have surveyed members of the public about accessing this data prior to consent, and none of those interviewed had any objections to this. Once patients attend the lung health check appointment and consent to participation, further data will be collected in a pseudonymised fashion.

The aim is to provide a realistic indication of uptake in a real-world clinical context. Therefore appointments will be framed as a pilot health service, meaning participants will initially be unaware that their attendance is being measured for research purposes until they get to the clinic. Recording attendance is already standard practice in a clinical context and knowing that participation is being recorded for research purposes would introduce observer bias and undermine the research question.

Participants will receive information about the lung health check with their invitation. The information sent out will introduce the medical tests and components of the lung health check and provide a direct telephone number should they have any questions or require further information. They will receive this information at least two weeks before the appointment allowing time to decide whether to attend, cancel or rearrange the appointment. At the appointment, the research nurse will explain in detail all aspects of the lung health check appointment and LDCT scan, answer questions and check understanding. Communicating the benefits and risks of a lung cancer screening test is complex. Those at greatest risk of lung cancer (and thereby a significant proportion of those invited) are overrepresented in socioeconomically deprived groups, who have lower literacy and numeracy skills. Our strategy for communicating information (through written and other visual and interpersonal channels) is intended to improve informed decision-making by taking account of the complexity of this decision and the high level of support needed by our participants to make this decision.

The nurse will also explain that the intention is to collect research data investigating the likely uptake of a lung health check service, its impact on health services and factors relating to patient acceptability and psychological impact. The nurse will then take written informed consent from the patient should they wish to participate, or continue with the lung health check and terminate data collection if the patient declines participation. If the patient wishes to take time to consider all or parts of the consent, they will be able to do so, and another lung health check and LDCT scan will be rescheduled for another day. The research nurse will be trained to ensure that at the patient is at no time under any pressure to make a decision.

A standard participant information sheet and consent form will be used with all patients. The nurse will explain participant rights and confidentiality, and check understanding. Signatures will be dated and version numbers used. The patient will keep one copy of the consent form, whilst the other will be scanned and saved to the study database. Where there is doubt, capacity to consent will be determined.
6.0 Intervention: A targeted, stepped and low burden invitation strategy

6.1 Intervention invitation strategy: approach and rationale

The intervention invitation strategy aims to improve uptake of lung cancer screening by high-risk individuals; specifically smokers from socioeconomically deprived backgrounds. It takes the form of a targeted, stepped and low burden approach to information provision prior to the appointment which, in principle, would be practically feasible to implement on a national scale. This has been developed in response to what is known about the characteristics and beliefs of the target group from our preliminary research and evidence from other screening programmes. The complexity of information that must be understood prior to screening and psychological theory of the effectiveness of different types of information at different stages of decision-making are key factors that have been considered. Materials have been tested during four patient/public engagement sessions to ensure acceptability and comprehensibility, and revised accordingly.

The targeted component aims to reduce fear, fatalism and stigma around lung cancer, by emphasising support, providing a lay explanation for how early treatment of lung cancer can work, and avoiding mention of smoking, smoking cessation and risk where possible at the invitation stage. The stepped approach to information provision is based upon the different stages of awareness, engagement, decision-making and action proposed by the Precaution Adoption Process Model. Given that the target group are likely to have no prior awareness of lung cancer screening, the first contact has been designed to introduce the service and engage them with the idea. Written communication provides a low level of information to promote consideration of the offer in a way that does not overwhelm or overburden. This low burden approach has been designed in response to the inherent challenges of communicating risk, uncertainty and overdiagnosis; something likely to be exacerbated by the low levels of literacy and numeracy anticipated for the target group, and which may be compromised by fear of lung cancer. Free and easy access to further information before the appointment will be clearly signposted on invitation materials (for both groups).

Once at the appointment, the nurse can provide a supported environment for the communication of complex information and can facilitate informed decision-making. The patient can then choose whether to have the tests the same day or on a different day and the nurse will ensure they do not feel under pressure to decide either way.

6.2 Control invitation strategy

In the absence of usual care screening invitation materials, the control invitation materials and strategy are based upon the best available materials and methods of existing cancer screening programmes. This is comprised of the following:

1. a pre-appointment letter notifying patients of the lung health check service and an information booklet mimicking those of existing screening programmes
2. an invitation letter with a pre-scheduled appointment plus the same information booklet
3. a reminder re-invitation letter for those who miss their appointment without cancelling.

The intervention group will receive the same stages of invitation materials. The two differences are i) instead of the information booklet they will received a targeted leaflet, and ii) the invitation and reminder letters will use indirect phrasing to explain that smokers and ex-smokers are being invited. Together, these manipulations aim to deliver a targeted, stepped and low burden approach to information provision prior to the appointment as just described. Table 3 provides a detailed breakdown of the content, delivery and staging of information by invitation group.
6.3 Monitoring of non-participation

Those phoning to cancel or change their appointment will be asked for their reason, which will be recorded if the person is willing. Standardised questions will be set to ensure uniformity of data collection for non-attenders.
Table 3. Information content and delivery by stage and invitation group

<table>
<thead>
<tr>
<th>DELIVERY (mode, messenger, recipients)</th>
<th>Control Arm (Group A)</th>
<th>Intervention Arm (Group B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-invitation</td>
<td>Pre-invitation letter notifying the patient of the lung health check service</td>
<td>Identical pre-invitation letter to control</td>
</tr>
<tr>
<td></td>
<td>Information booklet mimicking ‘the facts’ booklets for cancer screening programmes</td>
<td>Targeted information leaflet introducing the tests using a low burden approach including:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- content designed to reduce fear, fatalism, stigma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- explanation and diagram to show how early treatment can work</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- quotes from interview participants to address stigma and highlight benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- emphasis on non-judgemental service</td>
</tr>
<tr>
<td>Invitation</td>
<td>Letter inviting patients for a lung health check including:</td>
<td>Control letter with one exception:</td>
</tr>
<tr>
<td></td>
<td>- statement that smokers and ex-smokers are being invited</td>
<td>- statement changed to say that people who have ever smoked are being invited (rather than smokers and ex-smokers specifically)</td>
</tr>
<tr>
<td></td>
<td>- pre-scheduled appointment</td>
<td>Second copy of targeted information leaflet</td>
</tr>
<tr>
<td></td>
<td>- contact details to cancel/rearrange/further information</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- information to help journey planning (map/address/stations/buses)</td>
<td>Brief essential information on the reverse side of the letter including details for requesting free copy of information booklet (phone or online)</td>
</tr>
<tr>
<td></td>
<td>Second copy of information booklet.</td>
<td></td>
</tr>
<tr>
<td>Appointment</td>
<td>Information booklet mimicking those of existing cancer screening programmes. Nurse-led facilitation of informed decision-making</td>
<td>Identical to control</td>
</tr>
<tr>
<td>Reminder</td>
<td>Letter re-inviting the patient for a lung health check appointment with similar content to the invitation letter</td>
<td>Control letter with one exception:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- statement changed to say that people who have ever smoked are being invited (rather than smokers and ex-smokers specifically)</td>
</tr>
</tbody>
</table>
7.0 Participating Screening Centres

7.1 University College London Hospital NHS Trust
This NHS trust was keen to implement a screening demonstration pilot on the basis of emerging evidence following the NLST. It is an internationally acclaimed teaching hospital with a large department dedicated to the subspecialty of lung cancer diagnosis and management within the trust and a dedicated lung cancer research unit within University College London (the same institution as the grant holder). The department has been known for pioneering research in the fields of early diagnosis of lung cancer and lung cancer staging\textsuperscript{136-143}, and has successfully lead several clinical trials on time and on budget and therefore is an ideal leading unit.

The chest radiology department also has a dedicated team well suited to lead on reading and management of LDCT scans generated from the screening programme. There is an affiliated cardiothoracic surgical unit with the skills and expertise for the surgical management of lung cancer and an established oncology unit with state of the art chemotherapy and radiotherapy services.

The catchment area of this site covers two London boroughs with a heterogeneously distributed demography within the local population.

7.2 Homerton University Hospital NHS Trust
Demographically, the catchment area is more deprived and ethnically diverse. On the basis of this, there is likely to be a higher proportion of individuals that may have a lower baseline uptake of screening, thereby being highly appropriate for this study. Furthermore, given the potential lack of generalisability with the NLST given its lack of implementation in district general hospitals\textsuperscript{144}, it was felt, by addition of a second site the results of this study may be more applicable to the general UK population.

This site was chosen on the basis of the interest taken in the project by both the Respiratory Physicians and Radiologists. The Respiratory Physician at this trust is a pioneer of endobronchial ultrasound within London and has a subspecialty interest in lung cancer. The Thoracic Radiologist is well experienced at detecting and staging lung nodules and lung cancers.
8.0 Components of the ‘Lung Health Check’ appointment
An overview of the stages of the study following on from the initial recruitment and the patient journey can be seen in figure 2.

8.1 Co-ordination and scheduling of appointments
Initially, appointment slots will be given in batches to each GP practice. This will be coordinated by the research team, who will assist GP practice administrators in preparing batches of appointment letters in advance which will be posted weekly or fortnightly by DocMail on the practice’s behalf. CT scan appointments will be quadruple-booked with four lung health checks and one CT scan scheduled for each day. Depending on attendance rates and eligibility for CT rates, this process will be modified to aim for two CT scans to take place per day. Appointments will be rescheduled or cancelled by the research nurse on participant request. This booking process will be reviewed and amended if the attendance rates are not in accordance with such a structure.

8.2 Appointment summary
At each appointment, participants will be given written and/or visual decision aids to improve their understanding of the benefits and risks of screening. This will be followed by a discussion between the participant and the nurse to facilitate informed decision-making and consent (see section 5.2). The nurse will take a brief medical and smoking history to assess cancer risk, eligibility for the CT scan, and carry out a spirometry test to measure lung function. Those who are eligible for the CT scan will be offered to have it on the same day or to have one arranged for another day at their preference. The data fields to be completed at the lung health check are listed in table 4.

8.3 Spirometry
Spirometry will be used to measure participants’ lung function. Nurses will receive training in advance to enable them to measure and document patient’s FEV₁, FVC and FEV₁:FVC ratio. They will be given basic guidance in determining a reading consistent with COPD or non-normality. A report of the spirometry result will be sent to the GP following the lung health check appointment to enable any abnormal findings to be flagged to the GP and enable Quality and Outcomes Framework (QOF) accreditation. Patient information leaflets on Chronic Obstructive Pulmonary Disease (COPD) and other lung conditions will be available. If a new finding of COPD or other abnormal result is detected in the absence of any prior known respiratory diagnosis, the patient will be recommended to contact their GP for further advice. Where possible, prior known diagnoses will be ascertained and only if a new diagnosis is picked up, will the patient be advised to see their GP. All results will be sent to the GP.

8.4 Biological sampling
The nurse will be trained to take a peripheral blood sample, sputum sample and exhaled breath sample and buccal swab. Various analyses will be carried out on these samples to collect data relating to proteins, antibodies and molecules present within the samples and of DNA and RNA of cells. The samples will also be stored and may be used in future studies (beyond the remit of this protocol). This anonymised data may be shared with external organisations (academic and commercial) both to validate current biomarkers and to explore new approaches within ethically approved research studies.
Study protocol: Lung Screen Uptake Trial v4 27.06.2016

Identification, recruitment and randomisation via GP surgery administrator

Group A: control invitation strategy
Group B: intervention invitation strategy

Sending of invitations ± reminder letters

Consent + lung health check appointment

Smoking cessation randomisation

Group C: Information only
Group D: Opt out scheme

A/B

Eligible for CT scan

Any abnormality detected

Normal scan

Write to patient & GP

Discharge to GP or internal 2WW referral
Request GP referral to respiratory or other services

A / AC / AD / B / BC / BD

No scan
Normal scan
Indeterminate findings
Abnormal scan
Incidental findings on scan

Follow up for up to 1 year

Inclusion/ exclusion criteria for database search

Randomise sub-sample of patients (n=210) to film + booklet vs. booklet

GP summary of outcome and spirometry result

Eligibility criteria

Result letter and subsequent psychological impact and informed decision making assessment questionnaire

Figure 2. The patient journey through stages of the study. Letters A&B denote initial randomisation group (relating to control or intervention invitation), and C&D denote second randomisation (relating to brief smoking cessation advice with or without the opt out referral to a local service).
Table 4. Components of the Lung Health Check

<table>
<thead>
<tr>
<th>Consent obtained</th>
<th>Demographic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID number</td>
<td></td>
</tr>
<tr>
<td>Age/ dob</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>IMD score &amp; rank; Townsend score</td>
<td></td>
</tr>
<tr>
<td>Accommodation</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Lives alone/ with anyone</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Highest level of education</td>
<td></td>
</tr>
<tr>
<td>Verify smoking status and history (Pack years)</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide reading</td>
<td></td>
</tr>
<tr>
<td>If quit smoking, ascertain years since quitting</td>
<td></td>
</tr>
<tr>
<td>Randomised to group C or D</td>
<td></td>
</tr>
<tr>
<td>Accepted smoking cessation intervention</td>
<td></td>
</tr>
<tr>
<td>Local service referred to / number given</td>
<td></td>
</tr>
<tr>
<td>Quit confidence and nicotine dependence (Heaviness of Smoking Index)</td>
<td></td>
</tr>
<tr>
<td>Lung cancer risk/ Medical History</td>
<td></td>
</tr>
<tr>
<td>Asbestos exposure</td>
<td></td>
</tr>
<tr>
<td>History of malignancy, if yes details including when</td>
<td></td>
</tr>
<tr>
<td>Family history of lung cancer, age&lt;60</td>
<td></td>
</tr>
<tr>
<td>Comorbidities especially previous respiratory disease (COPD, pneumonia, ILD)</td>
<td></td>
</tr>
<tr>
<td>Drug history</td>
<td></td>
</tr>
<tr>
<td>Factors required for lung cancer screening, cardiovascular and thoracic surgical risk scores</td>
<td></td>
</tr>
<tr>
<td>Measurements/ CT eligibility factors</td>
<td></td>
</tr>
<tr>
<td>BM1/ weight/ Height</td>
<td></td>
</tr>
<tr>
<td>Spirometry, FEV1 (absolute, % predicted), FVC (absolute, % predicted), FEV1/FVC</td>
<td></td>
</tr>
<tr>
<td>Ability to lie flat</td>
<td></td>
</tr>
<tr>
<td>Performance status (ECG)</td>
<td></td>
</tr>
<tr>
<td>NYHA/ MRC breathlessness scale</td>
<td></td>
</tr>
<tr>
<td>Psychological assessment and informed decision making</td>
<td></td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td></td>
</tr>
<tr>
<td>Cancer worry scale</td>
<td></td>
</tr>
<tr>
<td>Low Literacy Decisional Conflict Scale and satisfaction with decision</td>
<td></td>
</tr>
<tr>
<td>Subjective &amp; objective knowledge scores</td>
<td></td>
</tr>
<tr>
<td>Length and quality of nurse discussion</td>
<td></td>
</tr>
<tr>
<td>CT attendance</td>
<td></td>
</tr>
<tr>
<td>Eligible for CT scan (if ineligible- state reasons against inclusion/ exclusion criteria)</td>
<td></td>
</tr>
<tr>
<td>CT performed today (if no- when rebooked for)</td>
<td></td>
</tr>
<tr>
<td>CT attended</td>
<td></td>
</tr>
<tr>
<td>Willingness to be screened among those who are ineligible</td>
<td></td>
</tr>
<tr>
<td>Any other condition diagnosed or suspected e.g. COPD, asthma</td>
<td></td>
</tr>
<tr>
<td>Communication with GP</td>
<td></td>
</tr>
<tr>
<td>Recommendations for pulmonary rehabilitation</td>
<td></td>
</tr>
<tr>
<td>Report for GP of lung health check completed for GP</td>
<td></td>
</tr>
</tbody>
</table>
8.5 Smoking cessation referral intervention

All patients attending for the lung health check will be asked to have a Carbon Monoxide (CO) screening test, which will be carried out using a handheld CO monitor. Those who self-report smoking or have a CO reading ≥10 parts per million (ppm) will be eligible for the smoking cessation referral intervention. Patients will be advised that the best method of quitting is a combination of treatment and behavioural support, and that local, expert and friendly support is available. This approach is based upon the latest evidence and is advised by Dr McEwen, Executive Director of the National Centre for Smoking Cessation and Training (NCSCT). Using a web-based randomisation tool, patients will be individually randomised (again, with blocking by practice) to groups C or D to receive one of two types of smoking cessation referral:

i) **Group C — opt-in referral:** Smokers will be provided with contact details of their local stop smoking service and advised to self-refer should they want support with stopping smoking. Note that this represents usual care and is the most common route of referral to stop smoking services.

ii) **Group D — opt-out referral:** Smokers will be informed that it is the policy to refer all smokers to the local stop smoking service for help with managing their smoking and asked if they are content for this referral to take place. They will be advised that it is routine care to be put in touch with their local stop smoking service, but that it is their choice whether they want the referral to take place, or indeed to accept what the stop smoking service will offer them. A member of the respective stop smoking service will contact the patient to discuss the support available, the ways of accessing it and will attempt to engage the patient with their service.

Stop smoking services will be asked to provide follow-up data on attendance rates and quit rates set for patients who attend from both groups. Where possible, and where individual service information governance allows, data will also be collected on medication use, smoking history behaviour and quit attempts, including four-week quit rates. A report by the NCCST (supported by), provides evidence that abstinence at four weeks is a good predictor of long-term abstinence at 52 weeks. Patient consent for data collection from stop smoking services will be obtained by the nurse carrying out the Lung Health Check and by the stop smoking service (included within existing service consent forms in relation to third party data sharing). For patients consenting to take part in psychological follow-up questionnaires (see section 10.0), smoking status and quit attempts will be measured three months after their lung health check appointment. For patients who are being followed up within the pilot on the basis of abnormal findings on their scans, longer term quit rates will be recorded where possible. The results letter sent to GPs following the lung health check will include details of which services patients have been referred to.

Nurses will have completed the NCSCT online training module on delivering very brief advice on smoking. Dr McEwen will provide training to nurses on CO screening. CO monitors will be calibrated according to usage and ongoing support with their use will be provided by the NCSCT.

8.6 Eligibility screen for CT scan

Nurses will take a detailed medical and smoking history and record factors relevant in determining eligibility for a CT scan. The information will be collected as in table 3. Patients must fulfil the below criteria in order to have a CT scan, which will be scheduled to take place shortly after the lung health check or on another day, according to the patient’s preference.
Study protocol: Lung Screen Uptake Trial v4 27.06.2016

**Inclusion criteria:**
- ≥30 pack-year smoking history AND quit ≤ 15 years ago AND age 60-75 years
- OR LLP 5 year lung cancer risk > 2.5% OR PLCO 6 year lung cancer risk > 1.51%

**Exclusion criteria:**
- Participant does not have capacity to give consent
- CT scan within the last 12 months
- Weight exceeds restrictions for scanner (>200Kg)
- Participant unable to lie flat
- Poor physical fitness such that radical treatment would be contra-indicated

**8.7 Patients who are ineligible for a CT scan**
It is important that those attending, who are ineligible for a CT scan also benefit from the appointment. These patients will be offered all other components of the 'lung health check,' including spirometry and smoking cessation advice. It is the perfect context in which to raise awareness of lung cancer symptoms in at-risk groups and validate help-seeking by smokers. Therefore nurses will talk these patients through the symptoms and encourage them to visit their GP should they notice anything suspicious, even if seemingly minor. It is hoped this information will be exchanged through their wider social networks too. Where appropriate further input with smoking cessation and pulmonary rehabilitation will be recommended outside of the context of the study.

Communicating ineligibility in the correct way is paramount, especially for current smokers, so as not to provide a false sense of security with regards to lung cancer risk. The approach taken will depend on the reason for exclusion, as specified in the table below:

<table>
<thead>
<tr>
<th>Reason for ineligibility</th>
<th>Explanation to patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant smoked &lt;30 pack-years, quit smoking ≥ 15 years ago AND PLCO/LLP risk score lower than threshold for recruitment into study</td>
<td>Communication of current and future risk</td>
</tr>
<tr>
<td>Age outside recommended age bracket</td>
<td>Communication of current and future risk</td>
</tr>
<tr>
<td>Participant has contraindication</td>
<td>Harm-benefit ratio for them</td>
</tr>
<tr>
<td>Participant has physical limitations (i.e. weight &gt;200kg, unable to lie flat)</td>
<td>Harm-benefit ratio for them / Symptom awareness education</td>
</tr>
<tr>
<td>Participant cannot give consent</td>
<td>Symptom awareness education for relative / carer</td>
</tr>
<tr>
<td>Participant has never smoked (GP records inaccurate)</td>
<td>Apology and explanation of error</td>
</tr>
</tbody>
</table>

**8.8 Patients presenting with respiratory symptoms or infection**
Respiratory infection can increase the probability of a false positive result. Consequently, those attending who present with respiratory infection and qualify for a CT scan will be booked in for a delayed appointment in 6 weeks' time, allowing time for the infection to clear.

The nurse will screen for evidence of respiratory infection at the lung health check appointment. If there is any doubt, a respiratory clinician will be available for advice. The following definitions and guidelines will be used to screen for lower respiratory tract infection (LRTI), exacerbations of COPD and red flag symptoms of lung cancer.

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The SIGN guidelines for LRTI\(^{146}\) state that a diagnosis of LRTI encompasses a range of symptoms and signs, varying in severity from non-pneumonic LRTI in the young healthy adult through to pneumonia or life-threatening exacerbation in a patient with severe disabling chronic obstructive pulmonary disease (COPD). The most common symptom is cough, which is new or changed in character. Other symptoms include new or changed sputum discoloration or volume, breathlessness, wheeze, chest pain, fever, sore throat and coryza.

The GOLD definition\(^{150}\) of an exacerbation of COPD is “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication”.

Red flag symptoms in the context of lung cancer include haemoptysis, weight loss, loss of appetite, facial swelling or distended thoracic neck veins, hoarse voice and severe new chest pain\(^{151}\).

8.9 Requests for lung cancer screening for/by friends or family members of participants

This screening pilot is currently only being run as part of a trial. If there are any patients who have friends or relatives seeking LDCT screening, they will be informed of this and advised to speak to their GP should they be concerned that they have symptoms of lung cancer or that their risk of lung cancer is very high. Advice and support for GPs will be provided by a specialist respiratory clinician within the research team.

8.10 Communication of results to GP and patient following lung health check

The patient’s GP will receive a letter informing them of their patient’s attendance of the lung health check and enrolment in the screening demonstration pilot. GPs will also be notified of results from the CT scan, the spirometry test and any information on smoking cessation interventions carried out by letter. Continuous support and advice for GPs will be provided by the Clinical Research Fellow via a direct telephone line. Patients will be informed that their GP will receive all of this information prior to their consent.
Study protocol: Lung Screen Uptake Trial v4 27.06.2016

9.0 Lung cancer screening: The low dose CT scan
(adapted from UKLS protocol[52])

9.1 CT Equipment and software requirements
Sixteen channel (or preferably higher) 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. A volumetric software package will be used for assessment of pulmonary nodules. Where repeated scans are required (either within or outside the study), the software should remain constant to allow accurate comparison of volumes.

9.2 CT Image Acquisition Protocol

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

Localiser
Sites should use their standard scanogram to localise the start and end positions of the scan. The frontal localiser should be performed in the PA projection and at the lowest possible setting to minimize 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. Thin detector collimation (0.5 mm) will be used.

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

Image reconstruction
Thin collimation and overlapping 1mm-volumetric data. Image reconstruction should be standardised and used for any subsequent follow-up examinations.

Table 6. Reconstruction parameters for LDCT

<table>
<thead>
<tr>
<th>Reconstruction Algorithm</th>
<th>Reconstruction Slice thickness</th>
<th>Reconstruction Increment</th>
<th>Reconstruction FOV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate spatial frequency / soft tissue</td>
<td>1mm</td>
<td>0.7mm</td>
<td>Entire lung parenchyma</td>
</tr>
</tbody>
</table>

The height and weight of patients will be used to enable accurate selection of exposure factors. Patients will be asked to lie supine in the scanner with their arms above their heads. A scanogram will initially be carried out to localise start and end points of the scan. The reconstruction parameters will be as per table 6 above.

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9.3 Image Interpretation
A Radiologist or Radiographer should check appropriate segmentation of nodules. Image interpretation should be performed on 3D CT workstations which permit scrolling through the data set with variable thickness and orientation using multi-planar reformations (MPR) and Maximum Intensity Projection (MIP). 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. All scan data acquired from trial participants will be archived and retained at the local site.

9.4 Methodology for CT Reading and Quality Assurance
The main read for each scan will be by a local Chest Radiologist at the same site that the CT scan has taken place. All Radiologists have significant expertise with evaluation of pulmonary nodules and other findings. As the nodule cut off is fairly high at 8mm³ a high sensitivity and specificity are likely. In addition 5-10% of total cases, selected at random will be second-read by a Radiologist from the alternative participating site. Radiologists will provide detailed reports with the data outcomes to be recorded as per table 7 and plans for further management will be determined from this.

In addition to the above reading protocol, an additional read will take place by a suitably trained Chest Radiographer (who will be completely independent from the Radiologist readers). The Chest Radiographer will read the scans and they will use CADe as a second reader. The number and position of nodules will be compared across the readers. Any scans with excess nodules detected by Radiographer + CADe will be re-reviewed by the original Radiologist Reader, in order to accept the excess nodules as “true positives” or reject them as “false positives”. Any nodules noted by the Radiologist reader but missed by the Radiographer + CADe combination will be automatically recorded as “false negatives”.

Weekly quality assurance practices are required for the CT scanner, using a water and body phantom. All doses must be recorded at the time of acquisition. During the process of CT reading, if the Radiologist is not happy with the quality of the image, due to defects in the acquisition quality of any CT, such as image degradation due to breathing artefact, a decision should be made as to whether or not to repeat the CT, with participant permission.

9.6 Lung Nodule Characterisation and Volumetric Analysis
A nodule is an abnormal, rounded (or nearly-rounded), focus of opacification with or without calcification surrounded by aerated lung. Each scan will have up to two nodules characterised in detail with respect to site (lobe, juxta-pleural, perifissural), volume, density and presence or absence of spiculation or a benign pattern of calcification. Nodule type will be classified as solid (SN), part-solid nodules (PSN) or pure ground glass nodules (pGGN). SN with benign features (such as popcorn calcification, perifissural position, intrapulmonary lymph nodes etc.) will be disregarded and will not be recorded. The total number of nodules and other findings will also be recorded. Table 7 shows the fields that will be recorded for each scan.

Any subsequent scans will also record the same fields for any new nodules and a VDT will be calculated for any nodules with an increase in volume of ≥25% since the last scan.

9.7 Lung Nodule Management and Follow-up/Further Diagnostics
The protocol for management of patients undergoing the CT screen will be in accordance with the BTS 2015 pulmonary nodule guidelines which are currently under final review before publication. The likely management plan is as follows, however any changes to the final published BTS guideline will be reflected in the present trial management of screening findings and will not constitute a substantial amendment.
Study protocol: Lung Screen Uptake Trial v4 27.06.2016

### Table 7. LDCT Data Recording Fields

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader (e.g., Radiologist 1-4/ Radiographer + CAD concurrent vs second reader)</td>
<td>Time taken to read scan</td>
</tr>
<tr>
<td>Type of scan (e.g., screening, baseline/interval)</td>
<td>Age</td>
</tr>
<tr>
<td>Smoking history (PY)</td>
<td>Sex</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>Family history of lung cancer</td>
</tr>
<tr>
<td>Nodule size (mm³)</td>
<td>Nodule size (mm³)</td>
</tr>
<tr>
<td>Nodule size (mm)</td>
<td>Nodule size (mm)</td>
</tr>
<tr>
<td>Nodule type (e.g., pGGN, PPN, SN)</td>
<td>Nodule type (e.g., pGGN, PPN, SN)</td>
</tr>
<tr>
<td>Nodule density (HU)</td>
<td>Nodule density (HU)</td>
</tr>
<tr>
<td>Nodule shape (e.g., round, lobulated, linear, ovoid)</td>
<td>Lobar position</td>
</tr>
<tr>
<td>Margin (e.g., smooth, spiculated)</td>
<td>Margin (e.g., smooth, spiculated)</td>
</tr>
<tr>
<td>Benign features (e.g., diffuse, central, laminated, or popcorn calcification, fat, perifissural location)</td>
<td>Suspicious Features (e.g., bubble like appearance, pleural indentation, pleural retraction)</td>
</tr>
<tr>
<td>Suspicious Features (e.g., bubble like appearance, pleural indentation, pleural retraction)</td>
<td>Position (e.g., perifissural, juxta-pleural, upper lobe)</td>
</tr>
<tr>
<td>Total number of nodules detected</td>
<td>Incidental findings (e.g., none, UI, heart, liver, lung parenchymal, pulmonary vascular, anterior mediastinum, pleura, bones)</td>
</tr>
<tr>
<td>Emphysema (yes, no)</td>
<td>Any other findings</td>
</tr>
<tr>
<td>Impression</td>
<td>Follow up recommendation (e.g., d/c; f/u CT at 3/9/12 months; referred to MDT; incidental finding to be followed up)</td>
</tr>
<tr>
<td>Brock score</td>
<td>Volume doubling time (VDT) if previous imaging available</td>
</tr>
</tbody>
</table>

- Patients with nodules <5mm in diameter or <80mm³ or clear features of benignity can be discharged to the GP.
- Patients with incidental non-pulmonary findings can be discharged to their GP and specialist referral will be advised if appropriate.
- For lung parenchymal disease or other findings (other than malignancy), the GP will be advised of these changes and to refer to the local respiratory service if appropriate.
- For pulmonary nodules 5-6mm, a 12 month interval scan will be recommended and further management will be based on VDT as discussed below. For pulmonary nodules >5mm or 80mm³, interval scans at 3 months and 12 months (from the baseline scan) will be recommended. Following interval scans the VDT should be used to determine further management.
- Nodules with VDT>600 days can be considered stable while nodules with VDT<400 days should be further investigated (e.g. percutaneous biopsy, lung resection) and the patient should be discussed in the multidisciplinary meeting where further decisions should be in line with the BTS guidance. For
nodules with VDT 400-600 days, either approach (surveillance or biopsy/ resection) is considered appropriate and should be dependant on patient preference.

- For nodules >8mm or 300mm³, the Brock tool should be utilised (at the baseline scan for SN and at the 3 month interval scan for pGGN and PSN) to calculate risk of malignancy, and a risk >10% should lead to further assessment with FDG-PET scanning. Following this, the Herder tool should be utilised to calculate risk of malignancy and the patient should be discussed in the thoracic oncology multidisciplinary meeting where further decisions should be in line with the BTS guidance.

- For stable SN (i.e. <25% growth, or VDT<600 days) follow up can be restricted to one year if based on volumetry.

- For PSN and pGGN, any change in morphology or growth of solid component (≥2mm) as well as a Brock risk of malignancy of >10% should favour definitive histological diagnosis or radical treatment. The Brock score may at times underestimate risk and other radiological and clinical factors may need to be considered and discussed in the setting of a multidisciplinary team. Interval surveillance scans for stable PSN and pGGN should occur at 1, 2 and 4 years.

The Brock nodule risk prediction calculator 15 (for on-line calculator follow link: Brock tool) is a validated tool for assessment of risk of lung cancer taking into account clinical and radiological factors as per table 7 above. The Herder tool is another such calculator that incorporates findings from FDG-PET scans (on line calculator link: Herder tool).

9.8 Communication of results

CT scans will be read within 2 weeks and the results will be communicated to patients by one of four standardised letters. The results will be communicated as either “normal”, “indeterminate”, “warranting further investigation” or that “another incidental finding has been noted”. The patient will be required to contact their GP for the latter. For indeterminate nodules that require further surveillance, an internal referral to the respiratory team will be made to discuss the findings. Where possible, the management of these nodules will be discussed in a “nodule MDT meeting”. For those with suspicious findings, an urgent internal 2-week-wait referral will be generated and the imaging will be discussed in the thoracic MDT.

The GP will also have a letter sent with a summary of the CT result, what advice has been given to the patient and any subsequent follow up that has been arranged for the patient. If an incidental finding has been noted, the GP will be made aware, however the onus will be upon the patient to seek a referral from the GP.

For participants who are being given a “normal” result, care will be taken in framing of results to the participants and their GPs. It has been reported that participants receiving an “all clear” result in the context of negative tests for cancer may get short-lived or even long-lasting effects of over-reassurance that may undermine help-seeking in the context of perceived or associated symptoms in the future 153. The population being studied is at continued risk of lung cancer after screening and this must be made clear to both the participant and their GP to ensure appropriate medical investigations are carried out if appropriate in the future.

Following delivery of the results, a questionnaire will be sent to evaluate decision satisfaction, psychological well-being and current smoking status and desire / ability to quit.
10.0 Psychological impact of screening and informed decision-making

Three questionnaires combining the below outcome measures have been compiled for each time point to be assessed. The tentative versions of these questionnaires are available and appended to the ethical submission.

10.1 Measurement of the psychological impact of screening

Validated questionnaire measures will be used to investigate the psychological well-being of patients, namely the Hospital Anxiety and Depression Scale (HADS)\textsuperscript{104}, the EQ-5D\textsuperscript{105}, and the Cancer Worry Scale\textsuperscript{106}, which will be adapted for lung cancer.

Measurement will take place at the following three time points:
1) Baseline: At the lung health check appointment prior to screening
   Patients will be asked to report their levels of lung cancer worry, anxiety and depression over the last month (not currently) to provide a pre-screening assessment.
2) Post-appointment: Patients will be given a questionnaire at the appointment and a freepost return envelope, which they will be asked to complete the following day as a post-screening assessment.
3) 3 months follow-up: Patients will be mailed a questionnaire and a freepost return envelope three months after their lung health appointment as a follow-up assessment.

10.2 Measurement of informed decision-making

Validated questionnaire measures will also be included to examine whether an informed decision has been made about screening by eligible participants attending the lung health check appointment, and their satisfaction with that decision. This will allow us to, i) assess the information on screening provided at the appointment and ii) ensure the targeted invitation strategy is equally effective as the standard invitation strategy at supporting decision-making at the appointment. Items will be adapted from existing scales to measure subjective and objective knowledge relevant to the decision\textsuperscript{107}, decisional conflict\textsuperscript{108} and decisional satisfaction\textsuperscript{109}.

Measurement will take place at the following three time points:
1) Baseline: At the lung health check appointment prior to screening to determine differences in baseline knowledge
2) Post-appointment: To determine the impact of any decision aids and/or discussions with the nurse.
   Patients will be given a questionnaire at the appointment and a freepost return envelope, which they will be asked to complete the following day as a post-screening assessment.
3) 3 months follow-up: To assess longer term retention of information and satisfaction with decision.
   Patients will be mailed a questionnaire and a freepost return envelope three months after their lung health appointment as a follow-up assessment.

10.3 Testing the information-film (Substantial amendment June 2016)

It is acknowledged that the information required to make an informed decision about lung cancer screening is complex and is not always easily understood. Informed decision-making (IDM) requires processing of complex information that may be challenging particularly for individuals with low levels of health literacy\textsuperscript{110}. There is evidence to suggest that the understanding of the complex issues in cancer screening such as overdiagnosis and false positive rates\textsuperscript{111}, is generally poor. It has been reported that patients often do not read written materials\textsuperscript{112} and individuals of varying demographic background have different preferences in how this information should be presented in terms of content and graphics\textsuperscript{113}.  

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A number of studies have evaluated the efficacy of delivering patient education using a variety of communication tools. It is noted that use of these tools, particularly when interactive and tailored to the individual, results in improved patient understanding\textsuperscript{165}. Several randomised studies have been carried out comparing film with standard methods of delivering information, most commonly written. The majority of studies\textsuperscript{155-158} (including one in lung cancer screening\textsuperscript{155}) have found a significant improvement in various components of IDM with use of this method while a few, rather underpowered studies\textsuperscript{170-172} have not.

Extra funding has been granted to the research team by the Roy Castle Lung Cancer Foundation, to use qualitative research methods to inform the development of an information-film that can be used to present the potential benefits and harms of screening in order to promote informed decision making in those considering taking part. This is a previous ethically approved study entitled "Addressing the Information needs of lung screening participants" (INLS) (IRAS 192823).

The information film has been scripted and is currently undergoing a final round of feedback in the form of focus groups from members of the public who would qualify for lung cancer screening as well as written feedback from a variety of health professionals involved in the care of lung cancer patients. The proposed story-board and script (which may have minor changes following the feedback) are attached to the substantial amendment submission. The film will be completed at the end of July 2016.

In a sub-sample of the participants of the Lung Screen Uptake Trial (n=210), a third randomisation will take place allocating participants to receiving either the control information booklet (previously given to all participants on arrival to the lung health check appointment) or the information booklet plus the newly developed information-film (Groups E and F).

It will be explained to patients that these assessments are to test the effectiveness of our information materials and not them.

In order to test the effectiveness of the film, two additional knowledge assessments, before and after the patients receive the information materials, will take place as indicated below. Between these assessments, patients in both groups E and F will be given 10 minutes to read the control information booklet ± watch the information film.

Measurement will therefore take place at the following four time points:

1) Baseline: At the lung health check appointment prior to screening and before information-giving in clinic, to determine baseline levels of knowledge

2) Post information materials: To determine the impact of the written and/or audio-visual information materials

3) Post-appointment: To determine the added impact of the discussion with the nurse.

4) 3 months follow-up: To assess longer term retention of information and satisfaction with the decision.
11.0 Data Management

11.1 Data handling and Record Keeping
Access to data will be restricted to appropriate trial personnel for the purposes of the research and analysis of the results. All data will be handled in adherence to the Data Protection Act 1998 and Information Governance (IG) legislation. An IG Toolkit is being obtained with UCL’s IG department. Audit trails will be in place in order to be able to fully trace data entry and edit.

Specific personnel acting on behalf of the trial sponsors, and national regulatory authorities, may access data.

Inputting of data will comply with information governance legislation. Contracts of non-disclosure will be in place where appropriate. An audit trail of documentation and data collection will be kept to enable monitoring by the research team and external regulatory bodies, and to protect against unintentional or unauthorised modification. Data will be obtained fairly and appropriately from participants. At the time of consent participants will be informed of the purpose of data collection and intentions for its use.

In order to minimise risk of data breach, all data will be stored securely and keys to identifying the participant’s GP, name and other identifiable data will be kept in a separate database within UCL’s information data safe haven.

11.2 Data sharing plan
In line with Cancer Research UK’s (funder) policy on data sharing, we intend to make our data available to others in a timely and transparent manner for the benefit of the research community. As our research involves human participants, we will initiate appropriate precautions to ensure the privacy of participants such as anonymising data. All participants will be required to provide informed consent and this will be in place to allow data sharing at an appropriate time. We will follow guidelines outlined under the Data Protection Act (1998) to ensure confidentiality and adhere to ethical principles at all times. We will also adhere to the School of Life and Medical Sciences IG framework which aligns with the Health and Social Care Information Centre IG toolkit.

Analysis of biological samples may be carried out by third parties. Where third parties are to be involved, appropriate data sharing agreements will be in place. Biological samples may be used for scientific research at a later date. These would be regarded as a gift from medical research. All transferred data will be anonymised, the key will not be shared and will be retained securely. Radiological images will also be anonymised and shared with the radiology software company. Participants’ consent will be sought prior to carrying out this. Information from the National Health Service Care Register, the Office of National Statistics and/or Cancer Registries may be used to follow the patient’s progress.

We will follow the principles of metadata to support the data sets arriving from the research, in order to ensure the data can be interpreted accurately when required. This information will include definitions of variables, units of measurements, assumptions and any other relevant information. We anticipate that data will be available following final acceptance for publication of the findings (unless intellectual property protection restrictions apply). Following requests for data, we will securely send data ‘under the auspices of the Principal Investigator’, although in the course of the study we may adapt our strategy to include other methods of data sharing suggested by CR-UK (e.g. data endave). Following a request, we will develop a data sharing agreement to ensure that data will be used appropriately. For example, we will require information about objectives, timelines for use and intellectual and publication rights.
Once the projects have finished, we will ensure to preserve all the data for a minimum of fifteen years or as stipulated by the study sponsor. We intend to monitor our data sharing policy, and discuss issues around intellectual property rights with relevant organisations as they arise.

With consent, the participant’s GP will be notified of their participation in the trial.
12.0 Statistical considerations

12.1 Sample size calculation
A total of 2000 patients will be invited for a lung cancer screening appointment, 1000 in each arm. This is based on our primary outcome (screening attendance). Our best estimate from similar studies is 35% uptake in the control group which will increase to 42% with the intervention materials. The 7% difference is based on studies examining the effect on screening uptake of ‘psycho-educational’ materials; although the literature is scarce. We found a 5% difference in uptake with an illustrated booklet in deprived participants in the UK Flexible Sigmoidoscopy Trial\textsuperscript{73}, and a study of FOBT found a 5.9% difference compared with a letter only condition and a 11.8% difference compared with usual care\textsuperscript{74}. As we are addressing both SES- and smoker-specific factors in uptake, we believe 7% is a reasonable estimate and a figure that would deliver clinically significant benefit if implemented on a national scale. 1000 patients per group will provide 90% power to detect a significant difference of 35% vs. 42%, with 5% significance level and two-sided testing.

12.2 Statistical analysis plan
12.2.1 Baseline demographic data
- Observational baseline demographic data of invited participants in the control and intervention arms including age, sex, ethnicity, deprivation score and rank, smoking status (including previous quit attempts) to be collected.
- Consort diagram.

12.2.2 Primary outcome analysis
- The association between uptake and invitation group will be analysed using Chi square and multivariate logistic regression analyses.
- Interaction terms will be included to investigate if sociodemographic (age, sex, ethnicity, deprivation score and rank) and smoking-related (smoking status, quit confidence, tobacco dependence) predictors of uptake are differentially associated with invitation group.
- Sociodemographic and smoking-related characteristics of attenders within each invitation group will also be compared with those of the overall invited patient group (i.e. all those identified and invited initially in primary care).

12.2.3 Secondary outcome analysis
- Eligibility for screening:
  - Number eligible for CT screening; number screened.
  - Number would be eligible for screening using alternative eligibility criteria i.e. 6 year PLCO risk > 1.51% / 5 year LLPv2 risk > 2.5%
  - Univariate analysis (Chi squared test) to determine if there is any significant difference in the numbers of patients eligible using differing criteria [95% powered to detect small effect size of 0.18].

- Smoking cessation intervention:
  - Numbers in both groups of clinic attendees, quit dates set and 4 week quit rates
  - Univariate analysis to explore association between likelihood of attending clinic/ setting quit date/ achieving abstinence at 4 weeks in both groups using logistic regression. (Assuming 75% of 770 attendees are still smokers, projected sample size is 289 in each group. This would result in 90% power to detect difference of between 10% and 20% abstinence at 4 weeks, and 80%
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- power for a difference between 5% and 12% abstinence at 4 weeks, with two-sided testing and a 5% significance level.
- Multivariate analysis of associated variables adjusting for demographics (such as age, sex, ethnicity, and smoking history)- to be attempted but note low power.

- **Observational findings from CT/ Lung health check interventions**
  - Numbers of cancers and other incidental findings eg emphysema, pulmonary fibrosis, cardiac abnormalities, pleural abnormalities, mediastinal lymphadenopathy, proportion new incidental diagnoses made.
  - Numbers of patients with new diagnosis of COPD on spirometry at lung health check.
  - Numbers of investigations and treatments generated by screening (projected numbers from UKLS data for our sample of 693 scans noted in figure 5 below).

- **Observational findings on local healthcare costs and impact on service and univariate comparison with historical controls in same institution**
  - Cost incurred per patient who required additional investigations beyond baseline scan (mean, s.d.)
  - Number of extra CT scans generated by screening over a 1 year period
  - Total number of referrals generated for nodule follow up
  - Total number of referrals to MDT
  - Total number of subsequent PET, biopsy, PFT, EBUS, bronchoscopy, LN biopsy, further CT and other imaging
  - Total number of generated referrals to oncology/ thoracic surgery and other specialties
  - Costs of smoking cessation intervention compared in both arms
  - Impact on GPs from screening process- Total number of generated patient queries/ consultation requests

![Diagram](image)

Figure 5. Expected numbers of investigations modelled from UKLS.

- **Appraisal of radiology follow up and reading protocols**
  - Number of false positive and false negative nodules detected per scan by the Radiographer (with and without use of CADE). False positive nodules will be defined as any nodules detected
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by the Radiographer ± CADe combination, that are subsequently rejected by the Radiologist as true positives when the scans are re-reviewed. False negative nodules will be defined any nodules picked up on the initial read by the Radiologist but not by the Radiographer. The false positive and false negative values for the Radiographer ± CADe combination will be calculated against the Radiologist performance. It is acknowledged that the Radiologist may not achieve 100% specificity and sensitivity, however such analyses will establish non-inferiority of performance.

- Risk of malignancy within the dominant nodule as calculated by Brock Score
- Outcome and management plan advised by scan read
- Numbers of incidental findings detected
- Reading time and cost per reader
- Numeric outcomes can be compared between the 2 groups by unpaired students 2-tailed t-test. Categorical outcomes can be compared by chi-squared test. There is sufficient power with this sample size to detect a small effect, and so no detected effect may be considered to be suggestive of non-inferiority.

- Psychological burden of screening
  - Levels of cancer worry, anxiety and depression will be explored in relation to the screening result, sociodemographic characteristics and smoking-related factors using chi square analyses and multivariable regression modelling.
  - Analyses will be carried out in relation to absolute thresholds and changes over time, adjusting for baseline levels.

- Informed decision making
  - Observed levels of subjective and objective knowledge of concepts relating to lung cancer screening at baseline, post CT screening appointment and over time
  - Scores relating to decisional conflict, satisfaction with decision and coherence of decision making with own values and general anxiety and psychological well being
  - Comparison between such scores across different time points, across groups (i.e. in response to different invitation strategies) and association between different sociodemographic factors can be explored in chi square analyses and multivariable regression modelling.
  - Impact on quality, ease and length of discussion with the nurse and numbers of patients making informed consent to screening (vs. those making an informed refusal)

- Adverse events from screening process and subsequent investigations
  - Observed adverse events (if any) from screening and subsequent investigations
  - All cause and lung cancer related mortality rate at 1 year

12.2.4 Testing the effectiveness of the information-film (Substantial amendment June 2016)

Previous studies assessing the effect on patient knowledge of information provided by film compared with written information are scarce. Those that do typically do not expose the participants to the film under controlled conditions in the way we are doing so in the present study.
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The effect size of the intervention in studies testing the impact of film on patient knowledge is generally moderate to large. Three well designed studies report intervention related improvements in knowledge scores by 24% \(^{165}\), 21% \(^{166}\) and 78% \(^{166}\). Other studies have failed to detect a significant effect, however, these were heavily underpowered. The sample size in this study will confer more than 90% power for a difference of 10% vs 30% in the two groups, and approximately 80% power for a difference of 10% vs 25% (5% significance level, two-sided testing).

Statistical analyses comparing mean score for the objective and subjective knowledge, decisional conflict and decision satisfaction within and between each group at stages 1-3 will be carried out by way of 2-tailed t-tests. Chi-squared tests will be used to compare categorical outcomes between groups.

12.3 Procedure(s) to account for missing or spurious data
All attempts will be made to minimise any missing data. At the time of consent to the study, we will take consent from the patient to access their secondary care health records so that any patients managed within secondary care, will continue to have data recorded. For any patients leaving the geographical area or seeking treatment from another hospital, attempts will be made to get the complete data.

Missing data will be continually monitored to identify if there are any problematic measures which need to be adjusted or removed. If a significant amount of data is missing, imputation will be carried out where appropriate to minimise any bias, under the supervision of a statistician. Where possible, the order of questionnaire items will be rotated to reduce order bias in participants’ responses.

13.0 Compliance

13.1 Subject Compliance
As the primary outcome for the study (uptake) will be measured at enrolment, subject compliance is not anticipated to be an issue. If response rates for the follow-up questionnaires are low, participants will be contacted by telephone to prompt or assist questionnaire completion and return (only for those participants consenting to be contacted by the research team in this way). Clinical secondary outcome measures will be recorded for one year after recruitment by the research team and therefore should not be subject to problems with participants’ compliance.

Patients with abnormal or unclear results who do not attend appointments for follow-up medical investigations will be contacted to determine the reasons for non-attendance. Where this prohibits the follow-up of serious findings, the patient and their GP will be notified.

13.2 Withdrawal of subjects
Patients wishing to withdraw from the study will be able to do so at any time. A discussion with a member of the research team will take place to ask if the participant would be willing to share their reasons for this (although a reason is not required) and ensure there are no adverse events or other issues that need resolving either within or outside of the study and/or study team.
13.3 Withdrawal of data
Participants wishing to withdraw their data will be able to contact the research team and request this at any time during the trial duration. Participants will not be required to give a reason, but will be asked for their reason for quality assurance purposes.
14.0 Ethical considerations

The study will be undertaken with strict adherence to recommended CONSORT guidelines and good clinical practice. The data will be held securely and information governance rules followed rigorously.

Special attention will need to be paid to ensure the primary care record search (used to identify eligible patients) is carried out with adherence to information governance legislation concerning the handling of personal data. The search will be carried out by a researcher in conjunction with a member of a general practice surgery staff to identify potential participants as defined by pre-set criteria (namely age and smoking status). Postcodes will be converted into deprivation scores and ranks and all identifiable data will be hidden at this time. Once the conversion has taken place, all sensitive and identifiable data will be removed from the list to be exported to the researchers. The only sensitive personal data extracted from these records will be ethnicity.

Achieving informed consent is a key priority in this study, both to participation in screening as well as participation in the trial. More information on the consent process is in section 5.2.

We have sought the opinions of members of the public and patients on the acceptability of using their pseudonymised data without consent for research purposes (as we will be doing at the GP database stage) and had no objections reported. We have also piloted the invitation materials and asked members of the public their views on consenting to the LDCT scan and the research study on the basis of these materials in advance of the appointment (together with contact details for further information and questions), and had a unanimous response that this would be entirely reasonable.
15.0 Trial audit and quality control

15.1 Ethical approval
Main Research Ethics Committee (MREC) approval, NHS Research Ethics Committee (REC) and NHS Research and Development (R&D) approval is being sought via the Integrated Research Application System (IRAS). Site Specific Information (SSI) is being submitted by each participating centre.

15.2 Declaration of Helsinki and Good Clinical Practice
The study will be conducted according to the recommendation of the Declaration of Helsinki (2000 Edinburgh, Scotland) and in accordance with the ICH principles of Good Clinical Practice.

15.3 Quality control and quality assurance
The Lungs for Living Research Centre and the Health Behaviour Research Centre will be responsible for the day-to-day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL/ UCLH/ HUH). The sponsor will be responsible for all duties relating to safety monitoring.

As a quality control measure (and in addition to measures set out by the sponsor), site visits will be carried out by the research team to ensure consent is being taken appropriately and that the necessary documentation is being completed and data entered. Conversations with patients will be observed to ensure patients are involved in decision-making and communication adheres to protocol. A quality control checklist will be prepared for the researcher to complete during these observations as an objective measure.

5% of all CT scans will be cross read for quality assurance. Any difficulties encountered will be reported to the Trial Management Group (TMG) on a regular basis concerning difficult decisions referred to them, as the study progresses. (See also section 9.5.)

Participating sites must agree to allow trial-related on-site monitoring and Sponsor audits by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

15.4 Trial Management
The TMG will include the Chief Investigator, clinicians and experts from relevant specialities. The TMG will be responsible for overseeing the trial. The TMG will review substantial amendments to the protocol prior to submission to the REC. All investigators will be kept informed of substantial amendments through their nominated responsible individuals.

An Independent Data Monitoring Committee (DMC) and Trial Steering Committee (TSC), both involving members who are independent of the investigators, funders and sponsors will be appointed. The study will be conducted according to Good Clinical Practice guidelines. The DMC and TSC will monitor data accrual and toxicity, trial progress and conduct and advise on scientific credibility. The DMC and TSC will meet regularly (for example every 6 months).
15.5 Trial management file

A trial management file will be kept at UCLH and an Investigator Site File at HUH. These will be composed in accordance with our sponsor's regulations and will be kept securely, but will be accessible to regulatory authorities. The maintenance of these files will be assigned to a dedicated researcher.

15.6 Indemnity & Compensation

The sponsor, will provide insurance against claims for compensation for injury caused by participation in this trial (ie non-negligent compensation). Patients wishing to make a claim should address their complaint in writing to the chief investigator in the first instance.

15.7 Publication policy

A summary of study findings will be available to participants on request.

We intend to disseminate any findings from our research in peer-reviewed journals. All clinicians and researchers involved in the project will be acknowledged in written papers.
Appendix 3- LSUT protocol paper

The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and ‘hard-to-reach’ patients

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Abstract

Background: Participation in low-dose CT (LDCT) lung cancer screening offered in the trial context has been poor, especially among smokers from socioeconomically deprived backgrounds; a group for whom the risk-benefit ratio is improved due to their high risk of lung cancer. Attracting high risk participants is essential to the success and equity of any future screening programme. This study will investigate whether the observed low and biased uptake of screening can be improved using a targeted invitation strategy.

Methods/design: A randomised controlled trial design will be used to test whether targeted invitation materials are effective at improving engagement with an offer of lung cancer screening for high risk candidates. Two thousand patients aged 65–75 and recorded as a smoker within the last five years by their GP, will be identified from primary care records and individually randomised to receive either Intervention Invitation materials (which take a targeted, stepped and low burden approach to information provision prior to the appointment) or Control Invitation materials. The primary outcome is uptake of a nurse-led ‘lung health check’ hospital appointment, during which patients will be offered a spirometry test, an exhaled carbon monoxide (CO) reading, and an LDCT if eligible. Initial data on demographics (i.e. age, sex, ethnicity, deprivation score) and smoking status will be collected in primary care and analysed to explore differences between attenders and non-attenders with respect to invitation groups. Those who attend the lung health check will have further data on smoking collected during their appointment (including pack-year history, nicotine dependence and confidence to quit). Secondary outcomes will include willingness to be screened, uptake of LDCT and measures of informed decision-making to ensure the latter is not compromised by either invitation strategy.

Discussion: If effective at improving informed uptake of screening and reducing bias in participation, this invitation strategy could be adopted by local screening pilots or a national programme.

Trial registration: This study was registered with the BICTIN (International Standard Registered Clinical/Social study Number: ISRCTN21774741) on the 23rd September 2015 and the NIP ClinicalTrials.gov database (NCT0255810) on the 22nd September 2015.

Keywords: Lung cancer, Cancer screening, Smoking, Health inequalities
Background

Worldwide, lung cancer kills more people than any other cancer, explaining over one fifth of all cancer-related mortality in the UK [1, 2]. Five-year survival is poor at just 11.1% for men and 15.0% for women [3], but prognosis improves significantly with earlier stage at diagnosis. For example, five-year survival estimates increase to 58–73% when non-small cell lung cancer (NSCLC) is diagnosed at the earliest stage (stage IA) [4]. However, close to 70% of patients are diagnosed with advanced stage disease [5] with around 40% presenting via emergency admission [6] and almost a third dying within 90 days of their diagnosis [7]. This is partly because detecting lung cancer early is challenging; early symptoms are typically non-specific and they may not even be manifest until the disease has progressed.

Data from the National Lung Screening Trial (NLST) suggest that screening individuals at high risk of lung cancer using low-dose computed tomography (LDCT) scans is a potential early detection strategy. A 20% relative risk reduction in lung cancer mortality and a 6.7% reduction for all-cause mortality was observed for patients aged 55–74 with a significant (≥30 pack-years) and recent (within 15 years) smoking history, who underwent three annual LDCT scans compared with chest X-rays [8]. Subsequently, the US Preventive Services Task Force (USPSTF) issued a grade B recommendation for screening high risk adults: a preventive service benefit now covered by Medicare and Medicaid Services [9].

For any screening programme to be effective, it must achieve a positive benefit-harm ratio, which in turn depends upon attracting the high risk population. Increasing the risk profile of participants has potential to reduce avoidable invasive follow-up tests and the number needed to screen [10]. Indeed, NLST participants categorised within the three highest quintiles of risk benefitted from 88% of screen-prevented deaths [11]. However, enrolment to screening offered within the trial context has been extremely low, ranging from 0.2–4.6% of the total age-eligible population invited [12–15], and biased toward former smokers, rather than current smokers, and towards higher socioeconomic status (SES) individuals [16, 17]. In the UK Lung Screening Trial (UKLS), the proportion of individuals with a high lung cancer risk score (using the Liverpool Lung Project model) [18] increased with socioeconomic deprivation, yet paradoxically response rates and subsequent clinic attendance decreased [19]. This suggests that despite their high risk, lower SES smokers are less likely to engage with an offer of screening or see it through a pervasive problem observed across other screening programmes [19–21] and healthcare services [22, 23].

It is essential that screening communication effectively engages this group if lung cancer screening is to be an equitable early detection strategy and attain adequate uptake. To date, methods of recruitment into trials have been heterogeneous, including mass-mailing, media advertisements, community outreach and GP enrolment (e.g. [12, 14, 24]). Some initially invited all individuals in the at-risk age group who were requested to complete risk assessment measures and engage in further correspondence to determine eligibility. Therefore, while we know uptake is poorer among low SES smokers, it is difficult to ascertain the denominator of eligible individuals invited to screening needed to reliably calculate levels of uptake among high risk candidates. Furthermore, these individuals have been invited to participate in a research trial evaluating the clinical effectiveness of LDCT screening: an invitation that is likely to be interpreted very differently from that for a lung cancer screening service. To our knowledge, no study has taken a targeted approach to the design of invitation and information materials for (and in consultation with) high risk and hard-to-reach groups, nor attempted to test such a strategy in the real-world context of a demonstration pilot lung cancer screening service.

Aims

The primary aim of this study is evaluate the impact of a targeted invitation strategy, compared with a control, on uptake of ‘lung health check’ appointments overall and in association with demographic and smoking characteristics.

The secondary aims of this study are to:

1. compare the demographic and smoking-related characteristics of attenders versus non-attenders for each invitation group, and with the overall invited group, to explore informed decision-making outcomes by invitation group to check that the information provided to each is equally effective in facilitating a patient’s ability to make an informed decision at the appointment,
3. ascertain figures to help gauge uptake of a national screening programme and inform the feasibility of recruiting to a LDCT programme via primary care.

Methods/design

Study design

This study will use a two-arm, between-subjects, individually-randomised controlled trial design to compare uptake of lung cancer screening appointments between two groups allocated to receive either intervention
or control invitation materials (see Fig. 1 for an overview of participant flow through the trial).

**Randomisation and allocation procedure**
The individual unit of randomisation will be the patient. A web-based randomisation programme has been constructed by an independent health research unit. This will randomise patients at a ratio of 1:1 using permuted blocks for each GP practice to ensure group allocation is evenly balanced by practice. Patient identifiable details will be concealed from the researcher carrying out the randomisation assignment using a pseudo-anonymised spreadsheet of eligible patient details exported securely to the researcher from the GP practice. Patients will be blind to their allocation and the research nature of the study, which would undermine the primary outcome.

**Setting and participants**
Patients will be identified from primary care practices falling within three Clinical Commissioning Groups (CCGs): Islington, Camden, and City and Hackney. These sites were chosen because they have demographically diverse patient populations. All patients will be invited by their GP (by letter, including a clinic telephone helpline) to a pre-scheduled ‘lung health check’ appointment with two weeks’ notice. This will include an eligibility screen (i.e. smoking and medical history), spirometry test, CO reading, smoking cessation advice (for current smokers), and for those eligible, a LDCT scan. The appointments will be run by research nurses in outpatient clinics at a central London tertiary referral hospital and an inner London district general hospital (University College Hospital and the Homerton University Hospital). Informed consent will be taken by a research nurse at the beginning of each lung health check appointment who will explain...
that the purpose of the pilot is to measure uptake and will describe all other data being collected. Data on secondary outcomes will not be collected for patients who do not give consent.

Eligibility criteria
Inclusion criteria
Patients will be eligible for invitation if they are aged 60–75 years and have been recorded by their GP practice as a current smoker at any point since April 2010. This threshold was chosen for two reasons: i) to identify a group likely to have accrued the 30 pack-year history conferring likely screening eligibility, and ii) to identify predominantly current smokers as this is the group most difficult to attract to screening.

Exclusion criteria
Patients will be excluded if they fulfil any of the following criteria: have an active lung cancer diagnosis or metastases, are on the palliative care register, have had a recent CT thorax (<12 months), lack capacity to consent, or GP deems them unsuitable due to a comorbidity contraindicative of screening for lung cancer or subsequent treatment.

Patient identification
The patient identification process will be supported during an initial site visit by a member of the research team. A standardised audit search will be imported and run by practice administrators to extract details of eligible patients from GP record databases with ease and consistency. The subsequent list of potentially eligible patients will then be screened by GPs for patients they deem unsuitable. To avoid contamination, only one eligible patient per household will be enrolled.

Invitation procedure and adherence
The printing and mailing of materials will be carried out via a secure third party company on behalf of each GP practice. A researcher will support practice administrators in uploading patient details, specifying the contents of mail packs and assigning mailing dates using the company’s electronic system. Allocation of appointments will have been carried out by the research team at the randomisation stage and input into the spreadsheet of patient details so that these automatically populate the invitation letters. This in-practice assistance will also allow monitoring of adherence to the mailing protocol. The mailing company’s activity will also be monitored via checking of reported mailings to ensure they are being sent as instructed.

Control invitation materials
Table 1 provides a detailed breakdown of the content, delivery and staging of information by invitation group. Invitations in both arms will be from the patient’s own GP. In the absence of ‘usual care’ invitation materials, control invitations will mimic so far as possible the best available materials and methods of established cancer screening programmes. These comprise the following:

1. a pre-invitation letter notifying patients of the lung health check service and an information booklet mimicking so far as possible, those of existing screening programmes,
2. an invitation letter with a pre-scheduled appointment plus the same information booklet that accompanied the pre-invitation letter,
3. a reminder re-invitation letter for those who miss their appointment without cancelling (sent ≥4 weeks following the missed appointment).

Intervention invitation approach: a targeted, stepped and low burden invitation strategy
The intervention group will receive the same stages of invitation materials as the control group. The two differences are: i) instead of the information booklet they will receive a targeted leaflet (see Additional file 1), and ii) the invitation and reminder letters will use indirect phrasing to say that smokers and ex-smokers are being invited. Together, these manipulations aim to deliver a targeted, stepped and low-burden approach to information provision prior to the appointment which, in principle, would be practically feasible to implement on a national scale. The group we are inviting will be far from homogeneous but as it is not feasible to ascertain each individual recipient’s characteristics prior to invitation, we are attempting to provide the best ‘one size fits all’ approach inclusive enough to target a variety of different characteristics but also conservative, so as not to unnecessarily deter one group at the expense of another’s uptake. Materials have been tested during four patient and public engagement sessions to ensure acceptability and comprehensibility and reviewed by our multidisciplinary team (psychology, respiratory medicine, radiology, smoking cessation, and primary care) and community-academic partners from our qualitative phase of work informing the invitation design ([25]; full paper in prep).

Targeted component
This has been developed in response to what is known about the characteristics and beliefs of the target group from our own and existing research ([25–29]; full paper in prep). It aims to minimise fear (particularly of an expected diagnosis at screening which actually has a low
probability), fatalism, stigma and blame around lung cancer by: i) emphasising a supportive and non-judgemental service, ii) providing a lay explanation for how early detection of lung cancer can work (using a diagram to illustrate that the lung is a treatable organ which need not be completely removed because early treatment can be focussed within a lobe), iii) acknowledging that the invited generation were previously not as informed of the risks of smoking, iv) avoiding mention of smoking, smoking cessation, and risk where possible at the invitation stage, vi) emphasising the salience for older adults, and vi) normalising the offer so as to not imply the reason for invitation as being that lung cancer is suspected or that the recipient is being singled out.

**Stepped approach**

This is guided by the Precaution Adoption Process Model (PAPM) which depicts different stages of awareness, engagement, decision-making and action for preventive health behaviours [30]. It is a useful framework from which to hypothesise at what stage different types of information could most effectively be communicated. Given that the target group are likely to have no prior awareness of lung cancer screening, the first contact is designed to provide a positive introduction to the service to engage them with the idea, without the pressure of yet needing to decide whether to attend. Previous research has shown that advance notification letters for bowel cancer screening which include a low level of information successfully increase participation [31], particularly among men from socioeconomically deprived backgrounds [32]. Written communication thereafter contains cues to action intended to minimise non-intentional factors that reduce participation (i.e. forgetting and procrastination). These include prescheduled appointments, maps with travel information, and for those who do not respond, reminder re-invitations, which have previously been shown to be effective [31–34].

**Low burden level of information prior to the appointment**

The materials have a relatively low level of information to promote consideration of the offer in a way that does not overwhelm or overwhelm. This takes account of the inherent challenges of communicating risk, uncertainty and overdiagnosis [35, 36]; the scientific uncertainty of estimates for lung cancer screening, its fast-moving evidence base, the application of population risk modelling to individual risk profiles, and new medical terminology [37], difficulties comprehending this information which are likely to be further exacerbated by the low levels of health literacy and numeracy anticipated for the low SES target group [38], and fear of lung cancer, which may influence receptivity to information and the ability to
weigh up information rationally [39]. Increased ambiguity of information has been shown to confuse, raise suspicion and promote risk aversion among individuals with low numeracy and low optimism [40, 41]. Furthermore, recipients' first impressions of the amount of information could be important for information engagement as perceived cognitive ease has been associated with more positive appraisal of the information content [42].

All these factors considered, it seemed appropriate to reduce the complexity of the information provided and the decision required by the individual to that of deciding whether to attend to discuss the tests. Free and easy access to further information before the appointment will be clearly signposted on invitation materials (for both groups). Once at the appointment, the nurse can provide a supported environment for the communication of complex information and can facilitate informed decision-making. The patient can then choose whether to have the tests the same day or a different day and the nurse will ensure they do not feel under pressure to decide either way.

**Social marketing**

The proposed approach, supporting evidence, and detailed draft content, were communicated to a social marketing team, who have used their expertise to creatively design engaging materials tailored for the target audience. The colour scheme and typography of the targeted leaflet is based on the brand identities of businesses that target low income customers. The images used are representative of a diverse population and range of ages, so as to reflect and engage the target audience. The leaflet uses a non-authoritarian conversational tone and includes quotes from our qualitative work to introduce a social presence to the information (255, full paper in prep).

**Methods of data collection and outcome measures**

**Demographics and smoking**

Data on age, sex, ethnicity, smoking status and postcode will be extracted from primary care records by practice administrators for all patients identified as eligible and invited. Postcodes will be converted to Index of Multiple Deprivation (IMD) scores and ranks on site by a researcher from a spreadsheet within which identifiable data fields have been hidden. A pseudo-anonymised spreadsheet containing all these data will then be compiled and exported to a researcher independent of the identification process for randomisation and entry into the study database. While developing this protocol, we surveyed members of the public and patients about accessing this data prior to consent and none interviewed had any objections.

At the appointment, these data will be verified by a nurse who will take informed consent for the collection of any further data post-attendance. Further data collection will include information on attendees' highest level of education (as an additional measure of SES) and measures of smoking behaviour and history. These will include current smoking status (self-reported and CO verified), usual number of cigarettes smoked daily, age started smoking, pack-year history, use of other nicotine and tobacco products (pipes, cigars, electronic cigarettes, waterpipes, smokeless tobacco) nicotine dependence (two item Heaviness of Smoking Index) [43] and quit confidence within the next six months.

**Primary outcome**

Uptake of the lung health check appointments will be recorded by the nurses running the lung health check appointments prior to consent. It will be measured by attendance because the outcome of interest is whether participants can be adequately engaged to consider lung cancer screening. The aim is to provide a realistic indication of uptake in a real-world clinical context. Recording attendance is already standard practice in a clinical context and knowing that participation is being recorded for research purposes would introduce observer bias and undermine the research question.

**Secondary outcomes**

To further explore interest and uptake of screening, willingness to be screened will be used as a proxy measure to gauge interest among those attending who are ineligible for a LDCT scan, and uptake of LDCT scans will be recorded among those eligible. Data on informed decision-making (i.e. objective and subjective knowledge, decisional conflict, decisional satisfaction) will also be collected at the appointment using a paper questionnaire. Items have been adapted from existing studies and measures, and low literacy scales have been chosen where available [44–46]. These measures will allow us to ensure the targeted invitation strategy does not compromise the ability of patients to make an informed decision about screening at their appointment. Scores on these measures will be compared by invitation group to ensure intervention participants achieve either similar or improved scores.

**Sample size**

The target sample size is 2000 patients. This is based on an estimate that 35% of patients in the control group will attend, similar to initial uptake of colorectal cancer screening (by FOBT) in London within the two most deprived IMD quintiles [47]. The aim is to achieve a 7% improvement in uptake on the basis of similar previous research. Studies testing targeted ‘psycho-educational’ invitations have achieved a 5.9% higher uptake of colorectal cancer screening (flexible sigmoidoscopy) in
deprived areas [48] and an 11.8% increase in FORT participation [49]. Also, a 7% increase would deliver clinically meaningful benefit if scaled to a national programme. With 2000 patients split equally into two groups, statistical power to carry out two-sided tests at the 5% significance threshold is 90%.

Statistical analysis methods

Primary analysis

The researcher carrying out the analyses will be blinded to group allocation. Un-blinding will occur after the primary data analysis is complete and has been checked and verified by a second researcher. Chi square associations and multivariate logistic regression analyses will be carried out to compare uptake between the intervention and control groups. These analyses will take an intention-to-treat approach, including all patients identified and randomised. Due to the nature of this study, there should be no missing data for uptake.

Secondary analysis

Interaction terms will be used in regression models to investigate if there are differences in demographic and smoking-related predictors of uptake and if there are associations with invitation group. The demographic and smoking-related characteristics of attenders from each invitation group will also be compared with those of the overall invited group to further test for any biases in uptake and to elucidate figures which could be used to help gauge uptake by the high risk in the event of a national lung cancer screening programme.

Further analyses will be carried out to explore willingness to be screened, uptake of LDCT scans and informed decision-making outcomes (i.e., knowledge, decisional conflict, decisional satisfaction) by invitation group. This will function as a check that the intervention invitation materials do not adversely affect the patients’ ability to make an informed decision, given their low burden approach to information provision.

Ethical approval, research governance and trial sponsorship

This study was approved by the City Road and Hampstead NHS Research Ethics Committee (REC reference: 15/LO/1186) on the 29th July 2015. Site-specific approval for the two hospital sites has been obtained via the Integrated Research Application System (IRAS), along with the necessary approvals from their Research and Development Departments. Any planned modifications to the protocol will be approved by the REC before they are adopted by the study.

This study has been adopted onto the NHS trial portfolio and is sponsored by University College London (UCL). The Joint Research Office (for UCL, UCH and the Royal Free) may carry out independent audits and on-site monitoring of the trial at any time and without notice; in adherence to UCL’s respective policies and the Department of Health’s Research Governance Framework for Health and Social Care.

Study management

This study is a collaborative effort, run by the Health Behaviour Research Centre (HBRC) and the Lungs for Living (L4L) Research Centre. The trial management group (TMG) is comprised of the Principal Investigator, academic and clinical collaborators, and key researchers, who will together monitor trial conduct and progress. Data management, patient confidentiality and the conduct of all clinical and trial personnel will adhere to the full clinical trial protocol (version 2.0 or subsequent approved versions). Good Clinical Practice guidelines, essential standard operating procedures, the NHS Code of Confidentiality and the Data Protection Act (UCL Records Office registration number: ZE364106/2015/10/34). Inputting of data will comply with information governance legislation. An audit trail of documentation and data collection will be kept to enable monitoring by the research team and external regulatory bodies, and to protect against unintentional or unauthorised modification. Formal involvement of a Clinical Trials Unit (CTU) was deemed unnecessary by the UCL Institute of Clinical Trials and Methodology (ICTM) portal review group.

A Trial Steering Group (TSG) comprised of independent expert and lay members will meet with key members of the TMG to oversee this study and agree any amendments to the protocol. There will be meetings at six month intervals (approximately) throughout the trial recruitment phase. An Independent Data Monitoring Committee (IDMC) will review data on secondary clinical outcomes and sub-studies (to be reported elsewhere). There will be no interim review of the behavioural data as the behavioural intervention tested here poses minimal risk to patient safety.

Trial status

This study began recruiting in October and is expected to recruit for 12 months.

Discussion

This study will test a novel, low-cost and targeted invitation strategy for lung cancer screening, which aims to improve engagement with a screening offer by the high risk, especially low SES smokers. If shown to be effective, the materials and strategy could be translated for use by local screening pilots and a national screening programme were one to be implemented. The results would act as proof of principle that grass-roots research
investigating psychosocial barriers to uptake within the local high risk community can effectively inform the development of engaging materials. Results will also inform the feasibility of inviting high risk patients to screening via primary care and provide figures to help estimate likely uptake of a screening programme. Findings from this study will be written in accordance with the CONSORT Statement [50], submitted for publication to relevant peer-reviewed journals and presented at conferences. A summary of results will provided to any participants who request this.

Additional files

Additional file 1: Targeted information leaflet (PDF 20.6 MB)

Abbreviations

Competing interests
AM has received travel funding, honorariums and consultancy payments from manufacturers of smoking cessation products (Pfizer Ltd, Novartis UK and GSK Consumer Healthcare Ltd) and hospitality from Nishi; who provide online and database services. AM also receives payment for providing training to smoking cessation specialists; receives royalties from books on smoking cessation and has a share in a patent of nicotine delivery device. AM is an Associate of the New Nicotine Alliance (NNA) that works to foster greater understanding of safer nicotine products and technologies. Reardon media (J and G); a specialist health behaviour change consultancy, was commissioned on a semi-commercial basis to provide social marketing services including copywriting and graphic design services for the creation of the health information leaflet "NUIO: for your lungs". John Littt, Director of Insight at Reardon, who is an honorary research fellow at UCL, gave consultancy time to the project free of charge. Copyright of the leaflet design and content is retained by Reardon. A universal license to use the leaflet for non-commercial use is granted by Reardon to UCL in perpetuity. The terms of the licence require preclude the transfer of this licence to any other party.

Authors’ contributions
JM, SWG, DBR, AM and SLQ conceived the study design and wrote the funding application. At the time this paper was written, JM was the PI and grant holder and SLQ was the CWI, SLQ, J and GI designed the intervention invitation materials. IW, SWG, SWO, DBR, RJS, AM, KS, MIB and SLQ have developed and refined the study protocol. All authors have contributed to the draft and critical review of the manuscript. All authors read and approved the final manuscript.

Acknowledgements
We are sad to announce that Professor Jane Wardle passed away while this paper was in preparation. Jane was the inspiration and driving force behind this paper and her intellect, wisdom, kindness and humour are deeply missed by all of her co-authors, colleagues and students. We would like to thank Selina Foroghi of NCIoT, for her help with developing and piloting the patient identification search process within primary care, and with GP practice recruitment. We would also like to thank Dr Lucía Grun and Dr Struan Hitchman for their help with recruiting GP practices for the study. The study is funded by a National Awareness and Early Diagnosis Initiative (NAEDI) project grant awarded by Cancer Research UK and a consortium of Funders (Department of Health (England), Economic and Social Research Council, Health and Social Care NI) Division, Public Health Agency, Northern Ireland, National Institute for Social Care and Health Research, Wales, Scottish Government, NI, MI, WB and AM are supported by Cancer Research UK, SM is a Wellcome Trust Senior Fellow in Clinical Science and is supported by the Roswell Trust, the Wellton Trust, the Gairdner Wellton Trust and UCL Charitable Foundation. This work was partially undertaken at UCL, which received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centre’s funding scheme (SM). SM is also funded by the Royal Castle Lung Cancer Foundation and is part of the CRUK Lung Cancer Programme of Excellence. SLQ is supported by the Medical Research Council. The funding sources have had no role in the design of this study and will not have any role in its execution, analyses, interpretation of the data, or decision to submit results.

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References


Appendix 4- LSUT lung health check script

LUNG HEALTH CHECK SCRIPT

OUTSIDE THE DOOR

- Introduce self as member of lung health check team/ lung health check nurse and thank them for coming
- As you know, you are here for a lung health check appointment.
- As this is part of a new service it is also part of a research study.
- What that means is with your permission we will ask you a few extra questions and record that data for research purposes.
- Depending on your answers, you may be invited to have a CT scan of your lungs afterwards
- The research isn’t compulsory and if you choose not to do that part (or any individual part of the study), you can still have a lung health check, but we are grateful to you if you can take part.
- The lung health itself check takes about 30-45 minutes.
- Give leaflet and ask them to read, and complete demographic info
- Offer tea/ coffee

Give them time to read, and check if they have a hospital number on CDR and start completing the recruitment log. Make sure the database and randomisation are logged on. Give them a few minutes to read but call them in when they have stopped reading.

START OF APPOINTMENT

- Ask them if they understood everything and if they have any questions
- Go through consent - side 1
  - This is to say that you have read the information sheet, and been able to ask questions.
  - That you are happy to have your data recorded on the computer. This data is just for the researchers and the health care team that will be looking after you. People who run quality checks on the research, may also view this data. We may also look at your medical records in the future as part of the research.
  - We may use/share this data anonymously for teaching, reports, presentations and publications in academic journals.
  - Your participation is voluntary and you may withdraw at any time and this won’t affect your medical or legal rights.
  - If you are happy to take part please sign here. (Initial 1-5 and sign

DATABASE

- Take demographic info
- Do smoking history (if smoker carry out randomisation while asking smoking questions)
• CO test

• At end of smoking section deliver VBA (very brief advice)
  o Research has shown that people who want to give up have a much higher chance of achieving this when given a combination of support and nicotine replacement and medications and both are available freely at an NHS service near you.
  o Whether or not you have thought about giving up smoking,
  o If C: We are routinely referring all smokers to their local stop smoking clinic and they will contact you within a few days. You don’t have to make any decisions now. Please say if you don’t want me to pass on your details.
  o If D: Here are the details for your local stop smoking service, it would be good if you could get in touch with them.
  o At end of clinical recordings

• Then go through
  o Symptoms and help seeking
  o Past medical history
  o Information resources and reasons for attendance

CONSENT PART 2
• If appropriate- tell them they have a higher than average risk of lung cancer due to their age, smoking and other history and that they are eligible to be offered a CT scan
• CT scan is a 3d x-ray test, not painful, like a big doughnut.
• Takes about 10 minutes with perhaps a little waiting before hand
• Important to hold their breath for a short time but they will be instructed.
• But before they decide whether to go ahead, they should be aware of the pros and cons and make their own mind up whether its right for them to go ahead.

Pros:
• Currently lung cancer is often diagnosed late due to symptoms occurring late. With screening we aim to detect lung cancer earlier which offers a higher chance of cure.
• A US study showed we might save 20% of lives that could have been lost from lung cancer if we screen high risk individuals

Cons:
• Radiation- the amount of radiation in 1 scan is about the same as what you’d get from the environment in a year, and isn’t too harmful. However many scans over a lifetime especially when young, can cause harm.
• Indeterminate results- about a quarter of all patients undergoing screening will have a “spot”. This will mean the need for further tests to check for growth. This can cause anxiety. If this does happen to you, try not to worry as about 90% of those with spots, will turn out not to have cancer. I.e. only 2 in every 100 screened will have cancer.
• Overdiagnosis- The screening test may pick up slow growing cancers that you may end up having tests or treatments, when they may be so slow growing that without the screening tests you may have gone on another 15-20 years without knowing there was cancer, and it may not cause symptoms.
• Very rarely, the test may miss small cancers
• Ask them if this is something they are want to have, and if so offer today or to reschedule.
• Then go through second part of consent form.
  o That if they are happy we will take blood and do tests for research purposes such as DNA which will help us to be able to predict risk of lung cancers
  o That they consent to having the CT scan
  o That they don’t mind if we share their images without their name with an external company that is developing software to detect lung cancers
  o That we may contact them for further research
  o That we let their GP know of the results
  o That we contact SSS for info on how they have got on

END OF THE APPOINTMENT

• Send email request for CT
• Thank them and take blood
• Explain results perhaps while taking blood:
  o You will hear from us within a couple of weeks (more over Christmas). If it is normal, we will let you know and nothing more will need to be done. If a spot or anything else shows up, you will be called to see a specialist doctor who will discuss the results and need for further test with you. Sometimes we find other things not relating to lung cancer, and if we do we may ask you to discuss this with your GP.
  o Ask them to complete questionnaire outside in waiting room
  o Encourage to do the one the next day and send back afterward in SAE
  o Direct them to CT scanner
Appendix 5- LSUT participant information sheet

UNIVERSITY COLLEGE LONDON HOSPITAL
235 EUSTON ROAD
NW1 2BU

SCHOOL OF LIFE AND MEDICAL SCIENCES
UNIVERSITY COLLEGE LONDON
5 UNIVERSITY STREET
WC1E 6JF

Participant Information Sheet V 4  17/06/2016

LUNG SCREEN UPTAKE TRIAL

You are being invited to take part in a research study. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please take time to decide whether or not you wish to take part and let us know if there is anything that is not clear or if you would like more information.

The study is approved by the National Research Ethics Committee.

What is the purpose of the study?
Research has shown lung cancer screening can save lives. The present study is being carried out to see if we can increase the numbers of people attending screening by altering the method and content of the information and invitations you received prior to attending the lung health check appointment.

Why have I been invited?
We are inviting people who would likely qualify for lung cancer screening and have been identified as previous or current smokers aged between 60 and 75.

What we will ask of you during this study:
Here is some basic information of what will be asked of you as part of the study. More information can also be found on the leaflets that you should have received earlier. If you need another copy or wish to discuss this further please ask the research nurse or use the contact details on the back of this form.
First a nurse will go through the details of the study with you and ask you to sign a form to say you are happy to participate. You can change your mind at any time.

You will be given a leaflet with information about lung cancer screening and/or shown a short film. The nurse will ask you to answer some questions to check what you already know about lung cancer screening. This is to test how good our information materials are so that they can be improved for future patients if needed.

The nurse will then carry out the lung health check. They will record information about your medical conditions, details about your smoking and any family history as well as some personal details such as age and occupation. The nurse will record your weight and height and carry out a breathing test to check the function of your lungs. It is not painful but will require you to blow into a machine. They will carry out a blood test and take samples of your breath. These samples allow researchers to develop new techniques for assessing the risk of lung cancer.

If you are assessed as meeting the criteria for lung cancer screening, you will be invited to have a CT scan today or if you prefer, at a later date. It is important you read the information about the scan and the screening process on the supplied leaflet on CT screening.

What are the possible benefits of taking part?
By having a lung health check and CT scan, we will have the opportunity to detect lung problems that you may not be aware of including conditions such as lung cancer and emphysema. If found you may be offered more effective and earlier treatment.

By taking part, you also help to improve our knowledge of how best to invite people for lung screening, how best to carry it out within the NHS and the development of new ways to assess risk of lung cancer.

Are there any disadvantages to taking part?
The procedure for obtaining the blood sample may cause a little discomfort. Blood will be taken by a qualified Nurse or a Health Professional and they will follow procedures and take appropriate precautions to minimise any discomfort. The breathing tests and collection of phlegm and cheek cells are painless. If you are uncomfortable at any point, you can ask to stop the tests.

The risks from the scan are relatively small, however some people may feel anxious while waiting for or receiving the results. The risks associated with the scan are further detailed in the leaflet on CT screening.
It is important that you fully understand the risks associated with screening and the possible outcomes that may follow the scan before going ahead. If there is anything you are not sure of, you will have the opportunity to discuss this before you decide whether or not you would like to take part.

**What will happen to the blood and other samples, and other information I provide?**

We will take a small 20ml sample (roughly three and a half teaspoons) of blood. Some of this will be processed in the hospital laboratory. The remainder of the blood, cheek samples and sputum will be processed to look for special cells, proteins, DNA and other molecules that could be markers of cancer. This research may be used to develop new techniques for detecting lung cancer early and the sample may be analysed at a university or at a specialist company. With your permission the samples may be sent anonymously (so your name and other personal details will be removed) for analysis and stored for use in future ethically approved studies.

We will also ask your permission for your CT scan images and the results of any future medical tests you have in relation to anything we find on screening, to be shared with a medical imaging software company to help further develop their product. The images may also be used for teaching and training purposes. All of the pictures and your medical information will be anonymised (so your name and other personal details will be removed) prior to sharing this information. It is your choice whether you agree to this and it will not affect any other care you receive.

**Will my taking part be kept confidential?**

Yes, your participation in this study will be kept confidential. All information you provide will be kept confidential in accordance with the 1998 Data Protection Act. Any shared samples or pictures will be anonymised and you will not be able to be identified from them.

We ask your permission to share your participation in this study and any results from the medical tests (but not results from any questionnaires you complete) with your GP. Again, it is your choice whether you agree to this and it will not affect any other care you receive.

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

We hope to report our findings in academic/health-related journals and present them at scientific meetings and conferences. You will not be identified in any report or publication arising from the study. If you are interested we will also send you a summary of our overall findings. The aims of our study are to improve early detection of lung cancer so more patients can be cured.
The events following the CT scan
If you do have a CT scan you will be contacted with the results and further advice within two weeks. Some people will be required to come back to the hospital for further tests, either in some weeks or some months. If you require any further tests, this will be at the same hospital as your initial screening test. We will record details of further tests and any results as part of the study. You may also be asked to complete questionnaires every few months which we will post to you. We may also contact you by phone or email to help with other research within this study or carried out by University College London. We will ask your permission prior to doing this and will not contact you if you do not want us to.

For more information on outcomes following the CT scan, please see the screening information leaflet.

Who is organizing the research?
The study is being led by a team of researchers at University College London. Staff from University College Hospital London (UCLH) and Homerton University Hospital (HUH) are overseeing the study. The study is funded by several charitable organisations including Cancer Research UK through a new project called the National Awareness for Early Diagnosis Initiative (NAEDI).

What if there is a problem or if something goes wrong?
It is important that you ask any questions you have at any time before and throughout the study. The research nurse will go through the details of the different tests and the research study with you at the lung health check appointment and you will have as much time as you need to discuss these. If you have any questions at any other time, please contact the research team using the number on the last page of this information sheet.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this.

In the unlikely event that you are harmed by taking part in this study, compensation may be available. If you suspect that the harm is the result of the Sponsor’s (University College London) or the hospital’s negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Professor Samuel Janes, who is the Chief Investigator for the research and is based at University College London. You can obtain the correspondence address for this from Dr Mamta Ruparel,
whose contact details are on the last page of this information sheet. The Chief Investigator will then pass the claim to the Sponsor’s Insurers, via the Sponsor’s office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

**To contact the research team:**

Dr Mamta Ruparel  
Lungs For Living Research Centre, Division of Medicine  
University College London  
Rayne Institute, S University Street  
London WC1E 6JF.

Telephone: 07969 118308  
Email: lungscreen@ucl.ac.uk

If you would like independent advice or information about taking part in research projects then please see the INVOLVE website: http://www.invo.org.uk/ Or contact: INVOLVE, Wessex House, Upper Market Street, Eastleigh, Hampshire, SO50 9FD. Telephone: 023 8065 1088. Email: admin@invo.org.uk

Or for advice from the NHS please contact: Patient Advice & Liaison Service, Hospitals NHS Foundation Trust, Ground Floor, University College Hospital, 235 Euston Road, London, NW1 2PQ. Telephone: 0207 3809975.

**Thank you for taking the time to read this information sheet. We hope you are able and willing to take part in this study.**
Need more information before your appointment?
For more information call our freephone advice service on 0808 281 9525 or call/text 07469 118 308 or email us at lungscreens@ucl.ac.uk

Lung Health Check:
Information on what’s involved

If you are unable to read this leaflet because English is not your first language, please ask someone who speaks English to telephone the freephone helpline on 0808 281 9525 for further information and help.

Engilsh

If you are unable to read this leaflet because English is not your first language, please ask someone who speaks English to telephone the freephone helpline on 0808 281 9525 for further information and help.

Appendix 6- LSUT Film study control information booklet
A new NHS Lung Health Check is being offered to people aged 60 to 75 who smoke or used to smoke.

This booklet is designed to help you decide whether to have a lung health check. It is your choice whether you attend.

It aims to answer the following questions:

Why am I being invited?

What happens when I arrive at the appointment?

What are the different tests?

What are the possible benefits and risks?

What is lung cancer?

Who can I contact if I have a question?

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**Signs and symptoms of lung cancer**

In the very early stages of lung cancer, there are often no symptoms. This is partly because the lungs are large and do not feel pain.

Warning signs to look out for include:

- a persistent cough or change in an existing cough
- feeling short of breath
- coughing up blood
- pain or ache when breathing or coughing
- unexplained tiredness or weight loss
What is lung cancer?

Lung cancer begins when cells in the lungs, windpipe (trachea) or airways (bronchi) start to grow abnormally.

The cells form a cluster (known as a nodule), which grows bigger and turns into a tumour.

In most cases this happens slowly and (without screening) can take up to five years before it is diagnosed.

How common is it?

Lung cancer is the second most common cancer in the UK. Survival from lung cancer improves the earlier it is found. Over eight out of ten lung cancers are caused by smoking. Risk of lung cancer is also increased in those who are older, have been exposed to other people's smoke, have been exposed to asbestos, or have been diagnosed with a lung problem like COPD (which includes chronic bronchitis and emphysema).

What can I do to reduce my risk?

The single best thing you can do to prevent lung cancer is not smoke. If you do smoke and would like to stop there is lots of help out there.

Ask your GP about free local support available, or contact NHS smokefree on 0800 0224 332 or visit www.nhs.uk/smokefree

What is a lung health check?

Lung health checks test for the early signs of lung conditions. Lung conditions and lung cancer are easier to treat when found early, and there is now good evidence that screening for early stage lung cancer using CT scans saves lives.

Why am I being invited?

Lung health checks are being offered to people aged 60 to 75 who smoke or used to smoke. These people are most likely to benefit because they are more at risk of lung disease. Medical records indicate that you are either a smoker or have smoked in the past.

It does not matter if you already have a lung problem. Please let the nurse know about this at your appointment.

What happens when I arrive at the appointment?

A nurse will greet you, discuss all the different tests and answer any questions. The nurse will help you choose which tests you would like by explaining how you might benefit from them. You can choose when you want to have the tests - then or at a later date. You may not be offered a CT scan if it is not suitable for you and the nurse will discuss this with you.
What are the different tests?

**Lung function test**

This is a simple test (called spirometry) for which you blow into a hand-held machine. The test checks for problems with the lungs that may be caused by conditions like asthma, lung tissue scarring, sarcoidosis and COPD (which includes chronic bronchitis and emphysema). It measures:

- How much air you can take into and blow out of your lungs
- How strong your breathing muscles are

**CO (carbon monoxide) test**

The nurse will ask you to hold your breath for 15 seconds (or as long as you can) and then blow into a hand-held machine. It measures the level of carbon monoxide in your breath, to find out how much there is in your blood. Carbon monoxide is a poisonous gas produced by tobacco smoke, unsafe gas boilers and pollution.

**Samples of blood, breath, sputum and cheek cells**

We are carrying out research to see whether the early signs of lung disease can be found in the blood, breath, cells from the lining of the cheek and sputum samples. These tests are not part of your lung health check and it is completely up to if you want to have them.

Samples of breath are taken by breathing normally into a machine

Cheek cells are collected by rubbing a swab (which looks a bit like a large cotton wool bud) against the inside of the cheek

Any sputum brought up by an existing cough is collected in a pot

How reliable is lung cancer screening?

Like all cancer screening tests, lung cancer screening is not completely accurate and some cancers will be missed. Nodules found in the middle of the chest and some small cancers are harder to see. Some cancers start to grow after screening.
What are the possible benefits?

When found early, lung conditions are easier to treat and lung cancer is more likely to be cured.

A study in North America has shown that using CT scans to find lung cancer early saves lives of people aged 55 to 75 who smoke or used to smoke. Screening using CT scans prevented 20% more deaths from lung cancer than using chest x-rays.

What are the possible risks?

The low dose CT scan will expose you to a small amount of radiation. It is the same as about one year’s worth of radiation from the natural environment. The risk of a CT scan causing a cancer is very low compared with the benefits of detecting lung cancer early. If a further CT scan is needed then this will expose you to more radiation.

In some cases, people will be diagnosed and treated for lung cancer that would never have caused the person harm. If they had not been screened, they would never have known about the cancer or have had any treatment.

Waiting for the results of these tests can be worrying. People with an unclear result will need to be monitored and have a further scan. This can be a worrying time and in most cases they will not have lung cancer. If you are confused about any of the tests or have any concerns at any point, please contact the lung clinic and we will help.

Further tests and treatment all carry risks as well as benefits. Should you be offered any of these, a specialist NHS doctor will discuss the risks and benefits. If you would like to know more information about these before having a CT scan, please speak to the nurse during your appointment.

Low dose chest CT (computed tomography) scan

A chest CT scan is a type of x-ray which takes detailed pictures of the lungs. These pictures are processed by a computer and then checked for the early signs of lung cancer by specially trained doctors (known as radiologists).

Whether or not you are offered a CT scan will depend on your lifestyle, medical and family history. The nurse will help you to choose whether the test is right for you and you may want to postpone it to a different day.
What is having a chest CT scan like?
The CT scan will take about 10 minutes. You will be asked to lie flat on the bed of the scanner. The bed will move slowly backwards and forwards while the scanner circles your chest. Specially trained staff will sit the other side of a screen where they can talk to you and control the scanner.

Only your chest will be scanned and you will not go into a tunnel (this is for a different scan called an MRI scan). The scan is pain-free and you will not need an injection. If you do have any concerns about the scan then please contact the lung clinic or speak to the nurse at your appointment.

RESULTS WILL BE SENT TO YOU & YOUR GP IN 2 WEEKS

Normal result This means that no signs of lung cancer or other abnormalities could be seen on the scan. Approximately three quarters of people will have a normal result. While this is good news, it is still possible that lung cancer could develop in the future or that the scan may have missed it. It is important to be aware of the symptoms of lung cancer and to go to your GP quickly if you have any concerns.

Unclear result This usually means the scan has shown a small area of white shadowing in the lung. This is probably something harmless but there is a chance it might be something serious. You will be invited to an appointment with a specialist doctor to discuss the result. The best way to make sure that there is nothing to worry about is to have another scan after an interval to make sure there are no signs of lung cancer. Most people with an unclear result will not have lung cancer.

Abnormal result This means there is something abnormal on the scan that needs more tests to find out what it is. It could be cancerous or it could be harmless. You will be invited to an appointment with a specialist doctor who will discuss the results and arrange further tests.

Incidental finding This means there are signs of other problems on the scan that may need treatment or medical advice. If you already have a lung problem, this might be why and you may not need any extra care. You may be advised to make contact with your GP to make an appointment to find out more.
Appendix 7- LSUT Consent form

Contact: Dr Mamta Ruparel
Lungs For Living Research Centre, Rayne Institute
Division of Medicine, University College London
5 University Street, London, WCIE 6IF
lungscreen@ucl.ac.uk | 07469 118308

HOSP-TPN: ______________________
Date: ________________________

CONSENT FORM (v7.0: 17/06/16)
Study title: Lung Screen Uptake Study

1. I confirm that I have read and understood the information sheet (version 4) for the above study and have had the opportunity to ask questions.

2. I consent to having my data reviewed by the research team, relevant health personnel and personnel carrying out quality checks on the research study. I also consent to having my medical records (including after the trial has terminated) reviewed by the research team and data recorded where relevant to the research.

3. I consent to my data being anonymously used and/or shared with other organisations for teaching, reports, presentations and publications.

4. I understand that my participation in this trial is voluntary and that I am free to withdraw at any time and without giving any reason and without my medical care or legal rights being affected.

5. I agree to take part in the above trial.

Name of Participant __________________ Date ____________ Signature ______________

Name of Researcher __________________ Date (must match participant) ____________ Signature ______________

Participant consent form: Lung Screen Uptake trial v7.0 17/06/2016 Page 1 of 2
Lung Screen Uptake Trial

6. I consent to having a CT scan and have understood the risks and potential benefits.

7. I consent to my radiology images being anonymously used and/or shared with other academic organisations and collaborating commercial organisations for future ethically approved research studies, teaching, reports, presentations and publications and development of lung screening IT software.

8. I consent to having the following taken for analysis (please strikethrough if individual elements not agreed to): a blood sample, a buccal swab, a sputum sample and a breath test.

9. I consent to my samples (including DNA) being stored and/or anonymously shared with other academic organisations and collaborating commercial organisations for analysis, future ethically approved research and development. I am aware that my samples are considered as a gift to the research team.

10. I consent to being contacted by telephone, letter and/or email by the research team in relation to further research within this study.

11. I consent to my GP being informed of my participation and of any medical test results.

12. If I make a quit attempt with a stop smoking service following my lung health check appointment, I consent to data being collected about me and my quit attempt from that service.

Name of Participant __________________________________________ Date ___________ Signature ________________________________

Name of Researcher __________________________________________ Date (must match participant) ___________ Signature ________________________________

Participant consent form: Lung Screen Uptake trial v7.0 17/06/2016
Appendix 8- LSUT results letters

Patient letter - Normal

<<Participant ID>>
<<Date>>

RE: <<Participant Name / address/ dob>>

Dear <<Participant name>>

Thank you for participating in the Lung Screen Uptake Trial. As part of this study, you recently had a CT scan of your lungs. We are pleased to say there were no signs of lung cancer, nor any other abnormalities requiring further tests seen. Your GP has been sent a copy of the result.

This is very good news, however, it is important to note that if you have any concerning symptoms in the future, you should seek medical attention. Some of the symptoms to watch out for are: a persistent cough or change in an existing cough, coughing up blood, unexplained shortness of breath, a pain or ache when breathing or coughing and unexplained tiredness or weight loss.

If you would like to know more or have any worries or concerns, please telephone us on the contact number above which is available during Monday to Friday 9am-5pm.

If you smoke and would like help stopping, we know that the best way of quitting is with a combination of support and medication. Your practice or local pharmacist will be able to put you in touch with your free, friendly and effective stop smoking service or you can find the details of your nearest service below:

<<Smoking cessation clinic details>>

Many thanks,
Yours sincerely,
Patient letter - Suspicious finding

<<Participant ID>>
<<Date>>

RE: <<Participant Name / address/ dob>>

Dear <<Participant name>>

Thank you for participating in the Lung Screen Uptake Trial. As part of this study, you recently had a CT scan of your chest. Some abnormalities have been detected that may mean you require some further tests. An appointment has been made for you to discuss this further with a Specialist Lung Doctor. A letter with the date, time and location of this appointment is enclosed or will be sent to you within a few days.

If you would like to know more or have any worries or concerns, please telephone us on the contact number above which is available during Monday to Friday 9am-5pm.

If you smoke and would like help stopping, we know that the best way of quitting is with a combination of support and medication. Your practice or local pharmacist will be able to put you in touch with your free, friendly and effective stop smoking service or you can find the details of your nearest service below:

<<Smoking cessation clinic details>>

Many thanks,
Yours sincerely,
Dear <<Participant name>>

Thank you for participating in the Lung Screen Uptake Trial. As part of this study, you recently had a CT scan of your chest.

The scan has not shown any evidence of lung cancer.

It has however shown some other non-cancer findings that may require further attention. We have sent a report to your GP explaining what the scan has shown.

Please make a non-urgent appointment or telephone appointment with your GP to discuss this further.

If you would like to know more or have any worries or concerns, please telephone us on the contact number above which is available during Monday to Friday 9am-5pm.

If you smoke and would like help stopping, we know that the best way of quitting is with a combination of support and medication. Your practice or local pharmacist will be able to put you in touch with your free, friendly and effective stop smoking service or you can find the details of your nearest service below:

<<Smoking cessation clinic details>>

Many thanks,
Yours sincerely,
Dear <<Participant name>>

Thank you for participating in the Lung Screen Uptake Trial. As part of this study, you recently had a CT scan of your chest.

The scan has not shown any evidence of lung cancer.

It has however shown some other non-cancer findings that may require further attention if you have symptoms, though in some cases no specific treatment is required. We have sent a report to your GP explaining what the scan has shown.

Please make a non-urgent appointment or telephone appointment with your GP to discuss this further.

If you would like to know more or have any worries or concerns, please telephone us on the contact number above which is available during Monday to Friday 9am-5pm.

If you smoke and would like help stopping, we know that the best way of quitting is with a combination of support and medication. Your practice or local pharmacist will be able to put you in touch with your free, friendly and effective stop smoking service or you can find the details of your nearest service below:

<<Smoking cessation clinic details>>

Many thanks,
Yours sincerely,
Patient letter- Indeterminate pulmonary nodule

<<Participant ID>>
<<Date>>

RE: <<Participant Name / address/ dob>>

Dear <<Participant name>>

Thank you for participating in the Lung Screen Uptake Trial. As part of this study, you recently had a CT scan of your lungs, which showed a slight change that means that it would be sensible for you to have a repeat CT scan in 3 or 12 months’ time. An appointment has been made for you to discuss this further with a specialist lung doctor. A letter with the date, time and location of this appointment is enclosed or will be sent to you within a few days.

If you would like to know more or have any worries or concerns, please telephone us on the contact number above which is available during Monday to Friday 9am-5pm.

If you smoke and would like help stopping, we know that the best way of quitting is with a combination of support and medication. Your practice or local pharmacist will be able to put you in touch with your free, friendly and effective stop smoking service or you can find the details of your nearest service below:

<<Smoking cessation clinic details>>

Many thanks,
Yours sincerely,
Dear «Usual_GP»

You may recall that we let you know that some of your patients may be contacted and asked to participate in the Lung Screen Uptake Trial. The above patient attended their lung health check on «Date_of_lung_health_check_».

- The results of their spirometry and other clinical recordings are appended.
- The patient «Smoking_referral_Has__Hasnt» «Been_referred_given_details» to their local stop smoking service «Which_service» «Reason_not_referred»
- They «CT_Scan» have a lung cancer screening low dose CT scan.
- «Reason_not_had_CT»

<<Insert text as detailed on next page>>

Thank you for your participation in this study. If you need any further information or advice, please contact us on the telephone number or email address above.

Many thanks,
Yours sincerely,
**Lung Health Check Readings:**

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<th>FVC (l)</th>
<th>FVC (%)</th>
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<td>«Systolic_BP»</td>
<td>«Diastolic_BP»</td>
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**CT Report (if applicable):**

«CT_report»
Text to be inserted into GP result letter template:

1. Normal scan
The outcome from the scan was that this was a normal scan and no further action is required. Some incidental findings may have been noted and a summary of the report is appended. The patient still carries significant risk for lung cancer and any suspicious symptoms in the future should be dealt with appropriately.

2. Suspicious thoracic lesion
We have organised an internal 2 week wait referral to the local thoracic multi-disciplinary team. If you are able to provide a summary of the patient's medical history and give this to them to bring to their appointment, this would be most useful.

3. Incidental finding- needs further investigation/ treatment
The outcome from the scan was that a suspicious lesion has been found. A summary of the report is appended. We have advised the patient to make an appointment with you to discuss this further.

4. Incidental finding- COPD/ may not need any particular investigation/ treatment
The outcome from the scan was that an incidental finding has been identified. A summary of the report is appended. We have advised the patient to make an appointment with you to discuss this further.

Please note patients who were not aware of a diagnosis of COPD or emphysema when seen in the lung health clinic have been advised to see a GP to discuss this further. This may provide an opportunity for further smoking cessation advice and consideration for pulmonary rehabilitation and/or inhaled therapy if appropriate. Patients with CT findings of airway inflammation (bronchial wall thickening and mucous plugging) have also been advised to see a GP. This may provide an opportunity for inhaled bronchodilators. For further advice please contact the mobile number provided for advice from a respiratory clinician.

5. Indeterminate pulmonary nodule
The outcome from the scan was that an indeterminate pulmonary nodule has been detected. A summary of the report is appended. Whilst overall it is unlikely that this is malignant, we have arranged a thoracic outpatient appointment and further follow up as required. If you are able to provide a summary of the patient's medical history and give this to them to bring to their appointment, this would be most useful.
Appendix 9- LSUT Research Ethics Committee Approval letter

Health Research Authority
NRES Committee London - City Road & Hampstead
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Email: nrescommittee.london-cityroadandhampstead@nhs.net
Tel: 0117 342 1339

21 August 2015

Professor Samuel Janes

Dear Professor Janes

Study title: Randomised controlled trial to test novel invitation methods and materials targeted to increase informed uptake of lung cancer screening in individuals at high risk of lung cancer.

REC reference: 15/LO/1186
Protocol number: 2.0
IRAS project ID: 166426

Thank you for your submission of 21 August 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 29 July 2015

Documents received

The documents received were as follows:

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<tr>
<td>Participant information sheet (PIS)</td>
<td>3.0</td>
<td>30 July 2015</td>
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<td>Participant information sheet (PIS) [Tracked revised participant information sheet]</td>
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Approved documents

The final list of approved documentation for the study is therefore as follows:

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<td>Letter from sponsor [Sponsor letter]</td>
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<td>Letters of invitation to participant [Invitation letters and information sheets]</td>
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<td>3.0</td>
<td>30 July 2015</td>
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You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor’s responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/LO/1186 Please quote this number on all correspondence

Yours sincerely

[Signature]

REC Manager

E-mail: nrescommittee.london-cityroadandhampstead@nhs.net
Appendix 10- Protocol for qualitative study- Addressing the information needs of lung screening participants (INLS)

Information needs in Lung Screening: Study Protocol v3.0 1.3.16

Long title:
Addressing the Information Needs of Lung Cancer Screening Participants

Short Title:
Information Needs in Lung Screening (INLS)

Chief Investigator:
Dr Jo Waller

Supported by:
Roy Castle Lung Cancer Foundation

Sponsored by:
University College London (UCL)

(Draft) Protocol version number and date:
V3.0: 1st March 2016

R&D / Sponsor Reference Number(s):
15/0954
IRAS number: 192823

Study Registration Number:
PROTOCOL VERSIONS

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<td>Dr Mamta Ruparel</td>
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DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

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

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:................................................................................. Date:.........../......./......

Print Name (in full): Jo Waller

Position: Career Development Fellow

On behalf of the Study Sponsor:

Signature:................................................................................. Date:.........../......./......

Print Name (in full):.................................................................................

Position:..................................................................
### STUDY SUMMARY

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| Full (Scientific) title          | Addressing the Information Needs of Lung Cancer Screening Participants |
| Health condition(s) or problem(s) studied | Lung Cancer Screening |
| Study Type i.e. Cohort etc       | Qualitative        |
| Target sample size               | 68                 |

### STUDY TIMELINES

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<td>End of Study definition and anticipated date</td>
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| Key Study milestones | Identification of potential participants Recruitment Focus groups round 1 Feedback focus groups Data analysis and reporting Production of final decision aid |

### FUNDING & Other

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### STORAGE of SAMPLES (If applicable)

| Human tissue samples | N/A |
| Data collected / Storage | N/A |

### KEY STUDY CONTACTS

<table>
<thead>
<tr>
<th>Chief Investigator</th>
<th>Dr Jo Waller</th>
</tr>
</thead>
<tbody>
<tr>
<td>Researcher</td>
<td>Dr Mamta Ruparel</td>
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KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins, that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than one site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.
KEY WORDS
Informed decision making
Decision tool
Decision aid
Information film
Lung Cancer Screening

LIST OF ABBREVIATIONS

ACR  American College of Radiology
AE   Adverse Event
AR   Adverse Reaction
CI   Chief Investigator
GP   General Practice/ General Practitioner
ICF  Informed Consent Form
LDCT Low radiation Dose Computed Tomography
NLST National Lung Screening Trial
PI   Principle Investigator
PIS  Participant Information Sheet
QA   Quality Assurance
QC   Quality Control
RCT  Randomised Clinical Study
REC  Research Ethics Committee
SAE  Serious Adverse Event
SAR  Serious Adverse Reaction
SDV  Source Data Verification
SOP  Standard Operating Procedure
SSI  Site Specific Information
TMF  Trial Master File
UCL  University College London
USPSTF United States Preventative Services Task Force
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1 INTRODUCTION

There is a growing body of evidence to support lung cancer screening and much research is underway to determine the best methods of implementation. In the United States, screening for lung cancer is underway, and the American College of Radiologists (ACR) suggests a shared decision making process is imperative. The risks and benefits to lung cancer screening are complex and aids to facilitate understanding of these facts are needed. People in the more deprived socioeconomic groups are at higher risk of lung cancer and may have more difficulty understanding these facts enough to make a truly informed decision. Film or video have been used with success as decision aids in the past in other areas, however within lung cancer screening there is a paucity of evidence to inform the composition of decision aids and very few to date have been validated.

The present study aims to use qualitative research methods to explore the information needs of participants in a lung cancer screening pilot. We will also explore what experts in the field of decision making, and those with experience of lung cancer patients, find relevant to the content of an information film. The information film will be tested and further developed in a programme of work in lung screening participants.

This research will inform the content and format of a film. The story-boards to this film will undergo further evaluation by participants, and the final product will be quantitatively assessed in a further study. If scientifically validated, such a tool may be utilised by NHS centres carrying out lung cancer screening in the future.

![Flow chart summary of study](image)

**Figure 1. Flow chart summary of study**
2 BACKGROUND AND RATIONALE

Improving early detection by screening

Lung cancer is the most common cause of cancer mortality worldwide and has a mortality to incidence ratio, at 0.87[1]. This is largely due to the fact that around 70% of patients present with advanced disease[2]. Low radiation Dose Computed Tomography (LDCT) screening for early stage lung cancer resulted in a 20% relative risk reduction in lung cancer mortality in the National Lung Cancer Screening Trial (NLST)[3]. Consequently, screening via this modality has been recommended in the United States (US) and standards for those carrying out screening have been set by several medical organisations[4,5] including the US Preventive Services Task Force (USPSTF)[6]. The National Screening Committee in the United Kingdom (UK) is due to make a decision on lung cancer screening in 2016, pending the results of the Dutch Belgian randomised screening trial (NELSON)[7,8]. Nevertheless, UK lung cancer mortality rates continue to be far higher than other European countries[1].

Complexity of information to be communicated to patients

The Department of Health has released a statement on the importance of informed consent in screening and urged health services to produce strategies to develop, pilot and evaluate materials to aid this[9]. While the evidence for screening as a means to detect and treat lung cancer early is compelling, there are important risks which must be given full consideration by patients if they are to make an informed decision. These include overdiagnosis, false positive scans and radiation-induced cancers. These concepts are complex and challenging for patients to comprehend for numerous reasons, such as the information burden and the perceived effort required to read the materials. Furthermore different cultural groups have different preferences in how this information should be presented in terms of content and graphics[10].

We have carried out some patient and public involvement work by piloting screening materials, containing all the relevant information required to make an informed decision on lung cancer screening, on members of the public from the desired age-group. The patients interviewed largely expressed dislike of this format, thought it unlikely that they would read such a booklet and had difficulty comprehending some of the information. This work highlighted to us the need for the present study.

Anxiety associated with screening surveillance

An additional complexity of the screening process is that it will discover “pulmonary nodules” (small white spots) that are likely to be non-serious and due to inflammation, but will require a series of surveillance CT scans to determine this. This surveillance process can cause significant anxiety and distress for patients[11], however, there is potential to minimise patient distress if it can be successfully communicated that despite the need for surveillance, their overall risk of cancer is very low.

To date, few qualitative studies have been carried out with respect to communication of the significance of pulmonary nodules. Those that have, show that this is poorly understood by patients[12], often because this information is poorly communicated by their physicians[13,14]. In lung cancer screening studies, the impact on anxiety and distress has been evaluated[15], however, to our knowledge, the effectiveness of information-giving has not been evaluated qualitatively or quantitatively.
Suitability of video format

A number of studies have evaluated the efficacy of delivering patient education using a variety of communication tools. It is noted that use of these tools, particularly when interactive and tailored to the individual, results in improved patient understanding[16]. Several randomised studies have been carried out comparing film with standard methods of delivering information, most commonly written. The majority of studies[17–20] (including one in lung cancer screening[21]) have found a significant improvement in measures of informed decision making (such as subjective and objective knowledge, anxiety, decisional satisfaction and conflict) with use of this method while a few, rather underpowered studies[22–24] have not.

There are very few studies exploring the issues around informed decision making in lung cancer screening and even fewer exploring patients' and clinicians' preferences regarding the content and format of decision aids. The present study will explore the views of a sample of lung cancer screening participants and lung cancer survivors as well as decision scientists and clinicians who have experience in treating lung cancer patients. The findings of this study will inform the production of a video which will also undergo a round of feedback testing with the same participants prior to final production.

3 OBJECTIVES

3.1 Primary Objectives

To produce an information film for individuals considering participation in lung cancer screening by LDCT using data collected using qualitative methods. More specifically:

- To determine the information-needs of participants considering LDCT screening for lung cancer.
- To determine clinicians' perspectives on what should be included in an audio-visual format and how it may best be presented.
- To develop an information film aimed at people from varying educational and socioeconomic backgrounds, that facilitates understanding of the risks and benefits of lung cancer LDCT screening to enable informed decision-making.
- To test the acceptability, comprehensibility and effectiveness of the information-film concept with participants and health professionals.
- To produce an information film which acknowledges the support of the Roy Castle Lung Cancer Foundation and to subsequently test the impact on informed decision making of the written materials and a nurse-led discussion with and without the information film.

4 STUDY DESIGN

The qualitative study will use both focus groups and one-on-one interviews to achieve the study objectives. The focus groups will be with members of the public who may be potentially eligible for screening, and the interviews will be with clinicians involved with the diagnostic pathway of lung cancer patients. The data collection will be carried out in two phases. The first phase will be
exploratory and the second phase will seek feedback on concepts and ideas developed for the decision aid, which will then undergo further refinement to produce a finished product.

The data will be collected by audio recordings which will be transcribed and analysed thematically.

5 STUDY SCHEDULE

5.1 Focus groups
Participants will be identified from general practice and invited to participate by a letter from their usual GP together with the participation information sheet (PIS). A pre-defined search will aim to identify suitable participants. The letter will advise them that the research team will contact them within two weeks. If they wish not to be contacted, they can opt out by completing an ‘opt-out’ slip and sending this to the research team in a stamped addressed envelope provided, or opt out by phone, text or email.

Those who do not opt out, will be contacted by telephone by a member of the research team to further discuss the study and confirm participation. The potential participants will have the opportunity to ask any questions and consider their decision. Those who are agreeable will also be asked questions to compile the demographic and smoking data required to formulate the focus groups. They will then be sent a confirmation letter with the details of the location and time and date of the focus group and a copy of the PIS once again.

The aim will be to carry out maximum diversity sampling (a form of purposive sampling), that aims to include a heterogeneous group of individuals that represent the ‘at risk of lung cancer’ population. Groups will be as heterogeneous as possible with respect to age and ethnicity and divided by smoking status and educational background. If any particular demographic group is under-represented within those responding, further attempts to recruit such individuals using methods such as snowballing will be utilised.

Individuals will then be invited to focus groups with an aim to have between four and eight focus groups of 6-8 individuals per group, until saturation of themes is achieved. The first round of focus groups will be exploratory. The data collected will be used to produce some materials that may form the audio-visual decision aid. The same participants will then be invited to a second round of focus groups to give feedback these materials.

5.2 Clinician interviews
Experienced clinicians from a variety of backgrounds relating to the diagnostic pathway for lung cancer will be invited to participate with a view to recruiting 4-5 individuals from each specialist area, or until saturation of data is achieved. The clinicians will be identified by snowballing by partners of the research team. They will be invited by letter or email to participate. Attempts will be made to ensure individuals within each specialist group are from varied the geographical areas (urban vs. rural) and organisations (teaching hospital vs. district general hospital vs. primary care).

Specialists to be included are:

- General Practitioners
- Lung cancer nurse specialists
• Pulmonologists
• Public health consultants

Participants will then be interviewed in person or by (video)-teleconference in an exploratory manner, followed by a request for written feedback on preliminary materials produced as with the public focus groups.

5.3 Participant withdrawal
Participants will be free to withdraw from the study at any time. Where possible, reasons for this will be recorded.

5.4 End of study
The end of the study will end with the completion of the information film.

6 CONSENT
Participants will have had a chance to read the PIS and ask questions prior to committing to participate in the study. They will have a further opportunity to read the PIS and ask any questions prior to having informed consent taken in writing before commencing the focus group.

The exclusion criteria for the study includes those who may be unable to consent, and measures will be in place to ensure such participants are not contacted for participation, by excluding participants with the exclusion criteria listed to be identified in the initial GP database search, and also by allowing GPs to screen the list of participants to be contacted and excluding those not deemed suitable.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria
• Age 60 to 75
• Individuals recorded as smokers within the past 15 years on their GP database

7.2 Exclusion Criteria
• Active diagnosis of lung cancer or metastases
• Inability to consent to study (including those with dementia or severe mental health disorders or unable to speak English)
• Individuals on the palliative care register
• GP's alert to patient not suitable for research study

8 ANALYTICAL METHODS
Data will be collected by audio recording and transcribed verbatim by a transcription company. After familiarisation of the recordings and transcripts, the transcripts will be coded into themes and subthemes. 10% of transcripts will undergo double coding, carried out by two researchers of varied research backgrounds (psychology and medical) and the remainder will be single coded. Principles of framework analysis, a matrix based approach, will be used. The sample size will be as described above and until saturation of themes is achieved.
9 FUNDING AND SUPPLY OF EQUIPMENT

The research costs for the study have been supported by the Roy Castle Lung Cancer Foundation (grant awarded 1st September 2015). The grant covers the cost of refreshments and travel reimbursement for the participants, transcription of interviews, production of a film and relevant staff costs for 1 year.

10 DATA HANDLING AND MANAGEMENT

Data will be collected following informed consent from participants. The transcripts will be anonymised and the key to the participant identifiers will be retained on UCL’s data safe haven. Hard copy of consent forms will be kept in a locked, secure environment. The data will be transferred securely when necessary (for example between UCL and the transcription company), and no identifiable data will be shared outside of the research team. The data will be held by the chief investigator, and confidentiality, data protection and information governance procedures will be adhered to.

11 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCL/UCLH.

- The Sponsor considers the procedure for obtaining funding from Roy Castle Lung Cancer Foundation to be of sufficient rigour and independence to be considered an adequate peer review.

The study was deemed to require regulatory approval from the following bodies. Each approval will be obtained before the study commences:

- Health research authority/ NHS Research ethics committee
- NHS Research and development office (Joint research office at UCL)

12 ASSESSMENT AND MANAGEMENT OF RISK

No significant risks are anticipated with this study. Care will be taken to ensure any sensitive issues are discussed with participants with due care and consideration. Participants will be reimbursed for travel expenses where necessary.

13 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

13.1 Definitions of Adverse Events

Adverse events are not anticipated due to the nature of the study. Any such events will be recorded with participant consent.
13.2 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree —
(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

14 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

15 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that the study team will archive the study master file for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his respective site’s study documents for 5 years and in line with all relevant legal and statutory requirements.

16 PUBLICATION AND DISSEMINATION POLICY

The results of the study will be submitted for presentation and publication at conferences and in peer reviewed journals. To comply with the terms of the funder, they will be notified about all such events.
Appendix 11- INLS Research Ethics Committee Approval letter

10 March 2016

Dr Jo Waller

Dear Dr Waller

<table>
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<th>Study title:</th>
<th>Addressing the information needs of lung cancer screening participants</th>
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Thank you for your letter of 07 March 2016, responding to the Proportionate Review Sub-Committee’s request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact REC Manager Carolyn Hallwell, NRESCommittee.EastofEngland-CambridgeEast@nhs.net

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.
“Conditions of the favourable opinion” above).

Approved documents

The documents reviewed and approved by the Committee are:

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<th>Document</th>
<th>Version</th>
<th>Date</th>
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<td>01 March 2016</td>
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<td>Letters of invitation to participant</td>
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<td>Research protocol or project proposal [Protocol v3]</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:
• Notifying substantial amendments
• Adding new sites and investigators
• Notification of serious breaches of the protocol
• Progress and safety reports
• Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

16/EE/0089 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project.

Yours sincerely

Email: NRESCommittee.EastofEngland-CambridgeEast@nhs.net

Enclosures: “After ethical review – guidance for researchers” [SL-AR2]

Copy to: Smaragda Agathou, Joint Research Office
Appendix 12- INLS focus group discussion guide and interview schedule

DISCUSSION GUIDE: FOCUS GROUPS

Introduction/Ethics/Consent

- Greet participants as they arrive and take consent for participation in the study.
- Allow participants to take refreshments and then start the focus groups once all have arrived. Then, open with introduction below.
- The reason I’d like to talk with you today is to find out about your knowledge and experience of cancer screening and lung cancer.
- I am carrying out a number of these group sessions to get an overview from different individuals.
- I do understand that some people may not feel comfortable talking about cancer or may have had experiences that can be difficult to talk about. If at any time you are not feeling comfortable, please let me know.
- Does any one have any concerns about any of that so far? [Option of going away and thinking about it, or declining]
- So that I do not need to take notes, I will record our conversation using this device. This will later be typed up and I will delete the recording. Everything you say will remain strictly confidential and completely anonymous. Other researchers may read our conversation, but nobody else. I hope to write a report of my findings to publish in a scientific journal. This would summarise opinions from everyone I have spoken to and may include some of your quotes. However, your name will never be included, and you will not be identifiable in any way.
- I have a few questions noted down here of things I’d like to ask you but I’d like you to do most of the talking.
- I want to hear your views so please feel free to be as frank and open as you wish. There are no right or wrong answers. We don’t have to talk about anything that you feel uncomfortable about and you are free to withdraw at any time, without giving a reason.
- I expect the session to last between 60 and 90 minutes, but if you need to leave, please let me know
MAIN DISCUSSION POINTS

**NHS CANCER SCREENING PROGRAMMES**
1. Discuss what experiences they have had with other NHS cancer screening programmes.
   a. Purpose of screening.
   b. Reasons for going for screening (or not).
   c. Are they aware of any possible drawbacks or harms from screening?
   d. Do they feel taking part in screening is a positive thing to do for their health?

**LUNG CANCER**
2. What have they heard about lung cancer and its treatments?
   a. What it is and how it is caused.
   b. How frequently it occurs in the general population.
   c. Have they had any experience of lung cancer in anyone you know?
   d. How curable it is, and what affects curability.
   e. What sorts of treatments do you think are available for lung cancer?
   f. How long might someone with lung cancer expect to live?

**LUNG CANCER SCREENING**
Interviewer: “Research in the US has shown that if we carry out a CT scan (a detailed sort of X-ray) once a year on people who have a higher risk of lung cancer due to the amount they have smoked in the past, we may save 20% of lives by detecting the cancer early and giving a higher chance of cure. There are more trials underway, and depending on the results of those, we may start doing lung cancer screening in the UK in a few years. As with the other screening programmes we have discussed, there are pros and cons to screening for lung cancer. Here are some leaflets on lung cancer screening. I will give you some time to read through them and then, if it’s ok, I’ll ask you for your thoughts on them.”

3. Explore views on the contents of the leaflets.
   a. Initial thoughts / reactions to the leaflet
   b. Discuss radiation, over diagnosis, false positives.
   c. Discuss their feelings around having tests and treatments that may later prove to have been unnecessary vs potential to save life by early diagnosis. Do these harms influence their decision of whether to be screened?
   d. Discuss the benefits of reassurance from a normal result.
   e. Discuss understanding around numeric data [2% detection rate, 25% indeterminate results]
   f. Who should decide if screening is the right thing to do? How would their decision be influenced by the health professional’s opinion?
RESPONSE TO DECISION AIDS

We are planning to make a short video that could explain the concepts we have discussed today that would help people considering having lung cancer screening make a decision of whether or not to be screened. I would therefore be grateful for your opinions and feelings about some written materials or clips from films used for the same purpose in lung and other screening programmes and also some of the ideas we have thought about for our film.

4. Gauge thoughts on:
   a. Leaflet used in UCL lung cancer screening pilot: “lung health check – information on what’s involved” and similar bowel and breast screening leaflets.
   b. Show general video clips, pictures or read vignettes, and get opinions and thoughts as above
      i. Especially what they feel about the methods to explain concepts such as metaphors or numeric person indicators.
      ii. Do they help to make a decision one way or the other?
      iii. Do they convey all the facts we discussed today? If not, what is not clear that they think is important?
      iv. What ideas do they have that they think would make them feel more empowered to do positive things to impact their health- eg scenes, metaphors, messages, ideas?
   c. Discuss (and view if available) concepts from creative team.
   d. Discuss the idea of health professional speaking or a person speaking about personal experiences and who should be conveying what facts?
   e. What should we say about smoking if anything?

CLOSE AND DEBRIEF

• Is there anything else you would like to mention that you feel we haven’t covered?
• I really appreciate your time today and thank you very much for sharing your views with me, these are really interesting and helpful. We are hoping to have some more ideas or clips from our produced film that we would like to show you and get feedback on in 4-6 weeks time. Could you please let me know if you are happy to be invited back for this?
• Thank participants for their time and input and reassure about confidentiality.
• Answer any questions and provide with debrief information sheet and researcher contact details.
• Offer copy of transcript and report.
INTERVIEW SCHEDULE: CLINICIAN INTERVIEWS

The following questions are intended as a rough guide. The questions chosen, and the order in which they are asked, will depend on responses to preceding questions.

Introduction/Ethics/Consent

“The reason I’d like to talk with you today is because we are trying to produce an information film to help people considering undergoing lung cancer screening make an informed decision. This will be in the form of a short information film (3-5 minutes long). As you have experience with diagnosing/looking after patients with lung cancer, we would be very grateful for your thoughts and opinions. I will ask questions but I’d like you to do most of the talking. It should take about 20-30 minutes depending on how much time you have.”

“I will record our conversation and it will be typed up later. Everything you say will remain strictly confidential and anonymous. I hope to include my findings which may include some anonymised quotes in my thesis and in publications in scientific journals. Would that be ok?”

MAIN INTERVIEW QUESTIONS

1. What do patients/individuals know about lung cancer? Can they give me some examples of experiences they have had with patients who have been newly diagnosed with lung cancer or indeterminate pulmonary nodules?
   o Can you tell me what you usually tell patients about lung cancer and/or indeterminate nodules?
   o Can you tell me what questions people usually ask?
   o Do they find any particular concepts difficult to understand?
   o Do you find anything particularly challenging to communicate to them? How do you get around it?
   o Do you think patients have an accurate idea of curability and risk?
   o When you talk about stage, what do they understand by it?
   o Do they understand how stage implicates treatments and prognosis?

2. Imagine you are carrying out screening in your institution.
   o Can you think of patients that you know that may have made an informed decision not to be screened?
   o If so, what concerns do you think they might have about the screening process? Do you think it may be based on true fact or mis-information/misconceptions?
   o If they have patients who they think might not have chosen to be screened? Can they tell me more about them?

3. Can they give examples of patients where they have had to consider or discuss issues such as overdiagnosis and surgical risk (operability vs. resectability)? What worked well? What worked badly? Give example of pulmonary nodules.
4. What concepts/facts about screening do you think are most important for patients to understand?
5. What techniques do they use to explain things? Examples of metaphors.
6. Check response to:
   - Patients giving experience of lung cancer/treatment
   - Clinician/expert explaining lung cancer screening
   - Smoking cessation
   - Concepts from film company
   - Examples of other decision aids - what works well and what doesn’t

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**CLOSE AND DEBRIEF**

“Is there anything else you would like to mention that you feel we haven’t covered?”

“I really appreciate your time today and thank you very much for sharing your views with me, these are really interesting and helpful. Based on what we have learned from interviewing yourself and other experts as well as from members of the public that would be eligible for screening, we will be developing the ideas and a script for the final information film. Would you mind if we send you a summary of these ideas in a few weeks time and get you to fill in a feedback form on your thoughts on what in your opinion works well and what doesn’t?”

Answer any questions and provide with debrief information sheet and researcher contact details. Offer copy of transcript and report. Thank participant and end interview.