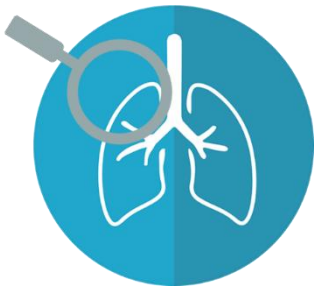
RESEARCH PROTOCOL



SEARCH

Screening for Early detection of second cancers After Radiotherapy and Chemotherapy for Hodgkin lymphoma

Implementing and Evaluating Lung Cancer Screening for High-risk Hodgkin Lymphoma Survivors within the NHS National Lung Cancer Screening Programme

Chief investigator: Professor Kim Linton

Sponsor: The University of Manchester

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STUDY SYNOPSIS

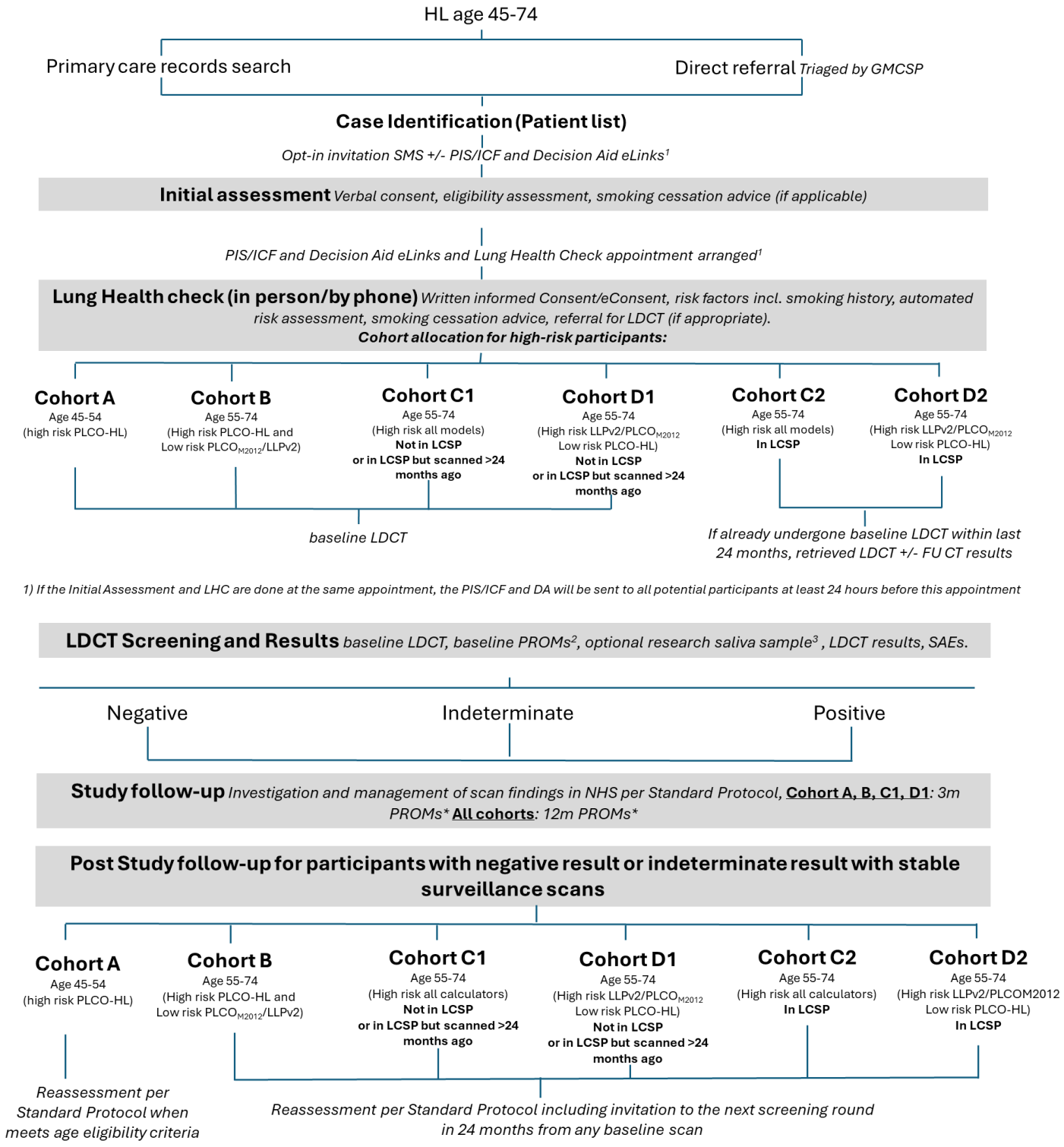
Study identifiers	**Full study title:** Implementing and Evaluating Lung Cancer Screening for High-risk Hodgkin Lymphoma Survivors within the NHS National Lung Cancer Screening Programme **Protocol version and date:** 0.7_02 June 2026 **Sponsor:** The University of Manchester **IRAS ID:** 357604 **Trial Registration Number:** ISRCTN 11668189 **Device Investigation reference:** TBC
Study Purpose	To implement and evaluate a targeted lung-cancer screening pathway for high-risk Hodgkin lymphoma (HL) survivors within the NHS Lung Cancer Screening Programme (LCSP), using PLCO-HL, an independently implemented version of the PLCOm2012 statistical model calibrated specifically for this high-risk population, in order to determine feasibility, effectiveness, and acceptability (including early-stage detection rates, screening outcomes, health inequalities, process and economic impact), and to generate evidence to inform NHS policy on national adoption.
Study Design	A multicentre, real-world evaluation study integrating a risk-adapted lung cancer screening pathway for high-risk HL survivors into the NHS LCSP. Eligible ever-smokers aged 45-74 undergo a Lung Health Check with automated risk assessment (PLCO-HL, PLCOm2012, LLPv2). Individuals meeting PLCO-HL high-risk criteria (or high-risk by standard LCSP models where applicable) are offered a baseline low-dose CT (LDCT). LDCT acquisition, reporting, and follow-up follow standard LCSP governance. Additional study assessments include patient reported outcomes (PROs), optional saliva sampling for genotyping, and collection of service, process, and health-economic data. Participants are followed for 3–12 months for screening outcomes, interval diagnoses, and treatment.
Population	Hodgkin lymphoma (HL) survivors aged 45–74 years, previously treated with combined-modality therapy and/or chemotherapy, who have a current or former smoking history and are eligible for low dose CT (LDCT) screening under the PLCO-HL risk model. Participants must be fit for potential curative-intent lung-cancer treatment and able to undergo LDCT scanning
Objectives	**Primary Objective** To determine the early-stage (stage I–II) lung cancer detection rate among high-risk Hodgkin lymphoma survivors who meet PLCO-HL criteria and undergo LDCT screening

	Secondary Objectives 1. To describe screening outcomes (detection rate, stage distribution, histology, false-positive/false-negative rates, curative treatment rates, incidental findings). 2. To compare the predictive performance (e.g. sensitivity, specificity, calibration) of PLCO-HL with PLCOm2012 and LLPv2 in this population. 3. To assess participation and acceptability at each step of the pathway (invitation, LHC, LDCT, saliva sampling, PROs). 4. To identify and address health inequalities in access, engagement and screening outcomes. 5. To evaluate feasibility and operational delivery of a PLCO-HL risk-adapted screening pathway across diverse NHS Cancer Alliances. 6. To undertake a health-economic evaluation, including ICER, net benefit, ROI, cost per early-stage cancer detected and QALYs gained. 7. To assess environmental (net-zero) impact, including carbon emissions per participant screened and emissions avoided via early diagnosis.
Endpoints	**Primary Endpoint** Proportion of early-stage (stage I–II) lung cancers detected among high-risk Hodgkin lymphoma survivors who meet PLCO-HL criteria and undergo LDCT screening. **Secondary Endpoints** • Screening performance: Overall lung-cancer detection rate, stage distribution, histological subtype, false-positive and false-negative rates, incidental findings, and proportion receiving curative-intent treatment. • Risk model comparative performance: Sensitivity, specificity, calibration, and predictive accuracy of PLCO-HL versus PLCOm2012 and LLPv2. • Participation and acceptability: Uptake and completion rates across the participant pathway (invitation → LHC → LDCT → saliva sampling → PROs), reasons for ineligibility or dropout, and participant experience. • Health inequalities metrics: Differences in identification, invitation, uptake and outcomes across demographic and socioeconomic groups. • Feasibility and implementation: Deliverability of the PLCO-HL pathway across diverse NHS settings; operational barriers and facilitators. • Health economic endpoints: Incremental cost-effectiveness ratio (ICER), net benefit, QALYs gained, cost per early-stage cancer detected, programme-level cost-effectiveness, and return on investment (ROI). • Environmental endpoints: Carbon emissions per participant screened and estimated emissions avoided by earlier diagnosis.
Study Procedures	Participants are identified through primary care searches or direct referrals, then receive an invitation to opt into the study. A brief initial assessment

	confirms eligibility and provides study information. At the Lung Health Check, written/e-consent is obtained and automated lung-cancer risk assessment (PLCO-HL, PLCOm2012, LLPv2) determines lung cancer risk. High-risk participants undergo a baseline LDCT delivered under LCSP governance, with surveillance and clinical management following standard pathways. Participant-reported outcomes are collected at baseline, 3 and 6 months, and optional saliva samples may be provided for genomic analysis. Screening outcomes are collected as 3 and 6 months and at the end of the study, whichever occurs soonest.
Sample size	The study will screen approximately 500 high-risk HL survivors across multiple NHS Cancer Alliances.
Statistics	Analyses will be primarily descriptive, focusing on estimates of the early-stage lung-cancer detection rate, screening performance metrics, and participation across the pathway. Detection rates, false-positive and false-negative rates, and stage distributions will be summarised with confidence intervals. Comparative performance of PLCO-HL versus PLCOm2012 and LLPv2 will be assessed using sensitivity, specificity and calibration, acknowledging limited follow-up and event numbers. Health-economic and process-evaluation data will be analysed separately using established modelling frameworks.
Safety summary	LDCT screening is an established procedure, and the study introduces no investigational treatments. Safety monitoring will be limited to Serious Adverse Events occurring during, or on the same day as, the LDCT scan or pre-scan appointment, as specified in the protocol. All subsequent diagnostic or treatment-related issues are managed through routine NHS care, not as study SAEs. Equipment, data-security or system-failure incidents will be reported via standard governance routes to the Chief Investigator and Sponsor.
Ethical summary	The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and the UK Policy Framework for Health and Social Care Research. It will obtain approval from a UK Research Ethics Committee and the Health Research Authority before commencing. All participants will provide informed consent through a staged process, with clear information on risks, benefits and data use. LDCT scans will follow Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) requirements. Any protocol amendments, safety issues, or serious breaches will be reported per regulatory standards.
Data governance summary	Participant data will be collected and stored in the secure SEARCH database on the iMedidata RAVE platform, with pseudonymised study IDs used for all analysis. Identifiable data are held only where essential and accessed solely by authorised trial location staff. Electronic consent and PRO data are captured via LifeGuide and securely linked to the study database. All data handling complies with GDPR, NHS information-governance standards, and Sponsor policies, with controlled access, audit trails and defined retention periods.

Oversight roles	Study oversight will be provided by the Chief Investigator and a multidisciplinary Study Management Group, including clinical, radiology, statistical, health-economic and patient-representative members, with quarterly review of progress. Oversight of data capture and database management will be delivered by the Southampton Clinical Trials Unit (SCTU). Each participating Cancer Alliance will appoint a Principal Investigator responsible for local conduct, governance and compliance. Safety incidents, protocol deviations and data-quality issues will be escalated to the Chief Investigator and Sponsor under established governance processes.

STUDY SCHEMA



1) If the Initial Assessment and LHC are done at the same appointment, the PIS/ICF and DA will be sent to all potential participants at least 24 hours before this appointment

2) Baseline PROMs is mandatory. Cohorts C2 and D2 only complete one PROM equivalent to the 12m PROM but can complete this at any point.
3) Saliva sample can be collected at any time point in the study.

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AER	Absolute Excess Risk of lung cancer (or other outcome), expressed per population and time
AE / SAE	Adverse Event / Serious Adverse Event. In this study, only SAEs occurring during or on the same day as the LDCT scan or pre-scan appointment are reportable
AUC	Area Under the Curve (ROC); a measure of risk-model discrimination
BTS	British Thoracic Society
CAPA	Corrective and Preventive Action to address repeated deviations or systemic issues
CAT	COPD Assessment Test; a patient-reported measure
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CT / LDCT	Computed Tomography / Low-Dose Computed Tomography
CTU (SCTU)	Clinical Trials Unit (Southampton CTU) supporting database hosting, monitoring and data management
DA	Decision Aid for supporting informed choice
DPIA	Data Protection Impact Assessment
eCRF	Electronic Case Report Form
eConsent	Electronic informed consent completed via LifeGuide
eLink	Secure link used to access eConsent or ePRO forms
ePRO / PRO	(Electronic) Patient-Reported Outcomes collected at baseline and follow-up timepoints
GDPR	General Data Protection Regulation governing data protection and privacy
GP	General Practitioner
HInM	Health Innovation Manchester
HL	Hodgkin Lymphoma
HRA	Health Research Authority
ICB	Integrated Care Board
ICER	Incremental Cost-Effectiveness Ratio
IR(ME)R	Ionising Radiation (Medical Exposure) Regulations
ISRCTN / NCT	Public trial-registry identifiers (ISRCTN or ClinicalTrials.gov)
LCSP	NHS Lung Cancer Screening Programme
LHC	Lung Health Check
LifeGuide	Platform used for eConsent and ePRO collection
LLPv2 / LLPv3	Liverpool Lung Project risk models (v2 validated; v3 investigational)

MDT	Multidisciplinary Team responsible for reviewing findings and planning management
MPR	Multi-Planar Reformation (CT image interpretation method)
NCRAS / NDRS	National Cancer Registration and Analysis Service / National Disease Registration Service
NHS Spine	National service used to check vital status prior to invitation
PACS	Picture Archiving and Communication System for CT image storage
PERFECTS	Radiology performance-review programme
PI	Principal Investigator at each trial location
PIS / ICF	Participant Information Sheet / Informed Consent Form
PLCO-HL	PLCO lung-cancer risk prediction SaMD calibrated for HL survivors
PLCOm2012	Validated 6-year lung-cancer risk model used in LCSP
PRS	Polygenic Risk Score derived from genotyping of saliva samples
QALY	Quality-Adjusted Life Year
QMS	Quality Management System supporting device lifecycle and regulatory compliance
RAVE (Medidata)	Secure cloud platform hosting the SEARCH database and eCRFs
RCR / BSTI	Royal College of Radiologists / British Society of Thoracic Imaging
REC	Research Ethics Committee
ROI	Return on Investment
SaMD	Software-as-a-Medical-Device
SCHARR	The University of Sheffield Centre for Health and Related Research
SIR	Standardised Incidence Ratio
SMG	Study Management Group providing oversight
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms; the national structured clinical vocabulary used in NHS primary care and screening systems for standardised coding of diagnoses, procedures and variables (e.g. HL diagnosis codes, CanPredict variables).
SOP	Standard Operating Procedure
SPECTRA	LCSP data-entry and reporting system
UKCA	UK Conformity Assessed marking
UKNSC	UK National Screening Committee
VDT	Volume Doubling Time used for nodule-growth assessment

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1. PURPOSE

SEARCH is a multicentre study designed to determine whether targeted lung-cancer screening for high-risk Hodgkin lymphoma survivors is feasible, effective and acceptable, evaluating the PLCO-HL risk model within an adapted NHS Lung Cancer Screening Programme pathway to generate evidence on early-stage detection, screening outcomes, health inequalities, process and economic impact, and to assess suitability for wider national implementation.

2. BACKGROUND

Lung Cancer Risk in Hodgkin Lymphoma Survivors

Hodgkin Lymphoma (HL) is clonal B cell malignancy with bimodal incidence peaks in young adults aged 20-29 years and older adults aged over 75[1]. It is a highly curable cancer, especially in young patients, with 10-year survival rates exceeding 90% in those diagnosed under the age of 34[2,3]. Treatment frequently involves radiotherapy incorporating thoracic (chest) structures and/or multi-agent chemotherapy, including alkylating agents such as procarbazine, dacarbazine, and mechlorethamine. While effective, these treatments significantly increase the risk of developing second malignancies, with a cumulative incidence of 33% at 30 years and 49% at 40 years. Breast and lung cancers are the most common second cancers, each accounting for 20% of cases[4]. Importantly, lung cancer is the leading cause of second cancer mortality in this survivor population[5-7].

The risk of lung cancer in HL survivors is significantly higher than the general population, with a standardised incidence ratio (SIR) of approximately 6.4 and an absolute excess risk of 24.6/10,000 person years[4]. A younger age at HL diagnosis is associated with higher relative risk[8] and this elevated relative risk persists for decades following treatment[9]. Absolute risk of lung cancer increases with age[8] and over time[10], reaching a cumulative incidence of 6.4% at 30 years post-HL treatment[4].

Risk Factors for lung cancer in HL survivors

Radiotherapy to the chest and alkylating-agent chemotherapy, especially regimens like MOPP, MVPP and ChlVPP, independently increase lung cancer risk, with the highest risk observed in people receiving combined modality (chemotherapy and radiotherapy) treatment[10-12]. Statistically significantly elevated risks of lung cancer occur early, within 1-4 years after treatment with alkylating agents and within 5 years after treatment with radiotherapy[11].

Smoking is well established as the main risk factor for lung cancer in the general population, and while HL survivors who have never smoked have an elevated risk due to treatment alone, smoking multiplies treatment-related risk more than 20-fold[11]. For example, HL survivors treated with combined modality treatment who are current smokers have a relative risk (RR) of 49.1 for lung cancer compared to a RR of 7.2 for non/light smokers treated in the same way. Even among HL

survivors who are former smokers, the relative risk remains substantially elevated (RR = 5.7) compared to never-smokers[11].

Effectiveness of Lung Cancer Screening in the General Population

Many studies have demonstrated the effectiveness of LDCT screening in reducing lung cancer mortality in high-risk populations[13-15]. Mortality reductions of 20% and 24–33%, respectively, were reported in the National Lung Screening Trial (NLST) and NELSON trials[13,14] with 80% 10-year survival reported for all screened participants and 88% for stage I cancers in the International Early Lung Cancer Action Program (I-ELCAP)[16]. Importantly, these studies did not specifically include HL survivors, whose risk profile differs significantly from the general population.

The NHS LCSP, formerly the Targeted Lung Health Check Programme, was launched in 2019 as a national initiative for early detection of lung cancer in high-risk individuals aged 55–74 with a history of smoking. It uses LDCT scans to detect lung cancer at an early, more treatable stage. To date, the programme has invited over 1.5 million people and achieved 75% early-stage detection and low false positive rates (~2%), aligning well with the NHS Long Term Plan to diagnose 75% of cancers at stage I or II by 2028[17]. LDCT screening is embedded in community settings to improve access, especially in deprived areas. The programme has been shown to be cost-effective and acceptable to patients, leading to a formal UK National Screening Committee (UKNSC) recommendation for targeted lung cancer screening on 29 September 2022.

The LCSP currently uses the LLPv2[18] and PLCOm2012[19]models to identify individuals with an elevated risk of lung cancer over a 5- and 6-year time horizon, respectively. High-risk individuals with a ≥ 1.5% risk over 6 years and/or ≥ 2.5% over 5 years are recommended for LDCT screening. Despite a very elevated risk of lung cancer, most HL survivors do not benefit from screening as they are largely ineligible by current LCSP criteria. In our previous studies[20,21] and an unpublished analysis of a survivor cohort (n=120) at The Christie NHS Foundation Trust (The Christie), only 3.3–8% of HL survivors met current LCSP eligibility criteria due to both a lower age at diagnosis of lung cancer than the general population and an underestimated risk using the PLCOm2012 model[19]. As a result, many HL survivors, particularly those who are younger, female, or light/never smokers, are excluded from current screening programmes, representing a significant health inequality. Without screening, the majority (57-74%) of lung cancers are diagnosed at advanced, incurable stages[11,22,23] and outcomes are dismal with a median survival of just 5-10 months[23-25]. Poor survival is compounded by an inherently inferior prognosis for lung cancer as a second cancer after HL compared to first primary lung cancers[22].

HL survivor views on lung cancer screening

Studies conducted at The Christie showed that HL survivors are receptive to lung cancer screening[20,26]. A qualitative study[26] found that most HL survivors were unaware of their elevated risk but were highly supportive of screening once informed. They believed that early detection could lead to curative treatment and valued the opportunity to provide reassurance and monitor their

health as a logical extension to survivorship care. Most said they would attend screening, but some had concerns about radiation exposure, false positive screening results, and logistical barriers like travel and time off work. A subsequent quantitative study[20] confirmed high willingness to participate in a lung cancer screening programme, with 98% of respondents saying they would likely attend if invited. Hesitancy was more common among men, those living in deprived areas, and in individuals with lower self-efficacy. These studies highlight the need for targeted programmes with tailored education and accessible services to ensure equitable uptake.

Pilot study of lung cancer screening in HL survivors

A pilot study conducted at The Christie[21] demonstrated that targeted lung cancer screening using LCSP LDCT protocols is both feasible and effective in detecting early-stage lung cancer in HL survivors.

The pilot included asymptomatic individuals of all ages, as well as current, former and never smokers who were at increased risk due to prior treatment for HL. Of 218 individuals invited to participate, 127 responded, resulting in a response rate of 58.3%. Among respondents, 123 were eligible, and 102 underwent a baseline LDCT. Screening detected three cases of lung cancer, representing a detection rate of 2.9%. Two were early-stage cancers (stage 1A adenocarcinoma and stage 1B small cell lung cancer) and both were treated with curative surgery. The third case was a stage 3 small cell lung cancer managed with palliative chemotherapy. Additionally, one individual who declined screening was later diagnosed with stage 3B non-small cell lung cancer following clinical presentation. The pilot study reported a false positive rate of 2%, and 2.9% of participants had clinically significant incidental findings.

Participants showed high levels of engagement and acceptability, with 91% making informed decisions using a tailored decision aid developed for the study[27]. Factors such as age, gender, time since treatment, and socioeconomic status did not significantly influence participation, indicating broad acceptability across demographic groups.

Population-based lung cancer risk modelling in HL survivors and development of a PLCO-HL risk model

To improve the accuracy of lung cancer risk prediction in HL survivors, we developed PLCO-HL, an independently implemented version of the PLCOm2012 statistical model calibrated specifically for this high-risk population using data from 24,665 HL survivors in England diagnosed with HL over a 20-year period (1997–2020), sourced from the National Cancer Registration and Analysis Service (NCRAS).

The NCRAS cohort had 398 cases of lung cancer, yielding a standardised incidence ratio (SIR) of 2.37 (95% CI: 2.14-2.61) and confirming a significantly elevated risk compared to the general population regardless of the recorded treatment received. Age-group specific SIRs showed that younger age at HL diagnosis was associated with higher relative risk, as expected, and 117 (29%) of lung cancers

occurred within 1-5 years of HL diagnosis. To generate lung cancer risk scores using the PLCO HL algorithm, 6- year risk estimates from the PLCOm2012 model were multiplied by the age at HL diagnosis SIR. In this calculation, the 'personal history of cancer' variable in PLCOm2012 was fixed at '0' and replaced by the age specific SIR in the PLCO HL model. This adjustment allowed the model to better reflect the elevated risk in HL survivors. The PLCO-HL model identified 44% of HL survivors in the pilot cohort as eligible for screening in the LCSP - 69% more than identified by PLCOm2012[21]. Notably, two of the three lung cancers detected in the pilot fulfilled PLCO-HL but not PLCOm2012 criteria[28].

The analysis also showed that HL survivors consistently met the screening risk threshold (≥1.51% six-year risk) between ages 45 and 50, regardless of age at diagnosis and gender, meeting screening criteria 10 years earlier than the general population. This provided the rationale for lowering the screening age from 55 to 45 for the current study.

Regulatory status of the PLCO-HL risk model

PLCO-HL is an investigational Class I Software-as-a-Medical-Device (SaMD), Safety Class A, developed as a standalone web-based tool for estimating 6-year lung-cancer risk in Hodgkin lymphoma survivors with a smoking history. It will undergo clinical investigation within SEARCH to support future UKCA marking and NHS deployment and is labelled "Exclusively for Clinical Investigation" during the study.

3. RATIONALE FOR THIS STUDY

Second cancers are a well-recognised late effect of HL treatment, yet global screening efforts remain limited. While targeted screening for breast cancer in high-risk female HL survivors was embedded in the NHS Breast Screening Programme in 2003 - enabled by the Manchester-led Breast screening After Radiotherapy Dataset (BARD)[29] - no equivalent exists for lung cancer, the most fatal second cancer in this group. This represents a critical gap in care. Despite the urgency, lung cancer screening for HL survivors is not routinely available anywhere in the world. Only two small trials in North America have explored this need, both now closed to recruitment but yet to report results[30,31]. The urgent need for a targeted, evidence-based lung cancer screening programme for HL survivors remains unmet.

SEARCH (**S**creening for **E**arly detection of second cancers **A**fter **R**adiotherapy and **C**hemotherapy for **H**odgkin lymphoma) is an overarching research programme. The current SEARCH study is evaluating lung cancer screening in HL survivors through the implementation and evaluation of the novel PLCO-HL risk model within an adapted LCSP pathway.

An impact evaluation will determine early lung cancer detection rates for HL survivors fulfilling PLCO-HL criteria, aimed at furthering the NHS Long Term Plan[17] to diagnose 75% of cancers at stage

I or II by 2028. Health economic and process evaluations will determine cost-effectiveness and offer a scalable model for integrating risk-adapted screening into existing NHS infrastructure. A health inequalities sub-study will investigate barriers to engagement and develop, implement, and evaluate targeted strategies to improve engagement. A risk sub-study will assess the comparative performance of PLCO-HL and validated models (PLCOm2012[19] and LLPv2[32]) in HL survivors, the performance of investigational models with potentially enhanced accuracy (including CanPredict[33] and LLPv3[32]) and model updating strategies to evaluate whether additional variables can improve predictive precision.

If successful, study results will provide evidence to the UKNSC on the feasibility and value of targeted screening to inform NHS policy changes.

The study will be conducted across up to ten Cancer Alliances in England. Potential participants will be identified through primary care records and direct referrals. Following a lung health check, those at high-risk of lung cancer will be invited to undergo LDCT screening.

The study is funded by SBRI Healthcare under the NHS Cancer Programme Innovation Open Call 3 (Reference: NCPC03015).

4. STUDY DESIGN SUMMARY

4.1 Study Design

SEARCH is a multicentre, prospective clinical study evaluating a new lung cancer risk prediction model (the PLCO HL investigational device) designed to identify Hodgkin Lymphoma (HL) survivors aged 45-74 with a history of smoking who may benefit from low dose CT (LDCT) screening. The aim is to support integration of this approach within the NHS Lung Cancer Screening Pathway (LCSP), enabling earlier detection of lung cancer at a more treatable stage in this high risk population.

The protocol outlines extended eligibility and risk assessment criteria, a tailored patient pathway, and additional research assessments for participants enrolled in this study. The study deviates from the LCSP Standard Protocol for research purposes but adheres to the clinical governance standards set out in the LCSP by the Lung Clinical Expert Advisory Group 2502-B1647-quality-assurance-standards-prepared-for-the-lung-cancer-screening-programme.pdf; it should be used alongside this document: LCSP standard protocol

4.2 Study Population and Cohorts

The study population comprises individuals aged 45-74 who have previously received treatment for HL and who have a history of smoking. Although non-smoking HL survivors also have an elevated risk of lung cancer, the NHS LCSP currently invites only ever-smokers, and the PLCOm2012 model

upon which PLCO-HL is modelled, is validated only in ever-smoker populations. For this reason, eligibility for the present study is restricted to HL survivors with a history of smoking.

Five hundred eligible high-risk HL survivors from up to 10 participating Cancer Alliances will undergo LDCT screening in this study.

Based on prior research and national smoking prevalence data, to achieve a target of 500 screened participants the study aims to identify approximately 4,400 HL survivors aged 45–74. This cohort will be identified through two main routes: around 3,300 via primary care records, and approximately 1,100 through direct referrals. With an anticipated 60% response rate and 40% prevalence of ever-smokers, it is expected that 1,056 individuals will complete a Lung Health Check (LHC). Of these, approximately 528 are projected to fulfil PLCO-HL criteria for screening, resulting in 500 participants undergoing LDCT screening.

Study participants fulfilling eligibility criteria for LDCT screening in this study (or with a valid thoracic CT performed within the previous 24 months) will be allocated to cohorts based on their age, risk, and previous participation in the NHS LCSP, as illustrated in Figure 1 and described in the table below. Cohort allocation will take place during the LHC (section 4.9.2 of the protocol).

Cohort	Age	PLCO-HL risk	PLCOm2012 risk	LLPv2 risk	Not in LCSP or in LCSP and baseline LDCT ≥24m ago	In LCSP and baseline LDCT <24 months
A	45-54	High	-	-	-	-
B	55-74	High	Low by both		-	-
C1	55-74	High	High by either		Yes	-
C2	55-74	High	High by either		-	Yes
D1	55-74	Low	-	High	Yes	-
D2	55-74	Low	-	High	-	Yes
"-"not applicable						

4.3 Objectives

Primary Objective

To evaluate the early-stage (stage I-II) lung cancer detection rate in high-risk HL survivors meeting PLCO-HL criteria and scanned per protocol.

Secondary Questions/Objectives

1. To evaluate screening outcomes in high-risk individuals by any model (PLCO-HL, PLCOm2012, LLPv2), reporting stage distribution, histological subtypes, false positive and negative rates, curative treatment rates, and smoking cessation impact. Outcomes will be compared to historic controls in the general population and non-screened HL survivors.

2. To evaluate the performance of lung cancer risk prediction models (PLCO-HL, PLCOm2012, LLPv2), including predictive accuracy and calibration.
3. To evaluate participation rates and acceptability at each stage of the pathway (invitation, LHC, LDCT, saliva sampling, PROs).
4. To identify and address health inequalities in access, engagement, and outcomes among HL survivors, including underserved and marginalised groups.
5. To evaluate the feasibility and operational implementation of the PLCO-HL model and adapted screening pathway for high-risk HL survivors within the NHS Lung Cancer Screening Programme, including its scalability and sustainability across diverse healthcare settings.
6. To undertake a health economic evaluation, including Incremental Cost-Effectiveness Ratio (ICER), Net Benefit (monetary value of health gains minus costs), Return on Investment (ROI) ratio (if applicable), Cost per early-stage cancer detected, QALYs gained.
7. To evaluate environmental (net zero) impact, including carbon emissions per patient screened and emissions avoided through early diagnosis.

Exploratory Questions/Objectives

1. To explore enhancements to the PLCO-HL model using additional predictor variables.
2. To assess performance and adaptability of the CanPredict and LLPv3 models for HL survivors
3. To explore polygenic risk scores for improved lung cancer risk prediction
4. To explore QRisk2 scores in HL survivors stratified by risk of lung cancer

4.4 Endpoints

Primary Endpoint

Proportion of early-stage (stage I–II) lung cancers detected among high-risk Hodgkin lymphoma survivors who meet PLCO-HL criteria and undergo LDCT screening.

Secondary Endpoints

1. **Screening performance**:
   Overall lung-cancer detection rate, stage distribution, histological subtype, false-positive and false-negative rates, incidental findings, and proportion receiving curative-intent treatment.

2. **Risk model comparative performance:**
   Sensitivity, specificity, calibration, and predictive accuracy of PLCO-HL versus PLCOm2012 and LLPv2.

3. **Participation and acceptability:**
   Uptake and completion rates across the participant pathway (invitation → LHC → LDCT → saliva sampling → PROs), reasons for ineligibility or dropout, and participant experience.

4. **Health inequalities metrics:**
   Differences in identification, invitation, uptake and outcomes across demographic and socioeconomic groups.

5. **Feasibility and implementation:**
   Deliverability of the PLCO-HL pathway across diverse NHS settings; operational barriers and facilitators.

6. **Health economic endpoints:**
   Incremental cost-effectiveness ratio (ICER), net benefit, QALYs gained, cost per early-stage cancer detected, programme-level cost-effectiveness, and return on investment (ROI).

7. **Environmental endpoints:**
   Carbon emissions per participant screened and estimated emissions avoided by earlier diagnosis.

Exploratory endpoints

1. **Enhanced risk-model performance:**
   Incremental value of additional clinical variables (e.g. age at HL diagnosis, previous HL treatment exposures, comorbidities) in improving PLCO-HL risk prediction.

2. **Comparative performance of investigational models:**
   Discriminatory accuracy, calibration, and classification agreement of CanPredict and LLPv3 in HL survivors, compared with PLCO-HL and standard LCSP models.

3. **Genomic risk contribution:**
   Association of polygenic risk scores (PRS) with lung-cancer risk and assessment of whether adding PRS improves predictive performance in HL survivors.

4. **QRisk2 analysis:**
   Distribution of QRisk2 scores among HL survivors and exploratory assessment of associations with lung-cancer risk categories.

4.5 Study Procedures

4.5.1 Schedule of Events

Study Activities	Pre-LDCT	LDCT		Post- LDCT
		Baseline	Nodule Surveillance	3m, 6m and end of study
Identification and Invitation				
Documented route of identification[1]	x			
Identification of individuals already known to LCSP[2]	x			
Invitation[3]	x			
Initial Assessment and study enrolment[4]				
Documented verbal informed consent[5]	x			
Eligibility Assessment[6]	x			
Patient demographics[7]	x			
Smoking cessation advice +/- referral, where appropriate[8]	x			
Patient information Sheet, Informed Consent Form and Decision Aid[9]	x			
Invitation to Lung Health Check[10]	x			
Lung Health Check[10]				
Written informed Consent /eConsent[11]	x			
Patient demographics, medical, smoking, alcohol, occupational and family history, height and weight[7]	x			
Automated risk assessment, cohort allocation and documentation of risk scores[12]	x			
Smoking cessation advice +/- referral, where appropriate[8]	x			
Referral for LDCT[13]	x			
Low Dose Computed Tomography (LDCT) screening[14]				
Consent for LDCT[15]	x			
LDCT scan and nodule surveillance[16,17]		x[16]	x[17]	
Baseline Patient reported outcomes (PROs)[18]	x			
Research saliva sample (optional)[19]	x			
Smoking cessation advice +/- referral, where appropriate[8]	x			

4.5.1 Schedule of Events

Study Activities	Pre-LDCT	LDCT		Post- LDCT
		Baseline	Nodule Surveillance	3m, 6m and end of study
Clinical management and follow-up				
Adverse event reporting[20]		x	x	
LDCT/thoracic CT scan results[21]		x	x	x
Referral and management of findings[22]		x	x	x
Participant follow-up[23]				x
Patient reported outcomes (PROs)[18]				X[18]

1. Potential participants may be identified from primary care records, direct referrals from patients/clinicians in England, or both, and the route(s) of identification must be clearly documented in the electronic Case Report Form (eCRF).
2. Potential participants who have already participated in the LCSP and had a valid LDCT within the previous 24 months (Cohort C2 and D2) may be eligible to participate in the study at investigator discretion; they will be invited to undergo a LHC and LDCT results will be retrieved for inclusion in the analysis.
3. Potential participants may receive the study invitation text message from their GP, the trial location or a third-party provider according to local practice and governance arrangements. Their identifiable data should be recorded in the eCRF for communication purposes - only the direct care team and authorised researchers with delegated responsibilities may complete and access this data.
4. The Initial Assessment may be done by phone or in person by a trained member of staff and may be done at a separate appointment or at the start of the Lung Health Check appointment, according to local practice.
5. Verbal informed consent to collect, analyse and retain data for the current and future ethically approved studies must be obtained from all potential participants who have opted in. This must be done at the Initial Assessment or the start of the LHC and clearly documented in the eCRF, specifying consent for non-identifiable for research +/- identifiable data to contact patients about future research.
6. Refer to section 4.8 for eligibility assessment. Ever smoking status must be verified for all potential participants – as a guide, an ever-smoking history may be defined as smoking ≥ 100 cigarettes (or equivalent, except vaping) in their lifetime. Subjects with exclusion criteria are not eligible to enrol and must not be offered a LHC appointment.

7. Demographic data can be collected at the Initial Assessment and/or the LHC.
8. Current smokers should receive smoking cessation advice by a trained professional and referral to smoking cessation services on an opt-out basis, per the LCSP standard protocol. This can be done at any point in the pathway and may be repeated as necessary.
9. Potential participants must receive a Patient Information Sheet and Informed Consent Form (PIS/ICF) and a Decision Aid to support informed choice about their participation in the study, including the benefits and risks of lung cancer screening. The PIS/ICF and Decision Aid can be provided in paper format or digitally via a unique eLink to the Lifeguide web-based platform and should be provided at least 24 hours before the LHC. A LifeGuide/RAVE data reconciliation step will ensure accurate data linkage with the eCRF for each participant.
10. Only potential participants satisfying eligibility criteria should undergo a LHC. If a participant is excluded, the reason(s) must be recorded. The LHC can be done by telephone, video call or in person by trained member of staff.
11. Written informed consent/eConsent to participate in the study is mandatory and must be taken by a suitably qualified member of staff trained in all the necessary procedures of the study before or at the start of the LHC, and before undertaking any research activities including LDCT, ePRO,saliva sampling.
12. Risk assessment is automated within the SEARCH database and investigational medical device; risk scores for the PLCOm2012, LLPv2 and PLCO-HL must be recorded in the eCRF. Participants fulfilling PLCO-HL criteria will be allocated into Cohort A, B, C1 or C2. Participants fulfilling PLCOm2012 and/or LLPv2 criteria, but not PLCO-HL criteria, will be allocated into Cohort D1 or D2
13. Cohort A, B, C1 and D1 participants should be invited to undergo a LDCT scan. Cohort C2 and D2 participants will have retrospective collection of baseline and follow-up LDCT scan outcomes if scans meet the quality standards set out in the Standard Protocol for the LCSP.
14. LDCT acquisition and reading, management of findings and communication of findings should comply with the clinical governance structure of the LCSP and be conducted in accordance with the LCSP standard protocol.
15. Consent for CT screening must follow the Standard Protocol for the LCSP and should be taken by a suitably trained clinician or non-clinician, familiar with the risks and benefits of the process and radiation exposure.
16. Baseline scan - eligible participants will receive one baseline LDCT in this study. Follow-up scans, management and investigation of findings and invitations to subsequent rounds of screening must be done in accordance with the Standard Protocol for the LCSP.
17. Surveillance scan(s) - participants with indeterminate findings on the baseline scan will undergo surveillance scans in routine NHS care in accordance with the Standard Protocol for the LCSP; outcomes will be recorded for the study.

18. Patient Reported Outcomes (PROs) will be collected at baseline pre-LDCT, 3 and 6 months post-LDCT. PRO questionnaires are available in both printed and electronic formats (ePRO - accessible via a unique eLink to the LifeGuide web-based platform). A LifeGuide/RAVE data reconciliation step will ensure accurate data linkage with the eCRF for each participant. Participants in Cohorts A, B, C1 and D1 must complete PROs at all timepoints. Participants in Cohorts C2 and D2 are only required to complete the 3 and 6 month PRO questionnaire; this can be done at any time.
19. Optional saliva samples for research will be collected into provided tubes, labelled and shipped in Royal Mail Special Delivery Bags to The University of Manchester Genomics laboratory. These can be collected at any point in the study.
20. Only serious adverse events occurring during or after the baseline +/- nodule surveillance LDCT(s) (on the same day as the scan) should be reported (see section 9). Serious adverse events may be reported by screening teams or self-reported by participants.
21. Results of baseline, surveillance LDCT scans and any interval thoracic CT scans performed within the study period must be obtained from hospital records and documented in the eCRF. Data for LCSP-eligible participants must also be recorded in usual LCSP systems (e.g. SPECTRA) to comply with LCSP reporting, management and next-round invitation requirements per the LCSP standard protocol.
22. Referral and clinical management of findings will depend on LDCT scan results and will be conducted in routine NHS care, per the Standard Protocol for the LCSP.
23. Participants will be followed at 3- and 12-months until the End of the Study, whichever comes first, for survival, screening outcomes, interval lung cancer diagnoses and lung cancer treatment.

4.6 Study Participants

4.6.1 Inclusion Criteria

Participants must meet all of the following:

1. Any previous treatment with chemotherapy +/- radiotherapy for Hodgkin lymphoma (HL)
2. No relapse of HL or treatment for HL within the previous 3 years, indicating a high likelihood of cure
3. Aged 45-74 years at the time of eligibility assessment
4. A current or former smoker
5. Suitable for LDCT (or had a valid thoracic CT within 24 months meeting study imaging reconstruction criteria; such individuals are eligible for inclusion of their screening outcomes, including those undergoing surveillance for suspected lung cancer or with a diagnosis of screen-detected lung cancer. They may be approached for inclusion at the investigator's discretion and should be invited to undergo a LHC, including risk assessment using the PLCO-HL tool, optional saliva sampling and completion of a 3-month ePRO questionnaire (see section 4.17 for further details). Where a participant is found to be deceased, the study team will seek to obtain the required retrospective information from GP records for risk-assessment purposes; these data will be collected outside of the SEARCH database.

4.6.2 Exclusion Criteria

All cohorts

1. Never smokers
2. Lacking capacity to provide informed consent
3. Self-referrals for/from individuals residing outside of England
4. A lymphoma diagnosis other than Hodgkin Lymphoma
5. Any diagnosis of lung cancer ≥24 months ago

Cohorts A, B, C1, D1 (i.e. those planned to undergo LDCT in the study)

1. Not suitable to undergo LDCT scanning (including weight > 200kg or unable to lie flat)
2. Poor physical fitness such that treatment with curative intent would be contra-indicated. This may require a second opinion or advice from the local lung cancer Multidisciplinary Team (MDT). This may include:
    a. Individuals registered on the palliative care register
    b. Individuals with severe frailty (electronic frailty index >0.36) – see NHS England Electronic Frailty Index

c. Individuals with metastatic cancer with a poor prognosis, where treatment for lung cancer with curative intent would be contraindicated
d. Individuals with mesothelioma

4.7 Recruitment

4.7.1 Identification of potential participants

Potential participants will be identified at participating Cancer Alliances from primary care records or via direct referrals (or both). The route(s) of identification must be clearly documented in the electronic case record form (eCRF).

Primary care records route

Primary care records may be queried by GP-run searches at individual practices or at aggregate level by Integrated Care Board/Cancer-Alliance/ trial location -led identification (centralised searches) using automated or manual methods, according to existing local procedures. Data Protection Impact Assessments (DPIAs) for centralised searches may need to be amended to identify and approach individuals aged 45-54 who fall outside standard eligibility criteria for the main LCSP. The LCSP Data Extraction Definition Document for this study will identify all HL survivors aged 45-74 using standard LCSP SNOMED CT (Systematized Nomenclature of Medicine Clinical Terms) codes plus additional codes for HL (see Appendix 1) and the CanPredict investigational risk model (see Appendix 4). An initial records query should be run at the start of the study, with a re-query performed at least 6 months later where feasible to identify newly eligible participants, particularly those who were previously ineligible due to age or risk score.

Direct referral route

To promote equitable access for participation, especially during the phased rollout of the LCSP, referrals will also be accepted directly from healthcare professionals and patients (self-referrals). All direct referrals must be directed by email to a single point of contact at Manchester Foundation Trust, lead Trust for the Greater Manchester Care Alliance, for initial triage. They will forward referrals to the closest participating Cancer Alliance based on the geographical location of the participant's home postcode. Trial locations are encouraged to facilitate research participation for both local and out-of-area individuals.

The study will be promoted to potential participants and clinicians for direct referral through a variety of channels, including targeted communication campaigns, social media, patient support websites (e.g. Lymphoma Action), the SEARCH website, cooperative research networks (e.g. UK Lymphoma Research Group, Oncology Translational Research Collaboration), and other appropriate platforms. These campaigns should emphasise the importance of referral for early detection, even for individuals who

feel well, and must clearly include eligibility criteria and referral contact details for those engaging via the direct referral route.

Direct referrals should be sent to:

Sara Waplington
SEARCHStudy@mft.nhs.uk

Trial location Participant Lists

Trial locations should maintain an internal log of individuals identified through GP and/or centralised searches prior to invitations being sent. This supports operational planning, workload management and monitoring of uptake and health inequalities.

Before invitations are sent, all names should be checked against NHS Spine to confirm vital status to ensure that no inappropriate invitations are sent.

At this stage, potential participants must *not* be registered on the study database, and no identifiable data may be captured electronically.

4.7.2 Study Invitation Text Message

Potential participants identified through GP-led searches may receive their study invitation text message directly from their GP practice. Alternatively, and in accordance with local governance arrangements, invitations may be issued centrally by the ICB, the trial location or an approved third-party provider. The same applies to individuals identified through central searches or direct referrals, where invitations may be sent by the ICB, the trial location or an approved third-party operating under locally approved data-sharing agreements.

For individuals not invited directly by their GP, DPIA requirements may differ by age group. Those aged 55-74, who fall within the existing LCSP eligibility range, can typically be contacted under current DPIAs, with an added research clause where needed. For individuals aged 45-54, trial locations may need to amend an existing DPIA or establish a dedicated research DPIA to permit identification and invitation of this younger cohort.

Standardised invitations will be delivered via an interactive opt-in text message using software such as AccuRx or equivalent, with embedded links to a short patient video, summarised patient information, and the Lymphoma Action helpline. These materials and resources are designed to provide information and support to help reduce anxiety for recipients, especially those who are unaware of their potential risk of lung cancer following treatment for HL.

Individuals opting in will be asked to provide their contact details along with at least two items of personally identifiable information to support cross-checking with LCSP records and communication about the study. Individuals who have previously taken part in the main LCSP programme may be eligible for inclusion in the study and retrospective collection of screening outcomes; they should be invited to participate at the investigator's discretion.

Whilst this is an opt-in invitation, recipients may choose to opt out. They will be invited to give their reasons and asked to provide consent to be contacted about future research, including participation in a health inequalities sub-study exploring barriers to engagement.

Opt-in and opt-out responses will be directed to a trial location-specific, secure study inbox and responses will be recorded on the eCRF.

A reminder text should be sent after two weeks to recipients who have not responded to the Study Invitation.

4.7.3 Registration of potential participants

Individuals who opt in must be registered on the study database and assigned a unique study ID; this is automatically assigned within the SEARCH database. Those who opt out but provide consent to data collection and processing should also be registered and assigned a study ID for health inequality monitoring and future research invitation purposes. No electronic data may be captured for non-respondents or individuals who opt out and decline consent for data collection and processing.

4.8 Initial Assessment

All potential participants opting into the study must undergo an initial assessment before or at the start of the lung health check to confirm eligibility for inclusion in the study. The initial assessment can be conducted by telephone and should be done by a member of staff who has received protocol training and is qualified to collect the required data and enquire about symptoms.

The following must be done:

- Provide a brief verbal explanation of the study and obtain verbal informed consent to facilitate data capture from individuals who do not proceed to a LHC and analysis of reasons for ineligibility as part of the health inequalities workstream. Verbal consent will follow a standardised format and *must be clearly documented* in the SEARCH database and recorded separately for identifiable and non-identifiable data. Consent procedures are outlined in section 4.13.

- Collect demographic data including date of birth, gender, ethnicity, education level, disabilities and main spoken language, as well as information on how they heard about the study and referral route.
- Perform an eligibility assessment to ensure all inclusion criteria are met and no exclusion criteria apply that would preclude study enrolment and referral for a LHC, including medical history and any new or urgent clinical symptoms that require further assessment (see section 3.6 of the Standard Protocol LCSP standard protocol prepared by the Lung Clinical Expert Advisory Group, with escalation as appropriate to clinical colleagues and onward referral to primary or secondary care as needed. An ever-smoking history is crucial for participation in the study. As a guide, an individual is considered to have a history of smoking (ever smoker) if they have smoked at least 100 cigarettes, or the equivalent (except vaping), over their lifetime.
- Wherever possible, offer smoking cessation advice to all current smokers and refer to formal smoking cessation services.
- Send the Patient Information Sheet (PIS), Informed Consent Form (ICF) and a copy of the Decision Aid (DA) at least 24 hours prior to their LHC appointment, including when the Initial Assessment and LHC are scheduled at the same appointment. This ensures that potential participants have sufficient time to consider study participation and screening options. These materials support informed decision-making for individuals at high-risk and promote awareness among lower-risk participants about lifestyle changes that may reduce future risk, such as smoking cessation. Materials can be provided electronically via links to the PIS/ICF within LifeGuide or in printed format, depending on participant preference. Trial locations will provide this link to potential participants.
- Proceed to or book the LHC appointment for eligible participants.
- Send a standardised letter to the participant's GP informing them of their participation.

If a participant declines an invitation to a LHC or does not attend, the opportunity should remain for them to opt back into the study, provided they continue to meet all inclusion and none of the exclusion criteria.

To ensure accessibility and inclusivity, reasonable adjustments should be made for participants with physical or learning disabilities, mental health conditions, or language barriers. This may include providing easy-read materials, involving a key worker in the invitation process, or using NHS translation services where needed. Study information and participant materials, including the PIS/ICF, are also hosted on the Lymphoma Action website. The website features translation software capable of translating any material into over 100 languages, supporting accessibility for diverse populations. For further guidance, refer to the Standard Protocol developed by the Lung Clinical Expert Advisory

Group for the LCSP and the Lymphoma Action ReachDeck Toolbar Lymphoma Action Language Translation Tool.

Table 1. Risk variables collected in this study as featured in the multivariable risk prediction models under evaluation

Risk Models	PLCOm2012	PLCO-HL	LLPv2	CanPredict	LLPv3
Development status	**Validated**	**Research**	**Validated**	**Research**	**Research**
Age range *in this study*, years	**55-74**	**45-74**	**50-74**	**45-74**	**50-74**
Age (years)	Yes	Yes	Yes	Yes	Yes
Risk variables					
Sex at birth	-	Yes	-	Yes	Yes
Ethnicity	Yes	Yes	-	Yes	-
Socioeconomic status (Townsend score)	-	-	-	Yes	-
Education Level	Yes	Yes	-	-	-
Body Mass Index	Yes	Yes	-	Yes	-
Smoking duration (years)	Yes	Yes	Yes	-	Yes
Smoking Status	Yes	Yes	-	Yes	-
Average number of cigarettes smoked per day	Yes	Yes	-	Yes	-
Years having ceased smoking	Yes	Yes	-	-	-
Alcohol consumption	-	-	-	Yes	-
COPD/chronic bronchitis/emphysema	Yes	Yes	Yes	Yes	Yes
Asthma	-	-	-	Yes	-
History of pneumonia	-	-	Yes	Yes	Yes
History of tuberculosis (TB)	-	-	Yes	-	Yes

History of venous thromboembolism	-	-	-	Yes	
Personal history of any malignancy	Yes	-	Yes	Yes	Yes
Asbestos exposure	-	-	Yes	Yes	Yes
Family history of lung cancer	Yes	Yes	Yes	Yes	
Family history of lung cancer in a relative aged < 60 years	-	-	Yes	-	Yes
Family history of lung cancer in a first degree relative	-	-	Yes	-	Yes
Age adjusted standardised incidence ratio for lung cancer	-	Yes	-	-	-

Table 1 includes the variables that will be collected in this study that feature in one or more of the risk models. Additional variables not currently included in models that may be modify risk will be collected and analysed in the risk sub-study. Refer to Appendix 2 for online versions of the PLCOm2012 and LLPv2 risk models, Appendix 3 for continuous Standardised Incidence Ratios (SIRs) needed to compute PLCO-HL score and appendix 4 for the SNOMED-CT codes and variables used to calculate the CanPredict-lung score.

4.9 Lung Health Check (LHC)

All eligible participants, including those who have already participated in the LCSP, will undergo a LHC. Written informed consent must be obtained before conducting LHC. This includes the option of eConsent via the Lifeguide platform. Consent procedures are outlined in section 4.13.

The LHC can be done either remotely (via telephone or video call) or in person and should be conducted by staff who are trained on the protocol and qualified to obtain written consent, collect and document patient data, and request LDCT scans.

Individuals will be assessed by reviewing their medical, family and education history, and height and weight, to document risk factors for lung cancer, as summarised in Table 1 above. Information will be used to assess their risk of lung cancer over the next 5-6 years using the standard PLCOm2012 and LLPv2 tools and the PLCO-HL investigational device (outlined below). Results of risk assessment will inform eligibility for LDCT screening. Additionally, information collected, including details of prior HL treatment, will support modelling strategies aimed at improving the precision of future risk prediction tools.

4.9.1 Risk Assessment

Risk of lung cancer in HL survivors will be assessed using five models in this study - PLCOm2012, LLPv2, PLCO-HL, LLPv3 and CanPredict.

PLCOm2012, LLPv2 and PLCO-HL risk scores will be generated in real time for individuals within the age-range scope of each device for this study (summarised in Table 1); results will be used to guide LDCT decisions. Real time risk assessment will be automated within the SEARCH database/medical device and high-risk individuals will be auto flagged for action.

The performance of investigational tools with potentially enhanced precision, such as CanPredict[33] and LLPv3[32], will be evaluated in an exploratory risk sub-study.

Online links to the current LCSP recommended models are available as a backup in the event of IT issues (see Appendix 2). Standardised incidence ratios (SIRs) for lung cancer based on age at HL diagnosis are shown in Appendix 3 – in the PLCO-HL model, these SIRs replace the odds ratio for “personal cancer” in the PLCOm2012 tool. CanPredict variables and SNOMED-CT codes are shown in Appendix 4.

The risk thresholds for screening in this study are set at the same risk threshold as the main LCSP. An individual meeting the high-risk threshold from any of the risk assessment tools is eligible to undergo a baseline LDCT in the study:

- High-risk: 6-year risk ≥ 1.51% and/or 5-year risk ≥ 2.5%
- Low-risk: 6-year risk < 1.51% and 5-year risk <2.5%

4.9.2 Cohort Allocation

Participants aged 45-74 fulfilling PLCO-HL high-risk criteria for screening in this study will be allocated into one of four cohorts based on their age, risk assessment using standard models (PLCOm2012 and LLPv2) and participation in the LCSP, as follows:

- **Cohort A**: individuals aged 45-54 who fall outside the age eligibility range of the LCSP

- **Cohort B**: individuals aged 55-75 who fall within the age eligibility range of the LCSP and are low-risk by the standard models

- **Cohort C1**: individuals aged 55-75 who fall within the age eligibility range of the LCSP and are high-risk by the standard models, but have either not previously participated in the LCSP, or had a baseline LDCT ≥24 months ago

- **Cohort C2**: individuals aged 55-75 who fall within the age eligibility range of the LCSP, are high-risk by the standard models and have participated in the LCSP with a baseline LDCT performed <24 months ago or currently undergoing surveillance scans

Participants aged 55-74 fulfilling PLCOm2012 or LLPv2 criteria who are low risk by PLCO-HL criteria*, will undergo screening or retrieval of results for scans performed < 24 months. LDCT scans will be done within the LCSP, and outcomes will be recorded in the study for analysis of secondary endpoints. Such participants will be allocated into Cohort D, as follows:

- **Cohort D1**: individuals aged 55-75 who fall within the age eligibility range of the LCSP and are high-risk by the standard models and low-risk by PLCO-HL, and have either not previously participated in the LCSP, or underwent LDCT ≥ 24 months ago

- **Cohort D2**: individuals aged 55-75 who fall within the age eligibility range of the LCSP, are high-risk by the standard models and low-risk by PLCO-HL and have participated in the LCSP with a scan <24 months ago or currently undergoing surveillance scans.

* This situation is not expected to occur with the PLCOm2012 model, as PLCO-HL always replaces the 'previous cancer history' variable with a higher standardised incidence ratio (for people aged 45-74), making it more sensitive for HL survivors. However, it may occur with the LLPv2 model, which is less tightly calibrated to smoking history and tends to overestimate risk, particularly in light smokers, compared to both PLCO models.

4.9.3 Invitation to LDCT screening

Participants in cohorts A, B, C1 and D1 who satisfy all inclusion criteria without exclusions (as outlined in Section 4.6.2) will be invited to undergo LDCT screening in this study.

Participants in cohort C2 and D2 who have had a full thoracic CT scan within the past 24 months will not need to undergo another LDCT scan if the existing scan meets the study's image reconstruction criteria (see section 6.6.1 and the LCSP standard protocol). In such cases, results of the prior scan will be used as for study purposes. Similarly, participants under nodule surveillance with a scheduled upcoming scan will use the baseline scan performed within the LCSP and subsequent nodule surveillance scans for study purposes.

Participants who do not fulfil the criteria for screening in this study, i.e. assessed as low-risk using all models, will not undergo LDCT screening in this study. However, they should be informed that their risk of developing lung cancer may increase over time, particularly with continued smoking, and advised that they may become eligible for future screening under the LCSP. They should be advised to seek medical advice if they develop any concerning symptoms, such as a persistent or worsening cough, coughing up blood, unexplained breathlessness or wheezing, chest or shoulder pain, and recurring chest infections like bronchitis or pneumonia. Current smokers should also be referred for smoking cessation support.

4.10 LDCT Screening Appointment

Staff must confirm that written consent for study participation has been obtained and that no exclusion criteria apply prior to requesting a LDCT. Additional, separate consent for LDCT must be sought, in line with the Standard Protocol of the LCSP. Consent procedures are outlined in section 6.

4.10.1 Low Dose CT screening (LDCT)

LDCT acquisition and reading, management and communication of findings will comply with the clinical governance structure of the LCSP and be conducted in accordance with the Standard Protocol prepared by the Lung Clinical Expert Advisory Group. This is summarised below and outlined in full in Chapters 4, 5, 6, 8 and 9 of the LCSP standard protocol

4.10.2 CT Acquisition

Equipment Requirements

- Minimum: 16-channel multi-detector CT scanner (fixed or mobile), calibrated and tested.
- Volumetry software must be used for solid pulmonary nodules, capable of calculating:
  - Volume metrics
  - Percentage volume change
  - Volume doubling time (VDT)
- Software must be integrated with Picture Archiving and Communication System (PACS) and maintain version control.

Image Acquisition Protocol

- Positioning: Supine, arms above head, thorax centered.
- Breathing: Scans taken during suspended maximal inspiration.
- Localiser: PA projection at lowest setting to reduce breast dose.
- Scan Range: Entire lung parenchyma (apices to bases) in a single cranio-caudal acquisition.
- Field of View: Smallest diameter to include full lung parenchyma.
- No contrast is used.

Exposure Settings

- Radiation dose: ≤2 mSv (based on a 70kg adult).
- kVp and mAs adjusted for body habitus.
- Ultra-LDCT may be used if diagnostic sensitivity is equivalent.
- Medical physics input required for protocol setup.

Image Reconstruction

- Slice thickness: ≤1.25 mm (recommended: 1 mm).

- Reconstruction increment: ~0.7 mm.
- Algorithm: Moderate spatial frequency/soft tissue.
- Parameters must be consistent across follow-up scans.

4.10.3 CT Reading and Interpretation

Interpretation Tools

- Use of multi-planar reformations (MPR) and maximum intensity projections.
- Volumetric segmentation must be visually verified.
- All scan data archived and accessible for comparison.

Reader Requirements

- Radiologists must:
    - Report ≥500 thoracic CTs/year.
    - Participate in thoracic MDTs.
    - Be trained in nodule volumetry and BTS guidelines.
    - Complete NHS-approved RCR/BSTI CT screening course.
    - Engage in performance review via the PERFECTS (Performance and Evaluation Review for CT Screening) national radiology QA scheme.

Reporting Standards

- Diagnostic quality must be documented.
- Aim: 12–20 scans per programmed activity (PA), increasing with experience.
- Ergonomic standards for reporting environment must be met.

Nodule Assessment

- Threshold for characterisation: ≥5 mm or ≥80 mm^3.
- Record at least two nodules, including the largest and any >200 mm^3.
- New nodules ≥30 mm^3 or ≥4 mm must be reported.
- Volumetry preferred; manual measurements only if segmentation fails.
- VDT calculated from earliest acceptable scan.

Incidental Findings

- Only clinically significant findings should be reported.
- Non-significant findings should be excluded or clearly marked.

4.10.4 Screening outcome definitions

A **negative baseline LDCT** - no abnormal findings, no nodules found, clearly benign nodules or very small nodules below significant size thresholds, not requiring further evaluation

A **positive baseline LDCT** indicates a high suspicion of malignancy – large nodules, nodules with suspicious features requiring immediate referral to a lung MDT for further evaluation.

An **indeterminate baseline LDCT** – nodules found that do not fit the criteria for benign or malignant requiring further surveillance per the nodule management pathway described below, but no immediate evaluation.

- A **positive screening** result is defined as either a referral to a lung cancer multidisciplinary team (MDT) after a positive baseline LDCT scan or an indeterminate baseline CT followed by a positive, indeterminate, or missing follow-up CT.
- A **negative screening** result is defined as no suspicious findings on the baseline LDCT or an indeterminate baseline CT followed by a stable or resolved nodule on follow-up.

Screen-Detected Cancers are defined as lung cancers diagnosed after MDT referral due to abnormal CT findings. These are categorised as immediate screen-detected cancers diagnosed after a positive baseline scan or surveillance screen-detected cancers diagnosed after an indeterminate baseline scan followed by a positive follow-up CT.

Interval Cancers are defined as cancers diagnosed clinically between baseline and the 3/12-month follow-up in participants not referred to an MDT.

Cancer Confirmation should be based on histology when available, or MDT radiological consensus if invasive testing wasn't done. Staging should be done using the 8th edition of the TNM Lung Cancer Stage Classification. Pathological staging should be used for surgical cases, and clinical staging for non-surgically resected cases.

Incidental findings are unexpected abnormalities detected on any screening scan. Incidental findings include emphysema, interstitial lung abnormalities, bronchiectasis, respiratory bronchiolitis, consolidation, pleural effusion/thickening, pleural plaques, tuberculosis, bronchial wall thickening, coronary calcification, aortic valve disease, thoracic aortic calcification/dilatation, mediastinal mass, mediastinal lymph nodes, thyroid abnormalities, cardiac decompensation/pericardial effusion, oesophageal lesions, abdominal aortic aneurysm, breast nodules, liver lesions, renal lesions, bone

abnormalities, adrenal lesions are classified as life-threatening, urgent, non-urgent or clinically non-significant and should be managed according to standardised pathways outlined in the LCSP standard protocol:

1. Life-threatening (requiring immediate hospital admission)
2. Urgent (needing quick referral, including any possible cancer)
3. Non-urgent (requiring referral to primary or secondary care)
4. Clinically non-significant (not needing communication or action)

4.11 Management of Findings and Follow-Up

All participants will be managed in routine NHS care per the LCSP standard protocol, including communication of results and referral of participants with indeterminate findings or findings requiring further investigation. Out of region participants (direct referrals to the study) must be referred back to their local NHS services for management. Please refer to Appendix 5: Lung Health Checks Programme Pathway.

Negative screening result

Participants with a negative screening result do not require follow-up imaging. Their future participation in the NHS LCSP will follow the standard eligibility criteria, based on their cohort:

- Cohort A participants who are below the current age eligibility threshold for the LCSP will be eligible for reassessment in the LCSP when they turn 55
- Cohort B participants who are low-risk using standard models will be reassessed in the LCSP per Standard Protocol eligibility
- Cohort C and D participants who fulfil high-risk criteria using standard models should be invited to next LCSP screening round.

Positive screening result

- Participants with findings requiring further investigation must be referred to a specialist lung clinic.

All participants will be followed up on the study for clinical outcomes at 3 and 6 months and at the end of study.

Nodule Management

Management is based on nodule type, size, and risk

- Solid nodules:

  - <80 mm^3 or <5 mm: No follow-up.
  - 80–300 mm^3: 3-month scan, then 9-month follow-up if stable.
  - ≥300 mm^3 or ≥8 mm with Brock risk ≥10%: Refer for further investigation.
- Subsolid nodules:
  - <5 mm: No follow-up.
  - Ground-glass or part-solid nodules ≥5 mm: Serial scans over 3, 9, 12, 24, and 48 months if stable.
- New nodules:
  - ≥30 mm^3 or ≥4 mm: Surveillance or referral depending on growth and risk.

Significant Findings

- Nodules with volume doubling time (VDT):
  - 600 days: Annual LDCT.
  - 400–600 days: Surveillance or biopsy/resection.
  - <400 days: Further investigation if size allows meaningful intervention.
- Risk-based referral:
  - Brock score >10% or Herder score >10% (post-PET): Consider histological diagnosis and management.

Multidisciplinary Team (MDT) Review

- Screening Review Meeting (SRM): Discuss urgent findings and coordinate management.
- Lung Cancer MDT: Plan treatment for suspected or confirmed lung cancer.

Incidental Findings (Appendix 6)

- Management principles:
  - Only clinically significant findings are communicated.
  - Non-significant findings are not reported.
  - Findings already known to GP/patient are not re-communicated.
- Categories:
  - Life-threatening: Immediate referral.
  - Urgent: Referral to appropriate services.
  - Non-cancer: Managed in primary or secondary care.
  - Non-actionable: Not reported.

4.12 Communication of Findings

Per the LCSP, the communication of results must be timely, clear, and supportive, ensuring participants are well-informed and appropriately guided following their LDCT scan.

Once a participant undergoes a LDCT scan, the results should be communicated within a maximum of four weeks. This timeframe is supported by safety net systems that ensure urgent findings are flagged and acted upon immediately. For serious or potentially life-threatening findings, direct clinical action is taken without delay, while indeterminate results are followed up with appropriate surveillance.

Participants receive their results primarily through LCSP standardised letters. These letters are also sent to the participant's GP, preferably electronically, to facilitate audit and continuity of care. The letters to GPs include any recommended actions, and standard approaches such as SNOMED codes should be used to record outcomes in the participant's medical record. For participants, letters may be used to communicate routine findings, but serious results are not detailed in writing; instead, they are explained during clinic visits to ensure clarity and support.

In cases where clinical judgement deems it appropriate, results may also be communicated via telephone by a trained clinician. This is especially relevant for serious findings such as suspected malignancy. Additionally, participants must be provided with a contact number should they need further clarification or support after receiving their results.

To mitigate the risk of over-reassurance from a 'normal' result, communications should include reminders about the ongoing risk of lung cancer, the importance of reporting symptoms, and the benefits of smoking cessation. General information about the main LCSP programme is also available on the NHS website.

4.13 Informed Consent

The study uses an in initial opt-in approach followed by a two-stage consent procedure to ensure participants are fully informed and that data collection is conducted ethically and in accordance with GDPR requirements. Opt-in SMS invitation and DPIA modifications for 45–54-year-olds are proportionate and justified due to the high-risk nature of this survivor population and align with the transparency requirements of the amended UK Regulations.

All potential participants will have access to the Patient Information Sheet (PIS) - appended to which will be the University of Manchester Research Privacy Notice - and Informed Consent Form (ICF) at the time of the study invitation, via links embedded in the invitation text. These patient materials along with the Decision Aid (DA) will be provided again (in printed or electronic formats) to all participants who are eligible for a LHC, at least 24 hours prior to written consent.

Verbal and written informed consent must be obtained by a qualified member of staff and clearly documented in the SEARCH database. Staff obtaining written informed consent must also be trained on the protocol and study procedures.

Stage 1: Verbal Informed Consent

Participants undergoing an Initial Assessment should receive standardised verbal information about the study to facilitate informed consent. Documented verbal consent must be in place a) to collect and analyse non-identifiable data for this study and future ethically approved studies and b) to collect and analyse identifiable data for the purpose of contacting participants about future research opportunities; this includes the health inequalities sub-study where data will be used to explore health inequalities, identify barriers to participation, understand reasons for exclusion, and develop solutions to enhance equity of access.

Stage 2: Written Informed Consent/eConsent

Written informed consent must be obtained before undergoing any LHC assessments (outlined in 5.2.1 Schedule of Events). Separate consent for saliva sample collection for genomic analysis is optional.

Written informed consent may be obtained either in person during a face-to-face appointment or remotely via eConsent. The eConsent option via the web-based LifeGuide platform is available to facilitate timely consent for individuals who are not attending in person until late in the pathway e.g. when attending for a LDCT scan. Trial locations must ensure that participants providing eConsent have contact details to approach and discuss the study with member of staff who is trained on the protocol and can address their questions prior to giving informed consent. A LifeGuide/RAVE data reconciliation step will ensure accurate data linkage with the eCRF for each participant providing written informed consent.

Consent for LDCT scans

Institutional consent for CT screening must follow the LCSP standard protocol and be taken by clinicians or non-clinicians trained in Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) and familiar with the risks and benefits of LDCT and radiation exposure.

4.13.1 Participants who withdraw consent or lose capacity

Participants may withdraw from the study at any time.

Upon withdrawal, the study team will ask if the participant is willing to share their reason for withdrawing, but this is entirely optional, and record this in the eCRF. Previously collected data will be used in the analysis, but no further data will be collected from their medical records.

In cases where a participant loses mental capacity after initially consenting, the study team will withdraw them from the study as soon as the lack of capacity is identified. This may be communicated by the participant themselves, a representative, or observed by the study team. The protocol follows ethical guidance to ensure that participation is based on informed and ongoing consent, and that individuals who can no longer provide this are not included in further study activities.

4.14 Smoking Cessation Advice

Smoking cessation is a core component of the participant journey, aligned with LCSP standards and proactive steps for lung cancer prevention. All staff delivering this study must be trained to provide brief smoking cessation advice to current smokers and referral to cessation services on an opt-out basis, unless they actively decline. These efforts aim to support quitting through consistent, accessible, and effective interventions.

Smoking cessation information will be included in written communications, such as the study invitation text and result notifications. Where possible, advice must be delivered face-to-face, and participants provided with details of locally available support services. Enhanced interventions, including pharmacotherapy, are encouraged to improve quit rates.

Participants who currently smoke will be asked to self-report uptake of cessation services, strategies employed and smoking rates at 3 months after the LDCT scan (or after the date of consent for participants in cohort C2) to evaluate the impact of smoking cessation advice. Smoking habits will be captured via ePROs (see section 4.17).

4.15 Samples for research

Saliva samples for research will be collected at selected trial locations with capability and capacity to deliver this research component. Saliva samples are optional and should only be collected from participants who have provided written informed consent. DNA will be extracted from saliva samples for single nucleotide polymorphism (SNP) genotyping and calculation of polygenic risk scores (PRS) (see section 4.18.2).

Collection will take place during a face-to-face appointment at any feasible point in the patient pathway. Samples will be collected into saliva collection kits (e.g. Isohelix® or equivalent) that will be supplied to trial locations along with detailed instructions reiterated in the lab manual. Participants will be asked to spit into the collection tube to the required level marked on the tube. A buffer in the tube preserves DNA.

Each sample must be clearly labelled with the participant's unique study number and the trial location code. Barcodes on the collection tubes should be recorded. Samples should be packaged securely using double-bagging and absorbent material. Saliva sample collection must be recorded in the eCRF.

Samples may be stored at room temperature for up to five years. Trial locations have the flexibility to send samples individually or in batches, depending on local storage capacity. They will be processed and stored at The University of Manchester Genomics laboratory based at St. Mary's Hospital and must be shipped in boxed Royal Mail Special Delivery bags (or equivalent) to the address below. To support tracking, trial locations are required to submit a list of lab numbers prior to each shipment.

Mrs Helen Byers
The University of Manchester Research Assistant
Manchester Centre for Genomic Medicine
School of Biological Sciences
6th Floor, St. Mary's Hospital, Oxford Road
Manchester, M13 9WLPL

☎ 0161 7012305
✉ helen.byers@manchester.ac.uk

4.16 Data Sources and Electronic Data Capture in electronic Case Report Forms

A range of data sources and collections methods apply to the SEARCH study dataset.

- AccuRx SMS participant opt-in/opt-out responses are sent to trial locations via a secure email and then electronically captured on SEARCH database eCRFs by trial location staff
- eConsent forms signed by trial location Investigators and Participants and ePROs completed by Participants are hosted within the LifeGuide web-based platform with a link to the SEARCH database for participant study id reconciliation
- Raw variables are obtained from participants and SNOMED-coded primary care records during the Initial Assessment, Lung Health Check and LDCT screening visit and electronically captured on the SEARCH database eCRFs by trial location Staff
- Processed variables e.g. participant trial identifier number, body mass index, PLCOm2012 and LLPv2 risk scores are computed and recorded within the SEARCH database using automated processes
- PLCO-HL risk score is computed by the PLCO-HL investigational medical device and the result is manually recorded on the SEARCH database eCRFs by trial location staff
- Screening outcome data are retrieved from hospital records by trial location staff and recorded on the SEARCH database eCRFs for analysis by the independent study statistician
- Safety events reported by trial location staff are recorded on the SEARCH database eCRF; SAEs must be reported to the Chief Investigator and Sponsor within 24 hours via a secure email
- Safety events reported by Participants are sent via a secure email to the Southampton Clinical Trials Unit (SCTU) for assessment; SCTU will in turn redact and forward SAEs to the Chief Investigator and Sponsor within 24 hours
- Any SAE that may be causally linked with the investigational SaMD (PLCO-HL) must be captured and reported throughout the entire study period to the Chief Investigator and Sponsor within 24 hours
- Saliva samples are processed at the Manchester Centre for Genomic Medicine and results recorded on an internal, secure University of Manchester database for analysis by the SEARCH investigators
- Outcomes of stakeholder interviews, focus groups and other methods outlined in the process evaluation are recorded on secure, internal databases at The University of Sheffield for independent evaluation
- Outcomes of stakeholder interviews, focus groups and other methods outlined in the health economics sub-study are recorded on secure, internal databases at The University of Manchester for evaluation by the SEARCH investigators
- External NCRAS 1997–2020 cohort data are stored at The University of Oxford
- External pilot data are stored at The Christie NHS Trust
- External NHS LCSP programme data are recorded locally at trial locations and centrally in aggregated format at NHS England

- PLCO-HL investigational medical device data is contained within the quality management documentation and technical file for the PLCO-HL investigational medical device held securely at Digital Health Software and Platforms team at the University of Manchester
- QRisk2 is an exploratory endpoint captured on a separate CRF

The SEARCH database is hosted on the secure, cloud-based iMedidata RAVE platform managed by the Southampton Clinical Trials Unit (SCTU) under a subcontractual agreement. Access is restricted to delegated, trained staff with a research passport for the SEARCH study. Following initial account setup by SCTU, users will receive a study-specific email invitation with role-based permissions, ensuring they only view data relevant to their tasks. Single sign-on functionality provides convenience and security.

Trial location staff will enter data on electronic case report forms (eCRFs) within the SEARCH database including: demographic data (age, sex, ethnicity, socioeconomic indicators); clinical history (HL treatment, smoking history, comorbidities, family history); risk assessment data (variables and scores for PLCO-HL (derived by the PLCO-HL SaMD); PLCOm2012, LLPv2 (derived in the SEARCH RAVE database); CanPredict, LLPv3 (data will be entered but scores will be derived post study by the study statistician); screening participation details (invitation response, LHC and LDCT attendance, saliva sample provision); screening outcomes (LDCT results, lung cancer detection, stage, histology, incidental findings, planned treatment).

To comply with LCSP reporting, management and next-round invitations under the LCSP standard protocol, trial location staff must also record data and outcomes for study participants who are eligible for the LCSP in the usual programme systems (e.g. SPECTRA), following their local LCSP data collection protocols.

4.17 Electronic Patient Reported Outcomes (ePROs)

Participants will be asked to provide feedback through a PRO questionnaire administered at baseline, 3 and 6 months after the LDCT. Participants in Cohorts A, B, C1 and D1 must complete PROs at all timepoints. Participants in Cohorts C2 and D2 are only required to complete the 3- and 6-month PRO questionnaires; this can be done at any time.

PRO questionnaires are available in both paper and electronic formats. The electronic (ePRO) format is available on the LifeGuide web-based platform. Participants will access ePRO via a secure, unique link; they will receive an automated prompt from LifeGuide at the relevant time points notifying them when to complete each ePRO. A LifeGuide/RAVE data reconciliation step will ensure accurate data linkage with the eCRF for each participant.

PRO questionnaires will incorporate a combination of validated instruments and bespoke study-specific items to assess participants' views on lung cancer screening before their LDCT scan, as well as their experience, satisfaction with the screening pathway, and the adequacy of information provided before and after the scan. The questionnaires will also explore participants' willingness to continue in the LCSP programme (if eligible) and will collect longitudinal data on smoking behaviours to evaluate the impact of smoking-cessation advice on motivation to quit.

Anxiety, worry, and quality of life will be measured at baseline and following screening using validated scales. In addition, baseline PRO measures will capture health status and respiratory symptoms using the MRC Dyspnoea Scale and the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT).

4.18 Sub-studies

4.18.1 Health Inequalities Sub-study

The health inequalities sub-study embedded within this study is a dedicated effort to ensure equitable access and participation across diverse and underserved populations. Recognising that HL survivors who are current smokers, older adults, men, individuals from lower socioeconomic backgrounds and those with mental health conditions or learning disabilities face significant barriers to screening, the sub-study is designed to identify and address these challenges through a multi-pronged approach.

To enhance accessibility, from the outset the study will offer LHCs in community-based settings, reducing the need for travel and making participation more convenient. A travel budget will support out-of-area participants, and digital tools, including online surveys, PIS/ICF and a decision aid, and ePRO questionnaires will be used to minimise logistical burdens and promote environmental sustainability.

The sub-study will conduct qualitative focus groups and interviews with HL survivors and stakeholders to explore the success of inclusive strategies and other barriers and facilitators to screening uptake (for example, discussing themes such as digital exclusion and language barriers). These discussions will inform the development of tailored strategies to improve engagement, particularly among marginalised groups, and will be further explored in targeted focus groups based on geography and demographics. Patient and Public Involvement and Engagement (PPIE) will play a central role co-creating the qualitative enquiry.

The sub-study will also monitor participation rates across demographic groups using national datasets such as the Fingertips Public Health Outcomes Framework, the Health Survey for England, and the Cancer Patient Experience Survey. Equality impact assessments will be conducted to identify and address emerging disparities, and innovations to improve equity will be developed in collaboration with Cancer Alliances and Health Innovation partners.

Ultimately, the health inequalities sub-study aims to generate evidence-based recommendations for improving equity in lung cancer screening in high-risk HL survivors.

A separate ethics application and protocol will be developed and approved for the qualitative sub study.

4.18.2 Risk Sub-study

An embedded risk sub-study aims to assess and refine how lung cancer risk is assessed in HL survivors.

The sub-study will compare five risk prediction tools: the PLCOm2012 and LLPv2 models used in LCSP, PLCO-HL, CanPredict and LLPv3. Each model will be assessed for its ability to accurately identify individuals at high-risk of developing lung cancer, using metrics such as sensitivity, specificity, and area under the curve (AUC). The concordance between predicted risk and actual diagnoses will be a key measure of effectiveness.

To further improve predictive accuracy, the sub-study will explore the impact of adding clinical and genetic variables to these models. Additional risk variables will be collected from participants undergoing a LHC including variables from other risk prediction tools not included in the PLCO-HL model such as gender, asbestos exposure, socioeconomic status, comorbidity and alcohol consumption (summarised in Table 1) and risk factors relevant for people with HL such as age at HL diagnosis, and treatment received; specifically, alkylating agent chemotherapy, radiotherapy to the chest area, previous transplant for HL. Participants will provide optional saliva samples for genotyping of single nucleotide polymorphisms (SNPs), or common genetic variations, identified through genome-wide association studies (GWAS) for their links to lung cancer risk. A polygenic risk score (PRS) combines the effects of the SNPs to provide an individual-specific measure of an individual's genetic predisposition to developing lung cancer.

The sub-study will also track lung cancer detection rates among participants classified as high-risk by each model, including those who undergo screening and those who decline (if feasible), and those with an interval diagnosis of lung cancer. Results will identify the most effective risk prediction tools and evaluate the value (if any) genetic and clinical

enhancements, providing a blueprint for integrating precision risk assessment into future cancer screening programmes.

4.19 End of study

Recruitment for this study will run from May 2026 to May 2027. The end of the SEARCH study is defined as the point at which all participants have completed study-specific follow-up and all required data have been collected, verified, analysed and reported, culminating in submission of the final study report. The end of trial is not the last participant visit as additional time is required to collect outcome data from routine NHS records, data cleaning, analysis and reporting. No further participant visits occur during this period.

5. OUTCOME MEASURES

- **Early diagnosis impact**
  - Early-stage lung cancer detection rate in high-risk HL survivors meeting PLCO-HL criteria (primary outcome measure)

- **Screening outcomes** in all high-risk participants
  - Lung cancer detection rate
  - Stage distribution
  - Histological subtypes
  - Curative treatment rates
  - False positive rate
  - False negative rate
  - Incidental findings
  - Smoking cessation rate
  - Comparison with LCSP and non-screened HL benchmarks

- **Performance of lung cancer risk prediction models**
  - Predictive accuracy (sensitivity, specificity, AUC) of the PLCOm2012, PLCO-HL, LLPv2 models.
  - Exploratory: added value of clinical and/or genetic variables for improving risk prediction of the PLCO-HL model.
  - Exploratory: performance of the CanPredict risk model in the HL cohort.
  - Exploratory: performance of the LLPv3 risk model in the HL cohort.
  - Exploratory, if feasible: added value of clinical and genetic variables for improving risk prediction of models.

- **Participation and acceptability across the screening pathway**

- Participation rates at each stage of the pathway (Invitation, LHC, LDCT, saliva sampling, PROs, smoking cessation intervention).
- Comparison with pilot and LCSP benchmarks.
- Reasons for ineligibility and dropout.
- Participant views and experience.

- **Health inequalities in access and engagement**
  - Demographic and socioeconomic patterns in identification, invitation, and participation.
  - Effectiveness of new engagement strategies in reaching underserved groups.

- **Implementation and operational feasibility across diverse NHS settings**
  - The ability of Cancer Alliances to deliver the intervention.
  - Barriers, facilitators, and adaptations required for local delivery.
  - Staff and stakeholder feedback on acceptability
  - Scalability and sustainability.

- **Health economic evaluation**
  - Incremental Cost-Effectiveness Ratio (ICER)
  - Net Benefit (monetary value of health gains minus costs)
  - Return on Investment (ROI) ratio (if applicable)
  - Estimated cost per early-stage cancer detected and QALYs gained.
  - Cost-effectiveness and budget impact of national rollout.

- **Environmental (net zero) impact of the intervention**
  - Carbon emissions per patient screened.
  - Estimated emissions avoided through early diagnosis and reduced treatment burden.

6. DATA GOVERNANCE

Data will be managed in accordance with MHRA Good Clinical Practice and ICH E6(R3) principles of data integrity, ensuring all data are attributable, legible, contemporaneous, original and accurate, with audit trails maintained within RAVE and LifeGuide. Risk-proportionate controls will be applied to prevent transcription errors, ensure completeness and support reliable analysis.

The University of Manchester (UoM) is the data controller for the study and is responsible for overall data governance.

The Southampton Clinical Trials Unit (SCTU), acting as data processor under a formal agreement, has developed the SEARCH database and eCRFs on the iMedidata RAVE platform for electronic data capture. Electronic patient reported outcome (ePRO) measures will be captured using LifeGuide, also developed by SCTU. SCTU will receive study data, conduct automated and manual checks, and manage central monitoring. Missing or inconsistent data will be queried with trial location staff, with a dedicated data manager overseeing resolution before data lock and analysis.

SCTU manages user access to the SEARCH eCRF. Trial locations have secure access to participants' medical records, and only authorised, trained staff may enter or amend data in the SEARCH database in line with data protection requirements. Completion guidelines will support consistent entry, and trial location staff are responsible for ensuring accuracy, completeness, and timely updates. Delegated staff remain bound by professional confidentiality obligations.

To protect confidentiality, participant data is pseudonymised using a unique study identifier. This code is used for all communications between SCTU and trial locations. Limited identifiable information (NHS number, first name, surname, telephone number, email, postcode, GP code, name of GP practice) is stored in the SEARCH database for essential study purposes, including communication with participants, linkage with local LCSP systems, and collection of health inequality data. This occurs only with informed patient consent and in accordance with data-minimisation principles. Identifiable data is accessible only to local CSP and clinical care teams, and not to the Sponsor or non-delegated personnel and will be retained only as long as necessary.

Trial locations must maintain a secure, locally held code list accessible only to authorised staff. Identifiable data stored locally may be held for up to 25 years to support future ethically approved analyses before being deleted.

Pseudonymised data may be reviewed by the Sponsor, regulatory authorities, or trial locations for monitoring and audit. Data analysis will be undertaken within the UK by authorised researchers at the Universities of Manchester, Sheffield, York, Oxford and Queen Mary University of London. Fully anonymised datasets may be shared with other researchers under conditions approved by the Study Management Group.

The SEARCH database will remain active throughout the study, and SCTU will archive pseudonymised study data for 25 years in line with University of Southampton policies.

Access to archived data will be controlled by a designated SCTU representative, and all processing will comply with applicable Data Protection legislation.

UoM will digitally archive all study documentation including the Trial Management Folder with Research Data Storage for a period of 25 years.

7. STATISTICAL CONSIDERATIONS

7.1 Sample Size

The sample size for this study was determined based on the need to conduct a real-world evaluation across multiple NHS Cancer Alliances, each delivering LHCs in varied operational contexts. Rather than being powered to detect statistically significant differences in disease progression or mortality, the sample size was chosen to ensure sufficient precision in estimating key screening outcomes.

The study aims to screen 500 high-risk Hodgkin Lymphoma survivors across up to 10 NHS Cancer Alliances. This number is based primarily on the need to assess feasibility across a range of settings and the numbers of participants likely to be recruited from each participating Cancer Alliance. Using a target number of participants of 500 and the outcome rates observed in the pilot study, we can estimate the precision with which key screening outcomes will be estimated in the study. The study does not include a prospective comparison group, and comparisons are only possible with historical controls, epidemiological data or general outcomes in the LCSP. Furthermore, length of follow-up in the study period is limited. Hence, the sample size calculation is not based on power to detect statistically significant differences in disease progression or mortality between groups.

Based on prior pilot data, the study could conservatively expect to detect at least 14 cases of lung cancer in 500 participants, corresponding to a detection rate of 2.8% and a 95% exact binomial confidence interval of 1.5% to 4.7%. Similarly, the expected false positive rate is 2.0% (95% CI: 1.0% to 3.6%).

Population-level data from the NCRAS 1997-2020 dataset was used to support these estimates, including an annual lung cancer incidence rate of 0.5% in the target population and an expected 75% early-stage detection rate, consistent with LCSP benchmarks.

7.2 Screening Outcomes (Impact evaluation)

Screening outcomes will be assessed through a combination of quantitative metrics and outcome-focused evaluations. The primary objective is to assess the proportion of high-risk HL survivors identified by the PLCO-HL risk model who undergo LDCT screening and are diagnosed with early-stage (stage I or II) lung cancer.

Key components:

- **Lung Cancer Detection Rates**: The evaluation will measure the proportion of screened participants diagnosed with lung cancer at various stages:
    - Baseline LDCT
    - Surveillance LDCT(s)
    - Through interval diagnoses in symptomatic individuals

- **Stage Distribution:** A critical metric will be the proportion of lung cancers detected at an early stage, with a target of identifying early-stage disease in at least 75% of cases.
- **Histological Subtypes**: A breakdown of histological subtypes for screen-detected lung cancers.
- **Treatment Outcomes**: The proportion of patients receiving curative treatment will be tracked, alongside histological subtypes of lung cancers diagnosed.
- **Incidental Findings**: The study will also record other significant health conditions identified during screening, such as cardiovascular disease or other cancers.
- **Diagnostic Accuracy**: False positive and false negative rates will be calculated based on follow-up data, providing insight into the reliability of the screening process.
- **Comparative Analyses**: Outcomes will be benchmarked against national screening LCSP programme data for the general population. The 1997-2020 NCRAS HL cohort used for risk modelling in this study will serve as a non-screened control for lung cancer outcomes in HL survivors. The dataset includes information on gender, age at HL diagnosis, age at lung cancer diagnosis, lung cancer stage, survival after lung cancer diagnosis. Comparator data for non-screened individuals will also be sourced from the epidemiology literature.
- **Behavioural Impact:** Smoking status at baseline and at three-month and twelve-month follow-up will be evaluated, along with uptake, type and completion of smoking cessation interventions.

7.2.1 Statistical Analysis

The analysis will primarily consist of descriptive statistics and simple comparative metrics, rather than complex statistical modelling. Key screening outcomes such as lung cancer detection rate, stage at diagnosis, false positive rate, and treatment outcomes will be calculated using proportions and confidence intervals (e.g. exact binomial 95% CI).

Comparative analysis will benchmark SEARCH outcomes against national LCSP data and published literature.

Predictive performance of risk models (PLCO-HL, PLCOm2012, LLPv2) will be evaluated using sensitivity, specificity, Area Under the Curve (AUC), calibration plots comparing predicted vs. observed outcomes. Where feasible, concordance between predicted risk and actual lung cancer diagnoses will be assessed, acknowledging limitations due to short follow-up and small event numbers.

Comparisons across risk models and subgroups will be interpreted cautiously, with reporting of estimates and confidence intervals preferred to formal testing of differences. There is no anticipated need to formally adjust for multiple comparisons, due to testing not being the focus of the analysis and many comparisons being exploratory in nature. However, findings will be contextualised to avoid overinterpretation. Furthermore, subgroup analyses (e.g. by age, gender, socioeconomic status) will be reported descriptively, again with a preference for estimates and confidence intervals rather than inferential testing.

7.3 Process Evaluation

An independent process evaluation conduced at The University of Sheffield Centre for Health and Related Research (SCHARR) will examine how the programme is implemented across a range of complex settings, who it reaches, and how it performs in real-world conditions. A separate process evaluation protocol will be developed and submitted for HRA/REC approval.

In brief, the process evaluation will adopt a mixed-methods approach, grounded in established frameworks including the Medical Research Council (MRC) guidance for evaluating complex interventions. It will apply a Realist methodology to explore not only what works, but also how, for whom, and under what circumstances.

The evaluation will be theory-led, aiming to test and refine the assumptions underpinning the intervention. It will integrate principles from Utilisation-Focused and Developmental Evaluation, ensuring that findings are both relevant and actionable for stakeholders and decision-makers.

Quantitative methods will provide a broad overview of implementation patterns, while qualitative approaches, such as stakeholder interviews and case studies, will offer deeper insights into contextual factors, barriers, and facilitators. This dual approach enables the evaluation to explore:

- Patterns of successful implementation across diverse settings.

- Mechanisms of engagement, particularly in reaching high-risk populations equitably.
- Contextual influences on adoption, scalability, and sustainability.
- Local adaptations and service delivery models, including how Cancer Alliances manage additional activity and resource demands.

Key Components:

- **Identifying and Engaging the Target Population:** The evaluation will use data from the National Cancer Registration and Analysis Service (NCRAS) to compare expected versus actual identification rates. Demographic data and pathway-specific information (e.g. primary care vs. direct referral) will help assess who was reached and how. Participation rates in LHCs and LDCTs, along with completion rates for risk questionnaires and optional genetic profiling, will provide further insight into engagement levels.
- **Implementation and Feasibility:** Implementation will be assessed through both quantitative metrics and qualitative insights. Stakeholder interviews and focus groups will identify barriers and facilitators to delivery. Service delivery models, staff feedback, training records, and process improvement logs will offer a practical view of how the programme functions across different settings.
- **Scalability and Sustainability:** The evaluation will consider how many trial locations successfully implemented the intervention, the associated costs, and staff capacity. Longitudinal trends in uptake and stakeholder perspectives on sustainability, along with alignment with existing policies, will inform whether the programme can be scaled and maintained over time.

7.4 Health Economic Evaluation

An independent health economic evaluation will be conducted by the University of York to assess the long-term costs and health outcomes of lung cancer screening in high-risk HL survivors compared to current practice (no screening).

An evaluation framework will be applied to infer disease progression, determine expected impacts of screening on reducing late stage-detection, and evaluate cost-effectiveness from such reduction. The evaluation framework will combine different inferential and modelling activities, as follows:

- Step 1, main data analysis: a mathematical (inferential) analysis of the screening and control data (part of this project) will examine the natural history of disease and sensitivity of the screening strategy[34].

- Step 2, cohort modelling: the natural history model inferred in step 1 will be used predictively to determine predicted stage-shifts from a continued screening programme
- Step 3, cost-effectiveness modelling: the cohort model in step 2 will be extended to examine the long-term mortality and morbidity impacts of the predicted stage shifts

The evaluation framework is designed to compare lung cancer screening in high-risk HL survivors with current clinical practice (no screening). It will simulate long-term outcomes and cost-effectiveness in a population with elevated risk and unique clinical characteristics. A lifetime horizon is proposed to capture long-term costs and benefits of early detection and treatment. The approach used is flexible to accommodate data limitations and enables scenario analysis.

Main data sources are the primary data from the SEARCH study (smoking rates, screening uptake, detection rates, stage at diagnosis, true/false positives and negatives) and data from the NCRAS 1997-2020 dataset which will serve as control (detection rates, stage at diagnosis). Recognising that the numbers of cancers detected may be relatively small to obtain precise inference in Step 1, the modelling will likely use supplementary evidence from the literature to strengthen its inferences (for example, to identify reasonable constraints to the range of values of model parameters, or to be used as informative priors). Relevant evidence will be drawn from existing lung cancer screening models with a natural history component, like the ENaBL (Early Notification and Benefit from Lung screening) model used to support the LCSP (https://view-health-screening-recommendations.service.gov.uk/lung-cancer/) and national datasets (LCSP benchmarks).

The cost-effectiveness model will also draw on the NCRAS 1997-2020 dataset for short term mortality by stage at diagnosis. Wider evidence from the literature will also be used to derive longer term survival rates, quality of life metrics, healthcare resource use. A pragmatic literature review will seek to identify relevant evidence from published cost-effectiveness studies of lung cancer screening, epidemiological or burden of disease studies on HL survivors. Where evidence for this specific population cannot be identified, evidence on a general lung cancer population will be used to inform the modelling.

Assumptions and limitations

- Target population: HL survivors aged 45-74 who are ever smokers and meet the PLCO-HL or PLCOm2012/LLPv2 high-risk threshold.
- Counterfactual: No screening (current standard practice).
- Limitations:

- Potential small number of lung cancer events during the study period.
- Limited long-term outcome data specific to HL survivors.
- Use of proxy data for survival and QALY estimates.

Costs and Benefits to Be Included

Costs

- Screening delivery (LHC, LDCT)
- Follow-up investigations
- Treatment costs (curative and palliative)
- Programme implementation and staff time
- Infrastructure and IT systems
- Smoking cessation interventions

Benefits

- Life years (LY) gained
- Quality-adjusted life years (QALYs)
- Reduction in advanced-stage disease
- Reduction in lung cancer-related mortality
- Avoided treatment costs due to early diagnosis

Metrics for Benefit/Cost Calculations

- Incremental Cost-Effectiveness Ratio (ICER)
- Net Benefit (monetary value of health gains minus costs)
- Return on Investment (ROI) ratio (if applicable)
- Cost per early-stage cancer detected
- QALYs gained

Scenario and Sensitivity Analysis

- Probabilistic sensitivity analysis to account for uncertainty in model parameters.
- Scenario analysis to test different assumptions (e.g. uptake rates, cost inputs, survival estimates).
- Exploratory analyses examining other screening intervals (by modifying the step 2 model), the value of targeted screening (using subgroup analysis if data allow e.g. by age group, smoking status, socioeconomic status), and cost-effectiveness under lower PLCO-HL thresholds

Format of Outputs

- ICER values (e.g. £ per QALY gained)
- ROI ratio (if applicable)
- Budget impact estimates
- Graphical outputs (e.g. cost-effectiveness acceptability curves)

8. MONITORING AND QUALITY ASSURANCE

8.1 Study monitoring

A principal investigator (PI) at each participating Cancer Alliance will be responsible for overall planning, execution, and management of the study. This includes ensuring scientific and technical integrity, ethical conduct, and adherence to all relevant regulations and guidelines. The PI also manages the research team, oversees the budget, and reports on the progress and outcomes of the research. The PI may be the Clinical Programme Director, Responsible Clinician, Responsible Radiologist, Responsible Assessor or another suitably qualified and trained individual with an assigned clinical role in the LCSP.

Study oversight will be provided by the Study Management Group (SMG) comprising clinical experts in oncology, respiratory medicine, radiology, and genomics, independent evaluators, a patient representative, a representative from NHS England and a representative from the lead Cancer Alliance. The SMG will meet quarterly. This committee provides ongoing oversight and ensures that the study adheres to the highest standards of scientific and ethical conduct. The University of Manchester acts as sponsor and also provides oversight of the study.

Study progress will be monitored by the funder, including narrative progress reports, quarterly finance expenditure, a risk register and project metrics. An independent evaluation interim report will be submitted to SBRI after 240 participants have been screened.

8.2 Quality Management System

To uphold the highest standards of scientific and regulatory integrity, a dedicated Quality Management System (QMS) will be established to oversee the development and

implementation of the PLCO-HL risk prediction tool. A Technical File will be maintained to document adherence to QMS protocols. Together, the QMS and Technical File will provide the necessary evidence to support device classification, facilitate regulatory approval, and enable future market access.

This QMS will be aligned with the quality assurance standards set out for the Lung Cancer Screening Programme, available at: Quality assurance standards prepared for the Lung Cancer Screening Programme

The QMS will incorporate the rigorous standards outlined by the MHRA to ensure the integrity and reliability of electronic systems used in clinical investigations. Systems will be validated to confirm authenticity, accuracy, and consistent performance throughout their lifecycle. Procedures will cover system validation, functionality testing, data handling, maintenance, security, change control, backup and recovery, and contingency planning. Data will be attributable, complete, reliable, and logically consistent, with accurate reporting and robust audit trails. Security protocols will prevent unauthorised access, and access logs will be maintained. Authorised personnel will sign off on reported data, and users will be trained to safeguard blinding during data entry and processing. The QMS will also support the integration of software tools for participant identification and tracking, ensuring consistency and traceability across study trial locations. It will include procedures for protocol management, version control of study documentation, and oversight of participant-facing materials such as consent forms, questionnaires, and decision aids. In alignment with the NHS Net Zero agenda, the QMS will also promote environmentally sustainable practices, including the use of digital tools, virtual assessments, and community-based screening to reduce travel and resource consumption.

Training documentation and compliance tracking

All personnel involved in the study will be required to complete training as appropriate to their role. This includes but is not limited to:

- Good Clinical Practice (GCP) Certification
- Study-specific protocol training
- Electronic Case Report Form (eCRF) system training
- Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) training for those involved in LDCT consent
- Smoking cessation advice training
- Data protection and confidentiality training

Training records will be centrally maintained by the Sponsor or designated coordinating centre and stored securely in a dedicated training log. Each participating trial location will be responsible for submitting completed training records prior to trial location activation.

Compliance will be monitored through periodic audits and cross-checked against role-based access permissions within the eCRF system. Any gaps in training will be flagged and addressed promptly to ensure ongoing adherence to protocol and regulatory standards.

These standards will be embedded throughout the QMS, guiding all phases of the study, from initial setup through delivery and evaluation, and ensuring full compliance with NHS research governance frameworks and national regulatory requirements.

Operational oversight will be coordinated across trial locations, with mechanisms for staff training, performance monitoring, and delivery metrics. Continuous quality improvement will be supported through feedback loops involving patients, clinicians, and public involvement representatives.

9. SAFETY CONSIDERATIONS AND ADVERSE EVENTS

Safety evaluation within the SEARCH study follows a pragmatic and proportionate framework. Serious safety concerns within the study may relate either to participants or to staff delivering study procedures. The study adheres to established NHS and organisational processes for incident reporting, with additional study-specific mechanisms for monitoring equipment, data systems, and protocol compliance.

The Sponsor must be informed promptly of any event that may compromise participant safety, staff safety, data integrity, or the safe and compliant conduct of the study. Some events are managed fully by the study team, while others fall under local trial location responsibility with reporting onward to the Sponsor and Chief Investigator for oversight.

In accordance with MEDDEV 2.12-1 and ISO 14155-aligned vigilance requirements, any Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE), Unanticipated SADE (USADE), or Device Deficiency that may be linked to the investigational SaMD (PLCO-HL) must be captured, evaluated, and reported throughout the entire study period, regardless of timing or whether LDCT has occurred.

This includes any event for which a causal relationship with the device cannot be excluded.

Serious Harm or Risk of Harm to Participants

LDCT scanning is an established procedure, and all existing risk-management and safety protocols for scans will be followed. The additional study procedures do not pose a risk of physical harm. Accordingly, adverse event (AE) surveillance, evaluation, and reporting will be restricted to Serious Adverse Events (SAEs) that meet the regulatory criteria for seriousness (defined below) and that occur either during the pre-scan appointment or as

a result of, and on the same day as, LDCT scanning. These events must be reported to the Chief Investigator and Sponsor within 24 hours.

In addition, per MEDDEV requirements, any SAE occurring at any point in the study that may reasonably be associated with incorrect, delayed, or misleading device output (e.g. risk-score miscalculation, device malfunction, or usability error) must also be captured and reported as a SADE or USADE as appropriate, even if occurring outside the LDCT appointment window.

Any untoward clinical events occurring later in the patient pathway, for example, complications arising from subsequent diagnostic investigations if a lung nodule is detected, will not be considered AEs or SAEs for the purposes of this study and will be managed according to routine local practice in the treating centre. However, if such an event is judged by the investigator to be related to the investigational device (e.g. incorrect risk assessment contributing to delayed referral), it must be recorded and reported as a SADE or USADE.

- **Adverse Event (AE):** Any untoward medical occurrence in a participant who has undergone a research procedure, whether or not it is causally related to that procedure.
- **Serious Adverse Event (SAE):** An adverse event that:
  - results in death
  - is life-threatening*
  - requires in-patient hospitalisation or prolongation of existing hospitalisation**
  - results in persistent or significant disability/incapacity
  - consists of a congenital anomaly or birth defect or
  - is another medically important event* requiring intervention to prevent one of the above outcomes.
- **Serious Adverse Device Effect (SADE):**
  - A serious adverse event that is related to the investigational device.
- **Unanticipated SADE:**
  - A SADE not previously identified in nature, severity, or incidence.
- **Device Deficiency:**
  - Any inadequacy of the medical device, including malfunction, software error, output anomaly, usability issue, or labelling problem, whether or not it led to an SAE.

* “Life-threatening” refers to an event in which the participant was at immediate risk of death at the time it occurred; it does not include events that might hypothetically have become life-threatening.

** Hospitalisation refers to any inpatient admission, regardless of duration, including precautionary observation. Admissions for pre-existing conditions or elective procedures that have not worsened are not SAEs.

*** Other medically important events may be considered SAEs when, in the judgment of the investigator, they jeopardise the participant and may require medical or surgical intervention to prevent one of the serious outcomes listed above.

Harm or Risk of Harm to Staff

Any incident resulting in harm or risk of harm to study staff is the responsibility of the local Site to manage through established processes (e.g. Datix, Occupational Health). Trial locations must nevertheless notify the Sponsor and Chief Investigator so that study-level oversight is maintained.

Concerns About Staff Competence

Concerns regarding the competency or training of staff involved in delivering the study, where these concerns meet the definition of a safety incident, must be reported. Trial locations retain responsibility for initial management, but the Sponsor and Chief Investigator must be informed so that appropriate oversight and risk mitigation can be implemented.

Failure or Misuse of Equipment

Any failure, misuse, or concerns regarding the operation of study equipment, particularly the study medical device, must be reported. The SEARCH database includes an automated edit-check that triggers when implausible device values are entered. These triggers are logged in the system audit trail along with the user responsible. A weekly central review of audit-trail queries will identify repeated issues, which may indicate equipment misuse or staff training needs.

All device failures, malfunctions, anomalies in device output, or suspected software errors must be documented as Device Deficiencies and assessed for the potential to cause harm. Device Deficiencies that could have resulted in a SADE must be reported to the Sponsor and the MHRA in accordance with MEDDEV timelines.

Confirmed incidents must be notified to the Sponsor and Chief Investigator, and any external reporting (e.g. MHRA) followed per local policy.

ICT System Failures

Failures or malfunctions affecting essential ICT systems, such as Lifeguide, the SEARCH database or the PLCO-HL investigational medical device, are logged in the CTU's central

system issues log and reviewed routinely. Issues specific to the medical device software will be logged by the University of Manchester team. Any system failure that could affect participant safety, scheduling, consent, data integrity, or study delivery must be escalated promptly to the Sponsor and Chief Investigator.

Where ICT failures involve the investigational device or could influence device outputs, these must be recorded and evaluated as Device Deficiencies under MEDDEV requirements.

Breaches of Confidentiality or Data Security

All parties (trial locations, CTU, and University teams) are responsible for safeguarding participant data and reporting breaches of confidentiality. Staff follow institutional SOPs, are trained in information governance, data security, and GCP, and operate under NHS Data Security and Protection Toolkit (DSPT)-aligned policies. Any suspected or confirmed data breach must be reported immediately to the Sponsor and Chief Investigator, while simultaneously following local IG escalation procedures.

Protocol Deviations and Systemic Non-Compliance

- **Identifying and Logging Deviations**: Deviations from the SEARCH protocol, including systemic failures to comply with required procedures, must be recorded. Trial locations will maintain a deviation log, while a central deviation log will be maintained by the trial management team.
- **CAPA Triggers**: A corrective and preventive action (CAPA) process will be initiated when three or more deviations have been logged from a single trial location. Deviation reports generated from the database may also be downloaded by the CTU and shared with the study team to ensure accurate central logging. Alternatively, a shared log (e.g. via SharePoint) may be used for real-time collaborative management.
- Any deviation involving device handling, device output, data entry of device results, or device-related workflow must be assessed for classification as a Device Deficiency and reported accordingly.

Reporting Procedures and Timelines

- **SAEs involving participants**
  - All SAEs reported to study personnel or self-reported by participants must be reported to the Chief Investigator within 24 hours of becoming aware of the event.
  - Study personnel at trial locations must complete the Adverse Event eCRF and send a copy to the following secure email address: SearchTrial@securemail.soton.ac.uk. Access to this mailbox is restricted to the

SCTU SEARCH data team. Any SAE notifications received will be redacted and then forwarded securely to the SEARCH team.

- Participants self-reporting SAEs will be asked to send an email to the same secure email address: SearchTrial@securemail.soton.ac.uk. The participant information sheet provides guidance for participants on what to report and how to do this. Any SAE notifications received will be redacted and then forwarded securely to the SEARCH team.
- All SAEs will undergo review by the SEARCH team, including completion of the SAE form for self- reported SAEs, and clinical causality assessment reporting to the Sponsor and Chief Investigator within 24 hours of receipt.
- Events considered related to research procedures and unexpected: the Chief Investigator should report any SAE that is both related to the research procedures and is unexpected to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event. The CI will use the Health Research Authority (HRA) Non-CTIMP Safety Report form for this submission.
- In addition, all SADEs, USADEs, and Device Deficiencies that could have resulted in a SADE must be reported by the Sponsor to the MHRA Competent Authority within the MEDDEV-specified timelines (typically 2–7 days depending on severity and risk classification).
- Any SAE for which a causal link with the investigational device cannot be excluded must be treated as a SADE until proven otherwise.

- **Staff harm, competence concerns, equipment failures, ICT faults, confidentiality breaches, and systemic protocol failures**
  - Immediate notification to the Chief Investigator and Sponsor if safety-critical. Otherwise included in incident documentation within 5 working days.

- **Internal system logging (audit trails, system issue logs, deviation logs):**
  - Reviewed routinely and escalated as needed.
  - Any audit-trail flag indicating incorrect device output, unexpected behaviour, or user error during device interaction must be assessed for classification as a Device Deficiency.

10. PEER REVIEW

The study was informed by the results of a LDCT screening pilot study and a programme of quantitative and qualitative research by the study investigators which included the decision aid developed and reviewed by a steering group of HL survivors, clinicians and

other experts and tested in the pilot screening study. Feedback from the steering group informed the decision aid content.

The study was co-designed with national and regional stakeholders, including national clinical and radiology leads for the LCSP, The Greater Manchester Cancer Alliance (lead trial location), Health Innovation Manchester, independent evaluation partners and advisors from the UK Hodgkin Lymphoma Study Group, the Oncology Translational Research Collaboration, and Lymphoma Action as well as patient advocates from the EMERGE and VOCAL study groups. A patient and public involvement (PPIE) focus group provided input to co-design and review project methods and the study protocol. These partnerships contributed to the design, feasibility assessment, and planned implementation of the study, ensuring alignment with NHS priorities and infrastructure.

The scientific quality of the study was externally peer reviewed by the funder, Small Business Research Initiative (SBRI) Healthcare, which is directly funded and managed by NHS England.

11. ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 and the ICH-GCP E6(R3) guideline as implemented by the MHRA (effective 28 April 2026), as well as relevant legal requirements, the principles of the Declaration of Helsinki, and the UK Policy Framework for Health and Social Care Research (2017).

Approval will be sought from the National Research Ethics Committee (REC) and Health Research Authority (HRA) as well as the Research and Development Departments of all lead Trusts for participating Cancer Alliances before commencing this research. The study involves the use of ionising radiation and will comply with Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) 2017.

Any substantial amendments to the protocol will be reviewed and approved by the Chief Investigator and Sponsor and submitted in writing to the REC, the Health Research Authority and local R&D for approval prior to enrolment into an amended protocol. The Chief investigator will notify the REC when the study ends and take responsibility for submitting the Annual Progress Reports and Clinical Study Report (final report) within the required timeframes.

Deviations from the protocol may be taken by an investigator without prior approval from the Sponsor or regulatory bodies in order to eliminate an immediate hazard to a

participant. The rationale must be submitted to the Sponsor and the appropriate regulatory bodies as soon as possible after the deviation.

Any other study protocol deviation/violations and breaches of Good Clinical Practice (GCP) will be reported to the local R&D/Sponsor office immediately. The Sponsor will then advise of and/or undertake any corrective and preventative actions as required.

Should a protocol or GCP deviation be deemed by the Chief Investigator or Sponsor to meet the criteria for constituting a Serious Breach, this will immediately be reported to the REC (within 7 days of the Sponsor being made aware) and any other organisation as required.

12. RISK ASSESSMENT

This study has been designed following ICH-GCP E6(R3) Quality-by-Design principles, focusing on risks that could meaningfully affect participant safety, rights, wellbeing or the reliability of critical study data. Critical-to-quality factors (CTQs) include: accurate identification of eligible Hodgkin lymphoma survivors, correct application of the PLCO-HL risk model, informed consent, accurate LDCT referral and reporting within LCSP governance standards, and integrity of key outcome data.

Participant-related risks are low, as the study introduces no investigational treatment and uses established NHS Lung Health Check and LCSP processes. The main clinical risks relate to LDCT (radiation exposure, incidental findings, false positives/negatives), all of which are mitigated through adherence to LCSP protocols, IR(ME)R oversight, and management within routine NHS care. The restricted SAE definition (limited to events occurring during or on the day of the LDCT or pre-scan appointment) ensures proportionate reporting and avoids conflating clinical care events with study-related risks.

Operational risks include misclassification of eligibility or risk status, incorrect PLCO-HL score entry, delays in LDCT scheduling, incomplete follow-up data, and variable adoption of the adapted pathway across Cancer Alliances. These risks are minimised through automated score generation within RAVE, cross-checking of device and database scores, standardised LHC procedures, LCSP-trained radiology teams, central monitoring of completeness and timeliness of key fields, and defined escalation pathways for deviations.

Data-related risks include breaches of confidentiality, transcription errors and incomplete endpoint capture. These are mitigated through use of secure validated systems (RAVE, LifeGuide), pseudonymisation, role-based access, audit trails, predefined data-quality

checks and compliance with GDPR and institutional policies. Residual risks are considered acceptable.

Risks to Participants

Risk Category	Description
Radiation Exposure	LDCT scans involve low-dose radiation, which carries a small risk of inducing cancer.
Minor discomfort during LDCT scan	This is uncommon and may be related to incorrect positioning or scan duration.
False Positives and overdiagnosis	Indeterminate findings may lead to unnecessary follow-up scans, biopsies, anxiety or treatment for findings that would not have cause harm.
False negatives and underdiagnosis	Failure to screen a missed high-risk individual may lead to false reassurance and interval cancer diagnoses.
Incidental Findings	Detection of unrelated abnormalities may lead to further investigations and anxiety.
Physical Harm or complications from follow-up procedures	Additional invasive procedures may cause complications like bleeding, infection or pneumothorax.
Psychological Impact	Anxiety and distress from screening invitation, results, or awareness of cancer risk, cumulative radiation exposure and cancer risk.
Loss of Mental Capacity	Participants may lose capacity during the study, affecting consent validity.

Risks to Trial location Staff and Researchers

Risk Category	Description
Data management error	Risk or GDPR or privacy breach
Data Protection and Confidentiality	Risk of breaches in handling sensitive participant data.
Protocol Deviations	Risk of non-compliance with ethical or procedural standards.
Emotional Burden	Managing distressed participants may impact staff wellbeing.
Operational Stress	High workload may impact wellbeing
System failures causing burden	IT failures may delay work

Mitigation Strategies

Strategy Category	Mitigation Measures

Radiation Standard Operating Procedures	Use of LDCT with dose <2–3 mSv; medical physics oversight, operating within national framework, IR(ME)R approval in place.
Standardised management of findings, referral and follow-up procedures	Adherence to validated SOPs for volumetric analysis, MDT review of findings, LCSP referral and incidental findings pathways. Any additional tests (e.g. biopsies) are only performed when clinically indicated
Strict Participant Eligibility Criteria	Standardised Data Extraction Definition Document using SNOMED codes to identify participants, clear eligibility criteria with no waivers to ensure that only participants who meet defined inclusion/exclusion criteria are enrolled, reducing unnecessary exposure.
Informed Consent	Multi-stage verbal and written consent process; decision aids; clear communication of risks and benefits before agreeing to take part, participant education.
Participant Autonomy	Right to withdraw at any time without affecting their standard care, support for informed decision-making; opt-in options.
Psychological Support	Participants are provided with information and support to address anxiety or distress, including access to trained LCSP staff, tailored support and signposting to resources such as Lymphoma Action.
Staff experience, training and study oversight	All procedures are carried out by GDPR accredited staff trained on the protocol, adhering to the SEARCH and LCSP standard protocols, with full study oversight by trial location principal investigators, the study Chief Investigator and the Sponsor.
Clinical Governance	Defined roles for LCSP personnel and researchers; QA audits, findings managed according to NHS Lung Cancer Screening Programme standards, with multidisciplinary team (MDT) review for abnormal results.
Data Protection	Participant confidentiality is maintained through secure data handling and storage, anonymisation of data; restricted access to trained and delegated staff only; no sharing of personally identifiable data beyond the trial location staff, except where explicit consent is in place, compliance with GDPR and NHS standards.

Communication Protocols	Structured letters to participants and GPs and calls for results per the LCSP; escalation pathways for serious findings.
Incident Reporting	Defined SAE criteria; reporting to Chief Investigator and Sponsor within 24 hours; REC notification for serious breaches.

13. STATEMENT OF INDEMNITY

The Sponsor, The University of Manchester, takes full responsibility for insurance and indemnity.

14. FUNDING AND RESOURCES

The study is funded by a grant from the Small Business Research Initiative under the NHS Cancer Programme Innovation Open Call 3 (Reference: NCPC03015). The grant was awarded to the University of Manchester, commencing 02 June 2025. Additional funding to support the research was provided by the NIHR Manchester Biomedical Research Centre (NIHR203308).

Funding covers all projects costs, including staff resources at the universities of Manchester, Sheffield, York, Queen Mary University London, and Health Innovation Manchester. There is funding to support the Greater Manchester Cancer Alliance as lead trial location to roll out the project nationally, as well as funding for each individual Cancer Alliance to update software and invite and scan participants. Saliva sample research and analysis is fully funded.

15. PUBLICATION POLICY

The results of the study will be published in peer review journals and presented at relevant scientific conferences. Results will also be disseminated through patient organisations and charities to inform the wider community. Study investigators and funders will be acknowledged on all presentations and publications arising from this study.

Data will be analysed and published as soon as possible.

Individual investigators may not publish data concerning outcomes directly relevant to questions posed by the study until the Study Management Group has published its report. The SMG will form the basis of the Writing Committee and advise on the nature of

publications. All publications shall include a list of investigators, and named authors including the Chief Investigator, Co-Investigators, Project Manager, and Independent Evaluators involved in the study. Other individuals who have made contributions to the study design or made significant contributions to the manuscript will also be eligible for authorship on any resulting manuscripts. Named authors will be agreed by the CI and SMG.

The Chief Investigator will inform the Sponsor of any resulting publications.

Anonymous data will be available for request from three months after publication of an article, to researchers who provide a data sharing request to the SMG that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

16. REFERENCES

1. Cancer Research UK. Hodgkin lymphoma statistics. (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma).
2. Kwan A, Chadwick N, Hancock B. Improving Survival of Patients With Hodgkin Lymphoma Over 4 Decades: Experience of the British National Lymphoma Investigation (BNLI) With 6834 Patients. Clin Lymphoma Myeloma Leuk 2017;17(2):108-119. DOI: 10.1016/j.clml.2016.11.004.
3. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. Blood 2008;111(6):2977-83. DOI: 10.1182/blood-2007-10-115493.
4. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. N Engl J Med 2015;373(26):2499-511. DOI: 10.1056/NEJMoa1505949.
5. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;21(18):3431-9. DOI: 10.1200/JCO.2003.07.131.
6. Ng AK, Bernardo MP, Weller E, et al. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 2002;20(8):2101-8. DOI: 10.1200/JCO.2002.08.021.
7. Boivin JF, Hutchison GB, Zauber AG, et al. Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 1995;87(10):732-41. DOI: 10.1093/jnci/87.10.732.
8. Lorigan P, Radford J, Howell A, Thatcher N. Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. Lancet Oncol 2005;6(10):773-9. DOI: 10.1016/S1470-2045(05)70387-9.
9. Bright CJ, Reulen RC, Winter DL, et al. Risk of subsequent primary neoplasms in survivors of adolescent and young adult cancer (Teenage and Young Adult Cancer Survivor Study): a population-based, cohort study. Lancet Oncol 2019;20(4):531-545. DOI: 10.1016/S1470-2045(18)30903-3.
10. Ibrahim EM, Kazkaz GA, Abouelkhair KM, et al. Increased risk of second lung cancer in Hodgkin's lymphoma survivors: a meta-analysis. Lung 2013;191(1):117-34. DOI: 10.1007/s00408-012-9418-4.
11. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94(3):182-92. DOI: 10.1093/jnci/94.3.182.
12. Swerdlow AJ, Higgins CD, Smith P, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. J Clin Oncol 2011;29(31):4096-104. DOI: 10.1200/JCO.2011.34.8268.
13. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013;369(10):920-31. DOI: 10.1056/NEJMoa1208962.

14. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020;382(6):503-513. DOI: 10.1056/NEJMoa1911793.
15. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess 2016;20(40):1-146. DOI: 10.3310/hta20400.
16. Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355(17):1763-71. DOI: 10.1056/NEJMoa060476.
17. Earlier diagnosis NHS England. (https://www.england.nhs.uk/cancer/early-diagnosis/).
18. Field JK, Vulkan D, Davies MPA, et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. Lancet Reg Health Eur 2021;10:100179. DOI: 10.1016/j.lanepe.2021.100179.
19. Tammemagi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368(8):728-36. DOI: 10.1056/NEJMoa1211776.
20. Broadbent R, Armitage CJ, Crosbie P, Radford J, Linton K. Likely uptake of a future a lung cancer screening programme in Hodgkin lymphoma survivors: a questionnaire study. BMC Pulm Med 2022;22(1):165. DOI: 10.1186/s12890-022-01959-3.
21. Broadbent R, Crosbie P, Armitage CJ, et al. Pilot study of lung cancer screening for survivors of Hodgkin lymphoma. Haematologica 2023. DOI: 10.3324/haematol.2023.283287.
22. Lin L, Wang D, Chen H. The characteristics and survival of second primary lung cancer after Hodgkin's lymphoma: A comparison with first primary lung cancer using the SEER database. PLoS One 2023;18(5):e0285766. DOI: 10.1371/journal.pone.0285766.
23. Schoenfeld JD, Mauch PM, Das P, et al. Lung malignancies after Hodgkin lymphoma: disease characteristics, detection methods and clinical outcome. Ann Oncol 2012;23(7):1813-8. DOI: 10.1093/annonc/mdr551.
24. Behringer K, Josting A, Schiller P, et al. Solid tumors in patients treated for Hodgkin's disease: a report from the German Hodgkin Lymphoma Study Group. Ann Oncol 2004;15(7):1079-85. DOI: 10.1093/annonc/mdh273.
25. Laurie SA, Kris MG, Portlock CS, et al. The clinical course of nonsmall cell lung carcinoma in survivors of Hodgkin disease. Cancer 2002;95(1):119-26. DOI: 10.1002/cncr.10628.
26. Broadbent R, Gorman L, Armitage CJ, Radford J, Linton K. The perspectives of survivors of Hodgkin lymphoma on lung cancer screening: A qualitative study. Health Expect 2022;25(1):116-124. DOI: 10.1111/hex.13353.
27. Broadbent R, Seale T, Armitage CJ, Linton K. The development of a decision aid to support Hodgkin lymphoma survivors considering lung cancer screening. BMC Med Inform Decis Mak 2022;22(1):29. DOI: 10.1186/s12911-022-01768-y.
28. Broadbent R, Linton K. Performance of standard and PLCO-HL risk calculators in HL survivors from the ADAPT database at The Christie NHS Trust. 2024.

29. National Data Registration Service (NDRS). Breast screening After Radiotherapy Dataset (BARD). (https://digital.nhs.uk/ndrs/our-work/ncras-partnerships/breast-screening-after-radiotherapy-dataset-bard).
30. Hodgson D. Low Dose Chest Computed Tomography (CT) Screening. (https://clinicaltrials.gov/study/NCT01180010).
31. Ng AK. Low-Dose Chest Computed Tomography Screening for Lung Cancer in Survivors of Hodgkin's Disease. (https://clinicaltrials.gov/study/NCT00601146).
32. Field JK, Vulkan D, Davies MPA, Duffy SW, Gabe R. Liverpool Lung Project lung cancer risk stratification model: calibration and prospective validation. Thorax 2021;76(2):161-168. DOI: 10.1136/thoraxjnl-2020-215158.
33. Liao W, Coupland CAC, Burchardt J, et al. Predicting the future risk of lung cancer: development, and internal and external validation of the CanPredict (lung) model in 19.67 million people and evaluation of model performance against seven other risk prediction models. Lancet Respir Med 2023;11(8):685-697. DOI: 10.1016/S2213-2600(23)00050-4.
34. Uhry Z, Hedelin G, Colonna M, et al. Multi-state Markov models in cancer screening evaluation: a brief review and case study. Stat Methods Med Res 2010;19(5):463-86. DOI: 10.1177/0962280209359848.

APPENDIX 1: SNOMED CODES FOR HODGKIN LYMPHOMA

SNOMED Code	ICD Code 3CHAR	ICD Code
1091891000000106	C81	C819
118599009	C81	C819
118602004	C81	C819
118605002	C81	C810
118606001	C81	C813
118607005	C81	C814
118608000	C81	C811
118609008	C81	C812
118610003	C81	C813
1255666008	C81	C813
1255687003	C81	C813
1255726001	C81	C819
1255727005	C81	C819
1255728000	C81	C819
1255737000	C81	C814
1255738005	C81	C814
1255739002	C81	C814
1255743003	C81	C813
1255744009	C81	C813
1255745005	C81	C813
1255784000	C81	C810
1255785004	C81	C810
1255786003	C81	C810
1255788002	C81	C812
1255789005	C81	C812
1255790001	C81	C812
1255791002	C81	C811
1255792009	C81	C811
1255793004	C81	C811
1255797003	C81	C811
1255798008	C81	C819
1255802009	C81	C819
1255803004	C81	C819
1255804005	C81	C819
1255808008	C81	C813
1255811009	C81	C812
1255812002	C81	C811
125581400	C81	C814
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1255887000	C81	C810
1255888005	C81	C810
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188529007	C81	C810
188531003	C81	C810
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188579005	C81	C812
188580008	C81	C812
188582000	C81	C812
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188589009	C81	C813
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762690000	C81	C817
830057003	C81	C817
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93520007	C81	C819
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93527005	C81	C819
93528000	C81	C819
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93531004	C81	C819
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93547002	C81	C813
93548007	C81	C813
93549004	C81	C813
93550004	C81	C813
93551000	C81	C813
93552007	C81	C813
93554008	C81	C813
93555009	C81	C813

APPENDIX 2: USEFUL ONLINE LINKS

- LCSP standard protocol
- Lymphoma Action Language Translation Tool
- PLCOm2012
- LLPv2
- QRisk2
- Townsend deprivation score
- GP Practice Code Lookup
- COPD Assessment Test
- MRC Dyspnoea Scale
- Body Mass Index for adults
- NHS England Electronic Frailty Index

APPENDIX 3: CONTINUOUS SIRS BY AGE AT HL DIAGNOSIS FOR COMPUTING PLCO-HL RISK SCORE

Age at HL diagnosis	SIR	SIR_rounded
15	7.68632611	7.69
16	7.4860663	7.49
17	7.29102406	7.29
18	7.10106346	7.1
19	6.9160521	6.92
20	6.73586103	6.74
21	6.56036467	6.56
22	6.38944069	6.39
23	6.22296998	6.22
24	6.06083649	6.06
25	5.90292724	5.9
26	5.74913217	5.75
27	5.59934407	5.6
28	5.45345856	5.45
29	5.31137396	5.31
30	5.17299123	5.17
31	5.03821393	5.04
32	4.90694813	4.91
33	4.77910233	4.78
34	4.65458742	4.65
35	4.53331664	4.53
36	4.41520544	4.42
37	4.30017152	4.3
38	4.1881347	4.19
39	4.07901689	4.08
40	3.97274204	3.97
41	3.86923607	3.87
42	3.76842686	3.77
43	3.67024413	3.67
44	3.57461946	3.57
45	3.4814862	3.48
46	3.39077943	3.39
47	3.30243594	3.3
48	3.21639416	3.22
49	3.13259411	3.13
50	3.05097739	3.05
51	2.97148712	2.97
52	2.89406789	2.89

53	2.81866574	2.82
54	2.74522812	2.75
55	2.67370385	2.67
56	2.60404307	2.6
57	2.53619724	2.54
58	2.47011907	2.47
59	2.4057625	2.41
60	2.34308268	2.34
61	2.28203592	2.28
62	2.22257967	2.22
63	2.1646725	2.16
64	2.10827405	2.11
65	2.053345	2.05
66	1.99984708	2
67	1.94774299	1.95
68	1.89699642	1.9
69	1.84757201	1.85
70	1.7994353	1.8
71	1.75255275	1.75
72	1.70689168	1.71
73	1.66242026	1.66
74	1.61910751	1.62
75	1.57692322	1.58
76	1.53583801	1.54
77	1.49582323	1.5
78	1.456851	1.46
79	1.41889415	1.42
80	1.38192623	1.38
81	1.34592148	1.35
82	1.31085479	1.31
83	1.27670173	1.28
84	1.2434385	1.24
85	1.21104191	1.21

APPENDIX 4: CAN PREDICT VARIABLES AND SNOMED CODES

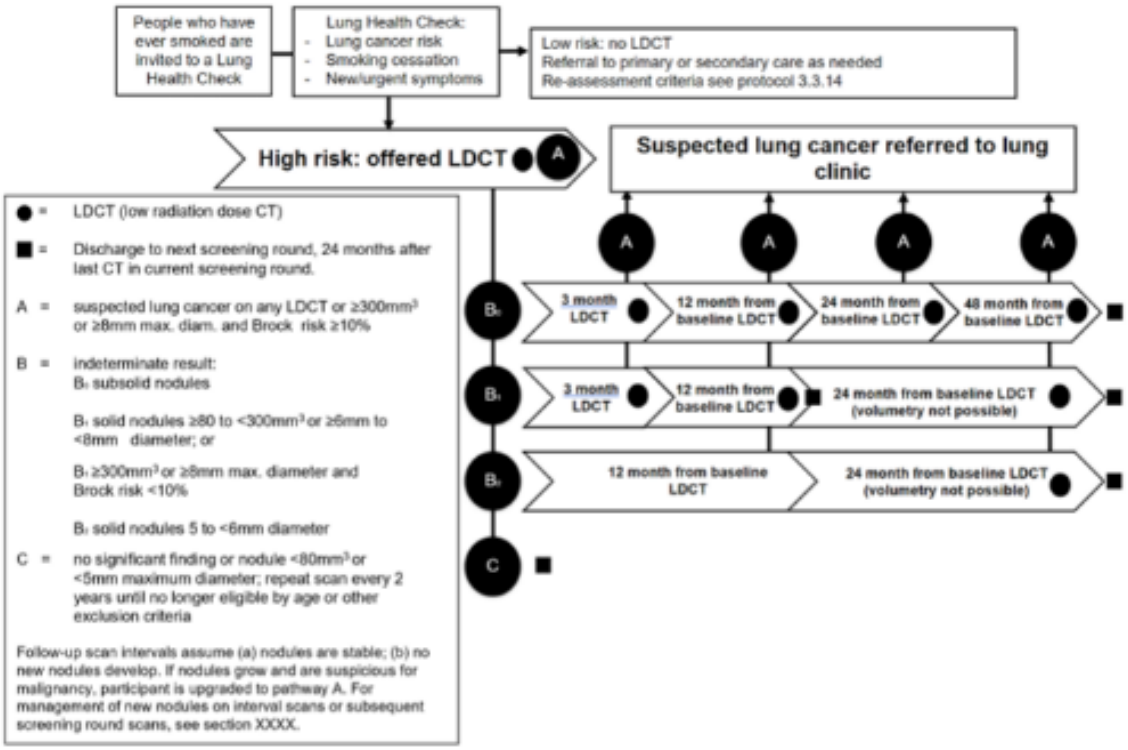
Please see https://www.qresearch.org/data/qcode-group-library/ for contents of each code group

Variable	Code Group ID on QWeb	comments
Age (single year)	n/a	Integer derived from year of birth and date of search. Valid ages 25-84 years.
Sex	n/a	Integer derived from gender. 1=male; 0=female
Ethnic group	17 categories	This can then be mapped to the 10 categories needed for calculation
Smoking status	2238-2244	6 groups – non-smoker; ex-smoker; light smoker (1-9/day); moderate smoker (10-19/day); heavy smoker (20+/day)
Alcohol status	17064-17070	Non-drinker; trivial (<1u/day); light (1-2/day); moderate (3-6/day); heavy (7-9/day); very heavy (>9 day)
Asthma	16760	yes=1; no=0
Blood cancer	58	yes=1; no=0
Breast cancer	52	yes=1; no=0
Cervical cancer	55	yes=1; no=0
COPD	29	yes=1; no=0
Oral cancer	222	yes=1; no=0
Ovarian cancer	53	yes=1; no=0
Colorectal cancer	2009	yes=1; no=0
Gastro-oesophageal cancer	2013	yes=1; no=0
Renal cancer	57	yes=1; no=0
Uterine cancer	54	yes=1; no=0
BMI (body mass index)		Numeric value associated with Snomed code
Family history of lung cancer	1389	yes=1; no=0
Townsend deprivation score	n/a	Derived from output area associated with postcode.

		See Townsend deprivation score Lookup
Asbestos	1415	

APPENDIX 5: LUNG HEALTH CHECKS PROGRAMME PATHWAY

This diagram is reproduced from Figure 1 of the QA standards prepared for the Lung Cancer Screening Programme by the Lung Clinical Expert Advisory Group Quality assurance standards prepared for the Lung Cancer Screening Programme



APPENDIX 6: INCIDENTAL FINDINGS, REPORTING AND MANAGEMENT

This table is reproduced from Annex 2 of the QA standards prepared for the Lung Cancer Screening Programme by the Lung Clinical Expert Advisory Group Quality assurance standards prepared for the Lung Cancer Screening Programme

This list is not exhaustive and other, less common findings, may be reported according to normal radiological practice. The evidence for this table was based on a systematic review of incidental findings in LDCT screening with review recommended for new evidence in January 2026. This table assumes no clinical information is available.

Finding	**Reliability of detection and characterisation by LDCT (Low Dose Computed Tomography)**	**Radiology report and management recommendations** *If reporting is recommended this means that the chance of the finding being harmful is significant, although any action may be associated with both benefit and harm*		**Potential consequences for participant** ***(benefit/harm)***
		Report content	**Management if baseline or new**	
Emphysema	Good	Classify as: • mild (<25%) • moderate (25-50%) • severe >50%	Inform participants with moderate to severe radiological emphysema about the findings and recommend they seek advice from primary care if they have symptoms. Do not refer participants with known diagnosis of COPD or if LHC establishes the participant is not impacted by dyspnoea and or cough. Smoking cessation referral for all current smokers. Further emphasis on smoking cessation in results letter	Early diagnosis and treatment of symptomatic COPD. Increased incentive to quit smoking. *No benefit and extra worry where no symptoms or no response to treatment.*

			in those with moderate or severe emphysema.	
Interstitial lung abnormalities (ILA)	Good	Report all ILA as an estimated percentage of whole lungs.	Further scanning within the lung cancer screening programme may flag progression for all ILA not referred. ILA involving more than 10% of either the whole lungs should be referred for specialist review / reviewed at the Screening Review Meeting (SRM).	Early diagnosis and treatment of ILD. *No benefit and extra worry. Unnecessary treatments and investigations with no benefit.*
Bronchiectasis	Good	Report bronchiectasis when moderate or severe (more than 2X the diameter of the artery and involving more than one segment).	Review at screening review meeting if moderate or severe. Ensure clinical assessment to check for symptoms either via existing records, lung health check or direct assessment in primary or secondary care.	Identification and treatment of symptoms including prompting early treatment of future infections. Identification of an underlying cause. *No benefit if asymptomatic and not underlying cause. Unnecessary treatment.*
Respiratory bronchiolitis (RB)	Good	Do not report.	Smoking cessation will be offered to all current smokers irrespective of the presence of RB-ILD.	
Consolidation	Good	Classify as: • possibly inflammatory • possibly malignant	If cancer more likely than inflammation refer to SRM. Inflammation more likely than cancer refer to SRM consider repeat CT Repeat CT at 6 weeks or 3 months depending on concern (within or outside screening programme). Do	Early identification and treatment of malignancy / other diagnosis. *Unnecessary worry, further imaging or work up and treatment for self-limiting resolving lesions.*

			not report minor areas of consolidation or tree in bud that are clearly inflammatory.	
Pleural effusion/ thickening	Moderate	Report size and laterality and whether malignant features present.	Refer directly via SRM for clinical assessment and work-up if suspicious appearances including a new effusion, pleural thickening suspicious for malignancy or mass lesion. This includes schwannomas.	Early identification and treatment of malignancy / other diagnosis. *Unnecessary worry, further imaging or work up for benign findings.*
Pleural plaques.	Good	Do not report or do so only as a note. Reporting is only recommended in context of screening where compensation is available (i.e. Scotland and Northern Ireland).	No clinical activity should be generated for benign appearances.	In some UK countries, compensation is available to people exposed to asbestos who have pleural plaques.
Tuberculosis (TB)	Good	Report if active TB likely and differential diagnoses.	Referral into local TB service.	Opportunity for treatment and contact tracing.
Bronchial wall thickening	Good	Do not report.	No action required.	
Coroonary calcification (CAC) *Note: all participants should have had a Q-risk or similar assessment*	Good	Report CAC, classify (using simple visual scoring) as: • Mild • Moderate • Severe	Cardiovascular (CV) risk assessment reminder if moderate or severe CAC present, unless already on lipid lowering therapy or known to have ischaemic heart disease. Note: it is not established that mild CAC confers extra risk over Q-risk or similar assessment.	Should provide an extra prompt for CV risk assessment in those at markedly increased risk of CV events. However with current entry criteria, almost all participants will be eligible for primary prevention regardless of coronary calcification.

Aortic valve disease	Good	Report aortic valve calcification (AVC) if moderate or severe. Classify using simple visual scoring. Isolated specks of calcification do not require reporting.	Refer those with moderate or severe AVC for evaluation with echocardiography via SRM.	Earlier assessment of aortic valve disease. *No benefit and extra worry, unnecessary further investigations.*
Thoracic aortic calcification/	Good	Do not report dilatation thoracic aortic calcification. Report thoracic aorta diameter if ≥ 45mm.	Referral for further assessment for those with thoracic aorta > 45mm diameter according to local guidelines/ pathways; if >50mm urgent referral.	Earlier option for medical treatment / monitoring / surgical intervention. *No benefit in outcome, extra worry / harm from work-up.*
Mediastinal mass	Moderate	Report size, morphology, position, and density / texture, including whether cystic.	Refer all non-cystic lesions to SRM. Options for management include surveillance as part of the screening programme or work-up depending on clinical assessment.	Early identification of malignant or harmful lesion. *Extra worry and work up for benign disease.*
Mediastinal lymph nodes	Moderate	Report mediastinal and hilar lymphadenopathy ≥ 15mm short axis.	Refer to SRM for further assessment.	Early diagnosis of significant disease. *Worry and work up for harmless findings.*
Thyroid abnormalities	Poor	Report nodules with suspicious features such as local lymphadenopathy, punctate microcalcification.	Refer to thyroid MDT via SRM for nodules with suspicious features that are ≥ 20mm.	Early diagnosis of thyroid cancer. *Work up of benign or indolent disease.*
Cardiac decompensation / pericardial effusion.	Moderate	Report moderate or large pericardial effusion. Report features of significant decompensation.	Referral for echocardiography and clinical assessment via SRM or primary care; urgent referral may be indicated for concerning features.	Early diagnosis and treatment of pericardial disease / cardiac failure

				Unnecessary activity if already known
Oesophageal lesions	Moderate	Report diffuse wall thickening, or focal lesions.	Referral for further assessment via SRM.	Early diagnosis of oesophageal disease. *Unnecessary work up and worry for no significant disease or normal findings.*
Abdominal aortic aneurysm (AAA)	Moderate	Report all AAA.	Referral for further assessment / surveillance according to guidelines; 3-5cm, referral >5cm, urgent referral.	Early identification of AAA.
Breast nodules	Moderate	Report size, site, calcification, density, and interval change.	Refer any breast lesion (via SRM) that is NOT clearly benign, (i.e., stable, well-defined margins or multiple) to the breast service unless already known.	Early diagnosis of breast cancer. *Overdiagnosis; worry and harm from benign disease.*
Liver lesions	Poor (Including partial imaging)	Report size and attenuation Benign features: sharp margin and homogenous low attenuation (≤20 Hounsfield Unit (HU)), (focal) fatty sparing or deposition do not require further investigation or reporting Incompletely imaged lesions or lesions too small to characterize should not by itself prompt further investigation.	Lesions < 1cm: no further investigation Lesions ≥ 1cm and no benign features: referral via SRM: refer malignant lesions to the appropriate cancer pathway Indeterminate lesions: consider further investigation with CE CT/ ultrasound/ MRI.	Diagnosis of primary or secondary cancer. *Unnecessary worry, and work up for non-significant disease.*
Renal	Poor (Including partial imaging)	Report size, site, attenuation, calcification.	Homogenous hypodense cysts do not require further investigation. Soft	Diagnosis of primary or secondary cancer.

		Classify as malignant, indeterminate, and benign or incompletely imaged/ unable lesions to evaluate. Incompletely imaged lesions or lesions too small to characterise should not by itself prompt further investigation.	tissue, hyperdense or mixed density renal mass >1cm – or masses >3cm that show growth in comparison with prior imaging if available refer to SRM.	*Unnecessary worry, and work up for non-significant disease.*
Bone abnormalities	Moderate	Report >50% loss of vertebral height in at least one vertebra. Report any lesions suspicious for malignancy.	Refer via SRM to primary care or osteoporosis service for >50% loss of vertebral height Refer to SRM.	Prevention of fracture. *Worry and inconvenience.*
Adrenal lesions	Moderate	Report size and attenuation Lesions < 10mm or <10HU in density and 10-40mm diameter do not require reporting.	Refer to SRM lesions which are >10-40mm diameter with attenuation >10HU, or lesions with these characteristics growing on serial scans. Refer lesions >40mm	Early identification of adrenal disease. *Worry and work up of nonsignificant lesion.*