Lung cancer screening for survivors of Hodgkin lymphoma

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LIST OF ABBREVIATIONS

ABVD	A=doxorubicin, bleomycin, vinblastine, dacarbazine
AER	Absolute excess risk
ALK	Anaplastic lymphoma kinase
ASCT	Autologous stem cell transplantation
BEACOPP	Bleomycin, etoposide, A=doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone
BTS	British Thoracic Society
CAC	Coronary artery calcification
ChlVPP-EVA	Chlorambucil, vinblastine, procarbazine, prednisolone, etoposide, vincristine, A=doxorubicin
CI	Cumulative incidence
COM-B	Capabilities, Opportunities, Motivations, Behaviour
CT	Computed tomography
DA	Decision aid
DCS	Decisional Conflict Scale
ECOG	European Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FDG-PET	Fluorodeoxyglucose positron emission tomography
GP	General practitioner
HAPA	Health action process approach
HBM	Health Belief Model

HL	Hodgkin lymphoma
HLS	Hodgkin lymphoma survivors
IDM	Index of Multiple Deprivation
IPDASi	International Patient Decision Aid Standards instrument
IQR	Interquartile range
KRAS	Kirsten rat sarcoma
LCS	Lung cancer screening
LCSHBS	Lung cancer screening health belief scales
LDCT	Low dose computed tomography
LLP	Liverpool Lung Project
LOT-R	Life orientation test – revised
MMIC	Multidimensional measure of informed choice
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MVPP	Mechlorethamine, vincristine, procarbazine, prednisolone
NELSON	Nederlands–Leuvens Longkanker Screenings On- derzoek
NHS	National Health Service
NLST	National Lung Screening Trial
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PDMS	Preparation for decision making scale
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer

RR	Relative risk
SEER	Surveillance, Epidemiology and End Results
SIR	Standardised incidence ratio
SMN	Subsequent malignant neoplasm
S-TOFHLA	Short Test of Functional Health Literacy Assessment
SUNDAE	Standards for UNiversal reporting of patient Decision Aid Evaluation
TDF	Theoretical Domains Framework
UK	United Kingdom
VAPEC-B	A=doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisolone
95%CI	95% Confidence interval

THESIS ABSTRACT

Hodgkin lymphoma survivors (HLS) are at excess risk of lung cancer. There is a rationale for developing a targeted LCS programme for HL survivors, however there are gaps in the literature pertaining to its' feasibility, specifically: the views of HLS; the motivators and barriers to participation; how to inform and invite HLS to screening; and the likely uptake rate. This programme of research aimed to address these gaps in the literature.

In the first study, the views of HLS on LCS were sought. Key findings were a lack of awareness of lung cancer risk, and high levels of willingness to undergo LCS motivated by positive beliefs around cancer early detection.

The second study surveyed HLS to identify the psycho-social factors associated with willingness to undergo LCS. Being male, living in a less deprived area and lower levels of self-efficacy were associated with hesitancy to undergo LCS.

The third study used mixed methods to test a novel LCS decision aid (DA) among HLS and practitioners. The DA improved knowledge and reduced decisional conflict among HLS. The study identified ways in which the DA prototype could be improved prior to use in an LCS pilot.

The fourth study was a pilot of LCS for HLS which utilised the DA. The overall response rate was 58%. Decision-making outcomes supported the use of the DA. The prevalence of screen-detected lung cancer screened was 2%. Rates of clinically significant incidental findings were low, but there were high rates of coronary artery calcification.

The fifth study explored drivers of LCS uptake among HLS invited to the pilot. Drivers of uptake included the belief that early detection of lung cancer is associated with better outcomes, desire for reassurance and knowledge and altruism. Concerns around radiation-induced cancers drove the decision to decline screening.

This body of work suggests that a larger study of LCS would be acceptable and feasible and supports the future use of the novel DA.

DECLARATION

I declare that no portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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RATIONALE FOR SUBMITTING AN ALTERNATIVE FORMAT THESIS

This thesis is presented in the alternative format. From the outset of the research, my supervisors and I felt that the individual studies would be suitable for publication. I therefore wrote the thesis chapters as papers and was successful in publishing the papers contained within Chapters 2, 3 and 4 in the journals 'Health Expectations', 'BMC Pulmonary Medicine' and 'BMC Medical Informatics and Decision Making' respectively. After successfully publishing these chapters, my supervisors and I decided that the journal format would be the most appropriate and efficient way of presenting the thesis. Chapters 5 and 6 are also written in journal format with the aim of publishing them in the future. In chapter 1 I provide the background to the thesis in the form of a literature review, and in chapter 7 I discuss the findings of the whole thesis. References are provided at the end of each chapter in keeping with the format for publication.

CANDIDATE CONTRIBUTION TO THESIS AND JOURNAL ARTICLES

The candidate, Rachel S. Broadbent, designed each individual study contained within the thesis, wrote the first draft of the study manuscripts and the sub-sections in this thesis. The candidates' contributions and that of the co-authors for each study, including the published articles are detailed below:

Study 1 (Chapter 2):

The candidate, under the supervision of their PhD supervisory team, conceived of and designed the study. The candidate collected and analysed the data, with LG acting as a second coder. The candidate wrote the first draft of the study manuscript and the co-authors (LG, CA, JR, KL) provided feedback and contributed

to the re-drafting of the manuscript and approved the final version submitted for publication.

Study 2 (Chapter 3):

The candidate, under the supervision of their PhD supervisory team, conceived of and designed the study, including the study questionnaire, inputted and analysed the survey data and wrote the first draft of the study manuscript. The co-authors (CA, PC, JR, KL) provided feedback and contributed to the re-drafting of the manuscript and approved the final version submitted for publication.

Study 3 (Chapter 4)

The candidate, under the supervision of KL and CA, conceived of and designed the study. PC, a co-supervisor, was a member of the steering group that gave feedback on the decision-aid prototype, but did not contribute to the study conception, data analysis or the manuscript. The candidate collected and analysed the data, during which time TS was a second coder. The candidate wrote the first draft of the manuscript and all co-authors (TS, CA, KL) gave feedback and contributed to the re-drafting of the manuscript and approved the final version for submission.

Study 4 (Chapter 5)

The study in chapter 5 is not yet submitted for publication. The authors listed at the beginning of the chapter will be co-authors on a future paper.

The candidate, under the supervision of their PhD supervisory team, conceived of and designed the study. Co-authors BT, ST and JM are consultant radiologists based at The Christie NHS Foundation Trust who contributed to the study protocol and reported low-dose CT scans. The candidate collected and analysed the data and wrote the first draft of the manuscript. The PhD supervisory team gave feedback on the first draft, the revised version of which is included in this thesis.

Study 5 (Chapter 6)

The candidate, under the supervision of their PhD supervisory team, conceived of and designed the study, collected and analysed the data, during which time TS

acted as a second coder. The candidate wrote the first draft of the manuscript and co-authors KL and CA have provided feedback on the first draft, the revised version of which is included in this thesis.

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Dr Rachel Broadbent (MBBCh) is a specialty registrar in medical oncology who is undertaking her training at The Christie NHS Foundation Trust.

CHAPTER 1

1.1 An introduction to Hodgkin lymphoma

Hodgkin lymphoma (HL) is a lymphoid malignancy of clonal B cells. Since the 1990s, incidence rates have increased by 37% in the United Kingdom (UK). Between 2016 and 2018, there were around 2,100 new cases of HL in the UK, with a slight male predominance (890 cases in women and 1,200 cases in men). HL has a bimodal incidence, predominantly affecting the young and elderly, with incidence peaks at the ages of 20-24 years and 75-79 years of age.[1] Lymphomas are the commonest type of cancer diagnosed in young people and HL accounts for 68% of lymphomas in 15-24 year olds, thus HL represents a significant proportion of the cancer burden in young people.[2]

As a result of improvements in treatment, the prognosis for people diagnosed with HL has improved across all age groups in recent decades, although a wide difference remains. In those diagnosed aged 15-24, 5-year overall survival (OS) is 94%, but this falls to 59% in those diagnosed over the age of 60.[3] Therefore, whilst HL is a disease affecting the young and elderly to similar degrees, people diagnosed at a younger age are more likely to be cured of their disease and live to experience the late effects of treatment.

In the 1960s, the development of chemotherapy regimens combing alkylating agents and vinca alkaloids dramatically improved survival rates from HL. Prior to this development, HL carried a dismal prognosis - radiation alone cured just 40% of patients with early stage HL and had little utility in advanced disease.[4] The MVPP (mechlorethamine (also known as mustine), vincristine, procarbazine and prednisolone) (or MOPP, 'O' representing vincristine or Oncovin) chemotherapy protocol was developed in 1964. This was a major breakthrough – advanced HL patients treated with MVPP had a 68% 5-year relapse free survival.[5] Long-term follow-up of the first 188 patients who achieved complete remission with MVPP chemotherapy demonstrated not only an impressive rates of durable remissions, but also the significant risk of secondary leukaemia and other malignancies

especially in patients who also received radiotherapy.[6] Around the same time, the principles of the development of the MVPP protocol were applied to the development of the ABVD (doxorubicin (also known as Adriamycin), bleomycin, vinblastine, dacarbazine) regimen by the Milan group, led by Bonadonna. A trial of three cycles of MVPP versus ABVD followed by extensive radiotherapy in patients with advanced HL demonstrated the superiority of ABVD both in terms of PFS (87% versus 77%) and OS (67% versus 77%).[7] Other recent investigations suggest that although long-term survival rates between the two regimens are similar, ABVD is less toxic, particularly in relation to fertility, and less carcinogenic.[8,9] In recent years, trials have failed to show an improvement in PFS or OS when other non-MVPP multidrug regimens were compared with ABVD[10] or when ABVD was compared with a hybrid regimen, MVPP/ABV.[11] Over subsequent decades, ABVD became the gold-standard regimen against which other regimens were compared in clinical trials of treatment for both early and advanced stage HL. In the late 1990s, the German Hodgkin Lymphoma Study Group pioneered a novel dose-intense seven-drug regimen, BEACOPP (bleomycin, etoposide, doxorubicin (also known as Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone). The HD9 trial demonstrated that for advanced HL, the dose-escalated BEACOPP regimen (escBEACOPP) improved 2-year PFS when compared to standard BEACOPP or COPP/ABVD (COPP representing a regimen in which cyclophosphamide replaces mechlorethamine of MOPP) (89% versus 81% versus 72%). All arms included radiotherapy to areas of initial bulk or residual disease. However, there was no improvement in OS and escBEACOPP was more toxic.[12] Further trials also failed to demonstrate an improvement in OS using escBEACOPP[13,14] but a meta-analysis reported that in the front-line advanced HL setting, escBEACOPP improves 5-year OS by 7% when compared with ABVD (95% versus 88%).[15] The widespread uptake of escBEACOPP has been limited by its' acute and long-term toxicity, in particular the higher rates of development of second malignancies compared with ABVD (6.6% versus 0.9% at 10-years).[16] As discussed below in the description of modern treatment pathways, escBEACOPP remains widely used for high-risk patients and as part of response-adapted protocols. In the last few years, a novel regimen in which procarbazine is replaced by dacarbazine (escBEACOPDac) has been increasingly

used since non-randomised data has demonstrated its' efficacy and lower risk of infertility compared to escBEACOPP.[17]

Radiotherapy plays an important role in the treatment of HL and has been used alone or as an adjunct to chemotherapy. Until the early 2000s, radiotherapy was delivered to both involved and uninvolved nodal groups, known as the extended field. The supra-diaphragmatic extended field involved radiation to the cervical, thoracic and axillary nodes - known as the mantle field - whilst an infra-diaphragmatic extended field – known as the inverted-Y field – covered para-aortic, iliac and inguinal lymph nodes.[18,19] Around 2007, it was proven that for early-stage HL, radiation to the involved-field – when used alongside chemotherapy- was non-inferior and this became standard practice.[20,21] The involved-node technique was developed later, which reduces field size further but requires optimal pre-treatment imaging.[22,23] In addition to a reduction in field size, radiation doses have reduced from 40-44 Gray (Gy) used in the 1960s to 20-30 Gy in the modern era.[24,25] HD10 was one of the key trials to demonstrate that reduced-intensity treatment could be used in early-stage HL. In HD10, early-stage HL patients were randomised to receive either four cycles of ABVD followed by 30 Gy of radiation therapy, four cycles of ABVD followed by 20 Gy of radiation therapy, two cycles of ABVD followed by 30 Gy of radiation therapy, or two cycles of ABVD followed by 20 Gy of radiation therapy. There was no improvement in PFS or OS with more cycles of ABVD or a higher dose of radiation, and two cycles and ABVD followed by 20Gy of radiation therapy became a new standard for early-stage HL.[26]

In early-stage HL, trials have investigated the omission of radiotherapy following a negative *fluorodeoxyglucose*-positron emission tomography (*FDG*-PET) scan. In the UK National Cancer Research Institute (NCRI) RAPID study which enrolled HL patients with early-stage favourable disease, three-year PFS was reduced in patients allocated to no radiotherapy compared to radiotherapy after a negative PET following three cycles of ABVD (90% versus 94%).[27] Similarly, the H10 study randomised early-stage unfavourable patients to two cycles of ABVD and INRT (standard arm) or PET directed randomisation, whereby after two cycles of ABVD,

PET negative patients went on to have four further ABVD, and PET positive patients received two cycles of escBEACOPP and involved node radiotherapy. The PFS rate at 1-year for PET negative patients was 100% in the standard arm versus 95% in the experimental arm.[28] These studies demonstrate that with the omission of radiotherapy, PFS in early-stage HL is reduced even with the use of contemporary chemotherapy regimens. Radiotherapy is commonly recommended in the advanced setting to areas of initial bulk, or when there is an incomplete response to chemotherapy. In such patients, radiotherapy has been shown to improve PFS by up to 15% and OS by 5%.[29] However, a trial has shown that after initial treatment with BEACOPP, PFS rates in patients who have a complete metabolic response to treatment are similar to those who undergo radiotherapy to residual PET-positive masses of 2.5cm or greater.[30] Therefore in patients with advanced-HL and a complete response to chemotherapy, there is the option to omit radiotherapy.

PET-response adapted therapy has also been trialled in advanced-stage HL to guide escalation or de-escalation of chemotherapy. In the RATHL trial, advanced-HL patients underwent two cycles of ABVD followed by an interim PET scan. Patients with a negative PET scan were randomised to further 4 cycles of ABVD or AVD (bleomycin omitted). Those with a positive interim PET scan had their chemotherapy escalated to standard BEACOPP or escBEACOPP. Consolidation radiotherapy was not recommended for those with a negative interim PET scan. Patients who had bleomycin omitted after a negative interim PET had lower rates of pulmonary toxicity but similar 3-year PFS (85.7% in AVD group versus 84.4% in the AVD group).[31] The RATHL approach to escalating or de-escalating chemotherapy based on the interim-PET result is now a standard approach in the UK.

For patients under the age of 60 in the UK, there is some variation in contemporary first line treatment pathways for HL, but certain key elements are common to different centres. Early-stage disease is treated with 2-4 cycles of chemotherapy whilst advanced stage disease is treated with 6-8 cycles of chemotherapy. ABVD and BEACOPP are commonly used regimens in patients ≤60 years of age. In both early and advanced disease, the decision to escalate to a BEACOPP-like regimen or

de-escalate by omitting bleomycin is directed by the result of an interim PET scan after two cycles of chemotherapy. For many patients, radiotherapy remains an important adjunct to chemotherapy.[32]

In patients over the age of 60, ABVD is poorly tolerated and bleomycin in particular is not recommended beyond two cycles due to increased rates of bleomycin lung toxicity. Similarly, BEACOPP is too toxic for use in the over 60s. There is no established standard treatment for patients with HL over this age, but options for fit patients include: 2-4 cycles of ABVD (with bleomycin either omitted entirely or given for a maximum of two cycles); 3-4 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone); or VEPEM-B (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, bleomycin). Less fit patients should not be given ABVD and anthracyclines are often avoided. Chemotherapy regimens used for less fit patients include VEPEM-B + IFRT, or ChlVPP (chlorambucil, vinblastine, procarbazine, prednisone), which do not contain anthracyclines. As for younger patients, consolidation radiotherapy remains an important adjunct.[33]

The risk of subsequent malignant neoplasms in HL survivors

As a consequence of their treatment, HL survivors are at excess risk of developing subsequent haematological and solid malignancies. In fact, in teenagers and young adults, HL is the primary malignancy most commonly associated with development of one or more subsequent malignancies.[34] Risks of subsequent malignancies are commonly described in terms of standardised incidence ratio (SIR) - a ratio of the observed malignancies in the cohort over the expected number of malignancies in the general population matched for age - or absolute excess risk (AER) - calculated by subtracting the expected cases from the observed cases and dividing by the person years at risk. AER is commonly expressed as extra cases per 10,000 patient years at risk. In a study of 3,905 HL patients diagnosed between 1965 and 2000, with a median age at diagnosis of 28, the cumulative incidence of subsequent malignancies (both solid tumours and haematological malignancies) at 40 years of follow-up was 48.5%, more than twice that expected in the general population. After 35 years of follow-up the SIR for subsequent

malignancies remained elevated at 3.9 and the AER, which steadily increased with time, was 364 per 10,000 person years. The incidence of leukaemia fell during the study period, but the incidence of solid malignancies did not. The highest AERs were for breast cancer (54.3), cancer of the respiratory system (27.3) and cancer of the gastrointestinal tract (24.0).[35] At 30-years of follow-up the cumulative incidence of breast cancer and lung cancer was 16.6% and 7.1% respectively. Among the study cohort, 4.3% had died from cancer of the respiratory system. This is in keeping with another large population-based study which also reported breast, lung and digestive cancers as having the highest AERs in that order, although the AERs reported were smaller (9.7 for lung cancer), likely due to a shorter follow up period - 34% were only followed-up for 1-9 years.[36] Among participants in the Teenage and Young adult Cancer Survivor study, in which population-level cancer registries were used to collect information on subsequent malignancies, there were 1,606 subsequent malignancies in nearly 17,000 survivors of HL diagnosed aged 15-39 between 1971 and 2006.[34] The cumulative incidence of subsequent malignancies 35 years after HL diagnosis was 26% in women and 16.5% in men. AERs increased with time from diagnosis for any subsequent malignancy and for breast and lung cancers. In female survivors, at every period since treatment that was examined, the highest AER was for breast cancer and the second highest was for lung cancer (AERs 71.8 and 26.0 at ≥ 30 years of follow-up respectively, representing 42.6% and 15.4% of the total AER for subsequent malignancies). In male survivors, lung cancer was the subsequent malignancy with the highest AER (50.2 at ≥ 30 years follow-up representing 41.2% of the total AER for subsequent malignancies) at every time point examined. Other studies in young adults treated for HL provide further evidence for breast and lung cancers being the most common subsequent malignancies in survivors.[36–38]

Subsequent malignancies are the most common cause of death in survivors of HL, followed by cardiovascular disease.[39–42] One study found that when deaths from HL were excluded, 48% died of a subsequent malignancy and that two thirds of those deaths were due to solid malignancies.[39] Elsewhere it was reported that among patients who died more than 15 years after diagnosis, 64% of deaths were due to

subsequent malignancies.[40] The subsequent malignancies most commonly associated with mortality are cancers of the gastrointestinal tract and respiratory system (relative risk (RR) and AER of death for gastrointestinal cancers of 7.7 and 10.4 and 8.8 and 9.4 for respiratory cancers.)[39] Despite being the most common subsequent malignancy in female survivors, the RR of death from breast cancer is 2.5, which is likely to be a result of breast cancer screening programmes.[35,39] Thus, the literature demonstrates that survivors of HL are at excess risk of mortality due to subsequent malignancies, particularly lung cancer.

1.2 Lung cancer in survivors of HL

Risk Factors

Sex

A meta-analysis of lung cancer in survivors of HL found that lung cancer affected male survivors of HL at a higher rate than the proportion affected in the general population,[43] possibly reflecting smoking behaviours in men and women in the included study periods.

Age at primary treatment

The risk of developing lung cancer is affected by age at which treatment for HL was given. A meta-analysis found the RR to be highest in those treated aged 15-24 and lowest in those treated over the age 55.[43] A systematic review found that in most studies, the SIR for lung cancer decreases and the AER increases with increasing age at diagnosis of HL, with the highest AER in those treated at age 45 years or older.[44] However, the study reporting on subsequent cancers in the Teenage and Young adult Cancer Survivor study participants - which was published after the systematic review - did not find any association between AER and age at HL diagnosis. [34]

Time since treatment and attained age

The risk of lung cancer increases with increasing duration of follow-up.[34,35,44] In those diagnosed with HL aged 15-39, the cumulative incidence of lung cancer increases at every 5-year interval between 15 and 35 years since treatment, such

that at 30 and 35 years since treatment, the cumulative incidence of lung cancer is 2.5% and 3.8% in females and 3.1% and 5.1% in males.[34]

Decade of diagnosis

To explore whether the evolution of HL treatments has reduced the incidence of late effects, several studies have examined the risk of developing a subsequent malignancy in relation to the decade of diagnosis of HL. One study which compared SIRs for a variety of subsequent malignancies found little difference in the SIRs for the most common malignancies in the study period 1965-2000,[45] whilst another examined the same period and found that among survivors of HL diagnosed aged 15-50, treatment in the more recent decades was associated with a reduction in the risk of a subsequent malignancy overall but there was no difference in the risk of developing solid malignancies.[35] In this latter study, the cumulative incidence of lung cancer in women increased across the treatment periods whilst in men, the incidence was lower in the period 1989-2000 than the earlier two periods. This finding is supported by the aforementioned study which found that in survivors of HL diagnosed aged 15-39, the AER for lung cancer in male survivors decreased consistently across the periods 1971-79, 1980-89 and 1990 to 2006.[34] The authors of both studies propose that the difference seen between the sexes is likely to be a result of changes in smoking behaviours rather than the change in treatment for HL. A study examining the risk of a subsequent malignancy in patients treated in 1988-2009 did not detect a significant difference in the proportion of patients developing lung cancer when the 1988-1999 and 2000-2009 periods were compared, but median follow up in the 2000-2009 period was only 4.8 years, which is shorter than the median latency time for lung cancer.[46]

Lung cancer risks associated with HL treatments: chemotherapy

With regards to the risk associated with chemotherapy, there is substantial evidence that the alkylating agents procarbazine and mechlorethamine (also known as mustine) increase the risk of lung cancer in HL survivors. The MVPP regimen contains both these agents, whilst the BEACOPP regimen contains procarbazine. The ABVD regimen includes the alkylating agent dacarbazine, but as discussed later,

there is no evidence that this agent increases risk of lung cancer. A study which followed 5,798 patients with HL treated with chemotherapy in the UK in the period 1963-2001 found the risk of lung cancer to be elevated after chemotherapy alone (SIR 2.9, AER 10.7). When different chemotherapy regimens were compared, the SIR for lung cancer was 3.1 following MVPP alone (14 cases in 716 patients), and 5.5 for MVPP plus radiotherapy with a dose to the lung (17 cases in 708 patients).[47] A case control study examined 220 cases of lung cancer and 440 controls from a cohort of HL survivors treated between 1965-1994 and found that higher cumulative doses of procarbazine increased the RR of lung cancer with statistical significance (5400-7599mg/m2 = RR 6.2, >7600 = RR 10.5) and found a statistically significant increase in risk as the number of chemotherapy cycles increased beyond five. In this study the risk associated with alkylating agents decreased with time and was not significant after 10 years since treatment.[48] However, another study found a higher RR in patients who received six or fewer cycles of procarbazine or mustine containing chemotherapy, probably because patients who received less chemotherapy also received radiotherapy.[49] Another reported an increased risk from treatment with MVPP and a trend towards increased risk with increasing number of cycles,[50] whilst conversely another two found no association between risk and the number of cycles given or the cumulative dose of alkylating agent.[35,51]

In the study of 5,798 HL patients in the UK, no lung cancers were detected among 273 patients treated with ABVD alone, whilst one case was detected among 278 patients treated with ABVD plus radiotherapy. Patients who had received MVPP had been followed up for longer than those who received ABVD.[47] The following three studies report small numbers of lung cancer cases in patients treated with ABVD with or without radiotherapy but do not specify whether these cases received radiotherapy. A pooled analysis of 622 patients treated with ABVD and 605 patients treated with BEACOPP from four randomised trials reported four lung cancer cases in the ABVD trials and six in the BEACOPP trials. Radiation was given to 12.6% and 11.3% of the patients in the ABVD and BEACOPP arms respectively.[52] Another study of 604 patients treated between 1968 and 2012 detected two lung cancer cases in patients treated with ABVD, but most of the total cohort also received radiation.[53]

Finally, a conference abstract from 2018 reported 7 lung cancers in 94 patients treated with ABVD with or without radiation between 2001 and 2016.[54] The interpretation of data on lung cancer risk following ABVD is limited by the small number of cases, a lack of granular data regarding receipt of radiotherapy and the shorter follow-up time for patients treated with ABVD compared to MVPP in some studies. However, currently available data would suggest that the ABVD regimen alone carries a lower risk of lung cancer than the MVPP regimen.

Lung cancer risks associated with HL treatments: radiotherapy

In the aforementioned case-control study, most radiotherapy was delivered to the extended field. Radiotherapy alone at a dose of ≥5 Gy was associated with an increased risk of lung cancer and the RR increased with radiotherapy dose to the lung with statistical significance above 30 Gy. It was reported that: "among case patients who received radiotherapy, 26.3% of the lung cancers occurred in the unblocked treatment field, 19.2% were diagnosed in areas that received lower dose radiation (1.9% beneath the lung blocks and 17.3% out of the beam), and 53.2% occurred on the beam edge." [48] In a meta-analysis,[55] 5 studies reported the area in which the lung cancer had occurred in relation to previous radiotherapy.[36,56–59] Among them, 83-100% of lung cancers occurred within the radiotherapy field.

Two modelling studies have calculated significant reductions in lifetime excess risk of lung cancer when radiotherapy is delivered to the involved field compared to the extended field, with a further reduction when 20 Gy over 30 Gy is delivered.[60,61] However, a meta-analysis of second malignancies following treatment for HL within clinical trials with a sample size of 793 found no difference in risk between extended field and involved field radiotherapy.[62] Eight of the ten included studies gave identical chemotherapy in both arms. This meta-analysis alongside the data on risk according to decade of diagnosis discussed above suggest that the use of smaller radiotherapy treatment fields has not reduced lung cancer risk.

Lung cancer risks associated with HL treatments: combined treatment

A meta-analysis of lung cancer risk in HL survivors,[55] which included 21 studies (74,831 HL patients), reported the following RR values for lung cancer: any chemotherapy RR 2.39; radiotherapy RR 4.88; combined chemotherapy and radiotherapy RR 5.15, demonstrating that combining chemotherapy and radiotherapy has an additive effect on lung cancer risk.

Lung cancer risks associated with HL treatments: high-dose chemotherapy and stem-cell transplantation

For the small proportion of HL patients who relapse after first-line treatment, high-dose chemotherapy followed by an autologous stem cell transplantation (ASCT) is the treatment choice for fit patients.[63] Prior to undergoing ASCT, patients receive a further line of chemotherapy to induce remission and further myeloablative conditioning chemotherapy prior to stem-cell transplantation. Studies have investigated whether this additional chemotherapy, which usually includes alkylating agents, increases the risk of subsequent malignancies. A study which included HL patients who underwent ASCT (n=467, period of diagnosis 1982-1995) or did not receive an ASCT (n=1,179, period of diagnosis 1977-1990) found that on multivariate analysis, the risk of a subsequent malignancy was greater in patients who relapsed after first-line treatment (RR 5.22, 95% confidence interval (95%CI) 1.59-17), patients with primary refractory disease (RR 3.86, 95%CI 1.12-13), and patients who underwent ASCT (RR 2.04, 95%CI 1.10-3.79). Subsequent solid malignancies were more common in patients who underwent ASCT (RR 5.19, 95%CI 2.03-13.30).[64] However, another study with similar numbers of HL patients undergoing conventional treatment (n=1530) or ASCT (n=202) during a similar period (1976-2001) reported no difference in the 15-year cumulative incidence of subsequent malignancies between patients who received ASCT or did not (8% and 10% respectively, p value 0.48) and no difference in the incidence of solid malignancies between the two groups (p value 0.06).[65] Neither study reported specifically on lung cancer risk. Therefore, the literature on the risk of a subsequent solid malignancy after ASCT is both scarce and contradictory and there has not been a specific exploration of lung cancer risk following ASCT.

Smoking

Two studies have identified smoking as having a multiplicative effect on treatment related lung cancer risk. The case control study reported the RR of lung cancer according to treatment (alkylating agents and radiation to lung ≥5 Gy) and smoking category as recorded 5-years before lung cancer diagnosis (non-smoker, former smoker or light smoker (<1 pack per day), versus moderate to heavy smokers (more than one pack per day). The RRs of developing lung cancer were significantly higher in 'moderate to heavy' smokers compared to 'non/former/light' smokers (RR 20.2 vs 7.2 after radiotherapy alone, 16.8 vs 4.3 after an alkylating agent alone and 49.1 vs 7.1 after combined chemo-radiotherapy).[48]

Similarly, a cohort study found the hazard ratio for lung cancer in patients who received supra-diaphragmatic radiotherapy to be 2.96 in non-smokers and 14.38 in former or current smokers.[35] With regards to smoking behaviours among HL survivors, two studies have reported the rates of current smoking in survivors of cancer in teenage and young adulthood as 26%[66] and 33%[67], although these studies did not specifically report on smoking behaviours in HL survivors. A study of health behaviours in HL survivors with a median age of 26 at diagnosis and a median current age of 44, reported a rate of current smoking of 7%.[68]

Family history

A study investigating the influence of a family history of cancer on subsequent cancer risk in HL survivors reported an SIR for lung cancer in survivors with an affected first degree relative of 11.24, compared to 3.39 in those without a family history ($p<0.001$).[45]

Clinical features of lung cancer in HL survivors

The median latency between HL diagnosis and development of lung cancer has been reported as 11.5 years in a meta-analysis[43] - with a median age at lung cancer diagnosis of 45.9 - and the latency period appears to reduce with increasing age at HL diagnosis (17 years, 10.6 years and 6.7 years in those diagnosed with HL <40, 40-54, 55 or older respectively).[48] Around two thirds of lung cancers in HL survivors are advanced stage (stage 3 or 4) at diagnosis,[48,69,70] similar to lung cancers diagnosed in the general population.[71]

In two studies reporting on 222 and 377 lung cancer cases among HL survivors[48,36] the balance across main histological lung cancer subtypes is almost identical and mirrors the distribution in the general population in the United States as reported to the Surveillance, Epidemiology and End Results (SEER) programme; squamous cell carcinoma 39% and 38%, adenocarcinoma 21% and 24% respectively and small-cell lung cancer 16%. Notably, one of these studies found a statistically significant increase in the risk of developing squamous cell lung cancers and small cell lung cancer after receipt of alkylating agents.[48] Currently there is only one published study describing the presence of oncogenic driver mutations in lung cancers in HL survivors. Out of seven cases of lung cancer in HL survivors, this study found two epidermal growth factor receptor (EGFR) mutations, no Kirsten rat sarcoma (KRAS) mutations and no anaplastic lymphoma kinase (ALK) mutations.[72]

Survival from non-small cell lung cancer (NSCLC) among HL survivors is worse than in patients with de novo NSCLC. In a study reporting on 187 cases of NSCLC in HL survivors in which HL survivor cases were compared to >17,800 de novo cases, survival was significantly lower for HL survivors diagnosed with regional and distant disease compared to controls (regional 7.2 months vs 16.8 months; distant 2.9 months vs 4.8 months).[73] The median OS for localised disease was 28 versus 61 months, but the difference was not statistically significant. The hazard ratio for death among HL survivors was 1.60 for localised disease, 1.67 for regional disease and 1.31 for distant disease. An analysis of the factors associated with survival found that a history of mixed cellularity HL was associated with a three-fold improved OS from subsequent lung cancer compared to other HL subtypes and survival in HL patients treated with radiotherapy who developed regional NSCLC was two-fold worse than those who had not been irradiated.[74] Regarding this latter finding, the authors propose that this could be because these patients could not receive further radiotherapy to treat their regional disease. A case series examining the method of diagnosis of lung cancer in HL survivors found a median survival for symptomatic tumours of 9.1 months but median survival was not reached in incidentally diagnosed lung cancers after 39 months of follow-up, suggesting that

lung cancer screening could reduce lung cancer related mortality in this population.[69]

1.3 Lung cancer screening

Screening trials

In the last 10 years, major advances have been made in testing and developing lung cancer screening programmes for ever smokers (current or former smokers). In the United States (US), the National Lung Screening Trial (NLST) enrolled 53,454 current or former smokers aged 55-74, who had a smoking exposure of at least 30 pack years. Participants were randomised to three annual low dose CT (LDCT) scans of the thorax or chest radiography. After 6 years of follow up, there was a 20% reduction in lung cancer related mortality in the LDCT arm.[75] The Dutch–Belgian lung-cancer screening trial
(Nederlands–Leuvens Longkanker Screenings On- derzoek [NELSON]) randomised 15,792 current or former smokers (13,195 men and 2,594 women) aged 50-75 to four rounds of LDCT screening at intervals of 1 year, 2 years and 2.5 years, versus no screening. At 10 years of follow-up, lung cancer related mortality was reduced in the screening arm by 24% in men and 33% in women.[76] A meta-analysis which pooled lung cancer related mortality data from 9 trials, including NLST, NELSON and 7 smaller trials, found that compared to chest radiography or no screening, screening using LDCT scans significantly reduced lung cancer mortality (RR 0.83, 95%CI 0.76–0.90).[77]

Lung cancers detected through LDCT screening are found at an earlier stage than those presenting symptomatically. In NLST and the NELSON studies, 69% and 63% of lung cancers detected by LDCT screening were stage IA-IB. Surgical treatment for lung cancer was three times more prevalent in the LDCT arm than the control arm in NELSON, and in NLST, 92% of stage I cancers detected by CT were treated with curative intent surgery, either alone or combined with chemotherapy and radiotherapy.[75,76]

Lung cancer screening eligibility criteria

All nine lung cancer screening trials included in the aforementioned meta-analysis selected participants based on their age and the presence of a smoking history.[77] However, in NLST those belonging to the lowest risk quintile accounted for just 1% of screen prevented lung-cancer deaths.[78] In the US, lung cancer screening is recommended based on age and smoking history[79] but in the UK, lung cancer screening risk calculators - PLCOm2012[80] or LLPv2[81] - are used to determine eligibility in ever smokers aged 55-74 with the aim of selecting individuals most likely to benefit from screening.[82] These calculators, developed from the prospective Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial[83] and Liverpool Lung Project (LLP) case-control study[84] have greater sensitivity for predicting lung cancer risk in ever smokers than the age and smoking history based criteria recommended by the US Preventive services Taskforce.[85] In the UK, the National Health Service (NHS) in England recommends lung cancer screening for ever smokers aged 55-74 with a 6-year lung cancer risk of ≥1.51% according to the PLCOm2012 model or 5-year risk ≥2.5% according to the LLPv2 model.[82] The variables used to calculate lung cancer risk in PLCOm2012 and LLPv2 models are shown in Table 1.1.

Table 1.1: Variables in the PLCOm2012 and LLPv2 lung cancer risk calculators

	PLCOm2012	LLPv2
Age	✓	✓
Race	✓	X
Education level	✓	X
Body Mass Index	✓	X
Chronic obstructive pulmonary disease	✓	X
Pneumonia	X	✓
Occupational exposure to asbestos	X	✓
Personal history of cancer	✓	✓
Family history of lung cancer	✓	✓ (in a first degree relative <60)
Smoking history	✓ (cigarettes per day, duration of smoking, duration of quitting)	✓ (smoking duration only)

Although a personal cancer history is included in both risk calculators, the receipt of chemotherapies which increase lung cancer risk and radiation to the lung are not specifically considered. A later version of the PLCOm2012 calculator, PLCOall2014, can be used to calculate 6-year lung cancer risk in never smokers. When the PLCOall2014 calculator was used to calculate 6-year lung cancer risk in 65,711 never smokers in the PLCO cohort, the maximum risk observed was 1.47%, which is below the ≥1.51% risk threshold for screening.[85] In view of this and the literature suggesting low rates of current smoking among HL survivors, it can be argued that most HL survivors at risk of lung cancer will not be eligible for lung cancer screening programmes aimed at ever smokers in the UK.

1.4 Uptake of cancer screening tests by cancer survivors

Two meta-analyses have reported that cancer survivors are more likely to undergo cancer screening than non-cancer survivors (odds ratio 1.27 in both studies).[86,87] Breast cancer is the only cancer for which specific screening recommendations exist for HL survivors - screening for other cancers occurs via screening programmes aimed at the general population. Two studies have reported the percentage of HL survivors who had not undergone screening for breast cancer (44% and 32%), cervical cancer (32% and 19%) and colorectal cancer (77% and 62%).[88,89] Another study found that just 50% of female survivors of HL diagnosed in teenage and young adulthood who met the National Comprehensive Cancer Network guidance for breast cancer screening had undergone screening.[90] In 2003 in the UK, a recall exercise took place in which all female HL survivors treated since 1962 with radiation to the breast before the age of 35 were invited to discuss breast cancer screening. One centre reported a 58% clinic invitation uptake rate, with 18% of clinic attendees having no evidence of subsequent screening [91] whilst another centre reported a response rate to the recall exercise of 76%.[92] The rates of recruitment into prospective studies of breast cancer screening in female HL survivors in the United States vary between 32% and 75%.[93,94] Thus, despite evidence that cancer survivors are more likely to take up cancer screening tests than non-cancer survivors, uptake remains sub-optimal.

1.5 Barriers to uptake of cancer screening

There are sociodemographic differences in uptake of cancer screening, with variation across different screening programmes. There is no clear difference in uptake of colorectal cancer screening between men and women; although more women than men participated in faecal occult blood testing in one study [95], another study reported higher uptake of flexible sigmoidoscopy among men.[96] Lower levels of uptake have been reported in non-white ethnic groups in relation to breast cancer screening[97], cervical cancer screening[98] and colorectal cancer screening.[95] In the United States, Hispanics are less likely to participate in breast, cervical and colorectal cancer screening programmes than non-Hispanics.[99] Lower

socioeconomic status, which can be measured using markers such as income, education or occupation, has been consistently associated with reduced uptake of breast, cervical and colorectal cancer screening. [99,100]

Sarma *et al* [99] categorise determinants of cancer screening participation that relate to the individual (rather than the environment) as intrapersonal (e.g. knowledge, perceptions of risk) and interpersonal (e.g. social norms and support). Better knowledge of the rationale for and benefits of cancer screening is associated with cancer screening uptake.[101,102] In keeping with this, believing that screening is not necessary if one is asymptomatic is associated with reduced uptake.[103–105] A further barrier to screening is cancer fatalism - the belief that cancer is inevitably fatal if diagnosed.[92-95] Risk perceptions are included in many of the theories proposed to predict health behaviours- including uptake of cancer screening tests[106]- such as the Health Belief Model and the Health Action Process Approach. Higher deliberative risk perceptions, which require logical and reflective thinking, were associated with higher uptake of cancer screening in two meta-analyses with a small effect size.[107,108] Affective risk perceptions are analogous to cancer worry. The impact of levels of cancer worry on cancer screening uptake are less clear, but it has been proposed that both low and high levels of cancer worry are a barrier to screening.[109,110] A meta-analysis has shown that intention to be screened is associated with uptake of cancer screening across different screening tests and that self-efficacy appears to predict intention.[111] Further intrapersonal factors that are barriers to cancer screening include information avoidance[112–114] and lower levels of health literacy.[115]

Perceived social norms are an interpersonal determinant of screening uptake. Injunctive norms refer to the extent to which other people are considered to endorse a behaviour, whilst descriptive norms are the extent to which a behaviour is considered to be performed by others.[99] Injunctive norms have has been shown to predict uptake of prostate, colon and breast cancer screening,[116,117] and both injunctive and descriptive norms may influence uptake of breast[118] and bowel cancer screening.[119] In addition, a positive recommendation to take up cancer

screening by a healthcare provider has been shown to significantly improve screening rates and to a lesser extent, adherence to screening over time.[120]

Uptake of lung cancer screening in trials and pilots to date has not exceeded 50%.[121] Intrapersonal factors shown to be barriers to lung cancer screening uptake include higher levels of cancer worry,[122] fatalistic beliefs about lung cancer,[122,123] the desire not to know if one has lung cancer,[113] and being asymptomatic of lung cancer.[113,122,124] The influence of risk perceptions is less clear. In the NELSON study, higher perceived risk was associated with lung cancer screening uptake,[124] but had the opposite effect in the UKLS study.[113]

There were significant sociodemographic predictors of uptake in the UK Lung cancer screening study. Women, current smokers, and those older than 65 were less likely to participate and those in the lowest socioeconomic quintile were twice as likely to decline as those in the highest quintile.[113] Higher levels of deprivation and current smoking were also associated with non-participation in the UK based Lung Screen Uptake Study.[121] Finally, practical issues such as travel, caring responsibilities and comorbidities are frequently cited barriers to uptake of lung cancer screening.[113,122,124] The extent to which the barriers to participation in lung cancer and other cancer screening programmes are relevant to survivors of HL is unknown.

1.6 Summary of the evidence informing this thesis

This literature review has shown that survivors of HL who were treated with thoracic radiotherapy or certain alkylating agents are at excess risk of dying from lung cancer for many years after completion of treatment. In the last decade, lung cancer screening using LDCT scanning has been shown to reduce lung cancer related mortality in ever smokers and is being widely rolled out, but most HL survivors are unlikely to meet the risk threshold for screening as most lack a significant smoking history. The socio-demographic and psychological factors which impact the uptake of different cancer screening programmes have been investigated, but the factors which would impact the uptake of lung cancer

screening among HL survivors are not known. There is a rationale and clinical need to investigate the feasibility of a targeted lung cancer screening programme for HL survivors. Pertaining to the feasibility of delivering such a programme, there are multiple issues worthy of investigation. These include exploring the perspectives of HL survivors towards lung cancer screening, investigating the psycho-social predictors of lung cancer screening uptake, developing educational materials with which to invite HL survivors to lung cancer screening and testing screening methodologies which are established in ever smokers but untested in HL survivors.

1.7 Aims and objectives of the studies in this thesis

The aim of the research undertaken for this thesis is to understand the feasibility of lung cancer screening for survivors of HL. Table 1.2 below lists the specific aims and linked objectives of this thesis and chapters in which they are addressed.

Table 1.2: Thesis aims, objectives and chapters

Aim	Objectives:	Thesis chapter:
Aim 1: To understand the perspectives and psychosocial factors that influence willingness to undergo lung cancer screening in HL survivors	To explore the perspectives of HL survivors towards lung cancer screening and how these perspectives influence willingness to undergo screening	Interview study to address aim 1, objective 1 **(Chapter 2)**
	To measure willingness to undergo lung cancer screening in HL survivors To describe the sociodemographic predictors of willingness to undergo lung cancer screening in HL survivors To measure the prevalence of lung cancer screening related health beliefs in HL survivors and describe the psychological	Questionnaire study to address aim 1, objectives 2-4 **(Chapter 3)**

	predictors of willingness	
Aim 2: To develop lung cancer screening invitation materials targeted towards HL survivors	To develop a lung cancer screening decision aid tool for use in a trial of lung cancer screening for HL survivors which supports decision making around participation To evaluate the decision aid tool among stakeholders to explore its' suitability for use in a lung cancer screening trial	Decision aid development and initial evaluation to address aim 2, objectives 1 and 2: **(Chapter 4)**
Aim 3: To test the feasibility of using lung cancer screening methodologies established in ever smokers, and novel lung cancer screening educational materials, in HL survivors.	To report the uptake rate of lung cancer screening among HL survivors invited to participate in a lung cancer screening trial To test a novel decision aid tool targeted towards HL survivors considering lung cancer screening To report lung cancer screening outcomes using imaging protocols established in ever smokers To explore the barriers and enablers to participation in a lung cancer screening trial	A pilot of lung cancer screening for HL survivors to address aim 3, objectives 1-3 **(Chapter 5)** Interview study to address aim 3, objective 4 **(Chapter 6)**

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CHAPTER 2

TITLE: The perspectives of survivors of Hodgkin lymphoma on lung cancer screening: A qualitative study

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2.1 ABSTRACT

Background

Hodgkin lymphoma survivors (HLS) are at excess risk of lung cancer as a consequence of HL treatment. HLS without a heavy smoking history are currently unable to access lung cancer screening programmes aimed at ever smokers and there is an unmet need to develop lung cancer screening (LCS) programme. In this study we prospectively explored HLS perspectives on a future LCS programme, including motivating factors and potential barriers to participation, with the aim of identifying ways to optimise uptake in a future programme.

Methods

Semi-structured telephone interviews were conducted with HLS, aged 18-80 and lymphoma-free for ≥5 years, selected from a clinical database (ADAPT). Participants provided informed consent. Data were analysed using inductive thematic analysis.

Results

Despite awareness of other late effects, most participants were unaware of their excess risk of lung cancer. Most were willing to participate in a future LCS programme, citing the potential curability of early-stage lung cancer and reassurance as motivating factors, whilst prior experience of healthcare was a facilitator. Whilst the screening test (a low dose CT scan) was considered acceptable, radiation risk was a concern for some, and travel and time off work were potential barriers to participation.

Conclusions

Our results suggest that most HLS would participate in a future LCS programme, motivated by perceived benefits. Their feedback identified a need to develop educational materials addressing lung cancer risk and concerns about screening, including radiation risk. Such materials could be provided upon an invitation to LCS. Uptake in a future programme may be further optimised by offering flexible screening appointments close to home.

Patient or Public Contribution

In this study, participants were patients and potential future recipients of lung cancer screening.

Key words:

Hodgkin lymphoma, lung cancer screening, risk, attitudes, benefits, concerns

2.2 INTRODUCTION

Hodgkin lymphoma (HL) is a malignancy which predominantly affects young adults and the elderly.[1] With modern treatments, over 90% of those diagnosed at a young age are cured and live to experience the late effects of treatment.[2]

Alkylating agents and radiotherapy used to treat HL put survivors at excess risk of developing subsequent malignant neoplasms (SMN), with smoking having a multiplicative effect on lung cancer risk.[3–5] Compared to survivors of other primary cancers, HL survivors have the highest risk for developing SMNs with those diagnosed with HL in adolescence or young adulthood being at higher risk compared to those diagnosed in childhood or during older adulthood.[6] The most common SMNs are breast cancer, lung cancer and colorectal cancer, with 30-year reported cumulative incidences of 16.6%, 7.1% and 2.5%, respectively.[5] Lung cancer and gastrointestinal cancers (of the upper and lower gastrointestinal tracts) are the leading causes of SMN related mortality in HL survivors.[3,5,7]

Despite evidence of an excess risk of breast, lung and bowel cancer, the sole targeted screening programme currently available to HL survivors in England is the NHS breast screening programme for women at very high risk of breast cancer.[8] Through this programme, women who were treated for HL (and non-Hodgkin lymphoma) with radiotherapy to the breast tissue before the age of 30 are invited to undergo early annual breast cancer screening with an MRI (magnetic resonance imaging) scan and mammogram. In the case of bowel cancer screening, HL survivors aged 60-74 can access the national bowel screening programme in the same manner as the rest of the general population. With regards to lung cancer screening, several large trials conducted in the general population in the past decade have shown that low-dose CT screening of the thorax reduces lung cancer related mortality in ever smokers by detecting lung cancers at an early stage.[9–12] In England, lung cancer screening is being piloted in ever smokers aged 55-74 with eligibility to undergo screening being determined by lung cancer risk calculators.[13] Such pilots are unlikely to benefit HL survivors because the average age at lung cancer diagnosis (45 years)[14] falls below the screening threshold (55 years) and lung cancer risk calculators do not account for risk associated with HL treatments. Consequently, HL survivors without a heavy smoking history do not meet screening criteria for pilots aimed at ever smokers, even if eligible by age, creating a need for a lung cancer screening programme targeted specifically towards HL survivors.

Among ever smokers in the general population, research has shown that lung cancer screening is acceptable.[15] Uptake rates are variable, ranging from <5% in the United States[16] to 26% in a recent community based pilot in Manchester, UK.[17] In the UK Lung Screening pilot trial, higher socioeconomic status was associated with a positive response to a screening invitation and subsequent participation. Current smokers were less likely to participate than former smokers and practical barriers were the most common reasons for non-participation.[18,19] Qualitative studies have identified fatalistic attitudes towards lung cancer and smoking-related stigma as barriers to participation in lung cancer screening.[20,21] The views of HL survivors towards lung cancer screening have not previously been explored so it is not known

whether the barriers to LCS participation in ever smokers also apply to HL survivors or whether their views differ. By gaining an understanding of the motivating factors and barriers to LCS participation in HL survivors, it may be possible to design a future LCS programme which reduces barriers to participation, thus optimising uptake rates. Thus, an exploration of the perspectives of HL survivors towards a future LCS programme is warranted and is addressed by this qualitative study.

2.3 METHODS

This study employed a qualitative design, using semi-structured telephone interviews with survivors of HL. Ethical approval was granted by the North West Greater Manchester West Ethics Committee (ref: 20/NW/0025).

Recruitment

HL survivors aged 18-80 who were known to be at excess risk of lung cancer due to previous treatment and who had survived relapse-free for at least 5 years after completing treatment were eligible for inclusion, regardless of smoking status. The upper age limit for eligibility reflects the highest age threshold for eligibility to participate in lung cancer screening trials in ever smokers published to date, whilst the lower age limit reflects the fact that lung cancer cases have been detected at all time periods after 5 years since completion of treatment. The wide age range threshold for also eligibility also reflects the bimodal distribution of HL in the young and the elderly. Patients with a diagnosis of lung cancer at any time, or who had participated in a pilot lung cancer screening programme were excluded. We identified potential participants from a prospectively maintained database of lymphoma survivors with at least 5 years follow-up (ADAPT). 194 HL survivors were eligible for inclusion. Of these, 80 were randomly selected, stratified according to attained age, time since treatment, prior treatment, and smoking history (see Table 2.1 for stratification criteria).

Table 2.1: Stratification criteria to guide random selection of participants

Sex	No more than a 40:60 ratio between males and females
Attained age	Aim to include participants from each decade of age within the eligibility criteria
Time since treatment	Aim to include participants in the following ranges of years since treatment: 5-15, 16-25, 26-40
Treatment / smoking history	Aim to include participants who have been exposed to the following risk combinations: 1) Radiotherapy + alkylating agent 2) Alkylating agent alone 3) Radiotherapy alone (if possible) Within 1-3 we will aim to recruit ever and never smokers.

Potential participants were sent an invitation letter and the participant information sheet by post. The invitation letter was signed by a doctoral student working in their treating team. Prior to the interview, participants received brief written information on lung cancer screening, provided written consent and completed a short questionnaire. The purpose of the questionnaire was to collect sociodemographic data which was not available from the ADAPT database (ethnicity, employment status and education), to confirm smoking history, and collect other health-related data such as self-rated health and prior participation in cancer screening opportunities.

2.2 Data collection

The first author conducted telephone interviews lasting approximately 20 minutes between March and April 2020. The interview schedule explored perceptions of

lung cancer and lung cancer screening, with prompt questions to explore risk perception, the perceived benefits of lung cancer screening and potential barriers to attending.

2.3 Reflexivity statement

The interviewer was a clinician and doctoral student working within the participants' treating team. In the majority of cases, the interviewer had not been involved in the participants' care during treatment or follow-up. In questioning participants and answering their questions about lung cancer risk and screening, the interviewer adopted a non-judgmental and neutral stance. To respond to participants' questions about lung cancer risk and a future lung cancer screening programme, the interviewer referred to their knowledge acquired through review of the relevant literature, taking care to neither promote the benefits nor risks of lung cancer, or other cancer screening. Participants were aware that this study was being conducted with the view to eventually offering lung cancer screening to at risk-survivors.

2.4 Data analysis

Interviews were audio-recorded and transcribed verbatim by an external company. Transcripts were linked to a pseudo-anonymised study ID number. An inductive approach to thematic analysis was used to analyse the transcripts.[22] This began with familiarisation with transcripts. Whole transcripts were examined one by one and data pertinent to the research questions were identified and coded by the first author. Throughout this process, new data was applied to an existing code, or a new code was created. A second researcher followed the same process, coding 9 randomly selected transcripts. The two researchers discussed the codes they had independently developed, their relationship to each other and emergent themes, following which the first author finalised the coding framework. The second researcher was involved throughout the development of the thematic analysis. Participants have been sent a summary of the study findings but were not involved in the analytic process.

2.4 RESULTS

3.1 Participant characteristics

Thirty HL survivors took part in the study. Participants included men and women with a median age of 53 years. Most were white British. Around half had a university education and most were in employment. The majority had received both chemotherapy and radiotherapy in keeping with treatment guidelines and trends over the last 40 years. Around two thirds rated their health as fair to poor. Five reported a history of SMN. Two thirds reported a prior invitation to undergo cancer screening, reflecting the predominance of female participants in the study invited to early breast cancer screening. Never smokers were a large majority. Participant characteristics are detailed in Table 2.2.

Table 2.2: Participant characteristics

Participant characteristics (n=30)	
Gender (male:female)	12:18
Median age (range)	53 (38-73)
Ethnicity	27 English/Welsh/Scottish/Northern Irish/ British 2 Asian / Asian British 1 British (Greek)
Education	16- undergraduate/postgraduate degree 6- A levels /some college education 3 had GCSEs or O levels or equivalent 3 left school without qualifications 2 preferred not to say

Employment	21 employed/self-employed 2 looking after home or family 7 retired
Median number of years since treatment (range)	22.3 (12.8-43.1)
Treatment received for Hodgkin lymphoma	Radiotherapy alone: 1 Chemotherapy and radiotherapy: 24 Chemotherapy alone: 5
Self-rated health	Excellent- 5 Very good - 5 Fair - 12 Good - 7 Poor -1
History of SMN	Yes - 5 (3 breast, 1 thyroid, 1 kidney)
Prior invite to cancer screening	Yes - 19 (100% attended 1 or more screens) No - 8 Missing data - 3
Family history of lung cancer	Yes -1
Smoking history	Current - 1 Former - 11 Never - 18

3.2 Thematic analysis

The quotes presented here are linked to study ID number, patient gender (M/F), and age (study ID number-gender-age). Tables of quotes illustrative of each theme are available as Supporting Information.

3.2.1 Lung cancer risk perceptions

As most participants were not aware that their prior cancer treatment increased lung cancer risk prior to participation in this study, there are two subthemes. The first describes participants' risk perceptions unrelated to cancer treatment (beliefs held prior to participation in this study) and the second relates to the impact of their prior knowledge and experiences on risk perceptions.

Subtheme 1: Lung cancer risk perceptions prior to study participation

Most participants were not aware of their excess risk of lung cancer due to their cancer treatment prior to being contacted about the study. Several factors appeared to influence lung cancer risk perception. Participants associated lung cancer with smoking and a lack of smoking history reduced perceived risk. One participant referenced the association of lung cancer with occupation or secondary exposure to cigarette smoke: "I'm not a particularly at risk group for lung cancer. I've never smoked, I've never worked in industry or in a smoky environment." (P43, F, 66) Despite the association of lung cancer with smoking, several former smokers expected or hoped that quitting smoking abolished lung cancer risk:

"You know, I've managed to get away with it, if you like, 'cause I've packed in so long ago now, I hope anyway" (P23,F,60).

Living a healthy lifestyle was considered to reduce the risk of developing cancer; one participant said they would not attend routine cancer screening because their healthy lifestyle meant their risk of developing cancer was low. A lack of family history of cancer reduced risk perceptions and led participants to expect clear cancer screening results, as did a lack of symptoms.

"When I go for cancer screening I kind of go with the assumption that I'm probably alright, because nobody in my family has ever had that." (P63,F,69)

"I feel in quite good health and everything, so I would hope that, yeah, that everything was fine." (P20,F,50)

One participant reported being reassured by a healthcare professional that her cancer risk had normalised to that of the general population. Weighing up risk factors and lived experience was difficult for one participant:

"I do have *COPD*, so I really don't know. I mean there's no history of lung cancer and whatnot in the family, but having said that, like I've had Hodgkins and I don't know what that treatment has done, you know, to my body..." (P23,F,60)

Subtheme 2: The impact of knowledge and experience on lung cancer risk perceptions

On receiving information about the risk of lung cancer after treatment for HL in the study materials, participants considered this in the context of their prior knowledge or experience of the effects of cancer treatments. Despite being unaware of the excess risk of lung cancer, many participants recalled being told of the risk second cancers including leukaemia and breast cancer, cardiac problems or the general possibility of late effects in the future. For some, this seemed to mitigate the impact of receiving information on the risk of lung cancer:

"I think 'cause I was told such a long time ago, then it wasn't like a *nasty*, *nasty* surprise when the letter came and so yeah I'm…I would have preferred…I'm glad I was told then, rather than just being a surprise." (*P11,M,48).*

Women previously informed of their increased risk of breast cancer following chest radiotherapy understood the risk of lung cancer through the anatomical closeness of the lungs to the breasts: "It's all in the same area" (P74,F,50). Similarly, engagement in a long-term follow-up programme influenced participants' response to being informed of lung cancer risk, in that some expected to be contacted about late effects, surveillance or screening. Another participant described the new

information as “comforting” since they appreciated being informed of their risks in the context of ongoing follow-up. However, some participants were distressed by the information. One, who had suffered a heart attack attributed to radiotherapy, said:

“So, when I opened this and it said I could have lung cancer, I was just like oh for God's sake, is there anything else they're going to throw at me. Yeah, it was a like similar feeling of…well horror really” (P63,F,69).

Participants’ spoke of their personal experiences of a variety of late effects of cancer treatment. Symptoms such as breathlessness, cough and recurrent chest infections were commonly reported, and some had been diagnosed with asthma or bronchiectasis. Participants frequently attributed these issues to their cancer treatment and appeared to use this to make sense of their lung cancer risk:

“I think because I’m aware that the treatment I had increased my risk of breast cancer and I know I’ve got damage to my lungs that there seems to be a correlation between, I should probably keep track of what’s going on in my lungs.” *(P36,F,56)*

The language used to describe cancer treatment reflected this understanding. Radiotherapy was described as “crude” and as being “blasted” around the lungs, causing “scarring”. Likewise for chemotherapy: “it’s got to do something to your body over the long haul”.

3.2.2 Theme 2: Positive perceptions of lung cancer screening

Participants had a positive attitude towards a lung cancer screening programme for HL survivors and the majority expressed willingness to attend. Their positive attitudes were informed by views towards cancer screening in general and the personal perceived benefits of undergoing lung cancer screening.

Subtheme 1: General perceptions of cancer screening

Participants felt strongly that people should take up the offer of cancer screening and many could not comprehend why someone would decline the offer.

Undergoing cancer screening tests was described as "sensible" and "a positive cause". Several participants expressed their view that all types of cancer screening are beneficial. Many said they would always take up an offer of cancer screening. Cancer screening was described as a "routine MOT" test and compared to the "Well Man and Well Woman" health checks. Several viewed access to targeted screening tests as a benefit of being a cancer survivor – one participant described this as a "silver lining". For some, prior experience of cancer was a clear motivation for participating in cancer screening, whereas others felt they would have been enthusiastic about participating even without a prior diagnosis. Recommendation by a medical professional was a motivating factor for participating in screening programmes.

Subtheme 2: Benefits of lung cancer screening

Early diagnosis of lung cancer

An early diagnosis of lung cancer was a benefit of screening reported by all participants, who perceived early-stage lung cancer as treatable and curable, whilst late-stage lung cancer was perceived to have fewer treatment options and poor survival rates. Several knew people who had died of advanced cancer.

"The earlier you catch any of these things, the better you are of, you know, finding treatment" (P23, F,60).

Many reported that you could be asymptomatic of cancer and felt that cancer symptoms were associated with advanced cancer. It was felt that lung cancer was best detected whilst asymptomatic.

For some participants, perceptions of early diagnosis were informed by their previous experience of being diagnosed with cancer. Experiences of a protracted journey to a diagnosis of HL, preceded by multiple visits to the general practitioner

(GP) had led to a late-stage HL diagnosis for some, who felt their treatment could have been less severe had they been diagnosed earlier. Some participants' had already been diagnosed and treated for second cancers detected at an early stage. Similarly, one participant described being diagnosed with ischaemic heart disease at routine follow up prior to any serious consequences. In contrast, a participant who had suffered a heart attack "out of nowhere" lamented the lack of screening for ischaemic heart disease prior to the event. Several felt that their GP lacked knowledge about late effects:

*"…*a lot of GPs haven't really understood what any of the long-term side effects and things are." (P3,F,39)

Whilst the main focus of discussion was early diagnosis, several acknowledged the possibility of a diagnosis of advanced lung cancer as a result of screening. They perceived this to be a benefit of screening since it would allow them to plan and spend time with their loved ones: "at least you can do things and be with your family more".

Reassurance and information about one's health

The "peace of mind" and "reassurance" that lung cancer screening could offer was a benefit reported by all participants. Several reported that their spouse would also feel reassured. A prior cancer diagnosis influenced the degree of health-related concerns experienced by participants, who described being "hypersensitive" about their health. For one participant, developing thyroid cancer "convinced" her that she will develop cancer again in the future. Others denied worrying about their health, stating they felt "lucky" or "grateful" to have survived HL and that any time was a bonus, although they still reported reassurance as a benefit of screening.

Uncertainty over health was often expressed. The opportunity to gain information about one's health, and thus reduce uncertainty, seemed to increase enthusiasm for screening and imaging surveillance. Another was anxious to commence bowel cancer screening, despite not being of an eligible age. Several felt their GP lacked

knowledge about late effects, which might have increased enthusiasm for screening as a method of seeking information about their health.

"You don't know what's going on inside you, unless somebody's constantly checking you". (P5,F,51)

Several participants felt that a screening scan could provide information about future health issues, allowing them to take preventative action to improve overall health, for example through lifestyle change:

"If you know that something is going on, you can at least attempt to do something about it" (P40,M,38).

Participants commonly reported a proactive approach towards their health, adopting a healthy lifestyle through diet and exercise, motivated by their previous cancer diagnosis.

3.2.3 Theme 3: Concerns and potential barriers to participation

Whilst a CT scan was perceived as fast, painless and non-invasive test - which compared favourably to participants' experiences of other investigations such as MR scans and other diagnostic tests -many reported concern about the radiation associated with a CT scan, with some stating they would want more information about the level of risk involved. For one female participant who was participating in the breast screening programme for women at high risk, even a small risk associated with radiation could be a potential barrier to undergoing lung cancer screening. One participant was concerned about the possibility of false positive results, which could lead to unnecessary further investigations, although they, and one other participant, also perceived a CT scan to be less likely to produce false positives results than other tests. When other participants were probed about their views on the potential need for further investigations following the baseline screening test, such as a biopsy, the majority expressed that this would not a barrier to attending as it was seen as a necessary part of the screening process in

order to rule out cancer or make a diagnosis. Taking time off work was reported as a potential barrier to participation by two participants, one of whom had previously needed to take multiple days of work for biopsies following breast cancer screening. Other participants said that supportive employers and help from family could help overcome practical issues relating to time off work and travel.

Participants commonly wanted more information about the process, risks and benefits and potential outcomes of lung cancer screening. For one participant who had experienced difficulties obtaining information about breast cancer screening, easy access to clear and non-contradictory information was a crucial factor in deciding whether to participate.

"If I couldn't get the information I needed for this to just get a sense of what the various risks and issues were, then I would be definitely more likely to not have it than to have it." *(P18,F,44)*

Waiting for a screening result was frequently described as worrying time, although the severity of worry experienced varied between participants. Some said they would be "mildly worried" and able to "put it out of my mind", but others said the result would always be on their mind. Prior experience of waiting for scan results helped some people cope with worry, or to worry less.

"I had so many things in my life, so I guess I'm a bit used to it" (P68,M,50).

Similarly, having experienced clear screening results before meant one participant did not anticipate worrying about the lung cancer screening result. Several took the approach, "I'll worry when I have to" and felt that a positive attitude towards screening made it less traumatic and could even make a positive outcome more likely.

Almost all participants said that they would attend lung cancer screening despite their concerns. Explaining their willingness to undergo screening, many expressed

that it was better to know either way, reflecting uncertainty about their health and desire for surveillance and screening:

"To not know, is a greater fear than knowing, to me" (P33,M,71).

"Like, if I get worried about anything, I've got a lot of things to look back on that I've had. But I think that's why I'd rather know and be kept an eye on than not, than just forgotten." (P29,F,56).

Furthermore, screening was considered to be an important and necessary health intervention to the extent that many were prepared to accept more uncomfortable or invasive tests such as MRI or endoscopy.

"Like I said if it was the MRI scan, my mind-set would be different, but I'm still…I'm sure I'd still somehow get round it" (P5,F,51).

Reflecting the frequently expressed view that the potential benefits would outweigh the risks, one participant said:

"For all the things that I've mentioned, like convenience or uncomfortableness or, you know, having to have a CT scan, whatever that might be, none of that is of any relevance in the grander scheme of things" (P74,F,50).

2.5 DISCUSSION

In this study we explored the perspectives of long-term survivors of HL towards lung cancer screening. We report high levels of enthusiasm, possibly reflecting views in the general population towards cancer screening and the positive perceptions of screening held by cancer survivors,[23,24] who are known to be more likely to participate in cancer screening than non-cancer survivors.[25,26] Lung cancer screening research to date has focussed on ever smokers. In this study, we found that HL survivors differ from ever smokers in that they perceive early-stage lung

cancer as curable, thereby differentiating them from ever smokers who frequently report fatalistic attitudes as a barrier to undergoing lung cancer screening.[15,20,21] Such fatalistic attitudes towards lung cancer are more prevalent among smokers than non-smokers,[20] which may explain the lack of fatalism in our study where current smokers were under-represented.

For our participants, the reassurance provided by screening was an important benefit, in keeping with other studies of lung and prostate cancer screening.[20,21,27] Seeking reassurance could be a particularly important motivation in HL survivors due to the worry resulting from a prior cancer diagnosis; one study found that 77% and 72% of HL survivors are concerned about future health or developing another cancer, respectively.[28] In a future lung cancer screening programme, the delivery of lung cancer risk information to survivors who were previously unaware of their risk has the potential to exacerbate pre-existing health-related anxiety, especially given that lung cancer risk increases with time since treatment and is not negated by undergoing screening. Whilst the context in which this information would be delivered – within an offer to undergo lung cancer screening – might help to mitigate negative psychological outcomes, it will be important to provide psychological support to survivors following a lung cancer screening invitation. The potential for causing anxiety should be balanced against the potential benefits of lung cancer screening, most importantly the early detection of lung cancer.

In this study we identified a lack of awareness of lung cancer risk after treatment for HL, with participants perceiving their lung cancer risk to be low when considering risk factors such as smoking and family history. Notably, former smokers attached little significance to their smoking history, in keeping with a study showing that former smokers have a low personal perceived risk after quitting.[29] Although a CT scan was considered an acceptable test in our study, consistent with the views of ever smokers,[15,30] radiation was a frequently reported concern. Since better knowledge and higher levels of risk perception are associated with screening uptake,[31] participation in a future lung cancer screening programme may be optimised by educating survivors about risk through the provision of targeted

informational materials, which could additionally address concerns about radiation risk associated with a low-dose CT scan and the likelihood of false positives. Taking time off work and travelling were reported as potential barriers to participation in our study, consistent with reported barriers to participation in cervical and bowel cancer screening[32,33] and a lung cancer screening trial.[19] A future lung cancer screening programme for HL survivors should address these barriers - which may disproportionately impact those of working-age and lower socio-economic status – by offering flexible screening appointments and minimising the distance people are required to travel, potentially by offering screening in the community, or in local health centres or hospitals.

In the present study, most participants indicated an intention to participate if lung cancer screening was offered, but their enthusiasm may not reflect actual future participation rates. The gap between people's intentions and their subsequent behaviour is a well-known phenomenon[34] that is typically not considered in classical models of health behaviour[35], but are addressed in newer models such as the health action process approach (HAPA). The HAPA makes a distinction between the variables that influence intention - the motivational phase - and the volitional phase that ensures maintenance of behaviour.[36] Risk perception, outcome expectancies and self-efficacy, which were explored in the present study, are important in the motivational phase, but the hypothetical nature of lung cancer screening for HL survivors means that volitional phase variables may have been missed and would be worthy of further research.

4.1 Strengths and limitations

This study is part of a comprehensive project investigating the feasibility of delivering a lung cancer screening programme for HL survivors. We have shown for the first time that most HL survivors are willing to undergo lung cancer screening if available. We have identified gaps in survivors' knowledge about lung cancer risk, which should be addressed in educational materials provided to HL survivors as part of an invitation to undergo lung cancer screening. Our sampling strategy helped ensure that study participants were diverse in their current age and time since

treatment, with both genders represented. By recruiting using a clinical database with details of previous cancer treatment, we were able to select participants known to be at risk of lung cancer. The use of semi-structured interviews allowed the researcher to explore the beliefs and experiences, which informed participants' views towards screening and willingness to undergo screening. We have described discordant views in the data.

The findings are limited by the participant characteristics. Half the participants had college or university education, which is associated with higher uptake of cancer screening.[37] It is therefore possible that our findings, in terms of enthusiasm for screening and reported barriers, do not reflect the views of all HL survivors. In particular, those with fewer material resources, for example those who do not own a vehicle, and people with a lower than average reading age who might have difficulty accessing written lung cancer screening educational materials, are likely to experience greater barriers to participation than reported by our participants. Current smokers, who are at the highest risk of lung cancer, were significantly under-represented in our sample, which could reflect smoking practices in HL survivors; the rate of current smoking in HL survivors has been reported as 7%.[28] Nevertheless, we cannot report on the perspectives of HL survivors who currently smoke. The participants may be more enthusiastic about lung cancer screening than those who did not respond to our study invitation, which is likely to have introduced a response bias. HL survivors who remain in follow-up may have better knowledge of late effects than those discharged soon after completion of treatment, and our results may therefore not be representative of the national survivor population discharged from long-term follow-up. Finally, the invitation to this study came from a doctor who worked at the participants' treating centre, which could have led to social desirability bias, with fewer reported barriers reported as a result.[38]

5 CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH

Our findings suggest that HL survivors would be willing to attend lung cancer screening, motivated by perceived benefits of cancer screening tests, and that

uptake of a future lung cancer screening programme by HL survivors may exceed uptake by ever smokers. There is no established protocol for survivorship care for people treated for Hodgkin lymphoma, with follow-up care for those in remission varying widely throughout the country. Breast cancer screening for HL survivors is coordinated at a national level by Public Health England rather than individual treating centres and it is likely that a future targeted lung cancer screening programme would follow a similar structural approach. However, the most pressing challenge prior to implementation will be the identification of long-term survivors at risk of lung cancer, many of whom will be discharged from follow-up, which will require a coordinated effort by treating centres. Further steps towards delivering lung cancer screening include large scale epidemiological cohort analyses to determine an appropriate lung cancer risk threshold to guide eligibility for screening and the development of lung cancer screening educational materials to support decision making and reduce barriers to screening uptake. Future studies should address the feasibility of such a programme and explore barriers to participation in a real-life setting, particularly in current smokers and survivors discharged from routine follow-up.

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2.7 SUPPLEMENTARY DATA

Table s2.1: Quotes illustrative of theme 1: Lung cancer risk perceptions

Quote	Participant
Subtheme 1: Lung cancer risk perceptions prior to study participation	
"Yeah, and of the cancer returning, but yeah, I just didn't recall it being that…in fact I didn't recall it being any particular type"	P11,M,48
"Well, I knew about it because I knew about this as well as all the side-effects because of the radiotherapy. I had the ABVD as well, so those two would cause certain problems."	P68,M,50
"I hadn't realised there was a vulnerability or link there or if I had been informed I'd missed it. It's quite a long list of things I'm vulnerable to so I'd not really taken in it."	P15,M,54
"Not really no I don't smoke and I live a reasonably healthy lifestyle out in the countryside so it wasn't top of my list, no."	P15,M,54
"I'm not a particularly at risk group for lung cancer I've never smoked I've never worked in industry or in a smoky environment."	P43,F,66
"I suppose you just naturally think 'cause you've stopped doing something that it can't happen, even though that's not the case."	P11,M,48
"You know, I've managed to get away with it, if you like, 'cause I've packed in so long ago now, I hope anyway."	P23,F,60
Interviewer: "What do you think it is about you that makes you so willing to have screening tests?" Participant: "I don't really know, actually, because my parents both had heart disease, so it's not as though they had, you know, lung cancer or anything"	P67,F,73

"Recently, the doctor sent me for x-rays, he couldn't find anything. I've done the test with the peak flow meter, they've done all sorts, a few different tests, and they've not been able to find anything, and the doctor's not been able to pinpoint anything, they've just told me it could be some sort of a scarring from the chemotherapy."	P28,M,57
"I think because I'm aware that the treatment I had increased my risk of breast cancer and I know I've got damage to my lungs that there seems to be a correlation between, I should probably keep track of what's going on in my lungs."	P36,F,56
"If there's a risk of breast cancer, your lungs are just behind your breast anyway"	P80,F,52
"It just made a bit of sense because where the treatment is so strong and how many things it could, well, potentially people could get through the treatment, it made sense really because the radiotherapy was blasted around that area, like your lungs and everywhere."	P48,F,58
Subtheme 2: The impact of knowledge and experience on lung cancer risk perceptions	
"No not really it was neither of those it was more I suppose the word to use would be more comforting than anything else, because since I've been an outpatient is always nice to be able to know that there's those kinds of things going on that I could be directly affected by you see. So no I wasn't shocked by it, it was more it put a smile on my face really in that respect."	P8,M,50
"I wasn't surprised at all, because the [hospital] had been quite consistent in, you know, because of the after effects of the trial that I was on when I had the Hodgkin's disease, so it didn't scare	P74,F,50

me, it didn't bother me"	
"I think [nurse clinician] who I was under at one time, she said, in the future we might contact you for different things and would you be willing, I said, yeah, it's fine, so I've always expected it"	P58,M,53
"It didn't, because I'm on the…I was part of the heart study as well, and they did say it was because of the type of chemotherapy that I had, that obviously those kinds of things could be more likely in the future. So I just assumed it was for a similar reason."	P20,F,50

Table s2.2: Quotes illustrative of Theme 2: Positive perceptions of lung cancer screening

Quote	Participant
Subtheme 1: General perceptions of cancer screening	
"I think it's a good idea. I think anything that gets things as early as possible, I'd rather deal with that than you know wait head in the sand and then find out it's all too late."	P30,M,51
"Well I think any kind of screening is beneficial to people, and should take you up when anything, you know…and I know it's a study and [hospital] were absolutely fantastic with me. And anything I can do to help in return is…I will do, you know"	P23,F,60
"I think it's personally a good thing, I'm happy for all the follow ups I can get really"	P47,M,46
"Yeah, it's like I still go for smear tests, I've always gone for those, I know people put off things like that and they aren't pleasant, but I think anything that can detect anything is always definitely worth doing."	P72,F,42

“Yeah, if the screening test was available, I’d have it and that would be that, it would just be part of my Hodgkin’s life, and you’re grateful to be here really, although it can be hard work at times.”	P34,F,61
“Well, I personally just take whatever's offered, you know. So I do the breast cancer screening now because of radiotherapy of the chest, I do the bowel cancer screening that you get when you're over 60, you know, I do whatever there is really. I'm open to it.”	P69,F,64
“So, having another routine scan, it doesn’t matter at all to me. I think I’m used to it.”	P48,F,58
“I get blood tests and all sorts that most people don’t get. So it's like having a free Bupa health test every week, every year isn’t it.”	P40,M,38
“But if there is a test for something, then the test should be done, because without that test, why bother developing the test, because nobody’s going to use it.”	P33,M,71
“Yeah, I think it would be a bit daft to turn something like that down, because what harm is it going to do?”	P29,F,56
“I’m scratching my head to see any reason why somebody wouldn’t want to do it.”	P74,F,50
“I don’t want to make this sound too strong, but I’m just curious as to why it’s not a normal procedure. What…you know, why it’s not just a routine thing? If there is an enhanced risk of anything following any other condition, surely we should just test for that.”	P33,M,71
Subtheme 2: Benefits of lung cancer screening	

Early diagnosis of lung cancer	
"Given the fact that I've been through one cancer treatment and everything it's good that you can potentially then know that you could potentially be called in for a screening to assess whether possibly to find it early if it was already there."	P8,M,50
"The earlier you catch any of these things, the better you are of, you know, finding treatment."	P23,F,60
"I think, if they're tiny minute…well, you know, they know they can do something about it then."	P67,F,73
"I'd much rather it get caught early and go through treatment which is never fun but rather get through that than find out that it's a year later it's not treatable"	P30,M,51
"And even if there was something wrong, hopefully that they've got things early enough"	P29,F,56
"Yeah, and they said there was nothing wrong with me. When I read the symptoms, it could have been one of three things and Hodgkins was one of them. I was the right age, average age, 26, female, you know? All that fitted but my GP didn't even pick up on it. Nobody picked up on it. For two years I just went on and it was Stage 2B when they found it but it could have been a lot better if they'd picked it up earlier. I might not have had to have chemotherapy; I could have just had radiation treatment."	P80,F,52
"It could have been a different story, couldn't it, you know, if it had been a little bit later. So, you know, I had it in, like, nearly every lymph node going: the only place I didn't have it was in my bone marrow, and I think if it had been in my bone	P20,F,50

marrow, it would have been a completely different story, so yeah, I think early detection is really important."	
"The heart attack was completely out of nowhere, you know, that was just like woomph it arrived, and I had no previous symptoms or anything. But, you know, lung cancer's much more insidious and, you know, there are things that you can do very early on when I wouldn't even know I had it. Whereas a heart attack's a heart attack and you unfortunately know right away."	P63,F,69
"And also it gives me…would give me a chance, for example, to ensure that all the things that I do in the house, my wife would know how to do it and my grandchildren would know how to do it, or know how to get things done."	P33,M,71
"Yes, I think, it would, I mean, it'd give 'em a better chance of helping them to…even if they couldn't survive it but, I think, they could if they found it straight away."	P67,F,73
"The sooner I know that I am ill, the better off I am in terms of getting better, or not; but at least I can plan."	P3,F,39
Reassurance and information about one's health	
"I think when somebody's been through something no matter what it is you're always worrying I imagine and the reassurance I thought it's just great."	P45,F,67
"But an ongoing screening would be great, wouldn't it? It just reassures you that you're okay, personally."	P28,F,60
"I'm happy to go and just get that peace of mind really, and to know that nothing's happening"	P47,M,46
"If something comes up like a lump in your neck or anything	P58,M,53

like that, anything that you think is out of the ordinary, you automatically think, oh God, it's something is back or I've got cancer or something, because obviously you've had it in the past."	
"But luckily because I was so paranoid with everything, I caught it very, very early. I had a mammogram, and a reconstruction but because I was so keen and like, I don't know, checking myself and everything, well, it saved me actually."	P48,F,58
"I suppose I must worry to some extent but I think because of my experience when I was 17, and I can remember at the time thinking if I carry on worrying like this, I'm going to die of a heart attack so what's the point of that?"	P34,F,61
"I've kind of always lived my life as, you know, I could die anytime so I just fill it, you know what I mean, just keep busy because you're lucky to be here still. And if at some stage, you know, it's my time, it's my time, I'm still lucky to have had these extra 30-odd years."	P69,F,64
"I think I was very, very lucky to come through Hodgkins and…so no I don't worry about it at all."	P23,F,60
"Well I guess you can find out if something bad is going to happen in the future or not and take some steps to either ease it, help it, prevent it or whatever."	P40,M,38
"Just to see if there are any, like, lifestyle changes I would need to make, you know, earlier rather than later."	P20,F,50
"Yeah, I certainly look after myself a lot better, and yeah, I listen to my body and yeah, I've changed my lifestyle a lot in fairness."	P11,M,48

"Well, being a Hodgkins lymphoma survivor has meant that I've had to learn an awful lot about medical stuff myself because a lot of GPs haven't really understood what any of the long-term side effects and things are."	P3,F,39
"I find that GPs don't really know much. One GP said to me when I said I'm at risk of having breast cancer what do you think about…I just wanted to talk through an elective mastectomy. He told me to go home, stop worrying and get a life."	P34,F,61
"I mean, I've benefitted before, through things which may have caused from the treatment I've had for cancer and I don't know what else may be lingering inside me, you know what I mean, which maybe wanting to be looked at maybe, I don't know."	P28,M,57
"I'm over 50 now and I want the bowel screening thing done. My doctor was saying, it's when you're 55, and I'm thinking, God, that's three more years yet."	P80,F,52

Table s2.3: Quotes illustrative of theme 3: Concerns and potential barriers to participation

Quote	Participant
"A CT scan, it's not problematic. I mean you'd have a slight concern they'd find something, but that's a concern anyway so no there wouldn't be anything that would worry me."	P15,M,54
"There are a lot worse things than a CT scan, for definite, so even the procedure is not, in my view, particularly uncomfortable or concerning or anything like that, there are other things that I've had done, in my time, than are a lot	P74,F,50

worse, put it that way."	
"Back in the day I've had CT scans and it's actually, you know, apart from the injections, the CT scan was always more enjoyable than an MRI scan, and this looks like a very short CT scan, so the scan itself is fine."	P18,F,44
"In terms of having the scan, there's nothing like that for me in there, there's no nasty response to it at all."	P78,M,52
"But the only thing that would worry me really…okay then, I'd ask about the risks, the radiation risks. Which is very low, very slight, fair enough."	P29,F,56
"Another aspect I guess as well is about the radiation levels of a CT scan, because I'm aware that a CT scan has more radiation than an X-ray say or I would expect it to have more than mammography even."	P18,F,44
"Yes, I'd still have the test knowing that another test might be around the corner."	P34,F,61
"I understand there's a bit of radiation involved in that, I suppose that would be my only slight concern with it."	P47,M,46
"There would be the practicality of trying to juggle work, 'cause assuming I'd be coming down to the Christie is quite a hike for me and it means basically half a day off work, which is quite a precious thing."	P78,M,52
"The distance I might have to travel and driving on the motorway although I imagine that'll be quite easy at the moment."	P43,F,66
"Yes I mean if you were to tell me that there was a high percentage of false negatives in the test that would put me	P15,M,54

through procedures I didn't necessarily want that would make me less likely to do it yes."	
"I don't think, it's not like other tests with false positives is it really and things, you know it's a scan so it can lead onto further investigations to make sure, but my understanding is once you're scanned and there's something there then it'll be looked at further and ruled out or confirmed one way or the other."	P30,M,51
"Yeah, I don't tend to have that, no, like I say, if I got offered it, even if was feeling fully well, I would still take it up."	P72,F,42
"Yeah I probably would still go because I mean with the Hodgkins, I didn't know I had Hodgkins I was reasonably OK as far as I knew."	P45,F,67
"I don't find it worrying going for it and having it done but I do get nervous when I know that I'm due to get the letter with the results."	P36,F,56
"There would be a bit of nervousness whilst, yeah, absolutely, I think that's only human nature really, as well, isn't it? But yeah, definitely, there would be a bit of concern, during that period I guess."	P47,F,67
"Well, psychology of having a test itself, when you have a test then you can expect a couple of days waiting for the result, but then I know some people can get affected more. For my case again, I had so many things in my life, so I guess I'm a bit used to it, whenever I have a test, being a bit stressed, wait for the result. But that's the only downside of having the test I think."	P68,M,50
"If I couldn't get the information I needed for this to just get a sense of what the various risks and issues were, then I would	P18,F,44

be definitely more likely to not have it than to have it."	
"No, time and travel won't make any difference to me, because it's my health at the end of the day, I would travel to get my health looked at."	P28,M,57
"To be quite honest, no, I mean, I've had a CT scan and that was no problem, I've had MRI scans and I think they're absolutely horrendous, but I wouldn't stop going for them, I think if anything that can, you know, like I say, try and keep an eye on things I would always try and go for if possible."	P72,F,42
"My remembrance of the bronchoscopy was not very pleasant shall we say, but if it was a necessity then yes, it would just…it would just happen, you know, I'd have it done."	P25,M,55
"I'd rather be fully tested top to toe to be told I haven't got something and then have the possibility of finding that I have got something, rather than live my life not knowing and then finding that it's too late to do something about it."	P8,M,50
"I'd rather have the scan than find out I've got lung cancer and have to be treated for it. Yeah, definitely I'd prefer to have a scan and know either way."	P34,F,61
"And in any case, if you're being positive about it, you're less worried, it's less traumatic."	P33,M,71
"My attitude is if you think positive you'll get a positive outcome."	P43,F,66
"I think if you sit and dwell too much I think it can have an adverse effect can't it. I really believe in positivity."	P45,F,67
"I just have that sort of…well I automatically think it's probably going to be okay"	P68,M,50

CHAPTER 3

TITLE: Likely uptake of a future a lung cancer screening programme in Hodgkin lymphoma survivors: a questionnaire study

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3.1 ABSTRACT

Background

Many Hodgkin lymphoma (HL) survivors are at increased risk of subsequent malignant neoplasms (SMN), including lung cancer, due to previous treatment for HL. Lung cancer screening (LCS) detects early-stage lung cancers in ever smokers but HL survivors without a heavy smoking history are ineligible for screening. There is a rationale to develop a targeted LCS programme. The aim of this study was to investigate levels of willingness to undergo LCS in HL survivors, and to identify the psycho-social factors associated with screening hesitancy.

Methods

A postal questionnaire was sent to 281 HL survivors registered in a long-term follow-up database and at increased risk of SMNs. Demographic, lung cancer risk factors, psycho-social and LCS belief variables were measured. Multivariable logistic regression analysis was performed to determine the factors associated with lung cancer screening hesitancy, defined as those who would 'probably' or 'probably not' participate.

Results

The response rate to the questionnaire was 58% (n=165). Participants were more likely to be female, older and living in a less deprived area than non-participants.

Uptake (at any time) of breast and bowel cancer screening among those previously invited was 99% and 77% respectively. 159 participants were at excess risk of lung cancer. The following results refer to these 159. Around half perceived themselves to be at greater risk of lung cancer than their peers. Only 6% were eligible for lung cancer screening pilots aimed at ever smokers in the UK. 98% indicated they would probably or definitely participate in LCS were it available. Psycho-social variables associated with LCS hesitancy on multivariable analysis were male gender (OR 5.94 CI 1.64-21.44, $p<0.01$), living in an area with a high index of multiple deprivation (IMD) decile (deciles 6-10) (OR 8.22 CI 1.59-42.58, $p<0.05$) and lower levels of self-efficacy (OR 1.64 CI 1.30-2.08 $p<0.01$).

Conclusion

HL survivors responding to this survey were willing to participate in a future LCS programme but there was some hesitancy. A future LCS trial for HL survivors should consider the factors associated with screening hesitancy in order to minimise barriers to participation.

KEYWORDS
Hodgkin lymphoma
Lung cancer
Screening
Willingness

3.2 BACKGROUND

Hodgkin lymphoma (HL) is a lymphoid malignancy of clonal B cells predominantly affecting the young and the elderly and accounts for 68% of lymphomas in 15-24 year olds. [1,2] Whilst over 90% of patients diagnosed under the age of 50 are cured with chemotherapy and/or radiotherapy, five-year survival rates fall with increasing age at diagnosis.[1] As a consequence of treatment with alkylating agents –

specifically mechlorethamine (also known as mustine) and procarbazine - and radiation[3], survivors of HL are at excess risk of developing subsequent malignant neoplasms (SMN), which are the primary cause of death among long-term survivors. [4] The most common SMNs in HL survivors are breast cancer (cumulative incidence (CI) 35-years post-treatment 14.4%) and lung cancer (CI 35-years post-treatment 3.1% in women and 5.2% in men) [5]. However, the SMNs most commonly associated with mortality are gastrointestinal cancers and lung cancer, with an absolute risk of death of 10.4 and 9.4 respectively.[6,7] In the case of lung cancer, a large case-control study found the relative risks for lung cancer in HL survivors following alkylating agents, radiation to lung ≥5Gy, or both to be 7.2, 4.3 and 7.2 respectively in light or never smokers, increasing in a multiplicative fashion to 20.2, 16.3 and 49.1 respectively in moderate to heavy smokers.[3] Despite these excess risks, the only comprehensive screening programme for the detection of SMNs in the UK is the breast cancer screening programme for women at very high risk of breast cancer (defined by the NHS Breast Screening Programme as a lifetime risk of at least 40% due to a confirmed pathological germline variant or following radiotherapy to breast tissue under age 31 years for the treatment of lymphoma or, rarely, another cancer). This programme provides for annual breast screening starting 8 years after treatment and continuing until age 70 when the screening frequency reduces to every 3 years.[8]

Screening for lung cancer using a low-dose CT scan detects early-stage, asymptomatic lung cancers and has been shown to reduce lung cancer mortality in current and former smokers in two large randomised controlled trials.[9,10] In the United Kingdom (UK), lung cancer screening is being piloted by the National Health Service (NHS) in former or current smokers aged 55-74, who have a 6-year lung cancer risk of ≥1.51% according to the PLCOm2012 calculator or a 5-year risk of ≥2.5% according to the LLPv2 calculator. The variables entered into these risk calculators are listed in table 3.1. Although personal cancer history is included in both calculators, cancer treatments which increase lung cancer risk (thoracic radiotherapy and certain alkylating agents) are not.[11]

Rates of smoking among HL survivors are low,[12] and since the lung cancer risk calculators aimed at ever smokers do not take into account the risks associated with prior cancer treatment with radiation and alkylating agents, many HL survivors will not be captured by the lung cancer screening pilots aimed at ever smokers. For this reason, a future lung cancer screening programme for HL survivors must target this population, much like the approach to breast cancer screening.

Table 3.1: Variables entered into the PLCOm2012 and LLPv2 lung cancer risk calculators

	PLCOm2012	LLPv2
Age	✓	✓
Race	✓	X
Education level	✓	X
Body Mass Index	✓	X
Chronic obstructive pulmonary disease	✓	X
Pneumonia	X	✓
Occupational exposure to asbestos	X	✓
Personal history of cancer	✓	✓
Family history of lung cancer	✓	✓ (in a first degree relative <60)
Smoking history	✓ (cigarettes per day, duration of smoking, duration of quitting)	✓ (smoking duration only)

The positive attitudes of the general public to cancer screening in the UK[13] are reflected in the relatively high levels of uptake for NHS breast, cervical and bowel

cancer screening programmes compared to other countries in Europe.[14] However, uptake of lung cancer screening by ever smokers has been suboptimal; the UK-based Lung Screen Uptake Study reported a 53% uptake rate, the highest reported rate among historically low uptake rates for lung cancer screening pilots and trials.[15] That said, uptake of cancer screening is higher among cancer survivors than non-cancer survivors[16,17] and in a qualitative study in the UK, HL survivors were motivated to participate in a future lung cancer screening programme and reported few barriers to participation.[18] However, it is likely that some of the sociodemographic and psychological barriers to cancer screening in the general public will also apply to HL survivors. This area is worthy of further investigation because uptake of a future targeted lung cancer screening programme could be optimised by interventions designed to minimise known barriers to uptake. In the general population, sociodemographic variables associated with reduced screening participation include older age, male gender and lower socioeconomic status, although the association varies across different screening programmes. Lower levels of education and health literacy – which correlate with lower socioeconomic status – have also been associated with reduced screening participation.[19]

Theories such as the Health Belief Model (HBM) have been used to explain variation in screening participation. The HBM constructs of perceived susceptibility, perceived severity, perceived benefits and barriers and self-efficacy have been shown to predict cancer screening uptake.[20,21] Other factors predictive of non-participation in cancer screening programmes include worse self-rated health [22] and lower levels of dispositional optimism, [23] whilst higher levels of cancer worry are both a facilitator and a barrier to participation.[24,25] Smoking is widely understood by the public as being an important risk factor for lung cancer but current smokers are less likely to participate in lung cancer screening than former smokers.[26,27] The aim of this study was to use quantitative methods to describe the psychosocial factors associated with hesitancy to participate in a future lung cancer screening programme in HL survivors.

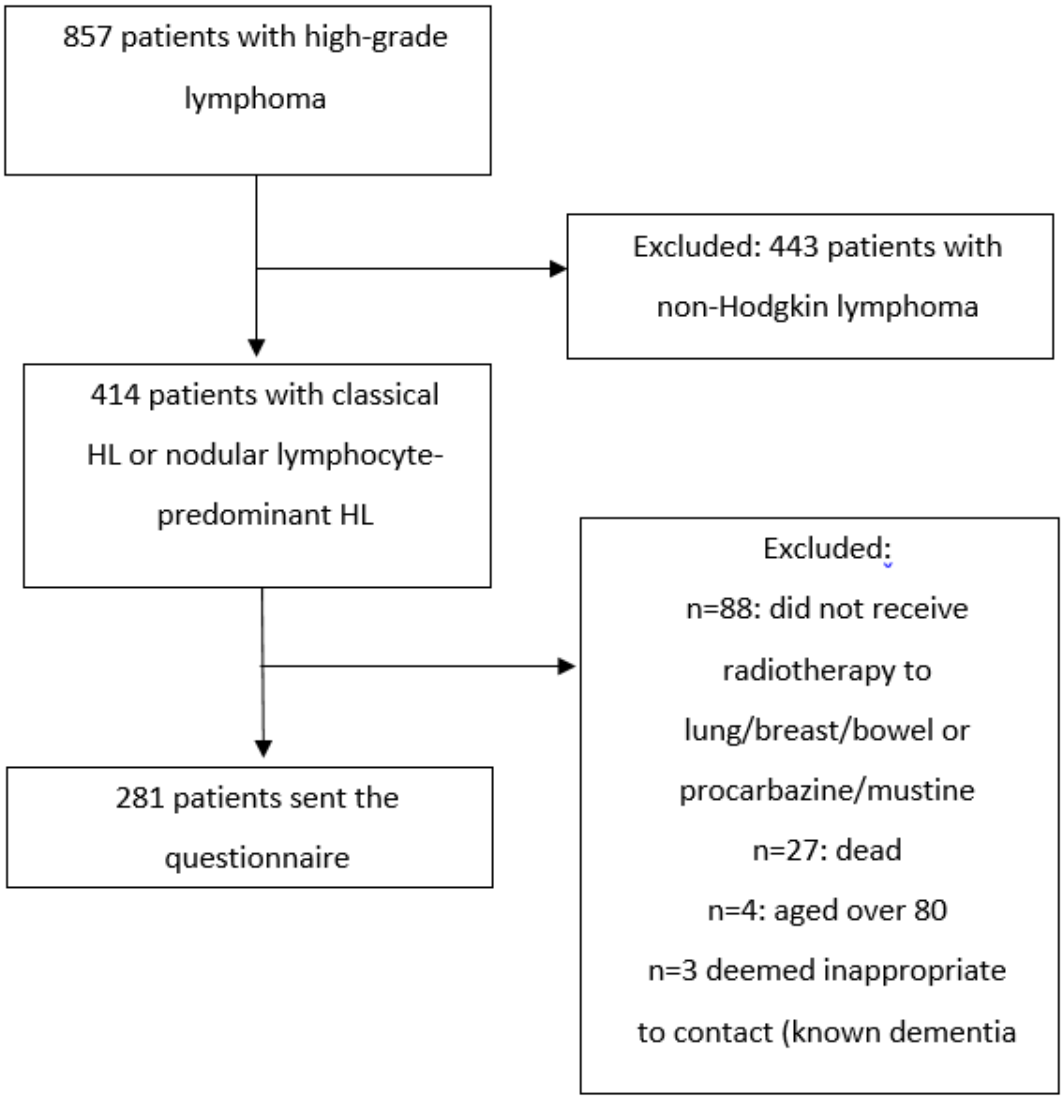
3.3 METHODS

Subjects and setting

Potential participants were identified from a prospective database of ≥5-year lymphoma survivors (ADAPT) held at The Christie NHS Foundation Trust. The ADAPT database contains the details of patients treated for high-grade lymphoma (or who were followed-up after completing treatment elsewhere) at The Christie NHS Foundation Trust. The database is prospectively maintained and contains details for patients treated since 1964. Patients are offered entry into the ADAPT GP-led follow-up programme if they remain in remission 5 years after completion of treatment, but they are not discharged from their clinical team. The database contains the names of the chemotherapy regimens received by patients and the anatomical sites which received a dose of radiation.

To identify individuals eligible for this study, patients with classical HL or nodular lymphocyte-predominant HL (n=414) were identified from the database, which held the records of 857 patients on 18th March 2021. The following patients were then excluded: patients who had died (n=27), patients aged over 80 (n=4), patients who had relapsed with HL within the last 5 years (n=5), patients currently being treated for metastatic cancer at The Christie (n=6), patients who it was deemed inappropriate to contact due to a diagnosis of dementia or learning difficulties (n=3), patients who had not received a treatment known to increase their risk of breast cancer (radiation to the breast tissue),[28] bowel cancer (procarbazine or radiation to the bowel)[29] or lung cancer (mustine or procarbazine or radiation to the lung)[3] (n=88). After applying these criteria to the database, 281 individuals were deemed to be eligible. Figure 3.1 demonstrates this selection process.

Figure 3.1: Diagram showing the process of selecting eligible individuals



A postal questionnaire and participant information sheet was sent to 281 eligible individuals followed by reminder letters to those who had not returned the questionnaire within three weeks. Return of the questionnaire was taken as consent to participate.

Measures

Willingness to undergo lung cancer screening

Participants were asked to rate the strength of their willingness to participate in a future lung cancer screening programme with the question 'If you were invited to go for a lung cancer screening test, would you go?' The response options were 'yes definitely', 'yes probably, 'probably not' and 'definitely not'.

Lung cancer screening related health beliefs

Lung cancer screening related health beliefs were measured using the Lung Cancer Screening Health Belief Scales (LCSHBS), developed to measure health beliefs impacting lung cancer screening uptake using the HBM framework and psychometrically tested in ever smokers.[30] The LCSHBS comprise four scales measuring perceived risk of developing lung cancer and perceived benefits, perceived barriers and self-efficacy (an individuals' belief in their capacity to execute a behaviour) for undergoing lung cancer screening. Although the Extended Health Belief Model includes separate constructs for perceived risk and perceived severity, the LCSHBS do not include a perceived severity scale because cancer is always perceived to be severe. To adapt the LCSHBS for this study population, items relating to cost, lack of a regular healthcare provider and booking a scan appointment were removed and never smokers were instructed not to complete the items in the perceived barriers scale which relate to a personal history of smoking. Prior to completing the scales, participants were provided with a short statement describing a lung cancer screening test.

Items in the perceived risk, perceived benefits and perceived barriers scales were scored using 5-point Likert scales indicating agreement (strongly agree/agree/neither agree nor disagree/disagree/strongly disagree). The self-efficacy scale had a 4-point Likert scale indicating level of confidence (very confident/somewhat confident/slightly confident/ not at all confident). The following are examples of items included in the scales: 'It is likely that I will get lung cancer in the next five years' (perceived risk scale); 'Having a lung scan would lower my chances of dying from lung cancer', 'Having a lung scan would help me plan for

the future' (perceived benefits scale); 'I might put off a lung scan because no one in my family had lung cancer', 'I might put off having a lung scan because I think I am too old to benefit from screening for lung cancer' (perceived barriers scale); 'How confident are you that you could find transportation to get to and from the clinic/hospital to have a lung scan?', 'How confident are you that you could get a lung scan even if you were anxious about the results?' (self-efficacy scale).

Cronbach's alpha was used to estimate internal consistency for each of the LCSHBS subscales and was found to be .90 for the 3-item perceived risk scale, .84 for 6–item perceived benefits scale, .89 for the 7-item self-efficacy scale, .94 for the 15-item perceived barrier scale for ever smokers and .91 for the 12-item perceived barrier scale for never smokers.

Demographic factors

Participants' age, gender and full postcode were extracted from electronic medical records. The questionnaire included questions about ethnicity, current employment status and level of education. Participants' postcodes were used to calculate area-level socioeconomic deprivation using the Index of Multiple Deprivation (IMD). The IMD combines seven domains of deprivation to produce a rank indicating the relative level of deprivation in a small area.[31] Participants' IMD ranks were categorised into deciles. The IMD has been used as a measure of socio-economic deprivation in studies examining sociodemographic predictors of cancer screening uptake, including lung cancer screening,[15,26,32] and researchers have previously categorised IMD ranks into quintiles and tertiles for statistical analysis.

Other psychosocial and health related factors

Cancer worry was measured using an item adapted from the Cancer Worry Chart [33] which is considered to measure cancer worry severity: '*In the last 4 weeks*, how often were you bothered by thoughts or worry about your chances of getting cancer again in the future?' (response options not at all / slightly / moderately / quite a bit / extremely).[34] Dispositional optimism was measured using the Revised Life Orientation Test (LOT-R), [35] in which a higher score represents a higher level of dispositional optimism. Self-rated health was measured with a single item taken

from the SF-12 Health Survey.[36] Optimistic bias was measured using an existing question relating to developing melanoma[37] adapted for this study: Compared to the average person of your age and sex, how likely is it in your opinion that you will develop [lung] cancer? (response options: much less likely / a bit less likely / about the same / a bit more likely / much more likely / I don't know). We developed items to measure presence of a close family history of lung cancer (in parents or siblings), prior uptake of breast or bowel cancer screening and prior knowledge of lung cancer as a late effect of HL treatment. To investigate 6-year lung cancer risk values in our participants, demographic and lung cancer risk factor data were entered into the PLCOall2014 (Prostate, Lung, Colorectal, Ovarian) lung cancer risk calculator. The PLCOall2014 calculator is analogous to the PLCOm2012 calculator designed for ever smokers which is currently used to determine eligibility to undergo lung cancer screening in the UK, however PLCOall2014 also calculates 6-year lung cancer risk in never smokers. When it was used to calculate 6-year lung cancer risk in 65,711 never smokers in the PLCO cohort, the maximum risk observed was 1.47% falling below the ≥1.51% risk threshold for screening.[38]

Statistical analysis

Descriptive statistics were used to analyse the demographic and clinical characteristics of participants at risk of lung cancer, their knowledge of lung cancer risk, cancer screening behaviours and future lung cancer screening willingness and responses to the LCSHBS.

The demographic characteristics of participants versus non-participants were compared using Chi-squared test for gender and Mann-Whitney U-test for age and IMD decile. In relation to the characteristics of participants and non-participants, effect sizes are presented using Cohens *d* values, which have been defined as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$).[39] To identify the psycho-social factors associated with lung cancer screening hesitancy - defined as those responding 'yes probably' or 'probably not' to the lung cancer screening willingness question - a binary logistic regression analysis was performed. The dependent variable was screening willingness and participants for whom complete data was available for the independent variables were included in the analysis. Independent

variables included socio-demographics, psychological variables (cancer worry and LOT-R scale score) and LCSHBS scores. Independent variables were entered into the multivariable logistic regression model regardless of whether they were associated with screening hesitancy on univariate analysis.

For the logistic regression, LCSHBS scoring for perceived risk, perceived benefits and perceived self-efficacy was reversed so that higher scores represented lower risk perception, lower perceived benefits and lower-self-efficacy. Scores for perceived barriers were retained so that higher scores represented higher perceived barriers. This change was made because we hypothesised that higher perceived barriers would increase screening hesitancy, whilst higher perceived risk, benefits and efficacy scores would reduce hesitancy. The following were treated as continuous variables: age, years since treatment, LOT-R score, self-rated health score, cancer worry severity score, perceived risk, benefits, barriers, and self-efficacy. Likert scale response values were converted to numerical values for the self-rated health and cancer worry severity score measures. The following variables were categorical: gender, IMD decile (categorised as low (deciles 1-5) or high (deciles 6-10)), family history of lung cancer (present or not present), smoking status (never smokers versus current or former smoker). IMD deciles were calculated by postcode using the English IMD 2019 data (276 recipients), Welsh 2019 data (4 recipients) and Scottish 2020 IMD data (1 recipient). A p value < .05 (two-tailed) was considered statistically significant for all analyses. Statistical analyses were performed using SPSS 23.0 (IBM, Chicago, IL)

3.4 RESULTS

165/281 questionnaires were returned (58% response rate). The characteristics of participants and non-participants are shown in table 3.2. Compared to non-participants, participants were more likely to be female ($p<0.01$), older ($p<0.01$) and living in a less deprived area (<0.05).

Table 3.2: Characteristics of participants and non-participants

	Participants (n=165)	Non-participants (116)	*p* value	Effect size (Cohens d value)
Gender Male Female	69 (42%) 96 (58%)	68 (59%) 48 (41%)	<0.01	0.16
Age (median)	55	49	<0.01	0.54
IMD decile (median)	7	5	<0.05	0.28

Participants at excess risk of lung cancer

159 out of 165 participants were at risk of lung cancer due to their treatment for HL (prior receipt of an alkylating agent known to increase lung cancer risk and/or a radiation dose to the lung.) Subsequent data presented in this paper refers to these 159 individuals. The median age was 55, 60% were female, 92% were of white British ethnicity, 38% were current or former smokers and 7% were current smokers. The median number of years since diagnosis and last HL treatment was 24 and 23 years respectively. In terms of treatment for HL, 144 (90.5%) had received radiotherapy, which was most frequently delivered to the mediastinum, and 150 (94%) had received chemotherapy, of whom 62% had received alkylating agents known to increase lung cancer risk (procarbazine or mechlorethamine (also known as mustine)). The cause of excess lung cancer risk was a combination of an alkylating agent and radiation to the lung in 49%, radiation alone in 41.5% and alkylating agent alone in 9.5%. The demographic and clinical features of the study participants at risk of lung cancer are shown in table 3.3.

Table 3.3: Characteristics of participants at excess risk of lung cancer

Clinical and demographic features of participants at excess risk of lung cancer n=159	
Current age: median (range)	55 (29-80)
Gender	Female: 96 (60.3%) Male: 64 (39.7%)
Ethnicity	White British: 147 (92%) Other[a]: 12 (8%)
Level of education (n= 156)	Education below university level: 86 (54.7%) University educated: 57 (37%) No educational qualifications: 13 (8.3%)
Employment (n= 158)	Full or part time employed (or in full time education / training): 101 (64%) Retired: 40 (25.3%) Other: 17 (10.7%)
HL classification	Classical HL: 150 (94%) Nodular lymphocyte predominant HL: 9 (6%)
Years since diagnosis: median (range)	24 (6-48)
Time since last treatment: median (range)	23 (6-44)
Sites of radiation (lung and non-lung) n=144	Mediastinal +/- other area: 95 (66%) Mantle field +/- other area: 28 (19%)

	Other area: 21 (15%)
Chemotherapy regimens[b] (n=150)	ChlVPP/EVA only: 46 (31%) ABVD only: 43 (29%) MVPP only: 19 (13%) Multiple chemotherapy regimens: 32 (21%) (of whom 17 underwent stem cell transplant and of whom 28 received procarbazine or mechlorethamine) VAPEC-B only: 10 (6%)
Cause of excess lung cancer risk by treatment modality	Radiation to lung and alkylating agent: 78 (49%) Radiation to lung only: 66 (41.5%) Alkylating agent only: 15 (9.5%)
Smoking history (n= 157)	Never smokers: 96 (62%) Former smokers: 49 (31%) Current smokers: 12 (7%)
Family history of lung cancer (n=159)	In parents or siblings: 12 (8%) Another family member: 20 (13%)
Self-rated health (n=157)	Excellent/very good: 46 (29.3%) Good/fair: 97 (61.8%) Poor/very poor: 14 (8.9%)
Revised Life-Orientation Test scores (possible range 0-24): median (range)	15 (0-23)
[a] Other ethnicities: 2 Indian, 2 Irish, 1 White and Black Caribbean, 1 Mixed (Arab and British), 2 Arab, 1 Bangladesh, 1 African, 1 Caribbean, 1 East African and Asian [b] ChlVPP-EVA: chlorambucil, vinblastine, procarbazine, prednisolone, etoposide,	

vincristine, doxorubicin, ABVD: doxorubicin, bleomycin, vinblastine, prednisolone, MVPP: mechlorethamine, vinblastine, procarbazine, prednisolone, VAPEC-B: doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisolone

Lung cancer knowledge, beliefs and willingness to be screened

31% of participants selected lung cancer as being a late effect of treatment from a list of health conditions. 82/158 (52%) of participants who answered the question about comparative risk of lung cancer believed that their personal risk was higher than the average person of their age and sex, 43 (27.2%) believed they were at equal risk, 8 (5%) at lower risk and 25 (16%) did not know. 52/158 (33%) of participants (32 women, 20 men) had previously been invited to undergo bowel cancer screening, of whom 40 (77%) had taken up the offer at least once (25 women, 15 men). Among female participants, 90/95 (95%) had previously been invited to undergo breast cancer screening, of whom 89 (99%) had taken up the offer at least once. Possible score ranges, median scores, range and interquartile range (IQR) for the perceived risk, perceived benefits, perceived barriers and self-efficacy scales are shown in table 3.4.

Table 3.4: Lung cancer screening health belief scale scores

	Median (range; IQR)
Perceived risk score (possible range 3-15) n=159	9 (3-15; 3)
Perceived benefits score (possible range 6-30) =158	24 (11-30; 5)
Perceived barriers score in ever smokers (possible range 15-75) n=59	23 (15-61; 14)
Perceived barriers score in never smokers (possible range 12-60) n=94	16 (12-40; 10)
Self-efficacy score (possible range 7-28) n=157	28 (17-28; 3)

Out of 157 participants who answered the question 'If you were invited to go for a lung cancer screening test, would you go?' 127 (81%) responded 'yes, definitely', 27 (17%) responded 'yes, probably' and 3 (2%) responded 'probably not'. There were no distinct commonalities among the three participants who indicated that they would probably not attend lung cancer screening compared to those responding yes probably/definitely. The single female responder who would probably not attend lung cancer screening was among the 1% of participants who had not participated in breast cancer screening despite being invited.

Eligibility for lung cancer screening programmes aimed at ever smokers

PLCOall2014 scores were calculable for 130 participants. The median 6-year lung cancer risk was 0.09% (range <0.001-8.2%). Thirteen (10%) participants - who were all former or current smokers - met the risk threshold for screening (≥1.51%), but when the age bracket for lung cancer screening in the UK (55-74) was applied, just 6% would be eligible for lung cancer screening in the UK through pilots aimed at ever smokers.

Factors associated with lung cancer screening hesitancy

A logistic regression analysis was performed to identify factors associated with lung cancer screening hesitancy. 158 participants with complete data for the dependant and independent variables were included in the model. The overall model was statistically significant when compared to the null model ($p<0.01$), explained 59% of the variation in screening willingness and correctly predicted 90.5% of cases. On univariate analysis, the following factors were associated with screening hesitancy: being male (odds ratio (OR) 2.52, 95% confidence interval (95%CI) 1.13-5.61) $p<0.05$), lower perceived benefits (OR 1.29, 95%CI 1.14-1.47, $p<0.01$), higher perceived barriers (OR 1.09, 95%CI 1.05-1.15, $p<0.01$) and lower self-efficacy (OR 1.45, 95%CI 1.27-1.65, $p<0.01$).

On multivariable analysis, the following factors were associated with screening hesitancy: being male (OR 5.94, 95%CI 1.64-21.44, $p<0.01$), living in an area with a high IMD decile (deciles 6-10) (OR 8.22, 95%CI 1.59-42.58, $p<0.05$) and lower levels of self-efficacy (OR 1.64, 95%CI 1.30-2.08, $p<0.01$). The results of the univariable and multivariable analyses are shown in table 3.5. For variables with statistical significance, OR, 95%CI and *p* value are in bold.

Table 3.5: Factors associated with lung cancer screening hesitancy (n=158)

	Univariable			Multivariable		
Variable	OR	95%CI	p value	OR	95%CI	p value
Male gender	**2.52**	**1.13-5.61**	**<0.05**	**5.94**	**1.64-21.44**	**<0.01**
Age	1.01	0.95-1.05	0.41	0.99	0.92-1.06	0.87
Years since treatment	0.98	0.93-1.03	0.44	0.91	0.83-1.00	0.06
LOT-R score	1.04	0.95-1.14	0.31	1.18	0.97-1.43	0.08
Living in an area with a high IMD decile	1.43	0.61-3.37	0.40	**8.22**	**1.59-42.58**	**<0.05**
No family history of lung cancer	1.23	0.25-5.96	0.78	0.17	0.01-2.20	0.17
Never smoker	1.21	0.53-2.74	0.64	0.80	0.20-3.17	0.76
Cancer worry sev erity score	0.84	0.59-1.20	0.35	1.01	0.51-1.98	0.97
Self-rated health score	1.11	0.75-1.63	0.59	0.60	0.27-1.31	0.20
Lower perceived risk	1.17	0.98-1.40	0.08	1.03	0.73-1.45	0.82
Lower perceived benefits	**1.29**	**1.14-1.47**	**<0.01**	1.23	0.98-1.53	0.06
Higher perceived barriers	**1.09**	**1.03-1.15**	**<0.01**	1.03	0.95-1.12	0.37
Lower self-efficacy	**1.45**	**1.27-1.65**	**<0.01**	**1.64**	**1.30-2.08**	**<0.01**

3.5 DISCUSSION

In this questionnaire study, a large majority of long-term HL survivor respondents at risk of lung cancer indicated willingness to undergo lung cancer screening, were the test available. The motivations for lung cancer screening reported by participants in our previous qualitative study[18] – namely perceived benefits and desire for reassurance in a population exhibiting high levels of health anxiety - may explain the high levels of positive lung cancer screening intentions reported in this current study.

Upon registration in the ADAPT programme – usually 5 years following completion of treatment – our standard departmental policy provides a written treatment summary to all patients, including information about an excess risk of lung cancer to HL patients treated with thoracic radiotherapy. Although the vast majority of our participants would have received this information, only 31% recalled and selected lung cancer as being a potential late effect. A larger proportion (52%) of our participants considered themselves to be at greater risk of lung cancer than the average person of the same age and sex. Knowledge of smoking as a lung cancer risk factor[40] and a perceptions by HL survivors of cancer treatments as being toxic[18] could have contributed to these comparative risk perceptions, particularly in participants who were not already aware that lung cancer can be a late effect of treatment. These findings demonstrate a lack of knowledge of personal lung cancer risk among HL survivors and reinforce the need for education about lung cancer risk upon invitation to a future lung cancer screening programme.

We hypothesised that few of our participants at risk of lung cancer would be eligible for screening through programmes aimed at ever smokers. Although the demographic characteristics of our participants do not fully reflect the HL survivor population overall (being older and female was associated with participation in the study), we found that just 10% met the $\geq$1.51% 6-year lung cancer risk threshold for screening, falling to 6% when the age eligibility criteria for lung cancer screening for ever smokers in the UK were applied. This finding supports our hypothesis and our

view that a targeted lung cancer screening programme for HL survivors should be developed. Survivorship care varies widely in the UK and many patients are discharged 2-5 years after achieving remission. Retrospectively identifying HL survivors at risk of lung cancer who have been discharged from their treating centres and who are eligible for lung cancer screening is likely to be time consuming and will require a significant effort from treating centres and potentially collaboration with primary care. A number of approaches have been used to identify and recruit ever smokers to lung cancer screening pilots and trials in the UK, including advertising and using electronic primary-care records, and a future targeted lung cancer screening programme for HL survivors may draw on the relative success of these approaches.[41]

The demographic variables associated with screening hesitancy were being male and living in a less deprived area. The impact of gender may be explained by the very high levels of breast cancer screening uptake among female participants. Although cervical screening uptake was not investigated in this survey, it is likely that many of the female participants would also have experience of cervical screening. On the other hand, few male participants had been invited or participated in bowel cancer screening, potentially increasing hesitancy due to reduced levels of awareness around cancer screening and risk. Furthermore, our prior qualitative research found that women viewed breast cancer screening as a norm and their awareness of an excess risk of breast cancer aided their understanding of lung cancer risk,[18] perspectives which could have increased their willingness to undergo lung cancer screening. The association between living in a less deprived area and screening hesitancy in this study contrasts with the literature showing that a lower socioeconomic status is associated with lower cancer screening uptake.[19] This discrepancy may be due to this study investigating willingness to participate in a hypothetical screening scenario as opposed to actual lung cancer screening uptake. In reality, people living in more deprived areas are likely to experience greater barriers to participation than those in more affluent areas, such as the ability to take time off work and to travel to a screening appointment.

Overall, our participants exhibited high perceived benefits scores, high self-efficacy scores and low perceived barriers scores. We are not able to compare the scores of our participants with those of other groups firstly because we adapted the LCSHBS for our population and secondly because there is a lack of published studies that have used the scales in their intended population of ever smokers. In our study, the only health belief model construct predictive of screening hesitancy on multivariable analysis was self-efficacy. Self-efficacy is widely considered to be an important predictor of behaviour and is incorporated into numerous theoretical models. The question items relating to self-efficacy used in our study related to finding time to attend, transportation and ability to cope with anxiety about the results and uncertainty about the procedure. Our participants have prior experience of navigating the healthcare system – experience which is likely to be ongoing for many due to the late effects of treatment – of undergoing scans and dealing with the associated anxiety. This prior experience and the fact that health is a priority for this group[12,18] may explain the high levels of self-efficacy in our participants.

A meta-analysis of health belief model variables in predicting behaviour found that outcome expectancies - perceived benefits and barriers – were the strongest predictors of behaviour.[21] However, neither perceived benefits nor perceived barriers were associated with screening hesitancy in the multivariable analysis in our study. It is possible that outcome expectancies predict intention to decline lung cancer screening by HL survivors, but as there were very few participants who indicated they would decline screening, we could not perform this analysis. With regards to perceived risk, our findings are supported by the aforementioned meta-analysis which did not identify a correlation between susceptibility (perceived risk) and preventative behaviours.

Strengths and limitations

This study is the first to use quantitative methodology grounded in behavioural theory to explore the psycho-social factors predictive of willingness to undergo lung cancer screening among HL survivors. The study complements and supports our previous qualitative work on this topic and provides further evidence of high levels

of willingness among this group to undergo lung cancer screening in the future. The resulting knowledge regarding the psycho-social factors which impact screening hesitancy could inform the design of a future lung cancer screening programme and its' associated informational materials, with the aim of optimising uptake rates. However, this must be balanced against the need to provide invitees with information about both the potential harms and benefits of screening in order to facilitate informed decision making.[42]

The extent to which the findings of this study can be applied to a national HL survivor population is limited by the characteristics of our participants who were registered in a long-term follow-up programme (most HL survivors who are in remission are discharged between 2-5 years after completion of treatment) and more likely to be female, older and living in a less deprived area than non-participants. In addition, a large majority of participants were of white British ethnicity and just over a third were university educated. Whilst the impact of gender and age on cancer screening participation rates is not always clear cut, a lower socioeconomic status (which correlates with lower levels of education and higher levels of smoking) has consistently been demonstrated to be a barrier to uptake[19] and people of non-white ethnicity face specific barriers to screening participation.[43] Therefore, the high levels of willingness to undergo lung cancer screening in this study may not reflect the entire HL survivor population, who would be expected to mirror the general population in terms of socioeconomic status and ethnicity. It is also possible that a greater proportion of non-participants to our study would decline lung cancer screening, compared to the participants. If this were the case, our study would have overestimated levels of willingness to undergo lung cancer screening. Although current smokers were poorly represented among our participants, the rates of current smoking in this study (7%), mirror the findings of another study,[12] so it may be that rates of current smoking among HL survivors among our participants reflect those in the HL survivor population.

CONCLUSIONS

In this study we have identified the psycho-social factors associated with lung cancer screening hesitancy in HL survivors asked to consider a hypothetical lung

cancer screening scenario and identified high levels of willingness to participate were lung cancer screening to become available. This study suggests that participation rates in lung cancer screening by HL survivors could be higher than in ever smokers and may exceed breast, cervical and bowel cancer screening uptake by the general population. Lung cancer screening is not routinely available for HL survivors and a trial of screening in this population is required to test lung cancer screening methodology established in ever smokers. Within such a trial, there would be value in exploring motivations and barriers to participation in a real-world setting. Further issues in this area worthy of exploration include developing lung cancer screening informational materials for HL survivors since current materials are aimed towards ever smokers and are not appropriate for use in this group. Developing a lung cancer risk calculator for this population is another important consideration to optimise selection criteria for lung cancer screening.

List of abbreviations:

HL: Hodgkin lymphoma

SMN: Subsequent malignant neoplasm

UK: United Kingdom

CI: Cumulative incidence

CT: Computed tomography

NHS: National Health Service

HBM: Health Belief Model

LCSHBS: Lung cancer screening Health Belief Scales

PLCO: Prostate Lung Colorectal Ovarian

IMD: Index of Multiple Deprivation

OR: Odds ratio

95%CI: 95% Confidence Interval

Declarations

Ethics approval

Ethical approval was given for this study by the Wales Research Ethics Committee 1 on 12th March 2021 (reference 21/WA/0071). The study methodology was designed in accordance with principles of the Declaration of Helsinki and in accordance with guidelines produced by the Health Research Authority and the principles laid out in Good Clinical Practice.

Consent to participate

In accordance with the Health Research Authority's guidance on informed consent, return of the postal study questionnaire was taken to indicate informed consent.

Consent for publication: Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing Interests

The authors declare that they have no competing interests.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RB. The first draft of the manuscript was written by RB. All authors read and approved the final manuscript.

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CHAPTER 4

TITLE: The development of a decision aid to support Hodgkin lymphoma survivors considering lung cancer screening

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Individual contribution:

I designed the study, collected the data, analysed the data and wrote the manuscript.

For clarity within this thesis, the references and supplementary data for this paper are presented at the end of this chapter.

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4.1 ABSTRACT

Background

Decisions aids (DA) can support patients to make informed decisions about screening tests. This study describes the development and initial evaluation of a lung cancer screening (LCS) DA targeted towards survivors of Hodgkin lymphoma (HL).

Methods

A prototype decision aid booklet was developed and subsequently reviewed by a steering group who provided feedback. Revisions were made to produce the DA tested in this study. HL survivors were recruited to an online survey and/or focus groups. Lymphoma practitioners were invited to an interview study. In the online survey, decisional conflict scales and knowledge scales were completed before and after accessing the DA. The focus groups and interviews explored acceptability and comprehensibility and the decisional needs of stakeholders. Focus groups and interviews were audio recorded. The framework method was used to analyse qualitative data.

Results

38 HL survivors completed the online survey. Following exposure to the DA, knowledge of LCS and risk factors and decisional conflict scores (total score and subscale scores) improved significantly. 11 HL survivors took part in two focus groups (n=5 and n=6) and 11 practitioners were interviewed. Focus group and interview results: The language, format and length were considered acceptable. Both groups felt the DA was balanced and presented a choice. Icon arrays were felt to aid comprehension of absolute risk values and for some survivors, they reduced affective risk perceptions. Among survivors, the impact of radiation risk on decision making varied according to gender and screening interval, whilst practitioners did not anticipate it to be a major concern for patients. Both groups expressed that a screening offer could mitigate anxiety about lung cancer risk. As anticipated by practitioners, survivors expressed a desire to seek advice from their clinical team.

Practitioners thought the DA would meet their informational needs regarding LCS when supporting survivors.

Conclusions

The DA is considered acceptable by HL survivors and practitioners. The DA reduces decisional conflict and improves knowledge in HL survivors, suggesting that it would support HL survivors to make informed decisions when considering LCS in a future clinical trial.

KEYWORDS

Hodgkin lymphoma

Lung cancer screening

Decision aid

4.2 BACKGROUND

People invited to undergo cancer screening must be provided with information to support informed decision making about participation, in keeping with the General Medical Council guidelines on decision making and consent.[1] In the UK, guidance issued by NHS Cancer Screening Programmes stipulates that screening programmes should provide patients with educational materials covering the purpose of the investigation, the risks, benefits and burdens of the screening test and the likelihood of the test outcomes.[2]

Decision aids are evidence-based tools which should support patients in their decision making when facing healthcare options and help patients to make explicit decisions in accordance with their personal values.[3] An updated Cochrane systematic review examined the use of decision aids in people facing healthcare or screening decisions and found that compared to usual care, decision aids improve knowledge and accuracy of risk perception, increase value-based decision making and reduce decisional conflict related to feeling uninformed, thus improving the quality of decision making.[3] A number of decision aids have been developed to

support patients making decisions about cancer screening, including ever smokers considering lung cancer screening [4–6] and those with low literacy levels considering bowel cancer screening.[7,8]

Hodgkin lymphoma (HL) is a malignancy of clonal B-cells which mainly affects young adults and the elderly.[9] Due to the carcinogenic effects of thoracic radiotherapy and chemotherapy, survivors of HL are at excess risk of developing lung cancer (30-year cumulative incidence 6.4%).[10,11] Lung cancer screening has been implemented for ever smokers over the age of 55,[12,13] but most HL survivors will not be eligible for screening as the majority are non-smokers.[14] Clinical trials of lung cancer screening for Hodgkin lymphoma survivors are underway,[15,16] but to our knowledge, educational materials to support decision making have not been developed. Existing lung cancer screening education materials are targeted towards ever smokers and are not appropriate for HL survivors as they do not address treatment related lung cancer risk. Prior research has found that HL survivors have a low perceived risk of lung cancer due to a lack of awareness of the risks associated with cancer treatment.[17] There is a need to develop educational materials targeted towards HL survivors considering lung cancer screening to use in future trials and screening programmes. To address this, we have developed a decision aid for use in a future trial of lung cancer screening. This paper describes the design and development process.

4.3 METHODS

The aim and scope of the decision aid

Our aim was to develop a decision aid for use in a future trial of lung cancer screening using low-dose CT scans in at risk HL survivors. The decision aid is intended to support HL survivors who are deciding whether to undergo lung cancer screening as part of the study.

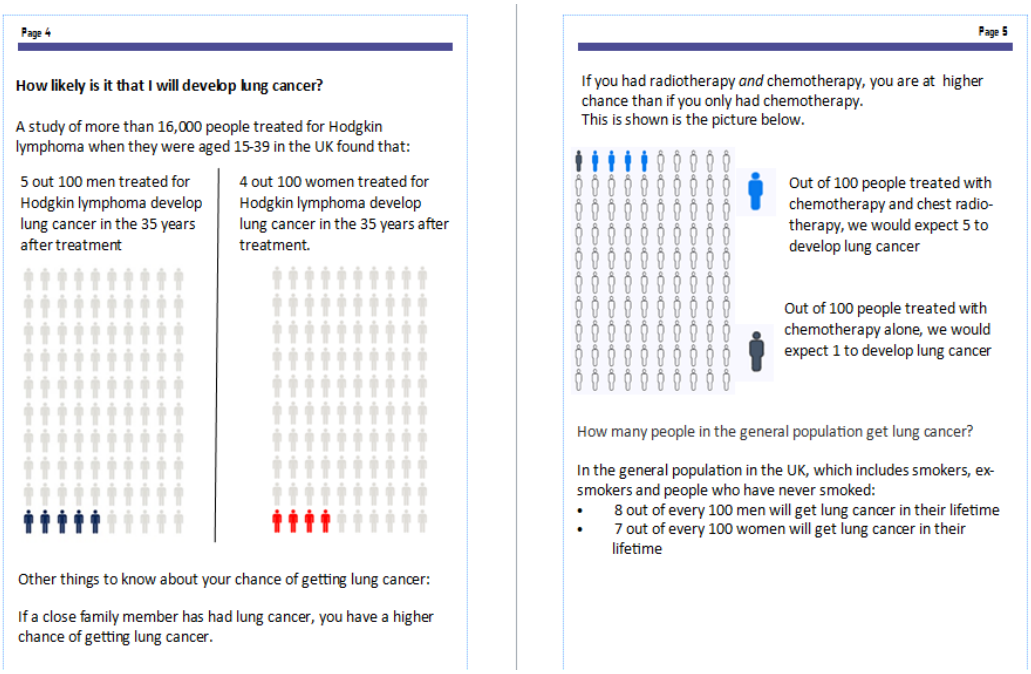
Content development

The International Patient Decision Aids Standards instrument (IPDASi) was used to guide content development.[18] Published literature informed the manner in which risk information is presented in the decision aid. Evidence has shown that

presenting absolute risk values improves accuracy of risk perceptions compared to relative risk values[19-22] and there is a consensus in the literature that the absolute risk format is the optimal method for presenting risk data.[20,21] Therefore, absolute risk values are presented in the decision aid where possible, avoiding the use of relative risk, or numbers needed to screen. Where absolute risk information was not published, the Winton Centre for Risk and Evidence Communication Real Risk-Make Sense of Your Stats website[22] was used to calculate absolute risk by extracting data from published literature. Absolute risk values are accompanied throughout the decision aid by visual aids in the form of icon arrays, which have been shown to improve accuracy and comprehension of risk perception.[19,23] There are instances where risk is presented qualitatively in the decision aid: firstly, to describe the greater likelihood of lung cancer in HL survivors who have smoked and secondly in HL survivors with a family history of lung cancer. In these specific examples, published data did not provide absolute risk values (or the raw data required to calculate these independently). In the example of smoking history, absolute risk values calculated from the sole paper providing raw data was misleading in that it suggested that HL survivors who are never smokers do not develop lung cancer. Since the literature suggests that most HL survivors who develop lung cancer have a history of smoking, we used the statement "most people who get lung cancer after Hodgkin lymphoma have smoked" in the decision aid.

There is strong evidence from a Cochrane systematic review[24] that personalised risk communication promotes informed uptake of screening tests and increases knowledge. For this reason, there are two icon arrays in the decision aid, which demonstrate absolute lung cancer risk in men and women and absolute lung cancer risk according to whether the survivor was treated with chemotherapy alone or chemotherapy and radiotherapy. The pages of the decision aid containing these icon arrays can be seen in Figure 4.1. In the absence of a lung cancer risk calculator for this population, it was not possible to provide individualised risk scores.

Figure 4.1: Screenshot of the pages in the decision aid containing icon arrays demonstrating absolute risk of lung cancer according to gender and treatment for



HL

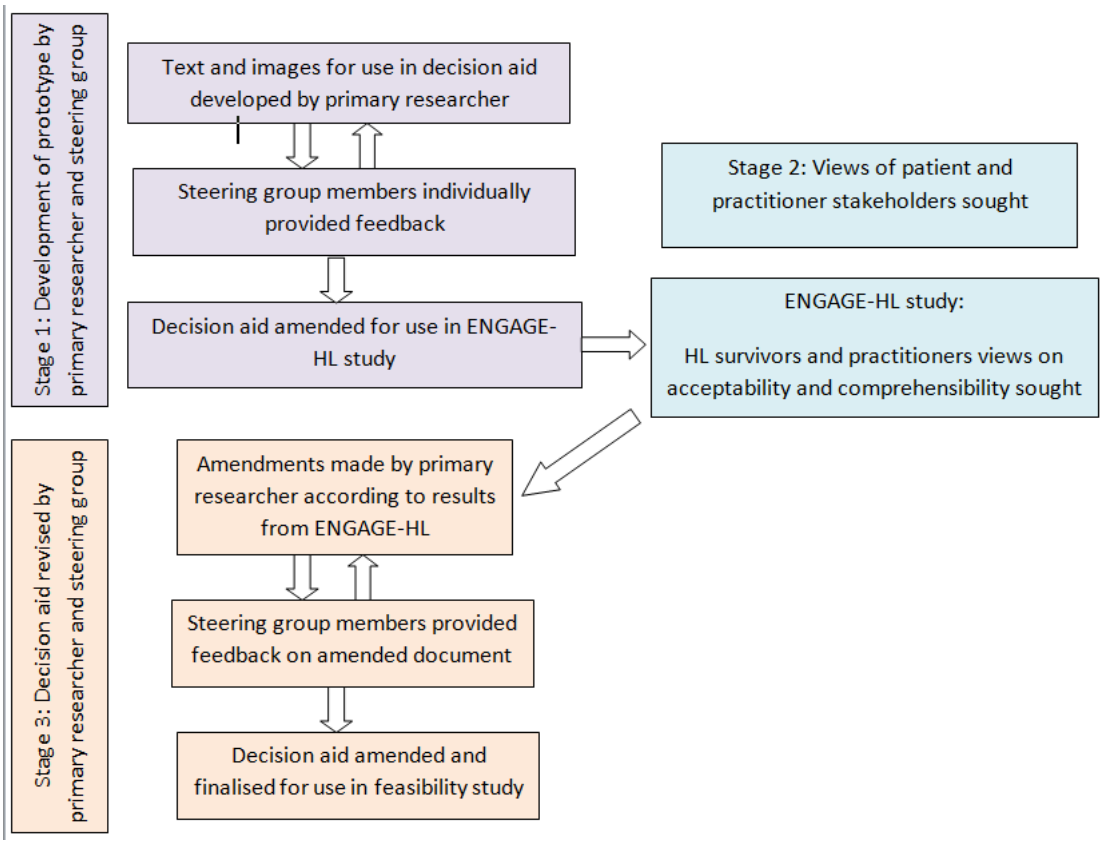
Published literature also informed the information in the decision aid regarding risk factors for developing lung cancer after treatment for Hodgkin lymphoma,[10,11,25,26] cumulative incidences and absolute risk levels.[25,27] Information about the lung cancer screening test was informed by publicly available information and an online lung cancer screening decision tool[28,29] whilst the information on the likelihood of a pulmonary nodule being detected on screening was informed by retrospective data on prevalence of pulmonary nodules in Hodgkin lymphoma survivors undergoing chest CT.[30] The Centre for Disease Communication 'Everyday Words for Healthcare Communication' booklet and online clear communication index tool guided the language used.[31,32]

Input of the steering group

A steering group of clinical experts and patients was set up, comprising 9 individuals with expertise in lymphoma late effects, lung cancer screening, risk and cancer communication and 3 survivors of HL (2 female, 1 male). Between November and December 2020, all members of the steering group provided feedback on an initial

prototype draft – developed by RB - which was subsequently revised to produce the version for further review by stakeholders. The steering group later commented on RB's proposed amendments to the decision aid following review by stakeholders in the ENGAGE-HL study, described below. A flow chart demonstrating the decision aid development process is shown in Figure 4.2.

Figure 4.2: Flow chart of the decision aid development process



The decision aid prototype

The decision aid prototype is a 16-page booklet, designed to be read in paper format, entitled *'Screening to find the early signs of lung cancer after treatment for Hodgkin lymphoma: Helping you decide'*. The features of the decision aid prototype are detailed in Table s 4.1 in supplementary data, but the decision aid is not publicly available at present.

Testing the decision aid among stakeholders: The ENGAGE-HL study

A study using mixed quantitative and qualitative methodology was developed to assess the decision aid among people treated for HL and practitioners. Mixed methodology was chosen to facilitate quantitative analysis of the impact of the decision aid using validated scales, whilst qualitative methods were used to explore the perspectives of stakeholders in depth.

The specific study objectives were:

1. To assess the acceptability and comprehensibility of the decision aid amongst HL survivors and practitioners
2. To explore the decisional needs of HL survivors and informational and support preferences with regards to a lung cancer screening invitation
3. To explore the needs of practitioners providing support to survivors making the decision.
4. To assess the impact of the decision aid on HL survivors' knowledge about lung cancer risk and lung cancer screening and on decisional conflict

Theoretical framework

The Ottawa Decision Support Framework[33] describes the interaction of decisional needs, decision quality and decision support and asserts that unresolved needs negatively impact decision quality, which can adversely impact emotions, behaviour and health outcomes. Decision support strategies can improve decision quality by addressing unresolved needs, which may include inadequate knowledge and unrealistic expectations. This framework and the 'Decisional Needs in Populations' workbook[34] were used to develop the questionnaire items and topic guides for interviews and focus groups.

Study design

There are two parts to the study. In Part A, HL survivors were recruited to take part in an online survey and /or a focus group whilst in Part B lymphoma practitioners were recruited to an interview study. Quantitative methodology was chosen to

assess the decision aid's impact on knowledge and decision making using validated scales and assessments, whilst the aim of the focus groups was to elicit the views of HL survivors' by allowing participants to debate and to discuss their shared and diverse experiences. Interviews with practitioners were chosen for ease of scheduling and to avoid the potential for any practitioners feeling less able to share their perspectives due to having less experience or due to professional hierarchy. Parts A and B of the study ran concurrently. HL survivors were eligible to participate if they were treated in the UK, were aged 18 or over and had not been diagnosed with lung cancer or participated in a lung cancer screening pilot. Practitioners were eligible if they worked in the UK in a clinical role treating or supporting HL patients.

Recruitment

To recruit HL survivors to part A, a study advert was placed on the Lymphoma Action charity Twitter feed on multiple occasions over a 4-week period and posted twice on the Lymphoma Action Facebook support page. The study advert was also included in the Lymphoma Action magazine and in an email to Lymphoma Action members. The study advert directed interested individuals to contact the researchers or access the study website, which hosted the participant information sheet, researchers contact details, and a link to the online survey.

To recruit practitioners to Part B, a separate study advert was placed on the Lymphoma Action charity Twitter feed and further information was available on the Lymphoma Action website. Study details were also listed on the British Society for Haematology website. Practitioners were sent the participant information sheet by email. All participants (in both Part A and B) were offered a £30 e-voucher for their participation (if a HL survivor participated in the focus group and completed the online survey, they received two £30 vouchers). Recruitment to Parts A and B took place between March and July 2021.

Part A study procedures

Online survey

Participants in part A completed an online consent form followed by a survey, hosted on the Qualtrics platform. The online survey captured demographic data and measured lung cancer screening knowledge and decisional conflict before and after the participant accessed a pdf version of the decision aid. Lung cancer screening knowledge was measured using a 16-item scale, adapted from a published scale,[35] and decisional conflict was measured using the low literacy Decisional Conflict Scale (DCS).[36] Additional novel questions explored aspects of decisional conflict, information and support preferences and acceptability of the decision aid. The Short Test Of Functional Health Literacy Assessment[37] (S-TOFHLA) was administered at the end of the survey.

Focus groups

Two focus groups, lasting 60 minutes, took place using Zoom teleconferencing and were audio recorded. Participants were required to complete an online consent form and short questionnaire to collect personal characteristics prior to the focus group and were sent a pdf version of the decision aid to view at least 48 hours prior to the focus group. The main researcher (RB) and a second moderator attended the focus groups.

Part B study procedures

Semi-structured interviews, lasting 25-45 minutes, took place over telephone or Zoom and were audio-recorded. Practitioners completed an online consent form prior to the interview. A topic guide covered questions relating to the decisional needs of HL survivors considering lung cancer screening, the comprehensibility and acceptability of the decision aid and practitioners' lung cancer screening informational needs.

Data analysis

Online survey (Part A)

Participant characteristics and their responses to questions exploring decisional conflict and support and information preferences are presented descriptively. To compare the difference in median total DCS scores and subscale scores and median proportion of correct answers given in the knowledge scale before and after exposure to the decision aid, the Wilcoxon signed rank test was used as the data did not meet tests for normality. McNemars test was used to compare screening intention before and after exposure to the decision aid. A significance level of 0.05 was used throughout. Effect sizes are presented using Cohens *d* values, defined as small (*d* = 0.2), medium (*d* = 0.5), and large (*d* = 0.8).[38] The percentage of correct answers given to each question or statement in the knowledge scale and the median DCS scores and interquartile ranges are also presented descriptively.

Focus groups with patients (Part A) and interviews with healthcare practitioners (Part B)

The focus groups and interview recordings were transcribed intelligent verbatim. Since the interview and focus group schedules covered similar topics, the framework method of content analysis was used[39] with the aim of identifying concordant and contrasting views among HL survivors and practitioners. NVivo 12 software was used to store and organise transcript files, codes and the framework matrix. The first author applied codes to the interview and focus group transcripts independently, producing two sets of codes, one for the interviews and one for the focus groups. This was an iterative process whereby codes were applied to the transcripts of the first seven interviews and the first focus group, and when the remaining interviews were transcribed and the second focus group had taken place, a further round of coding took place where previously developed codes, and new codes, were applied. Two researchers (RB and TS) met to discuss the codes and emerging themes, at which point any disagreements over coding were resolved. Subsequently, RB developed a coding framework which could be applied to both

focus group and interview transcripts. During the development of the thematic analysis, the RB and TS met on multiple occasions to discuss the emerging themes. The results of the study have been made available on the study website (engagehl.com) but participants have not been involved in the analytic process.

Reflexivity statement

Focus group participants and practitioners were aware that the interviewer (RB) had been involved in developing the decision aid that they were reviewing. Being aware of this, the interviewer took care to facilitate a safe environment in which participants could openly express their views towards the decision aid - including negative ones – by encouraging participants to share both positive and negative views and seeking their views throughout of ways to improve it. The interviewer was willing to answer questions that participants had on the topic of lung cancer screening and to discuss the rationale behind decisions that had been made during the development of the decision aid.

During the second focus group, the researcher (RB) explored issues which had not been addressed in the first focus group or which merited further exploration and additionally explored issues that had emerged from an interim analysis of the online survey. Thus, the direction and structure of the second focus group was influenced by the preceding research activities. Although this was a useful opportunity to discuss certain survey findings, this meant there was less time during the second focus group for discussion which could have generated new perspectives.

During the coding and development of the themes, two researchers discussed the challenges associated with running the focus groups, including group dynamics. They acknowledged the potential for their experience of running the focus groups to influence the resulting codes and themes, and efforts were made to remain unbiased in the weight attributed to the views of individual participants when developing the thematic analysis.

4.4 RESULTS

Part A

The online survey was completed by 38 HL survivors described in Table 4.1. In summary, the majority were female with a median age of 44, of white British ethnicity and were never smokers. There was a wide range of time since follow-up among participants and slightly more remained in follow-up than were discharged. All participants had adequate levels of health literacy according to S-TOFHLA.

Table 4.1: Personal characteristics of participants

	HL survivors		
	Online survey: participants personal characteristics n=38	Focus group 1: n=6	Focus group 2: n=5
Gender	Female: 30 Male: 8	Female: 3 Male: 3	Female: 5
Median age (range)	44 (21-71)	(26-60)	(21-71)
Ethnicity	White British: 30 Other white background: 5 (1 Spanish, 1 Portuguese, 1 Polish, 1 not stated, 1 Irish) Indian: 1 Pakistani: 1	5 white British, 1 Spanish	All white British
Smoking status	Never smoker: 25 Ex-smoker: 12 Current smoker: 1	Not captured	Not captured

Years since HL treatment:	<5: 17 5-10: 6 11-15: 3 16-20: 1 >20 years: 11	<5 years: 4 5-10 years: 2	<5 years: 1 5-10 years: 2 >20 years: 2
Follow-up status	21 remain in follow-up 17 discharged from follow-up	4/6 remain in follow-up	3/5 remain in follow-up
Treatment for HL	Not captured	All received chemotherapy alone	Radiotherapy only: 1 Chemotherapy only: 2 Both: 2
Level of education completed	Not captured	2: GCSE/O-level 1: A-levels 3: university educated	2: A-levels/other college education 3: university educated
	Practitioners n=11		
Role (number)	Consultant haematologist (3) Senior registrar (doctor) (1) Advanced nurse practitioners (haematology/lymphoma) (3) Clinical nurse specialist in lymphoma (4)		

Lung cancer risk and screening related knowledge

The median percentage of correct responses to knowledge questions and statements increased following exposure to the decision aid (68% pre exposure, 93% post exposure (p value <0.001). The effect size was 1.4. The percentage of correct answers given to each question pre and post exposure to the decision aid is shown in the Supplementary data file (Table s4.2).

Decisional conflict

In the decisional conflict scale and subscales, higher scores represent higher levels of decisional conflict, higher levels of uncertainty, feeling more uninformed, feeling more unsupported and feeling more unclear about personal values. Following exposure to the decision aid, median total DCS scores and median uncertainty, informed, values clarity and support subscale scores reduced indicating that the decision aid reduced levels of decisional conflict, reduced uncertainty, increased feeling of being informed, increased values clarity and feelings of being supported. Median scores, range, interquartile range, p-values for difference in pre-post median scores and effect size are shown in table 4.2.

Table 4.2: Decisional conflict median scores pre and post exposure to the decision aid.

	Pre: Median (range; interquartile range (IQR))	Post: Median (range; interquartile range) p value for difference in median pre and post scores	Effect size (Cohens d value)
Total DCS score	67.5 (0-100; IQR 40)	0 (0-80; 10) p<0.001	1.9
Uncertainty subscale score	50 (0-100; IQR 80)	0 (0-100; IQR 6.25) p<0.001	1.0
Informed subscale score	100 (0-100; IQR 37.51)	0 (0-66; IQR 0) p<0.001	2.0
Values clarity subscale score	75 (0-100; IQR 56.25)	0 (0-100; IQR 0) p<0.001	1.5
Support subscale score	33.33 (0-100; IQR 41.67)	0 (0-100; IQR 0) p<0.001	0.7

Intention to participate in a future lung cancer screening programme

Before and after accessing the decision aid, participants were asked: "If you were invited to go for a lung cancer screening test, would you go?" Prior to reading the decision aid, 33 (86.8%) participants responded 'Yes, definitely' and 5 (13.2%) responded 'Yes, probably'. After reading the decision aid, 29 (76.3%) responded 'Yes, definitely' and 9 (23.7%) responded 'Yes, probably'. The difference in strength of intention before and after reading the decision aid was not significant (p=0.21).

Decision making and information and support preferences

Participants answered the following questions before accessing the decision aid. Responses to the question, 'If you were invited to lung cancer screening, how easy would it be for you to make the decision?' were as follows: 'extremely easy'; 10

(26.3%), ‘quite easy’; 15 (39.5%), ‘neither easy nor difficult’: 10 (26.3%), ‘quite difficult’; 3 (7.9%). Participants rated their level of agreement to a series of questions assessing difficulties relating to decision making. The results are shown in Table 4.3.

Table 4.3: Responses to questions regarding difficulties in decision making

Statement	Response (n=38) n(%)		
	Strongly disagree / Disagree	Neither agree nor disagree	Strongly agree / agree
I would be unsure what to do	25 (65.8)	5 (13.2)	8 (21.0)
I would be worried what could go wrong	21 (55.3)	9 (23.7)	8 (21.0)
Trying to make the decision would upset me	31 (81.6)	3 (7.9)	4 (10.5)
I would be constantly thinking about the decision	26 (68.4)	5 (13.2)	7 (18.4)
I would delay making the decision	34 (89.5)	3(7.9)	1(2.6)

After reading the decision aid, 23 (60.6%) said they would not seek out more information, 13 (34%) would and 2 (5.3%) were unsure. Participants were asked to select the support options which might be useful to them. Responses were as follows: searching the internet: 25 (65.8%), charity or organisation webpage: 29 (76.3%), talking to a doctor or specialist nurse: 28 (73.7%), asking a support group: 5 (13.1%).

Nineteen respondents (50%) said they would involve someone else in their decision making and all those responding this way indicated they would involve their family

in the decision whilst 2 (5.3%) said they would involve their clinical team. When asked about the level of involvement of the doctor in decision making, 20 (52.6%) said they would decide on their own, 13 (34.2%) said they would decide after considering their doctor's opinion, 4 (10.5%) would decide with their doctor, and 1 (2.6%) said their doctor would decide after considering their opinion.

Acceptability of the decision aid prototype

Thirty-three (86.8%) said the length was 'just right', whilst 5 (13.2%) said it was 'too long'. Thirty-six (94.7%) participants said the amount of information in the decision aid was 'just right' whilst 2 (5.3%) said it was 'too much'. Participants were asked to rate the way the information was presented within the different sections of the booklet. Their responses are shown in table 4.4. Asked about the balance of the information, 28 (76.3%) said it was balanced, 9 (23.7%) said it was 'slanted towards having a lung cancer screening test' and 1 (2.6%) said it was 'slanted towards not having a lung cancer screening test'. All participants said they would find the decision aid useful if they had to make a decision about undergoing lung cancer screening.

Table 4.4: Ratings given to sections of the decision aid

Section of the decision aid	Response (n=38) n(%)	
	Excellent/good	Fair/Poor
How likely is it that I will develop lung cancer?	31 (81.6)	7 (18.4)
What does lung cancer screening involve?	37 (97.4)	1 (2.6)
What are the benefits of having a lung cancer screening test?	37 (97.4)	1 (2.6)
What are the disadvantages of having a lung cancer screening test?	36 (94.7)	2 (5.3)
Making a decision	31 (81.6)	7 (18.4)
What are the symptoms of lung cancer?	34 (89.5)	4 (10.5)
Information and Support	36 (94.7)	2 (5.3)

Thematic analysis of focus groups with HL survivors and interviews with practitioners

Focus group participant and practitioner characteristics

Whilst the first focus group was balanced in terms of gender, the second focus group was comprised of female participants only. The age range across both focus groups was 21-71 years of age. Most were of white British ethnicity. Of note, all the focus group participants had also completed the online survey. Practitioners were currently practicing as doctors or nurses. The nurses all held specialist roles (clinical nurse specialists or advanced nurse practitioners in the fields of haematology or lymphoma). Their characteristics are shown in Table 4.1.

Theme 1: Accessing and understanding the decision aid document

Acceptability

During the focus group, participants' perspectives on the language, length and format were explored, with probing questions to generate a deeper understanding of viewpoints. All groups agreed that the language was clear and jargon-free, especially by focus group participants experienced in patient and public involvement and engagement. The length of the decision aid (16 pages) was a cause for concern, however as information was felt to be "concise" and the layout "uncluttered" the length was generally considered manageable:

"Because it's written so clearly and in such simple language once you start reading it it's actually a lot quicker than you think" (Focus group 2 participant, female)

Linked to this, participants felt strongly that the decision aid document should be comprehensive despite its length and it was pointed out that recipients could "dip in and out of it". Across the two focus groups, suggestions were made to improve the readability through simple format changes, such as the use of bullet points and bold headings. It was suggested that videos or forums may be a better source of information and support for patients less likely to read written information.

Comprehension of lung cancer risk information

During the focus groups, it emerged that participants had become aware of the treatment-related risk of lung cancer for the first time through participation in this study and had therefore not been previously exposed to data relating to this risk. This lack of prior awareness impacted their perceptions of the absolute risk values

that were presented in the decision aid. Those who perceived the values to be lower than they had anticipated gleaned some reassurance, but this was not universal. A female focus group participant who was treated at a young age said she had not expected to get lung cancer, so the values still appeared "quite high". In relation to this, it appeared that using icon arrays to support textual information on absolute risk aided comprehension and reduced affective risk perceptions.

"With regards to it being simple for others to read, I definitely found the graphics useful from that perspective just to get a real insight. You can say 4 in 100 people, but when you see it in an infographic it's much more impressionable I guess, and you relax a bit more and your anxiety leaves, that actually the chances are that's probably not me." (Focus group 1 participant, female)

Practitioners also viewed the icon arrays positively, saying they were a simple but effective method of communicating risk.

Practitioners felt it was important for recipients of the decision aid to be able to identify the treatment related risk factors relevant to them. In keeping with this, there were multiple occasions when focus group participants correctly identified their personal risk factors using the information in the decision aid. When participants could not see their chemotherapy regimen listed as a risk factor, they sought clarification from the researcher running the focus group.

Whilst the decision aid provided information on risk factors and the absolute risks relating to single and combined modality treatments, it was not tailored to individual recipients. One participant expressed concerns about this, saying that the information was not sufficient for her to understand her personal risk factors.

"I think it certainly doesn't answer all the questions that I would have as to why I would be at risk personally. But you're never going to cover that off, that's the problem, in a leaflet. So, I think it does a good job of being quite generic and covering off the main reasons, without being specific; you'd have to reach out elsewhere." (Focus group 1 participant, female)

Both practitioners and focus group participants raised concerns that the inclusion of lifetime cumulative lung cancer risk values for the general population (7-8/100) was confusing. They felt that these data contradicted the text which stated that HL survivors were at higher risk than the average person, because the lung cancer absolute risk value for HL survivors 35 years after treatment was 4-5/100, seemingly less than the general population. Practitioners widely recommended that alternative data be used.

Facilitating informed decision making

Across both focus groups, participants felt that the decision aid presented lung cancer screening as a choice rather than a recommendation. It was widely agreed among practitioners and focus group participants that presenting pros and cons in textual and summary table format would help facilitate informed decision making by helping people identify the issues that were most salient to them. Being able to weigh up pros and cons during decision making held more importance for some focus group participants than others, for example one participant who perceived a prior lack of involvement in decision making relating to her cancer diagnosis, said:

"I think that's so important, especially when some of those decisions are taken completely out of your hands when you're diagnosed with cancer." (Focus group 1 participant, female)

In contrast, another participant indicated that the risks associated with screening were of minimal importance to them if there was any potential benefit:

"If I know it's going to help or it's going to try and help us I'll just do it." (Focus group 1 participant, male)

Participants in the second focus group were asked to consider whether the decision aid was slanted towards lung cancer screening, which had been reported in the online survey analysis. There was agreement among them that the document was balanced and that the pros and cons of screening were described in equal detail. One participant wondered whether it was biased to present pros before cons but

felt this was the “right decision” as presenting cons first may dissuade people from reading about the potential benefits.

Theme 2: Factors influencing lung cancer screening participation decisions

Perceptions of radiation risk associated with lung cancer screening

Participants were asked to consider the amount of information contained in the decision aid on the radiation risk associated with lung cancer screening. In the ensuing discussion, it emerged that the extent to which focus group participants were concerned about the radiation risk associated with screening was variable. In discussing this, two male participants agreed that although radiation could have adverse consequences, this knowledge would not prevent them from accepting a lung cancer screening test due to the potential benefits associated with early detection.

Another male participant said that whilst he placed more importance on radiation risk now that he was in remission, it remained a minor concern in view of previous cancer treatment:

“I guess from a fact point of view you can bombard me with anything else. You sign a form and bags of stuff arrive that say deadly on them with a skull and cross bone.” (Focus group 1 participant, male)

Conversely, one female participant said that as a young adult, her level of concern about radiation risk would be greater if regular screening was recommended over a long time period, whereas she would not be concerned about a single scan. For another female participant, the differing impact of radiation on men and women was an important consideration, for example in relation to fertility. In general, practitioners perceived that radiation risk would be a minor concern for patients in view of having undergone multiple scans*:*

“When you think of all the scans our patients have, it’s nothing really, is it?” (Clinical nurse practitioner)

A screening offer can provide a degree of reassurance about lung cancer risk

Health-related anxieties experienced by HL survivors, particularly regarding cancer recurrence but also about developing late effects of treatment, were discussed by both focus group participants and practitioners. Practitioners felt that anxiety and "hypervigilance" about their health would lead most survivors to take up an offer of lung cancer screening, making the decision a straightforward one.

"I think some people would bite your hand off to go and reassure themselves there's nothing wrong" (Advanced nurse practitioner)

Additionally, practitioners felt that although an offer of lung cancer screening could exacerbate anxiety, survivors could be reassured by a screening offer. In considering this, they cited their experience of patients' enthusiasm for surveillance imaging during follow-up. Focus group participants and practitioners went on to discuss the delivery of information about lung cancer risk. Both groups felt that delivering information about lung cancer risk in the context of an invitation to screening - accompanied by an explanation about the rationale - might somewhat mitigate the anxiety associated with becoming aware of this risk, although it was also said that reassurance could be short lived if regular screening were not available. Both groups noted that information on risk of late effects was often given without an offer of surveillance or screening.

"I'd find this arriving kind of reassuring cause it means someone's actually monitoring, checking up on you and not just leaving you to your own devices afterwards so you guys have assessed the risk and doing something about it which we don't get very much to be honest its more just, 'oh there's a risk' and they leave us alone."
(Focus group 2 participant, female)

Patient age at approach about lung cancer screening

Practitioners were asked about the challenges survivors might face when considering undergoing lung cancer screening. The age at which patients were

approached about lung cancer screening was felt to be an important consideration. Practitioners felt that younger patients' desire to "move on" from their illness might render them less likely to engage with information about late effects and screening. In contrast, they felt that people contacted about lung cancer screening at an older age would have better "emotional capacity" to understand late effects information and engage with screening because they or their peers may be experiencing health problems, making health a more salient issue and higher priority. In contrast with this, a focus group participant who was treated in their sixties and currently aged over 70 said that being treated at an older age led them to feel less concerned about lung cancer as a late effect, as they were not sure they would live long enough to be affected. Although the desire to avoid "remedicalisation" could reduce engagement with screening in all age groups, practitioners thought this may be particularly relevant to people diagnosed at a young age:

"I think there will be some who will have a real issue with that identity of being someone who's still…who can possibly still get ill from something serious again in the future" (Lymphoma doctor)

Theme 3: Information provision and support

Lung cancer screening discussions: past and future practice

There was a perception among practitioners that although late effects had not been widely discussed with patients in the past, this had improved in recent years. Nevertheless, there was evidence of variation in current follow-up strategies and timing of discussions about late effects and screening opportunities, which one practitioner attributed to a lack of guidance.

"I don't think we have clear enough guidance that we can use uniformly across our Hodgkin lymphoma survivors and that's tailored to each patient as well." (Consultant haematologist)

This was reflected in the focus groups, where participants described varied experiences of follow-up care and management of late effects. Participants

appeared uncertain about how to access support around late effects and the one participant who had accessed a late effects clinic had done it through "self-advocacy". Practitioners felt that if lung cancer screening were to become established in future, HL patients should be "forewarned" about future screening invitations whilst still in follow-up to mitigate the shock they might experience on receiving an invitation years later. Although practitioners did not offer a consensus as to the optimal time to deliver lung cancer screening information during the follow-up period, some perceived that patients would not be receptive to this screening information until they had achieved remission, as they would be focussed on getting through treatment.

"Screening would be something I would definitely want to talk about at the end of treatment rather than right at the beginning when they've already got those additional stresses." (Consultant haematologist)

Sources of information and support for HL survivors and their practitioners

When discussing support and information, practitioners anticipated that HL survivors would prefer to access support and advice through their own clinical team with whom they had established a relationship and would be likely to follow the recommendation of their lymphoma physician, whose view they would "trust". Indeed, focus group participants expressed their desire to seek advice from their clinical team and it appeared that a positive screening recommendation could be influential.

"If my consultant says to me take it, okay I'll be there in five minutes, that's my attitude." (FG1, male)

Practitioners acknowledged that patients long discharged from follow-up may not have an obvious point of contact, in which case they might seek support from a variety of other sources including a designated nurse specialist for their local area, their GP, or patient charities. Family members were considered to be important and influential sources of support during decision-making.

Practitioners were asked how they might be informed and supported should lung cancer screening become available for their patients in future. Clinical nurse specialists said that having access to the same decision aid document given to patients would fulfil their informational needs, whilst some doctors felt more detail on risk stratification would be useful for them to discuss risk with patients. Nurse specialists did not anticipate difficulties in providing psychological support to patients, saying that this was a key part of their role.

4.5 DISCUSSION

This paper describes our approach to developing a decision aid and shows that the decision aid significantly improved lung cancer risk and screening related knowledge and reduced decisional conflict among HL survivors. Although the decision aid improved participants' knowledge on treatment related lung cancer risk factors, the degree of improvement varied. For example, most participants were already aware of the lung cancer risk associated with radiotherapy, but far fewer had prior knowledge of the risk associated with chemotherapy. This may reflect the nature of information previously provided to participants about lung and other second cancer risks associated with radiotherapy. Nevertheless, it can be argued that even modest improvements in knowledge are of value because an improvement in knowledge around options and outcomes improves decision quality.[40] Decisional conflict scores reduced after accessing the decision aid across all subscales but the smallest change in pre-post median scores and the smallest effect size was seen in the 'support sub-scale', possibly reflecting the fact that more than half of participants remained in follow-up, retaining access to their clinical team for advice.

Participants in the online survey universally expressed willingness to undergo lung cancer screening if invited, even before accessing the decision aid. The utility of a decision aid in a population who are already highly swayed towards one option – screening - could be questioned, but it can be argued that recipients who strongly favour an option at the outset would benefit from feeling better informed, supported and clearer in their values, thus improving the quality of the decision-making process and quality of the choice made.[40,41] Notably, after accessing the

decision aid, a higher proportion responded that they would 'probably' attend lung cancer screening, as opposed to 'definitely'. The improvement in decisional conflict scores after viewing the decision aid would suggest that this change in strength of intention could be a result of participants being more informed of their level of lung cancer risk and of the risks of screening, as opposed to feeling less certain about the decision they would make. Although not statistically significant, this finding highlights the fact that becoming more informed can move screening intentions in both directions. This was demonstrated in the aforementioned Cochrane review of decision aids for people facing screening decisions, where there were mixed results in terms of uptake of breast and colorectal cancer screening after exposure to a decision aid.[3]

Our approach to the development of the decision aid – a schematic outline is shown in Figure 2 -diverged from the systematic approach recommended by Coulter *et al.* [42] Since the decision aid development took place as part of RB's doctoral research, the timeframe for development of the prototype was short and for this reason RB designed the prototype for review by the steering group. In addition, patients' needs relating to lung cancer screening decision making were not assessed prior to developing the decision aid prototype. Prior qualitative research exploring the perspectives of HL survivors on lung cancer screening showed that most survivors were unaware of lung cancer risk[17] and since there is no lung cancer screening programme for HL survivors, we anticipated that lung cancer screening related knowledge would be minimal in this group. We therefore opted to develop a prototype based on the comprehensive IPDASi and then explore the extent to which it met patients' needs, with the intention of amending the DA accordingly prior to further use.

Strengths and limitations

A particular strength of this work was that patient and practitioner stakeholders were involved at every level of the development process. Although our approach did not fully reflect the recommended systematic approach described by Coulter et al, stakeholder feedback influenced the decision aid design in that amendments were made following initial feedback from the steering group and then again - with

the input of the steering group - taking into account the results of the ENGAGE-HL study.

The use of mixed methodology allowed us to quantify the impact of the decision aid through validated scales and to explore the perspectives of stakeholders and the issues pertinent to patients when facing lung cancer screening decision, through qualitative methods. In addition, the use of mixed methodology led to specific insights. For example, the lack of personally tailored information caused ongoing decisional conflict for some focus group participants despite the online survey demonstrating a significant reduction in decisional conflict. The framework method of analysis allowed us to identify areas of concordance and discordance between patients and practitioners. For transparency and rigour, we have reported the evaluation of the decision aid according to the Standards for UNiversal reporting of patient Decision Aid Evaluation (SUNDAE) checklist[43] although not all checklist items were relevant in this early phase of evaluation.

A limitation of this study was the convenience method of sampling of HL survivors, which in turn limits the extent to which the decision aid can be considered acceptable and comprehensible to the wider population of HL survivors. We did not stipulate that patient participants received treatments that increased their lung cancer risk since this would require accurate recall of chemotherapy drugs and radiation site. Therefore, some participants were not at excess risk of lung cancer, meaning not all participants were representative of the intended target group for the decision aid. Nevertheless, a majority were considered to be at excess risk because of treatment trends in the last 40 years – this was the case for the focus groups where participants volunteered their treatment details – and the views of those who were not remain pertinent and relevant to our research questions. A further limitation of the convenience sampling strategy was that men, current smokers and non-white ethnicities were poorly represented among the patient participants meaning decisional needs unique to these groups would not have been identified. Health literacy levels were high among survey participants and more than half of focus group participants were university educated. Given that 42% of working-age adults in the UK cannot understand everyday healthcare information,

rising to 61% when numeracy is required for comprehension,[44] recipients of the decision aid within a future study may be less able to understand the decision aid than our participants. All participants accessed the decision aid in a digital pdf format due to the research being conducted virtually. However, in the future study, the decision aid will be in the form of a paper booklet. Recipients of the paper booklet may have different views regarding its' acceptability than our participants who accessed it online.

Conclusion

The findings of this study suggest that the decision aid developed here would support informed decision making when provided to HL survivors considering undergoing lung cancer screening. Its' suitability for use in a larger population who are more diverse in terms of ethnicity and educational level is uncertain and further research is warranted in those groups. Informed by the results of this study, the decision aid prototype tested here has been developed further by the steering group to produce a decision aid document which will be used in a future feasibility study of lung cancer screening in HL patients.[45] In this future study, the impact of the decision aid on knowledge, decisional conflict and preparedness for decision making will be tested in a larger sample.

List of abbreviations

DA: decision aid
HL: Hodgkin lymphoma
LCS: lung cancer screening
IPDASi: International Patient Decision Aid Standards instrument
DCS: decisional conflict scale
S-TOFHLA: Short Test of Functional Health Literacy Assessment
SUNDAE: Standards for UNiversal reporting of patient Decision Aid Evaluation

Declarations

Ethical approval: The University of Manchester proportionate research ethics committee granted ethical approval for the study on 21st January 2021 (ref: 2021-10619-17592).

Consent for publication: Not applicable

Availability of data: all data generated or analysed during this study are included in this published article and its' supplementary information files.

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Author contributions:

RB undertook data collection, data analysis and wrote the manuscript. TS undertook data analysis. All authors approved the final manuscript.

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Steering group members:

Dr Sally Taylor: researcher with expertise in patient-reported outcomes in oncology

Professor Diana Greenfield: professor of nursing with expertise in lymphoma late effects

Dr Philip Crosbie: respiratory physician with expertise in lung cancer screening

Dr Chris Keyworth: researcher with expertise in risk communication strategies

Anne Hook: publications manager at Lymphoma Action with expertise in patient directed publications

Tracy Howe: Lymphoma clinical nurse specialist, experienced in communicating with lymphoma patients

Dave Broadhurst: patient representative

Vicky Lee: patient representative

Gill Allan: patient representative

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Supplementary data

Table s4.1: Features of the decision aid prototype

Page	Content
Title page	'Screening to find the early signs of lung cancer after treatment for Hodgkin lymphoma: Helping you decide', followed by 'A lung scan can detect the early signs of lung cancer before symptoms have developed'. Cartoon of magnifying glass held over a lung
Page 2	Contents page
Pages 3-5	Text detailing risk factors for lung cancer following treatment for Hodgkin lymphoma

	Text and icon arrays describing: The 35-year post treatment cumulative incidence in men and women The absolute risks of developing lung cancer after chemotherapy alone or chemotherapy and radiotherapy combined. Data on the lifetime incidence of lung cancer in the general population is provided. Data on the lifetime incidence of lung cancer in the general population
Page 6	Text describing the low-dose CT scan procedure accompanied by image of person going through CT scanner Text detailing process for getting the results
Page 7	Text and icon array describing likelihood of negative (clear) result or needing extra tests to rule out lung cancer
Page 8	Text (2-3 sentences) addressing the following questions: What happens if the scan is clear? What happens if the scan result is uncertain? What happens if a possible lung cancer is seen? What else might the scan show? How often can I have a lung scan?
Pages 9-11	Text risks and benefits of undergoing lung cancer screening
Page 12	Common symptoms of lung cancer
Pages 13-14	Header: Making a decision Pros and cons table Suggested steps to help decision making
Page 15	Information and support sources
Page 16	Text boxes to write down pros and cons ‘that are important to you’ and any questions about lung cancer screening

Table s4.2: The proportion of correct responses to the knowledge scale pre and post exposure to the decision aid

Question / statement (response options with correct answer in bold)	Correct responses (%)	
	Pre exposure	Post exposure
A lung cancer screening scan will spot cancers 100% of the time (Yes/***No***/*I don't know)*	50	97
Most spots on the lung seen on a screening scan are cancerous *(Yes/**No**/I don't know)*	57	94
If a lung cancer screening test is clear (cancer is NOT found), you won't develop lung cancer in the future *(Yes/**No**/I don't know)*	84	100
Lung cancer found on a screening scan can always be cured *(Yes/**No**/I don't know)*	84	97
A lung cancer screening scan can tell you if you are likely to develop lung cancer in the future *(True/**False**/Unsure)*	23	65
How many people with an abnormal CT scan will have lung cancer? *(Most will have lung cancer / About half will have lung cancer / **Most will not have lung cancer** / I don't know)*	23	84
Can a CT scan miss a tumour in your lungs? *(**Yes**/No/I don't know)*	44	76
Will all tumours found in the lungs grow to be life-	55	97

threatening? *(Yes/**No**/I don't know)*		
Without screening is lung cancer often found at a late stage when cure is less likely? *(**Yes**/No/I don't know)*	73	100
How much does screening for lung cancer with a CT lower your chance of dying of lung cancer? *(About 95% / About 50% **/ About 20%** / I don't know)*	10	57
Can a CT scan find problems other than lung cancer? *(**Yes**/No/I don't know)*	97	100
Is radiation exposure one of the harms from lung cancer screening? *(**Yes**/No/I don't know)*	68	89
Can radiotherapy to your chest increase your risk of getting lung cancer? *(**Yes**/No/I don't know)*	89	97
Can chemotherapy increase your risk of getting lung cancer? *(**Yes**/No/I don't know)*	57	100
Are you still at risk of getting lung cancer if you have stopped smoking? *(**Yes**/No/I don't know)*	94	100
Can people treated for Hodgkin lymphoma who have never smoked get lung cancer? *(**Yes**/No/I don't know)*	92	100

Table s4.3: Changes made to the decision aid as a result of the ENGAGE-HL study

Section of the booklet	Change made to the decision aid
'Why should I think about lung cancer screening?' (page 2)	Addition: You have been identified as someone who was given one or more of the treatments that increase the risk of lung cancer. Rationale: Patients may not recall their treatment or may think they are expected to determine their risk themselves
'Which treatments increase the risk of getting lung cancer? (page 2)	Addition: There is no evidence that ABVD increases the risk of lung cancer Rationale: Patients who received this commonly used regime, but are at risk because of another regimen of chest radiotherapy, may wish to know whether ABVD also increases risk
Page 4	The graphic showing risk in men and women has been combined into 1 chart Rationale: to ensure length not increased by other additions
Page 4-5	Addition: Your chance of developing lung cancer depends on: 1. Whether you have ever smoked

	The chance of getting lung cancer is much greater in people who have smoked at any time. Most people who get lung cancer after Hodgkin lymphoma have smoked." Rationale: Ensure message about increased risk from smoking is clear
Page 5	Addition: Other things to know The risk of lung cancer in people treated for Hodgkin lymphoma is around 5 times higher than people in the general population who were not treated for lymphoma Rationale: providing lifetime incidence rates for the general population led to confusion over the excess risk in HL survivors
Page 9	Addition: Can I have more lung screening scans after this study ends? At the moment, lung cancer screening is not routinely available outside of this study. If lung cancer screening does become available for you in the future, you will be contacted. Rationale: after participating in the study, HL survivors

	would want to know if they could access further screening
What are the common symptoms of lung cancer? (page 12)	Addition: Occasionally, people treated for Hodgkin lymphoma have some these symptoms because of their cancer treatment, sometimes for many years after treatment. For them, some of these symptoms are 'normal'. However, if you experience these symptoms and they are **not** normal for you, or if your usual symptoms **change**, it is important for you to speak to your GP. Rationale: HL survivors can experience long-term respiratory symptoms after treatment, some of which are also symptoms of lung cancer
Pros and cons of lung cancer table (page 13)	The statement "You are less likely to die of lung cancer" was removed Rationale: Lack of evidence for this statement in this population
Page 16: More information and support	Addition: To be directed to the journal articles containing the data used in this booklet, please email… Please note, the articles are written in scientific language which may be difficult to understand.

	Rationale: Some survivors may wish to read the evidence behind the information in the booklet themselves
Worksheet (last page)	Separate text boxes removed so worksheet is blank Rationale: more flexibility

CHAPTER 5

TITLE: A pilot of lung cancer screening for survivors of Hodgkin lymphoma

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5.1 ABSTRACT

Background

Alkylating agents and thoracic radiation put survivors of Hodgkin lymphoma (HL) at excess risk of lung cancer (30-year cumulative incidence 6.4%). Lung cancer screening (LCS) using low-dose computed tomography (LDCT) reduces lung cancer mortality in higher-risk ever smokers by detecting early-stage disease. Here we report results of a LCS pilot in HL survivors. The primary outcome was uptake rate and key secondary outcomes were quality of decision making and clinical findings.

Methods

Individuals who had received treatment for HL ≥5 years ago, with mustine or procarbazine and/or thoracic radiation, were identified from a follow-up database (ADAPT, The Christie NHS Foundation Trust) and sent a letter of invitation. Study participants had a LDCT scan which was reported as negative/indeterminate/positive and actioned in accordance with national screening guidelines.

Results

Of 218 study invitees 54% were female, median age was 53 (range 25-80), median years since treatment 21 (6-45). 10 were found to be ineligible after invitation. The uptake among eligible responders was 83% (102/123). Participation was not influenced by age, gender, years since treatment or index of multiple deprivation decile. The decision aid improved LCS knowledge and decisional conflict scores were low (median 9). The median score on the preparation for decision making scale was 80/100. Baseline LDCT scan results in 102 participants were: 90 (88.2%) negative, 10 (9.8%) indeterminate, 2 (2.0%) positive. 3-month (n=9) surveillance LDCT scan results were: 2 positive, 7 negative (6 with stable nodule/s, 1 with resolution of changes). The other participant with an indeterminate baseline scan will undergo a 12-month surveillance scan. Among 4 participants with positive baseline or 3-month scans, 1 has been diagnosed with early-stage small-cell lung cancer and treated with curative intent, 1 has been diagnosed with stage 3 small

cell lung cancer, and 2 have not been diagnosed with lung cancer and are undergoing further surveillance. Coronary artery calcification was detected in 36.3%. Incidental findings including emphysema, bronchiectasis, pulmonary inflammation/infection, metastatic breast cancer and vertebral insufficiency fractures were seen in 64.7%, immediately clinically significant in 2.9%. Only 3/35 participants who were ever smokers met the age and risk criteria for LCS through the programme aimed at the general population.

Conclusion

LDCT scanning protocols tested in higher risk ever smokers appear to be appropriate for use in the HL survivor population in a future targeted LCS programme.

5.2 BACKGROUND

Around 48,500 new lung cancer cases are diagnosed in the United Kingdom each year, approximately 60% of which are stage 3 or 4. The predominance of advanced stage disease, which is associated with very poor survival outcomes, means the overall 5-year survival rate across all stages is just 16%.[1,2] Screening for lung cancer using low-dose CT (LDCT) scans leads to detection of asymptomatic lung cancers at an early stage, when potentially curative treatment may be offered and has been validated in the ever smoking population. In the National Lung Cancer Screening Trial which randomised current or former smokers aged 55-74 in the United States (US) to either a chest radiograph or LDCT scan of the thorax at 1-year intervals over a 2 year period, lung cancer mortality was reduced by 20% in the LDCT scan arm.[3] These results were corroborated in several large European lung cancer screening trials, the largest of which is known as the NELSON (Nederlands–Leuvens Longkanker Screenings On- derzoek) trial. In NELSON, 15,792 current or former smokers aged 50-75 were randomised to LDCT screening (the screening interval varied across study arms) versus no screening. At 10 years of follow-up, lung cancer related mortality was reduced in the screening arm by 24% in men and 33% in women.[4] In the NLST and NELSON studies, 69% and 63% of lung cancers detected

by LDCT screening were stage IA-IB and curative surgical treatment was more prevalent in the LDCT scan arms.[3,4]

Trials of lung cancer screening have been targeted towards current and former smokers and the eligibility for screening reflects this. In the US, individuals aged 50-80 with a 20-pack-year smoking history who currently smoke or have quit within 15 years are eligible,[5] whilst in the United Kingdom (UK) pilots are targeted towards 55-74 year-old ever smokers whose eligibility is determined using lung cancer risk calculators.[6] Despite the potential benefits of lung cancer screening, uptake by ever smokers has been sub-optimal. The UK based Lung Screen Uptake Study reported a participation rate of 53%, which exceeded uptake in previous trials.[7]

Survivors of Hodgkin lymphoma (HL) are at excess risk of lung cancer (standardised incidence ratio 6.4 and 30-year cumulative incidence 6.4%[8]) due to receiving the alkylating agents procarbazine or mustine and/or thoracic radiation,[9] but they are largely ineligible for UK-based lung cancer screening pilots because most lack a significant smoking history.[10,11] Among responders to a questionnaire study that surveyed HL survivors' willingness to undergo lung cancer screening, the proportion of HL survivors meeting the risk threshold for lung cancer screening aimed at the ever smoking population was just 6%.[11] A targeted lung cancer screening programme for HL survivors is therefore worthy of exploration. One issue pertaining to the feasibility of such a programme is uptake of lung cancer screening by HL survivors who may be previously unaware of their lung cancer risk and among whom potential barriers to participation - including male gender and concerns around the radiation associated with a LDCT scan - have been identified.[11,12] In addition, imaging protocols and pulmonary nodule reporting guidelines[13] have not been tested in HL survivors, many of whom were treated with pulmonary toxic anti-cancer therapies. To address the questions of uptake, decision making and clinical outcomes, we ran a pilot of lung cancer screening for HL survivors.

5.2 METHODS

Study design

Ethical approval for the study was granted by the Wales REC 7 ethics committee (21/WA/0137). This is a single-arm study which took place at a single participating site. HL survivors registered in a follow-up programme (ADAPT) and at risk of lung cancer due to previous treatment were invited to undergo a single round of lung cancer screening using a LDCT scan.

Primary outcome measures

1. The response rate to the initial invitation
2. The uptake rate among eligible responders

Secondary outcome measures

1. The characteristics of participants and non-participants
2. The impact of a decision aid on lung cancer risk and screening related knowledge
3. The impact of a decision aid on attitude towards lung cancer screening
4. Decisional conflict levels after receipt of the decision aid
5. Levels of preparedness for decision making after receipt of the decision aid
6. The proportion making an informed choice about screening
7. Participants' health and respiratory symptoms
8. The proportion of participants who would be eligible for lung cancer screening using risk prediction models used to determine eligibility for screening among ever smokers
9. LDCT scan findings including rates of coronary artery calcification and incidental findings

Eligibility criteria

The inclusion criteria are a history of HL (classical HL or nodular lymphocyte-predominant HL) with no relapse within 5 years prior to study recruitment, current age 18-80, treated with radiotherapy for HL with a radiation dose to the lung and/or a chemotherapy regimen containing procarbazine or mechlorethamine (mustine), and registered address within 40 miles of The Christie hospital. The following exclusion criteria applied: a CT scan of the thorax within the last 12 months, a previous diagnosis of malignant neoplasm of trachea, bronchus, lung, thymus or pleura, a current diagnosis of metastatic cancer, resident in a nursing home or housebound, pregnant women, and those known to have dementia or severe learning difficulties which would prevent them from providing informed consent.

Identification of potential participants

In July 2021, potential participants who fulfilled the inclusion criteria were identified from a clinical long-term follow-up database of lymphoma survivors held at The Christie NHS Foundation Trust known as ADAPT. Electronic patient records were used to confirm the patient met the inclusion criteria. The hospital data insights team performed a search of electronic patient records to identify patients ever treated for lung cancer or currently being treated for another metastatic cancer at The Christie NHS Foundation Trust, who were excluded. Individuals deemed potentially eligible were sent a study invitation letter by post with a baseline study questionnaire between August and December 2021.

The invitation procedure

Those interested in participating were asked to return the baseline study questionnaire, which contained measures to be recorded prior to the provision of more information about the study (see Table 5.1). Those who did not respond to the study invitation letter within 4 weeks were contacted by telephone. Upon return of the baseline study questionnaire, potential participants were sent a participant information sheet, a decision aid developed for this study[14] and a

second study questionnaire. The decision-aid was an A5 paper booklet which was 18 pages in length, entitled 'Screening to find the early signs of lung cancer after treatment for Hodgkin lymphoma: Helping you decide'. Those who had been sent the decision aid were asked to indicate their participation decision by contacting the study team, or by returning the second study questionnaire, in which they could indicate their decision.

Study visit and LDCT scan

Interested individuals were invited to attend an appointment at The Christie to confirm eligibility and obtain written informed consent, after which they underwent a baseline LDCT scan on the same day. At this appointment, participants completed a third study questionnaire and were offered the option to provide a saliva sample for a sub-study exploring the prevalence of single nucleotide polymorphisms associated with lung cancer.

Pulmonary nodule reporting and management

Pulmonary nodules detected on LDCT scans were reported according to the British Thoracic Society (BTS) Guidelines for the Investigation and Management of Pulmonary Nodules.[13] Scans were categorised as negative, indeterminate or positive. Coronary calcification (arterial (CAC) or valve) was reported as present or absent and graded in line with published guidelines.[15] Incidental findings were reported. Scan results were communicated to participants by telephone (if negative or indeterminate), or at a clinic visit if positive or showing another malignancy. Results were also communicated in writing to participants and their general practitioner. Participants with negative scans were not offered further screening, whilst participants with indeterminate scans were offered 3-month surveillance LDCT scans at The Christie, +/- a 12-month surveillance scan at their local hospital via a referral to a respiratory physician, as determined by the BTS guidelines. Participants with positive scans were referred to lung cancer services at their local hospital for further investigation and management.

Study follow-up

Participants will be followed-up by telephone 6 months following the baseline LDCT scan (if the LDCT scan detected an indeterminate nodule or an incidental finding requiring action) and 14 months following baseline LDCT scan (all participants).

Data collection

Prior to invitation to the study

The researchers who collected data on the participants were part of the treating team. Each person invited to the study was given a study ID number that they retained for all study activities. To identify the cohort to be invited to the study, personal details (name, date of birth, NHS number, last known address, gender) and clinical details (HL diagnosis, date of HL diagnosis, date treatment for HL commenced, last treatment date, receipt of radiotherapy to lung tissue) of individuals potentially eligible for invitation to the study were collected from the ADAPT database. Up to date addresses, phone numbers and registered GP details for those potentially eligible were obtained using NHS Spine. Electronic patient records were accessed to confirm receipt of a chemotherapy regimen containing procarbazine and/or mustine. The hospitals' data informatics team identified deceased patients, obtained addresses, phone numbers and registered GP details for those potentially eligible, and identified patients who had attended a recent Christie appointment so that electronic patient records could be checked to identify those with a metastatic cancer diagnosis, who were excluded. An online tool was used to identify the Index of Multiple Deprivation (IMD) decile for the postcode of each person invited to the study.[16]

Collecting the demographic and clinical data of participants

A study questionnaire was completed by participants in person at the study visit. It contained items to record the participants' demographic data and medical history (age, gender, ethnicity, height and weight, educational attainment, smoking history and other lung cancer risk factors, co-morbidities), their European Cooperative Oncology Group (ECOG) performance score) and their degree of breathlessness (using the medical research council (MRC) dyspnoea score, graded 1-5, a higher

score representing a higher level of breathlessness.) LDCT scan results were accessed using the electronic patient records. Clinical outcomes on patients with positive scans were collected through communication with patients and members of the lung cancer referral pathway teams.

Decision-making measures

Quality of decision-making and informed decision making were measured among those who received the decision aid and completed the first two study questionnaires. The first postal study questionnaire, sent with the study invitation letter, measured lung cancer risk and screening related knowledge and attitude towards lung cancer screening prior to the provision of the decision aid. The second, sent with the decision aid and participant information sheet, measured lung cancer risk and screening related knowledge, attitude towards lung cancer screening, decisional conflict and preparedness for decision making following receipt of the decision aid. Lung cancer screening risk and screening related knowledge was measured using a 16-item scale measuring lung cancer screening related knowledge adapted from a pre-existing questionnaire aimed at ever smokers.[17] Attitude towards lung cancer screening was measured using a 4-item attitude scale (possible range 3-21 where a higher score represented a more positive attitude) based on the work of Marteau *et al.*[18] Decisional conflict was measured using the decisional conflict scale (DCS)[19] and preparedness for decision making was measured using the preparation for decision making scale (PDMS).[20]

In the DCS, lower scores overall and in the sub-scales demonstrate lower levels of decisional conflict and uncertainty, feeling better informed, better supported and clearer about personal values. The possible range is 0-100 in the main scale and subscales. A higher score in the PDMS scale demonstrates greater preparedness for decision making and the possible range is 0-100. Table 5.1 shows the measures contained in the two postal questionnaires and the questionnaire administered at the study visit.

Table 5.1: Measures in the study questionnaires

	Study time-point		
Measures	First postal questionnaire (pre-decision aid)	Second postal questionnaire (post-decision aid)	Study visit questionnaire
Lung cancer risk and screening knowledge	X	X	
Attitude to lung cancer screening	X	X	
Decisional Conflict Scale (DCS)		X	
Preparation for decision making scale (PDMS)		X	
Medical history, smoking status, symptoms			X

Data analysis

Descriptive statistics are used to report the uptake rate, scan findings, results of the DCS and PDMS and the measure of informed decision making. Wilcoxon signed rank test was used to compare matched lung cancer screening related knowledge scores (which had been converted to the percentage of correct answers) and matched attitude scores – both measured pre and post exposure to the decision aid. The demographic characteristics of participants versus non-participants were compared using Chi-squared test for gender, the independent samples *t*-test for age and time since treatment (since the data met the tests for normality) and Mann-Whitney *U* for IMD decile and baseline knowledge score and attitude score (since the data did not meet the tests for normality). In the comparison between participants and non-participants, effect sizes are presented as Cohen's *d* values for age and years since treatment, Cohen's *W* for gender, and the *r* coefficient for IMD decile and attitude scores. In the comparison between matched knowledge scores and attitude scores

pre and post exposure to the decision aid, effect sizes are presented as the *r* coefficient. Effect sizes for Cohen's *d* are 0.2=small, 0.5 medium, 0.8 large and for Cohen's *W* and *r* coefficient small = 0.1, medium = 0.3, large = 0.5.

5.4 RESULTS

Characteristics of the invited sample

Two hundred and eighteen individuals in the ADAPT database fulfilled the study inclusion criteria and were invited to participate. Their demographic characteristics are shown in table 5.2. The invited cohort comprised 117 (54%) women and 101 (46%) men with a median age of 53 years (range 25-80). The median number of years since completion of treatment was 21 (range 6-45). The median IMD decile to which the invited individuals' postcode belonged to was 6 (range 1-10). Twenty (9.0%) were at risk of lung cancer due to having received procarbazine or mechlorethamine, 110 (50.5%) due to radiation to the lung only, and 88 (40.5%) due to receiving both these treatments.

The response rate and uptake rate

The response rate to the initial invitation was 58.3% (127/218). The uptake rate among 123 eligible responders (received the decision aid and participant information sheet and were eligible) was 82.9%. Response rate, uptake rate and the scan outcomes among participants are shown in figure 5.1.

Characteristics of participants and non-participants

Among 102 participants, 58% were female, the mean age was 52, the mean number of years since treatment was 22, 65.7% were never smokers, 27.5% were former smokers and 6.8% were current smokers. Among 106 non-participants (eligible non-responders and eligible responders who did not subsequently participate), 52% were female, the mean age 51, and the mean number of years since treatment was 20. The mean IMD decile for both groups was 6. Age, gender, IMD decile, time since treatment and baseline lung cancer risk and screening knowledge were not associated with participation in the screening aspect of the study. A more positive

attitude (measured as a continuous variable using the attitude scale) towards lung cancer screening at baseline (measured before exposure to the decision aid in 121 people) was associated with screening participation ($p<0.01$, effect size (*r* coefficient) 0.2 (small)).

Table 5.2 shows the characteristics of participants and non-participants, associated p values, and effect sizes.

Table 5.2: Characteristics of the overall invited sample, participants and non-participants

	Overall invited cohort (n=218)	Participants (P) (n=102)	Non-participants (NP) (n=106)	*p* value	Effect size
Gender: Male / Female	101 (46%) / 117 (54%)	43 (42%) / 59 (58%)	51 (48%) / 55 (52%)	0.47	<0.1 (Cohens *W*)
Mean age (range)	52 (25-80)	52 (26-80)	51 (29-80)	0.52	0.8 (large) (Cohens *d*)
Mean IMD decile (range)	6 (1-10)	6 (1-10)	6 (1-10)	0.14	0.1 (small) (*r* coefficient)
Mean number of years since last treatment (range)	20 (6-45)	22 (7-44)	20 (6-45)	0.08	0.2 (small) (Cohens *d*)
Ethnicity		White British 93 (91.2%), Asian (2) Black African (1), Black British (1) Irish (2), White and black Caribbean (1) White and Asian (1), Not divulged (1)			
Smoking status		Never smoker (65.7%), Former smoker (27.5%), Current smoker (6.8%)			
Educational attainment		No qualifications (9.8%);School/ college / further education but not a degree (52.9%);Undergraduate degree			

		(21.6%);Postgraduate degree (15.7%)			

Decision making outcomes

Pre-post measures: Lung cancer risk and screening related knowledge and attitude towards lung cancer screening

Matched lung cancer risk and screening related knowledge scores were available for 95 individuals measured pre and post exposure to the decision aid. The median percentage of correct responses to knowledge questions and statements increased following exposure to the decision aid (56% pre-exposure, 88% post-exposure (p value <0.001). The Cohens *d* effect size was 0.7 (large) as shown in table 5.3. The proportion responding correctly to each individual item in the knowledge scale pre and post exposure to the decision aid is shown in Table s5.1 in Supplementary information. Matched attitude towards lung cancer screening scores measured pre and post exposure to the decision aid were available for 95 people. Following exposure to the decision aid, attitude became more negative in 34, more positive in 33 and remained the same in 28. Among these 95, there was no statistically significant change in attitude towards lung cancer screening after exposure to the decision aid (p=0.44, Cohens *d* effect size <0.1). Table 5.3 shows the knowledge and attitude scores pre and post exposure to the decision aid, p values for the difference and effect sizes.

Table 5.3: Knowledge of and attitude towards lung cancer screening before and after exposure to the decision aid

Knowledge and attitude scores (n=95)			
	Pre-exposure to decision aid	Post-exposure to decision aid	p value for difference pre and post and effect size (Cohens *d*)
Median percentage of correct responses	56	88	p <0.001 Effect size 0.7
Mean attitude score	19	19	p value 0.44 Effect size <0.1
Median attitude score	21	21	
Range (IQR)	3-21 (2)	10-21 (3)	

Decisional conflict and preparation for decision-making: post receipt of the decision aid

Decisional conflict and preparedness for decision making were measured once, after receipt of the decision aid. Decisional conflict scores were calculable for 97 individuals, due to missing questionnaires and missing data for 5 individuals. The median total DCS score was 9, the median uncertainty score was 8, and the median score was 0 for the effective decision, informed, values clarity and support subscales. The DCS scale and subscales are scored out of a possible 100, with lower scores representing demonstrating lower levels of decisional conflict and uncertainty, feeling better informed, better supported and clearer about personal values. The median score on the PDMS scale was 80 (out of a possible 100, a higher score indicating greater preparedness for decision making). For the DCS and PDMS, there are no defined cut-off values to categorise scores.

Table 5.4 shows the median scores, range and interquartile range of the DCS and PDMS scales.

Table 5.4: DCS and PDMS scale scores following exposure to the decision aid

DCS scores (n=97)	
	Median (range; IQR)
Total DCS score	9 (0-42; IQR 25)
Uncertainty subscale score	8 (0-67; IQR 25)
Effective decision subscale score	0 (0-50; IQR 25)
Informed subscale score	0 (0-50; 25)
Values clarity subscale score	0 (0-67; IQR 25)
Support subscale score	0 (0-50; IQR 25)
PDMS scores (n=96)	
Total score	80 (35-100; IQR 18.5)

Informed decision making

Informed choice was measured using the multidimensional measure of informed choice (MMIC), with data collected after receipt of the decision aid. It was measured in 93 individuals who returned the second study questionnaire with complete knowledge and attitude data, who were eligible to participate and who selected a positive or negative

screening participation preference. Using the methods outlined by Marteau *et al* in their validation of the MMIC[21], attitude towards lung cancer screening was categorised as positive or negative, and knowledge as good or poor. A positive attitude was defined as scoring above the midpoint on the attitude scale (12), and good knowledge was defined as scoring above the midpoint (8) on the knowledge scale, measured after exposure to the decision aid. An informed decision was defined as a positive attitude + good knowledge + preference to participate, or a negative attitude + good knowledge + preference to not participate. Using this method, 91.4% were deemed to have made an informed decision. Table 5.5 shows the numbers deemed to have made informed and uninformed decisions based on definitions provided by Marteau.[18,21]

Table 5.5: Informed and uninformed choices by 93 individuals according to the MMIC

	Good knowledge	Positive attitude	Participation	Number	%
Informed choices					91.4%
Combination 1	✓	✓	✓	81	
Combination 2	✓	×	×	4	
Uninformed choices					8.6%
Combination 3	✓	×	✓	3	
Combination 4	×	✓	✓	5	

Participants' health and respiratory symptoms

In the study visit questionnaire, participants answered questions about their health. Fourteen (13.7%) had been diagnosed with another primary cancer following HL (6 carcinomas of the breast, 1 ductal carcinoma in situ, 1 thyroid, 4 skin (2 basal cell carcinomas, 1 melanoma and 1 not specified), 1 prostate, 1 cervical). MRC Dyspnoea Scores were grade 1 (58.8%), grade 2 (37.3%), grade 3 (2.9%), grade 4 (1.0%). Relating to

respiratory symptoms: 7.8% had received antibiotics or steroids for their chest within 12 months, 1.0% had been admitted to hospital for their chest within 12 months, 13.7% reported a cough most days/nights, 23.5% usually produce phlegm, 19.6% usually wheeze, 1.0% reported haemoptysis and 3.9% reported unintentional weight loss. Selecting from a list of 20 conditions, 38.2% reported no comorbidities, 53.9% selected 1-2 comorbidities and 7.8% reported 3 or more comorbidities. The frequently recorded comorbidities were asthma (21%) and hypercholesterolaemia (21%).

Eligibility of participants for lung cancer screening programmes aimed at ever smokers in the general population

Using data from the study visit questionnaire, 6-year lung cancer risk was calculated using an online PLCOm2012 calculator[22] for participants aged 40 or over (representing the scope of the calculator rather than the age-range eligible for lung cancer screening) who were current or former smokers. Six-year lung cancer risk was calculable for 29/35 participants who were ever smokers. The median risk was 0.3% and the range was 0.1-12.2%. Among the 35 ever smoking participants, only 3 (2.9% of all participants) met the age and lung cancer risk eligibility criteria for lung cancer screening aimed at ever smokers (a current age of 55-74 and a 6-year lung cancer risk of $\geq$1.51%).[6]

LDCT scan outcomes

The LDCT scan results of the 102 participants are shown in Figure 5.1. The baseline scan results were as follows: 90 (88.2%) negative, 10 (9.8%) indeterminate, 2 (2.0%) positive. One participant with an indeterminate scan requires a 12-month surveillance scan but not a 3-month scan. The 3-month surveillance scan results (n=9) were as follows: 7 were negative - defined as nodules of concern having disappeared or remained stable – (6 participants were referred for a 12-month surveillance scan and 1 did not require surveillance), and 2 were positive. One participant with an indeterminate scan result fulfilled the BTS guidelines criteria for proceeding to a 12-month surveillance scan without a 3-month scan.

The outcomes in patients with a positive LDCT scan are detailed in table 5.6. Two patients have been diagnosed with small-cell lung cancer, one of whom underwent surgical resection. Two patients remain under surveillance. One is felt to have benign changes due to

previous coronary artery bypass graft surgery and one has a stable nodule requiring 3-monthly surveillance which has not yet been confirmed to be cancer.

Table 5.6: Clinical outcomes in participants with a positive LDCT scan

Case	Timing and nature of positive scan	Personal demographics	Treatment, Time since treatment, Smoking history	Further investigations	Lung cancer diagnosis and treatment
1	Baseline scan	Female, age 53	Procarbazine 23 years Never smoker	2 surveillance CT scans at 3-month intervals, PET-CT scan, further surveillance CT scan planned at 3-months	None
2	Baseline scan	Male, age 66	Procarbazine Radiation to lung 24 years Never smoker	Pleural aspiration: no malignancy cells, CT thorax 6 months following baseline scan, no evidence of malignancy, further CT thorax planned at 3-month interval	None
3	3-month surveillance LDCT scan	Male, age 66	Procarbazine Radiation to lung 41 years Ex-smoker (30 pack years)	PET CT scan confirmed growing PET-avid nodule, biopsy could not be obtained; MRI brain post-surgery	Small cell lung cancer stage T2N0M0; wedge resection followed by adjuvant chemotherapy (curative intent)
4	3-month surveillance LDCT scan	Male, age 53	Procarbazine Radiation to lung 21 years	PETCT scan showed an avid node, confirmed to be nodal metastasis on biopsy	Stage 3 small cell lung cancer, for palliative chemotherapy

			Smoker (20 pack years)		

Coronary calcification

Coronary artery calcification (CAC) was detected on baseline LDCT in 36.3% of participants; categorised as severe in 4.9%, moderate in 6.9% and mild in 24.5%. Just 16.2% of those with CAC had a history of angina or myocardial infarction. Aortic valve calcification was present in 6 (5.9%). Among these 6 cases, 1 was severe and previously undiagnosed, 1 had previously undergone an aortic valve repair, 2 cases were moderate and 1 was mild. Mitral valve calcification was seen in 2 participants.

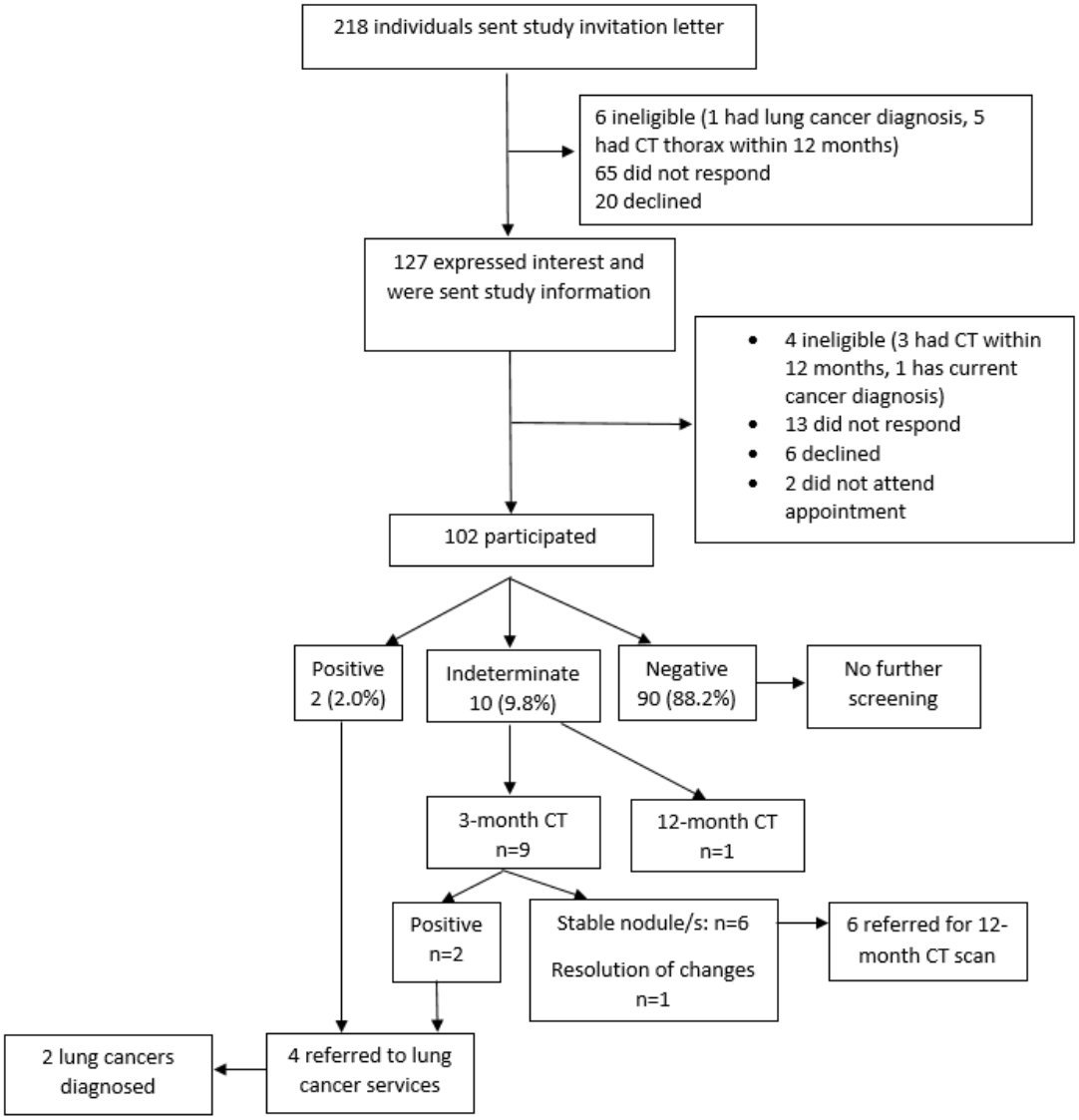
Incidental findings

Incidental findings were reported in 66 (64.7%) baseline scans. These were categorised as 'clinically significant' (requiring investigation and/or immediately impacting the participant), 'potentially clinically significant' (may require investigation or impact the participant in future), or 'not clinically significant' (unlikely to impact the participant) and are detailed in table 5.7.

Table 5.7: Incidental findings on LDCT scans: significance, nature and number affected

Category; number affected; (% of total cohort)	Nature of finding and number of participants affected
Clinically significant; 3 (2.9%)	Distended left pelvi-calyceal system (1)
	Pleural effusion (in a participant with a positive baseline scan in whom lung cancer is now considered unlikely) (1)
	Vertebral bone metastases (breast cancer recurrence) (1)
Potentially clinically significant; 15 (14.7%)	Emphysema (4)
	Cardiomegaly (2)
	Inflammation in the lungs (3)
	Bronchiectasis (2)
	Fatty liver infiltration (1)
	Vertebral wedge collapse / end plate fractures (2)
	Hiatus hernia (1)
Not clinically significant; 48 (47.1%)	Post-radiotherapy fibrosis / scarring (21)
	Residual nodes / mass at site of previous disease (usually calcified) (27)
	Vertebral body sclerosis (1)
	Adrenal myolipoma (1)
	Congenital vertebral fusion (1)
	Subpleural atelectasis (1)
	Liver cyst (2)
	Apical pleural thickening (1)

Figure 5.1: Lung cancer screening participation rates and scan outcomes



5.5 DISCUSSION

This is the largest lung cancer screening study performed in HL survivors to date. The rate of response to the initial invitation was 58.3% and the uptake rate among eligible responders was 82.9%. We report the impact of a lung cancer screening decision aid designed for HL survivors on decision making outcomes and rates of informed decision making. We have shown that the decision aid tool improves lung cancer risk and screening related knowledge, which is a key requirement for patient decision aid tools.[23] In addition, people who had received the decision aid had low DCS scores and high PDMS scores, demonstrating that recipients had low levels of decisional conflict and largely felt prepared to make a decision about screening after reading the decision aid, which suggests that the decision aid facilitates informed decision making. These scales were administered once, after exposure to the decision aid, so we cannot report whether the decision aid improved these scores, although the decision aid did improve knowledge and DCS scores when it was initially evaluated.[14] In addition, use of the MMIC showed that a large majority of those who received the decision aid booklet made an informed decision. However, there is no consensus as to how to define 'good' knowledge or a 'positive' attitude, both requirements of the MMIC. Whilst researchers continue to reproduce the methods used in the MMIC validation study[24] (using the midpoints of scales as cut-offs for categorising knowledge and attitude)[21], other MMIC adaptations have used expert consensus to determine a cut-off for adequate knowledge.[25] The use of subjective thresholds for measuring informed choice is one of several controversial issues surrounding the measurement of informed decision making.[26] Another issue, as described by Waller *et al,*[27] is that giving equal weighting to items within attitude and knowledge scales is unlikely to represent the perceived importance of these items by screening participants, who may regard certain knowledge items as being more important to make an informed decision. The authors propose alternative approaches when reporting informed decision making, including reporting individual item results from knowledge scales, testing associations between aspects of informed decision making (eg. knowledge / attitude and participation), and the use of other measures such as the DCS which we adopted in our study to enhance reporting of informed decision making.

The use of the BTS pulmonary nodule reporting and management guidelines[13] led to very few participants undergoing invasive tests to rule out lung cancer and there was no surgery for benign nodules. The prevalence of lung cancer after a single round of screening in this study was 2.0%. The rate of detection of indeterminate nodules on baseline LDCT was 10%, which is similar to the rate reported in the baseline screening round in the Manchester Lung Health check (12.7%), which also managed nodules in accordance with the BTS guidelines.[28] Had the participants undergone a further round of screening, the rate of indeterminate nodule detection on the second round would be lower, since benign nodules would have been identified during the first screening round. This pilot suggests that previous treatment for HL does not lead to higher rates of detection of indeterminate nodules, as compared with the ever smoking general population. Reassuringly, the majority of incidental findings were not clinically significant and just 3% required an immediate intervention. The presence of CAC scored using a simple visual scoring system was predictive of death related to coronary artery disease in the National Lung Screening Study.[29] Using the same visual scoring system for CAC, the Lung Screen Uptake Study found CAC in 61.9% of participants (ever smokers aged 60-75 years) which was moderate in 21.3% and heavy in 7.2%.[30] In comparison, CAC was only detected in around a third of our participants, probably because they were younger and largely never smokers. Nevertheless, 11.8% of our participants had moderate or severe CAC and given that cardiac events are the second most common cause of death in HL survivors,[31] CAC detection through lung cancer screening is an opportunity to initiate primary prevention, although this approach is not supported by national guidelines.

Whilst the uptake rate among eligible responders was high, the response rate was modest. This could be attributed to the fact that the invited cohort were being invited to undergo lung cancer screening for the first time and the initial invitation letter provided only brief information on the rationale for the invitation. In this study, the decision aid was not provided to invitees upon first contact as it was considered unethical to potentially provoke anxiety among those who would not wish to participate. However, providing the decision aid upfront within future studies might increase the initial response rate by providing information on the rationale and screening pros and cons on first contact. This would reflect the approach used by established cancer screening programmes in which participants may have minimal or no contact with healthcare professionals before the screening test, creating

a requirement for providers to facilitate informed decision making in advance of participation.[32,33] Future studies may also achieve higher uptake by making it less burdensome to participate. This could be achieved by minimising research procedures such as the pre-screening study questionnaires used in this study and offering flexible screening appointments close to people's home or work, especially as the HL survivor population are often of working age and may have childcare responsibilities. Incorporating interventions which have shown to increase uptake of other cancer screening programmes, such as telephone or written appointments reminders and small media[34] may also be valuable.

A limitation of this study was that we lacked data on smoking history and ethnicity for people who did not participate. We are therefore not able to comment on whether former or current smokers were less likely to participate than never smokers, as has been the case with other lung cancer screening trials,[7,35] or whether uptake differed between different ethnicities. It should also be noted that the HL survivors recruited to this study from the ADAPT programme database may be more engaged in late-effects monitoring, late-effects research and may have greater awareness of their lung cancer risk than other HL survivors who are not registered in a long-term follow-up programme. People registered in the ADAPT programme are sent an annual health questionnaire and some of those invited to this study had been invited to and/or participated in other late effects research studies, including studies exploring HL survivors' willingness to be screened for lung cancer.[11,12] Therefore, the uptake rate in our study may not be representative of the uptake rate by HL survivors who are not registered in a follow-up programme.

There are several challenges facing the development of a lung cancer screening programme for HL survivors. Long-term follow-up programmes like ADAPT are rare and most HL survivors at risk of lung cancer are discharged from follow-up care, so there is a need to develop methods of identifying and contacting them for lung cancer screening. A hybrid approach to identification and recruitment in which cancer centres are asked to provide treatment data for HL survivors identified from the National Cancer Registration and Analysis Service (NCRAS) database may be the optimal method for identifying the largest number of at-risk HL survivors but will require significant time and effort. A similar approach was used in the creation of the Breast Cancer After Radiotherapy Dataset (BARD)[36], which

has identified around 8000 women treated with radiotherapy under the age of 30 and at risk of breast cancer and we may learn from the successes of this project. A further challenge is the lack of lung cancer risk calculators for the HL survivor population. Currently, we are not aware of any datasets with the required data granularity for a lung cancer risk calculator to be developed and in its' absence, a targeted lung cancer screening programme will require a consensus on eligibility in terms of age, time since treatment, treatment, and smoking history. Nevertheless, the results of this pilot support the development of a larger study of lung cancer screening for HL survivors. In this larger study, there will be opportunities to assess the feasibility of methods to identify and contact survivors at risk of lung cancer, which is the first step in being able to offer lung cancer screening to HL survivors nationwide.

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5.7 SUPPLEMENTARY INFORMATION

Table s5.1: Correct responses to individual items on the knowledge scale pre and post exposure to the decision aid

Item on lung cancer risk and screening knowledge scale (response options with correct answer in bold)	Number who answered question; Percentage answered correctly before receiving decision aid	Number who answered question; Percentage answered correctly after receiving decision aid
A lung scan will spot cancers 100% of the time (True/**False**/Don't know)	125; 30.5%	98; 78.6%
Most spots on the lung scan are cancerous (True/**False**/Don't know)	125; 45.6%	98; 80.6%
If a lung scan is clear you won't develop lung cancer in the future (True/**False**/Don't know)	124; 84.7%	98; 94.9%
Lung cancer found on a screening scan can always be cured (True/**False**/Don't know)	124; 65.3%	97; 83.5%
A lung scan can tell you if you are likely to develop lung cancer in the future (True/**False**/Don't know)	125; 36.0%	97; 75.3%
How many people with an abnormal scan will have lung cancer (**Most will not have lung**	125; 14.4%	98; 66.3%

cancer/About half/Most will have lung cancer/Don't know)		
A CT scan can miss a tumour in your lungs (**True**/False/Don't know)	125; 25.6%	98; 64.3%
All tumours in the lungs will grow to be life threatening (True/**False**/Don't know)	125; 46.0%	97; 82.5%
Without screening lung cancer is often found at a late stage when a cure is less likely (**True**/False/Don't know)	125; 68.0%	97; 90.7%
A lung scan lowers your chance of dying of lung cancer by (**About 20%**/About 50%/About 95%/Don't know)	125; 5.6%	96; 40.7%
A lung scan can find problems other than cancer (**True**/False/Don't know)	125; 65.6%	96; 92.7%
Radiation is one of the possible harms from a lung scan (**True**/False/Don't know)	124; 37.9%	97; 83.5%
Radiotherapy to your chest can increase your risk of getting lung cancer	124; 69.4%	97; 82.5%

(**True**/False/Don't know)		
Chemotherapy can increase your risk of getting lung cancer (**True**/False/Don't know)	124; 46.0%	97; 82.5%
If you have stopped smoking you are still at risk off getting lung cancer (**True**/False/Don't know)	121; 84.3%	97; 95.9%
People treated for HL who have never smoked are at risk of getting lung cancer (**True**/False/Don't know)	122; 70.5%	97; 93.8%

CHAPTER 6

TITLE: A qualitative exploration of the factors driving (non)-uptake in a lung cancer screening pilot by Hodgkin lymphoma survivors

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6.1 ABSTRACT

Background

Hodgkin lymphoma survivors (HLS) are at excess risk of lung cancer and may benefit from lung cancer screening (LCS), which reduces lung cancer mortality in ever smokers. We report the results of a qualitative study which aimed to explore the drivers of (non)-participation in a LCS pilot for HL survivors. All participants received a decision-aid booklet.

Methods

Semi-structured telephone interviews were conducted with HLS who were invited to the LCS pilot. Eligibility criteria included no relapse of HL for ≥5 years, being aged 18-80, and at risk of lung cancer. Participants provided informed consent. Data were analysed using inductive thematic analysis and linked to Capability, Motivation, Opportunity, Behaviour (COM-B) model components.

Results

Nine LCS participants and 2 screening decliners participated. The extent of engagement and impact of the decision aid was variable, but it was felt to support informed decision making. Drivers of (non)-participation were linked to five COM-B components (reflective motivation, automatic motivation, psychological capability, physical opportunity and social opportunity). Participants were driven by the belief that early-stage lung cancer is treatable and associated with better outcomes, desire for reassurance and knowledge about lung health after treatment for HL and/or COVID, and the desire to help contribute to research. Decliners were driven by concerns about the radiation associated with LCS, due to their perceived susceptibility to further cancers. One decliner was driven by negative experiences associated with breast cancer screening.

Conclusion

HLS are driven to participate in LCS by their perceptions of the benefits of early detection of lung cancer, their desire for reassurance and knowledge, and altruism. Concerns about the risk of developing cancer as a result of radiation from LCS drove the decision to decline. Engagement with the decision aid was variable, but our findings support its' further use.

6.2 BACKGROUND

Hodgkin lymphoma (HL) is a lymphoid malignancy which is highly curable using multi-agent chemotherapy regimens with or without the addition of radiotherapy. With the development of more effective treatments over the past four decades, rates of long-term survival among people treated for HL have steadily improved across all age groups.[1] Although modern day treatments are associated with fewer late effects, the alkylating

agents and extensive radiotherapy fields that were widely used before the turn of the century have put survivors of HL at significant excess risk of late effects such as cardiovascular disease and subsequent cancers.[2] After breast cancer, lung cancer is the second most common subsequent cancer in female HL survivors (absolute excess risk (AER) 26.0 at ≥30 years since treatment) and the most common subsequent cancer in male HL survivors (AER 50.2 at ≥30 years since treatment).[3] Lung cancers are usually diagnosed at an advanced stage[4] and are the most common cause of cancer-related mortality in HL survivors along with gastrointestinal cancers.[5]

The early detection of lung cancer using low dose computed tomography (LDCT) scans reduces lung cancer mortality in high-risk ever smokers by detecting lung cancer at an early stage when treatments offer the possibility of cure.[6,7] In the United Kingdom (UK), lung cancer screening for ever smokers has been commissioned through a programme of Targeted Lung Health Checks. Ever smokers aged 55-74 whose 6-year lung cancer risk – calculated with one of two lung cancer risk calculators - meets the eligibility threshold (≥1.51% using the PLCOm2012 calculator or ≥2.5% using the LLPv2 calculator) are eligible to be screened.[8] Unfortunately, most HL survivors at risk of lung cancer will be ineligible for lung cancer screening pilots aimed at ever smokers because few have the required smoking history to reach the 6-year lung cancer risk threshold for screening.[9,10] A recent study that surveyed HL survivors at risk of lung cancer reported that just 6% of respondents were eligible for current lung cancer screening pilots in the UK based on their age and 6-year lung cancer risk.[10] Although smoking has a multiplicative effect on lung cancer risk among HL survivors, alkylating agents and/or thoracic radiation confer an excess risk even in never smokers.[11] These treatment related risks are not accounted for in existing lung cancer risk calculators and never smokers are ineligible for lung cancer screening. Therefore, most HL survivors are excluded from lung cancer screening opportunities despite their excess risk.

Uptake of lung cancer screening by ever smokers in clinical trials has not exceeded 50%,[12] which is lower than uptake of other cancer screening by the general population which ranges between 64% (bowel cancer screening) and 74% (breast cancer screening).[13] To date, two studies have reported on the perspectives and psychosocial factors that could influence lung cancer screening uptake by HL survivors.[10,14] These studies found that some

HL survivors are concerned about the level of radiation exposure associated with lung cancer screening,[14] and that being male, having lower levels of self-efficacy and a higher socioeconomic status is associated with hesitancy towards lung cancer screening.[10] Since lung cancer screening is not routinely available to HL survivors, both studies presented lung cancer screening as a hypothetical scenario, limiting the extent to which their findings can be understood to be true drivers of actual screening behaviour. In order to explore the factors which drive uptake or non-uptake of lung cancer screening in a real-life scenario, we incorporated an interview study into a lung cancer screening pilot for HL survivors.[15] The pilot was a single-arm, single centre study in which 218 HL survivors registered in a long-term follow-up database and at risk of lung cancer, were invited to undergo a single round of lung cancer screening with a LDCT scan at their treating centre (The Christie NHS Foundation Trust). All those interested in participating in the pilot were provided with a decision aid booklet[16] that described the risk factors for lung cancer after treatment for HL, the absolute risk of developing lung cancer, the screening test, and its' pros and cons including the risk of requiring further CT scans to monitor an indeterminate pulmonary nodule(s).

The Capabilities, Opportunities, Motivation, Behaviour (COM-B) model was used as a framework to guide data collection and analysis, with the aim of describing the drivers of (non-)uptake of lung cancer screening by HL survivors in greater depth and detail than has previously been done. The COM-B model is a behaviour change model that is designed to encapsulate 83 theories of behaviour change and guide researchers wishing to understand what needs to change in order to change behaviour effectively.[17] COM-B comprises six components - psychological and physical capability, physical and social opportunity and automatic and reflective motivation – which are underpinned by the following fourteen domains of the Theoretical Domains Framework (TDF): knowledge, cognitive and interpersonal skills, memory, attention and decision processes, behavioural regulation (psychological capability), physical skills (physical capability), social influences (social opportunity), environmental context and resources (physical opportunity), social/professional role and identity, beliefs about capabilities, optimism, intentions, goals, beliefs about consequences (reflective motivation), reinforcement and emotion (automatic motivation).[18] The COM-B and TDF models have been used to understand the factors

influencing a variety of health behaviours, including uptake of cervical cancer screening.[19,20] Here we present the results of a qualitative study which aimed to explore the drivers of (non)-uptake by HL survivors in a lung cancer screening pilot.

6.3 METHODS

This study employed a qualitative design, using semi-structured telephone interviews with survivors of HL who had been invited to a lung cancer screening pilot. Ethical approval for the study was granted by the Wales REC 7 ethics committee (21/WA/0137) as part of the approval for the lung cancer screening pilot.

Recruitment

Those eligible for the pilot were HL survivors with no relapse within 5 years of study recruitment, currently aged 18-80, who received a radiation dose to the lung and/or a chemotherapy regimen containing procarbazine or mechlorethamine (mustine), and whose registered address was within 40 miles of the Christie hospital. People who had undergone a CT scan of the thorax within 12 months, or who had a previous diagnosis of lung cancer, a current diagnosis of metastatic cancer, who were resident in a nursing home or housebound, pregnant, or unable to consent were excluded from invitation to the pilot. All those potentially eligible for the interview study had been invited to take part in the lung cancer screening pilot, had been sent the decision aid booklet and had returned a questionnaire indicating that they could be contacted about the interview study. Potential participants were invited to this study between 2 and 6 months after receiving the participation information sheet and decision aid booklet for the pilot. A total of 87 people gave permission to be contacted for interview, of whom one was ineligible for screening, two did not wish to undergo screening, one was unsure about screening and the remainder wished to participate in screening. As some of those of wished to participate did not subsequently participate, there were 80 screening participants who had agreed to be contacted for interview and two individuals who declined to take part in the pilot but agreed to be interviewed. Both screening decliners and 21 screening participants were invited to be interviewed in total. Screening participants were purposively selected with the aim of achieving approximately 50:50 balance in terms of gender and age ≤50 years of age versus > 50 years of age. Invitation letters and participant information sheets were sent by

post and £30 in vouchers was offered for being interviewed. Written informed consent was obtained prior to interview using an online consent form.

Data collection

Semi-structured telephone interviews lasting between 17 and 37 minutes were conducted by the primary researcher (RB) using an interview topic guide that was framed around the COM-B model.[17] The topic guide included questions to explore automatic motivation (e.g., Do you usually take up the offer of cancer screening tests?), reflective motivation (e.g., Did the decision aid booklet have any effect on your decision?), physical opportunity (e.g., Did you have means of travel?), physical capability (e.g., Did you anticipate any difficulties having the scan, for example getting on the scanner bed?), psychological capability (e.g., Did you have any concerns about coping with the wait for the scan results?) and social opportunity (e.g., If you work, did your employers support you taking time to come for the scan?). The full topic guide can be as a supplementary file (Table s6.1).

Data analysis

Interviews were audio-recorded, and the recordings were transcribed intelligent verbatim by an external company, linked to a pseudo-anonymised study ID number. NVivo 12 software was used to store transcripts and the associated codes. The approach to data analysis was neither entirely deductive nor inductive. The questions asked of the interviewees in accordance with the topic guide were based on the domains of the COM-B model. This use of the COM-B model as a theoretical framework for the study describes a deductive approach to the study design. However, during the process of coding the researcher aimed to apply a more inductive approach, in that codes were created without a pre-determined theoretical framework in mind.[21] This was to allow for the creation of codes – and subsequently themes – which did not clearly fit the TDF, which was subsequently used to index the codes. During coding, the primary researcher (RB), reviewing entire transcripts one by one and applying codes. New or existing codes were applied to subsequent transcripts. Coding began before all the interviews were complete. Once codes had been applied to all the transcripts, the codes were refined and deductively indexed into the domains of the TDF.[22] Then a second researcher (TS) reviewed the codes and RB and TS discussed the codes, their categorisation, and emergent themes. All queries

raised by the second researcher were resolved through discussion with the primary researcher who had conducted the interviews. Some codes were included in more than one domain of the TDF during the coding process. Participants were not involved in the analytic process.

Reflexivity statement

All the screening participants in this study had met the primary researcher (RB) upon attending for their scan and the two screening decliners had spoken to RB or another member of the lung cancer screening pilot study team prior to participation in this study. RB is a clinician working within the lymphoma team at The Christie, where all the participants were originally treated for HL. Therefore, the nature of the relationship between the interviewer and interviewee was a 'doctor-patient' one, although RB had not been involved in their care prior to the invitation to the lung cancer screening pilot. The approach used during recruitment to the lung cancer screening pilot focussed on allowing people to make an informed decision about participation based on the information provided in the decision aid, largely without the input of a healthcare professional. No attempts were made to persuade people towards participation and the interviewer took a neutral and non-judgemental stance when discussing the participation decisions with interviewees.

6.4 RESULTS

Both screening decliners who were invited to the study agreed to be interviewed. Nine of the 21 screening participants invited agreed to be interviewed (a response rate of 42.8%). After the screening decliners and the 9 screening participants had been interviewed, a decision was made not to recruit any additional screening participants. This was because after codes had been applied to these 9 transcripts and categorised according to TDF domains, the codes were consistently applied to 11 TDF domains (linked to 5 COM-B) components, and it was believed that further interviews with screening participants would be unlikely to yield novel or contrasting data. In coming to this decision, the primary researcher took into account their knowledge of the subject area and noted that the drivers of participation in lung cancer screening identified in this study largely mirrored those identified in an earlier study.[14] The demographic characteristics of the study

participants are described in table 6.1. Their current age and the years since they completed treatment are provided in 10-year brackets to reduce the chance of participants being identifiable.

Table 6.1: Demographic characteristics of interviewees

	Gender	Age bracket	Years since treatment	IMD decile of participants postcode
Screening decliner 1	Female	40-49	20-29	10
Screening decliner 2	Male	50-59	30-39	10
Screening participant 1	Male	50-59	30-39	6
Screening participant 2	Female	50-59	20-29	8
Screening participant 3	Female	40-49	20-29	3
Screening participant 4	Female	40-49	20-29	10
Screening participant 5	Female	40-49	20-29	8
Screening participant 6	Male	70-79	30-29	3
Screening participant 7	Female	30-39	10-19	10
Screening participant 8	Male	70-79	10-19	10
Screening	Male	50-59	20-29	8

participant 9				

Thematic analysis

There were three themes identified: theme 1 – the variable use and impact of the decision aid; theme 2 – motivators and facilitators of participation; theme 3 – barriers to participation.

Theme 1: The variable use and impact of the decision aid

This theme is about the extent of participants' engagement with the decision aid and its' impact on their decision. Participants generally found it easy to make the decision to participate. Many made the decision to participate after reading the first study invitation letter, prior to receiving the decision aid and patient information sheet. What is more, for some the decision aid booklet had little or no effect on their decision to participate.

"It was interesting to read, but not relevant to the decision that had already been made." (Screening participant 8)

Screening participant 8, quoted above, said that the brief information about the rationale for the study that was included in the first invitation letter was sufficient for him to decide to participate. On the other hand, the decision aid encouraged two participants to undergo screening. Participant 5 said: *"The booklet explained the procedure and the reason behind the study. So yeah, it made me want to take part even more." (Screening participant 5)*
Screening participant 3 said the decision aid made her "more enthusiastic" about taking part because after weighing up the pros and cons, she decided that the pros outweighed the cons. Receiving the decision aid was a prompt to take steps towards participating for screening participant 4. She said that she intended to participate after receiving the initial invitation letter, but it was not at the forefront of her mind. After reading the information about lung cancer risk in the decision aid, she said she thought: *"I really need to sort myself out and get this done." (Screening participant 4)*

The extent to which the interviewees had engaged with the decision aid varied. Most had read the booklet, considered the pros and cons, and had decided that the pros outweighed

the cons, although screening participant 7 felt there was "*no harm in [being screened]*". However, screening participant 2 did not recall reading the booklet at all, and screening participant 7 had asked their mother to read it for them for reasons explained in the quote below.

"Once a year I get a letter from the Christie and we call it my ten ways to die letter, because that's how it sometimes feels, they're saying, you know, we did this to you, so you might get this, and I think that's kind of why I stopped reading my letters from the Christie and my mum just handles them, because I just got fed up of reading that." (Screening participant 7)

The two screening decliners had engaged with the information in the decision aid, particularly the information about radiation associated with the CT scan, the risk of indeterminate nodules and the risk of false positives. They had used this information in coming to their decision not to participate.

"Was it 10 in 100 will get a positive result but they won't all have the cancer? That was really helpful in seeing that. I think if that was a lot lower that might have made me feel more kind of [...] if something was found on a scan that would be kind of like 99 per cent certain that was something that needs investigation, […] I might be more likely to do that." (Screening decliner 1)

"I suppose if I hadn't been aware of the risk [of radiation], then I probably would have signed up." (Screening decliner 2)

Both screening participants and decliners said that they appreciated being provided with information about the pros and cons of screening within the decision aid. They said that this information helped them to make an informed decision, even despite some having already made up their mind to participate.

"I think the fact that your booklet had both the benefits and the negatives as to why you should go ahead, and it helped you to weigh that information up, rather than it just being all, this is a really good idea, you should do this because of this." (Screening participant 4)

In weighing up the pros and cons, screening participants were aware of the risks associated with radiation, but they felt this risk was outweighed by the potential benefits of screening and a necessary risk associated with surveillance and screening.

"You do know what the risk is with radiation, but I think the benefits outweigh, you know…if you didn't…if you were bothered about radiation, you'd never get checked." (Screening participant 9)

Screening decliners also thought the decision aid helped them to make an informed decision. Screening decliner 1 said that the booklet was "really, really helpful in addressing concerns", but identified some areas where she felt more clarity was needed, for example the relative risk reduction in dying from lung cancer by being screened where she sought absolute risk values. However, she went on to say:

"I think the important thing is it didn't matter that the booklet wasn't kind of perfect and answered all the questions I have because it kind of gave permission to ask questions and talk about it, if that makes sense?" (Screening decliner 1)

Feeling able to contact the clinicians running the study to discuss concerns about lung cancer screening was particularly important to her, due to previously having trouble obtaining information about the risk of radiation associated with mammograms.

Regarding the influence of the decision on his decision not to participate, screening-decliner 2 said:

"It influenced my decision, and I think it was very…you know, it's so responsible of yourselves to…you know, that's the ethical way of doing research, isn't it? You know, I appreciated that it was set out like that. So yes, it did influence me, and I suppose if I hadn't been aware of the risk, then I probably would have signed up……I really appreciate, you know, that you gave people in your forms a choice." (Screening decliner 2)

Theme 2: Motivators and facilitators of participation

The speed and ease with which screening participants were able to decide was largely due to their beliefs about the potential benefits of undergoing lung cancer screening. They felt that if lung cancer was diagnosed at an early stage before symptoms developed, treatment could be accessed quicker, would be more effective and the chance of cure would be higher.

"Anything that might catch something earlier and give me a better chance is worth it to me." (Screening participant 7)

Screening participant 4 felt that treatment might less "harsh or aggressive" if cancer was detected early. Despite expecting a clear result, screening participants frequently said they would rather know if they did have lung cancer so that they could access investigations and treatment.

"Well, I think, yeah, it could have shown something, but I always think, I'd rather…even if it would've shown something, I'd rather be knowing now, than leaving it to, you know…if something was wrong. If I'd have left it, you know, it could be treatable now if there was something there, than leave it and not be treated for, it's gone past that stage."
(Screening participant 2)

The desire for reassurance was another important motivator among screening participants. Many saw lung cancer screening as an opportunity for a 'check-up' or 'MOT'. Several participants said that they had appreciated being followed-up in the years after completing treatment, finding it 'reassuring'.

"I feel so comfortable about [follow-up], because when I had my lymphoma, I went onto a trial and they checked me for…I think it was round about…they said that only problem is we have to keep checking you for up to about 15 years I think it was, and that's still fine with me, they could check me every year for the rest of my life, you know, that would make you more happier." (Screening participant 9)

A further motivating factor was the desire for knowledge regarding lung health. Some screening participants sought to know whether their treatment for HL had damaged their lungs and additionally, two were curious about whether they had sustained lung damage after contracting COVID-19.

"I don't know, obviously being 20 years down the line, if my treatment did actually have an effect on my lungs or not." (Screening participant 3)

Most screening participants did not expect that lung cancer would be found because they were asymptomatic and did not smoke, meaning they were not overly worried about participating.

"I was feeling quite positive, because I've not had any issues with my lungs, so…and I don't smoke as well, so that was obviously a positive thing. So, I was quite positive about the results would be okay, but even if they weren't, you know, it's better to know early and…so, that's why we wanted to take the opportunity to do the scan." (Screening participant 5)

Not all screening participants were optimistic about their lung cancer risk. Screening participant 3 said they had been concerned about developing lung cancer because of their treatment and passive exposure to smoking as a child. Some were already aware of their lung cancer risk, but a lack of prior knowledge in those who were not aware did not appear to be a barrier to participation.

"So, I was a bit surprised when I received the invitation, because I didn't know that I was more at risk, but I thought it would be a good idea to obviously go for the screening, it's better knowing than not knowing, kind of thing. And I found it quite easy and simple to do. Because I normally do screening, breast screening anyway, once a year. It was routine really." (Screening participant 5)

Interviewees were aware they were being invited to participate in a study. Many described their desire to help both future patients and researchers by contributing to the study.

When asked about their reason for participating, participant 7 said: "*I think mostly like a sense of duty that I should help future people in my situation*". (Participant 7)

The fact that the study invitation had come from the institution where participants had received cancer treatment was also important due to some participants perception of owing a debt towards the institution.

"*If it hadn't been for Christie's, I would be dead by now, and so the least I can do is try and help you". (Screening participant 8)*

Screening participant 8's primary motivation for participating was to contribute to the study and his excess risk of lung cancer was a less important motivation. Notably, screening decliner 2 said the decision not to participate wasn't easy, because he would have liked to contribute to "the development of new treatments for other people".

Returning to the site where they had undergone cancer treatment was not an issue and in fact several participants expressed that they would prefer to return to the Christie for the lung cancer screening test than attend another hospital because they trusted the institution. For participant 8, trust in the institution extended to trust in the NHS and this contributed to their positive feeling around participation:

"I have trust in you, Christie's and the NHS, and the individuals within the NHS. They are going to ask me to do something and they're not going to take a chance with my health or my life or my time or money, but you will possibly have something very good that comes out the end of it." (Screening participant 8)

Screening participants' prior experience of undergoing scans meant that they knew what to expect of a CT scan, which minimised anxiety about participating. The low-dose CT scan was perceived to be fast, non-invasive, and more straight-forward than a standard CT scan, MRI, or PET-CT scan, partly because intravenous contrast was not required. The physical aspects having CT scan were acceptable to both screening participants and decliners. Similarly, several screening participants were confident that any anxiety associated with

the wait for results would be manageable, since they had experienced this before during treatment or through the breast cancer screening programme.

"Definitely feel used to it now, so [waiting for scan results] doesn't worry me at all." (Screening participant 7)

Many of the participants had undergone screening for other cancers, for example breast cancer screening – often through the breast cancer screening programme for women at high risk – and bowel and cervical screening through the national screening programmes. For several participants, undergoing check-ups and cancer screening tests was habitual. For example, screening participant 5 described cancer screening as "routine" and referring to her attitude to screening and health checks, went on to say:

"I suppose, I'm in the mind-set already of getting check-ups. It worries you at the time, waiting for the results, but I feel better that I've done it and been pro-active about it…….And I have to get my bloods done once a year as well, so I try to make sure I keep on top of it all. I don't put it off. I try to get it done and over with really" (Screening participant 5)

In general, screening participants did not report difficulties relating to their other responsibilities when deciding to participate. Several said their employers were understanding about issues relating to their health, and others were self-employed, meaning taking time off work was not a barrier to participation for them. However, screening participant 7 acknowledged that had the scan appointment been on a different day of the week, it would have been "impossible" to attend due to work and childcare commitments. Screening participants often said that they had discussed the invitation to participate with their family who had been supportive of their decision. However, some said that they would not have changed their decision had their family advised them against participating.

Theme 3: Barriers to participation

This theme relates to the barriers to participation described by the two screening decliners who were interviewed. The radiation associated with the low-dose CT scan was their main reason for declining to participate, due to the potential for the radiation to cause another cancer. Underlying this, and common to both, was a sense of susceptibility to health problems, including developing another cancer. Screening decliner 1 was reassured to know that the level of radiation associated with the scan was "very low", but her previous radiotherapy treatment, and previous diagnosis of cancer in an irradiated region led her to feel more susceptible to the risks of radiation associated with the CT scan.

"My concern with this is because I've had this treatment in the past it's in my mind it's, kind of, I'm at high risk of cancer because I've had that much radiation in the past and if I haven't passed the threshold for triggering cancer then I'm probably not far beyond it."

Referring to her previous diagnosis of cancer in an irradiated region, she said: *"That seemed like quite a clear message that, yeah, there was some damage done here and I need to be careful".*

Screening decliner 2 also perceived himself to be an increased risk of another cancer. He described several different health problems since treatment for HL, including "radiation sickness" in the two years after treatment. He felt it was a "struggle to stay healthy".

"I don't think I've had the health of my peers during my life. For example, in my late twenties I developed an underactive thyroid, so I'm hypothyroid, and I believe that's a possible side effect of the treatment, particularly because, I mean, I was treated around the neck area. And obviously I'm on…with the NHS, I'm registered as someone with a lowered immunity because of my treatment. So although I'm not an expert on what my outcome would have been had I not been ill, but I don't feel as though my general health has ever been…has then been as robust as that of my peers."

His perceived poor health led him to feel more susceptible to the risks associated with radiation. He said, *"I feel like I'm, sort of, not especially robust and that I could be one of the…you know, I could be unlucky if I did have that exposure to radiation."*

Radiation exposure was also an important factor in determining their past or future participation in other cancer screening programmes. Concerns around radiation had led screening decliner 1 to decline breast cancer screening in the past - although she had participated on other occasions – and screening decliner 2 said that if radiation was involved in the bowel cancer screening programme, he would not wish to participate.

Relating to her likelihood of developing cancer again, screening decliner 1 did not glean reassurance from the absolute lifetime risk of lung cancer values presented in the decision aid. She said, "to me five out of 100, given my cancer history….there's no reason why that's not going to be me". Conversely, she also considered it unlikely that lung cancer would be detected if she participated in the screening study, both because she was a never smoker and because the study offered a single screening scan rather than ongoing screening, meaning that for her the study held "less risk but less benefit as well."

"I'm aware that because of I've had chemotherapy and radiotherapy I'm relatively high risk for problems, but then I'm a never smoker as well and how does that play out? I know that reduces the risk but how much…"

Considering that she felt it unlikely that she would have lung cancer detected, in discussing the risk of catching COVID-19 when attending for screening, she said "*there's no point putting yourself at risk for something when you might not have lung cancer*." The risk of contracting COVID would be something that she would bear in mind if she was invited to lung cancer screening again, but screening decliner 2 was not concerned about catching COVID during the screening process as he felt the hospital was a "more controlled environment".

Screening decliner 1 had participated in the breast cancer screening programme for women at high risk and she said that her experiences of it had influenced how she felt

about screening in general. Firstly, false positive results had led to anxious waits for biopsy results, multiple days off work and persistent pain after one biopsy. Referring to biopsies, she said:

"I don't see the follow up tests as being non-invasive. I see them being as really quite invasive and uncomfortable. And my perception of lung cancer biopsy is that it's probably more invasive than a breast cancer biopsy just of the location of where the lungs are. So, that was one kind of factor for me."

Secondly, she had had trouble communicating with and obtaining information from the breast cancer screening centre, including a lack of willingness to give biopsy results over the phone, which added to stress and anxiety associated with undergoing screening. Overall, her experience of the breast cancer screening programme had made her "wary" of screening.

"Experiencing it directly has kind of reinforced the point that screening doesn't always give you the yes/no correct answer."

These experiences were in the recent past, and as she had ongoing symptoms from other health problems, she described having "limited time and energy". She said that had the invitation to the lung cancer screening study arrived at another time, she might have been more willing to consider participating.

Categorisation of motivators, facilitators, and barriers by COM-B component and TDF domain

The drivers of (non-)uptake of the lung cancer screening pilot identified in the thematic analysis have been linked to TDF domains and COM-B components. There were eleven linked TDF domains (beliefs about capabilities; beliefs about consequences; optimism; intentions; identity; emotion; reinforcement; knowledge; memory, attention, and decision processes; environmental context and resources; and social influences) and five related

COM-B components (reflective motivation, automatic motivation, psychological capability, physical opportunity, and social opportunity). The results are shown in table 6.2.

Table 6.2: Motivators, facilitators and barriers to participation grouped by TDF domain and COM-B component

COM-B component	TDF domain	Motivators and facilitators to participation	Barriers to participation
Reflective motivation	Beliefs about capabilities	Previous experience of scans: • Accustomed to waiting for results • Knowing what to expect	Being low on energy and resilience
	Beliefs about consequences	Potential for early diagnosis • Getting treatment quicker • Less aggressive treatment • More effective treatment	Beliefs about consequences of participating: • Developing cancer due to radiation exposure associated with scan • Potential for false positives • Limited benefit from one screening round
	Optimism	Belief that scan probably won't show lung cancer	Belief that scan probably won't show lung cancer
	Intentions	Immediacy and stability of decision to participate	
	Identity	Regularly participating in other cancer screening programmes	
Automatic	Emotion	Trust in the NHS institution	Perceived susceptibility to the risks of radiation

motivation		The desire to give something back (or sense of duty to do so)	associated with the CT scan
		Would prefer to know if one has lung cancer	Previous negative experience of cancer screening programme
	Reinforcement (rewards / incentives)	Getting a check-up on lung health	
		Knowing that one has contributed to research • Debt towards institution/treating team • Benefitting future patients	
		Seeking reassurance through follow-up	
Psychological capability	Knowledge	Awareness of increased risk of subsequent cancers	Awareness that screening does not always produce clear answer
		Knowledge of the process of having a CT scan	
	Memory, attention, and decision processes	Belief that pros outweigh cons	
Physical opportunity	Environmental context and resources	Being able to take time off work	Taking multiple days off work for results
		Having own means of transport	Fitting in attending around other responsibilities

		Being within reasonable distance of screening location	
Social opportunity	Social influences	Positive views of close family and friends towards participation	

6.5 DISCUSSION

This is the first study to explore the drivers of (non-)uptake of lung cancer screening by HL survivors in a real-life scenario. Using the TDF and COM-B models we have identified motivators and facilitators among screening participants linked to eleven TDF domains and five COM-B components and barriers among screening decliners linked to six TDF domains and four COM-B components.

The prominence of motivational components within the thematic analysis, in particular reflective motivation, could be due to the interviewees having received a decision aid which aimed to facilitate informed decision making. The belief that detecting lung cancer at an early stage confers a greater chance of long-term survival was identified as an important driver of participation and it is notable that this message was contained in the decision aid.

Another driver of participation was the desire for reassurance and knowledge about lung health. The desire for reassurance is not unexpected. One study of HL survivors found that around three-quarters reported a degree of concern about future health and cancer risks,[9] and published literature suggests that many lymphoma survivors who have undergone curative intensive primary therapy find surveillance in the immediate post-treatment period reassuring.[23,24] Our study suggests that desire for reassurance through surveillance continues for years after remission and can be a driver of health behaviours such as cancer screening. Some participants reported being driven to participate by a sense of duty to help other cancer survivors. Altruism has been reported as a positive impact of experiencing cancer[25] and the desire to undergo screening to help others was also identified during the national recall exercise for women treated for HL and at risk of breast cancer, although that was not a research exercise.[26]

The interviews with two screening decliners revealed that their perceived high susceptibility to radiation-induced cancers was central to decision-making. The likelihood of developing a radiation-induced cancer after an LDCT scan (1 in 10,000 to 1 in 100,000) is much lower than the chance of developing lung cancer after HL treatment (4-5% absolute risk in the 35 years following treatment[3]). This information that was presented in the decision aid. However, both decliners assigned more importance to the radiation-related

cancer risk than to their risk of developing lung cancer, since they perceived that they were susceptible to developing radiation-induced cancer. It therefore appears that affective risk perceptions (their emotional response) and experiential risk perceptions ("gut-level assessments of vulnerability"[27]) were more influential than deliberative logic-based risk perceptions. Studies have shown that the majority of the general public are not concerned about exposure to medical radiation[28] and the majority underestimate the amount of radiation associated with a chest CT scan.[29] However, almost half of cancer survivors, including HL survivors, report high levels of worry about medical radiation, especially those reporting poor health[30] meaning that concerns about radiation could have been an important reason for declining amongst other HL survivors who did not participate in the pilot.

There were three important findings regarding participants' perceptions about the decision aid booklet and its influence on decision-making. Firstly, the ways interviewees utilised the decision aid during the decision-making process varied. Although many made their decision after considering the information in the decision aid, some decided to participate and later became informed about the screening test whilst others did not personally engage with the decision aid. These findings are in keeping with a study that explored the use of a medication decision aid for use during primary care consultations and found that decision aids were "flexible artefacts", which can be valuable in across a spectrum of decision-making models.[31] Secondly, the information in the decision aid encouraged some interviewees to take part whilst others were dissuaded. This should not be seen as a negative, rather, it is a consequence of providing people with the information and autonomy to make a decision about cancer screening, which is a regulatory requirement.[32,33] Thirdly, both screening participants and decliners perceived that they had made an informed decision after reading it and perceived that they were being provided with information with which to make a personal choice, demonstrating that the decision aid succeeded in improving the quality of informed decision making, as defined in the literature.[34] This latter point in particular supports the use of the decision aid in a future lung cancer screening study. Relating to our finding that knowledge about the benefits of early detection is a driver of participation, providing the decision aid with the first invitation to lung cancer screening (rather than after an expression of interest) might

improve uptake in a future study by educating HL survivors on their treatment-related risk of lung cancer and on the benefits of early detection of lung cancer earlier in the decision-making process. This could also improve the quality of decision making among those strongly inclined towards screening who decide to be screened before considering the risks. This is important because people participating in established cancer screening programmes have minimal or no contact with healthcare professionals before the screening test, so providers must facilitate informed decision making in advance of participation.

Most of the individuals who did not participate in the lung cancer screening pilot did not respond to the initial invitation letter and were not eligible to be interviewed for this study. Consequently, this study did not explore the barriers to participation in these non-responders. The non-responders are likely to have experienced different barriers to participation than the two screening decliners interviewed in this study. For example, the screening decliners interviewed had sought information on the study and largely engaged with the information in the decision aid booklet whereas non-responders may have experienced barriers to seeking or understanding information. Supporting this possibility, a study of barriers to flexible sigmoidoscopy participation found that 'non-responders' were less likely to fully engage with information about the test than 'active decliners'.[35] Therefore a limitation of this study is our inability to describe the barriers to uptake among those who did not respond to the invitation to the lung cancer screening pilot.

The interviewer had been the lead research on the lung cancer screening pilot, and through this work she had been in contact previously with the people invited to take part in this interview study. In particular, she had met all the screening participants when they took part in the pilot and had been in contact by letter and/or phone with the screening decliners. This prior contact may have influenced the uptake to this study by screening decliners, since they may have felt uncomfortable discussing their participation decision with a person closely associated with the study. In addition, the participants in this interview study would have been aware of the interviewers' involvement in the pilot and may not have wished to express negative views. This relates to the concept of 'access' in qualitative research. Riese argues that the data produced through qualitative research depends on how the researcher and participant "position themselves in relation to each

other", which is in turn influenced by power dynamics.[36] The power balance in this study will have varied according to the interviewer and participants' perceptions of their relationship to one another and of their contribution to the research process. Here, the interviewer was both a doctor within the participants' treating team and the lead researcher in the lung cancer screening pilot and the potential impact of this upon the way in which the interviewer and participants related to one another must be acknowledged.

Conclusion and directions for future research

In this study we have described the drivers of uptake and non-uptake of lung cancer screening by HL survivors who had been provided with a decision aid, and the heterogeneous ways in which the decision-aid was used and influenced screening decisions. Future research should aim to explore the barriers to lung cancer screening uptake among individuals who are not inclined to participate after a first invitation and to explore the acceptability and impact of providing a lung cancer screening decision aid upfront.

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6.7 SUPPLEMENTARY DATA

Table s6.1: The interview topic guide

Questions	Construct
Could you talk me through your decision to have / not have the lung cancer screening test?	N/A
When you get invitations to have medical tests, what do you usually do? Do you usually take up the offer of cancer screening tests?	Automatic motivation
Did you want to have a screening scan before you read the decision aid booklet?	Reflective motivation

Did the decision aid booklet have any effect on your decision? Did it make you more or less keen on having the screening test?	
Did you anticipate any difficulties getting to the hospital? Did you have means of travel? Did *you anticipate any difficulties having the scan for example getting on the scanner bed?*	Physical opportunity *Physical capability*
How easy / hard did you find it to understand the information you were given about lung cancer screening? For example, what is the rationale, benefits and risks? Was it an easy decision to make or did you deliberate? Did you feel you understood the information about the possibilities of what the scan could show? Did you have any concerns about being inside the Christie? For example, bringing back bad memories / getting lost in the hospital I know you'll have had scans before, how did this impact your decision – were you	Psychological capability

worried or did it help because you knew what to expect? Did you have any concerns about coping with the wait for the scan results?	
Did you discuss attending lung cancer screening with anyone? Were they supportive? Did you feel you wanted someone to attend the hospital with you? Was there anyone to come with you? Did COVID restrictions around having someone with you concern you? If you work, did your employers support you taking time to come for the scan? Did you encounter any difficulties?	Social opportunity

CHAPTER 7

DISCUSSION

7.1 PARTICIPATION IN LUNG CANCER SCREENING BY HL SURVIVORS

A key aspect of the feasibility of delivering a lung cancer screening programme for HL survivors is uptake by those at risk. In chapters 2, 3, 5, and 6 I explored the factors influencing HL survivors' willingness to undergo lung cancer screening and the socio-demographic factors associated with hypothetical future participation and actual participation. Here, I discuss the findings relating to uptake across the entire thesis.

Across all the thesis chapters, there was evidence for the factors which motivate HL survivors to accept the offer of lung cancer screening and the factors which facilitate having the screening test. The desire for reassurance and knowledge about one's health was a motivating factor identified in the qualitative studies undertaken in chapters 2, 4 and 6. In chapter 2, I found that participants were affected by differing degrees of health-related uncertainty and anxiety, which underpinned their desire for reassurance through screening. My findings presented in chapter 2 and 6 indicate that the desire for clinical and imaging surveillance persists in HL survivors many years since treatment. As discussed later, this motivating factor could be influential in optimising lung cancer screening participation in future studies.

The second key motivating factor which emerged strongly during the qualitative work undertaken in chapters 2 and 6 and to a lesser extent in chapter 4, was the belief that detecting lung cancer early is beneficial. Furthermore, qualitative findings from chapters 2 and 6 in which HL survivors expressed the view that the benefits of screening outweigh the risks, are supported by the high median score on the perceived benefits subscale from the lung cancer screening health belief scales (LCSHBS) and the low median score on the perceived barriers subscale in chapter 3. These motivating factors were reported by HL survivors who held positive views of screening and who largely went on to participate and I cannot report whether the non-responders to the lung cancer screening pilot would hold these same positive views. However, I can conclude that among those interviewed in chapters 2 and 6 there was no evidence of fatalistic attitudes towards lung cancer (the

belief that lung cancer is inevitably fatal). The HL survivors interviewed in chapter 2 were well-educated and mostly employed or retired, whilst most of those interviewed in chapter 6 lived in a less socio-economically deprived area. It has been hypothesised that such fatalistic attitudes are more prevalent among low socio-economic status groups, where smoking and its' negative health consequences are more common.[1,2] In addition, most interviewees were never smokers. These factors may contribute to their positive attitudes towards lung cancer screening. On the one hand, it is important to acknowledge that the absence of fatalistic attitudes towards lung cancer differentiates HL survivors from ever smokers in the general population where fatalistic views have been the target of lung cancer screening communication strategies.[3] On the other hand, the absence of such attitudes among participants in the studies conducted in this thesis does not preclude its presence and influence in non-participants, particularly current smokers.

The desire to participate in the lung cancer screening study to help future cancer survivors and researchers within their treating institution is described in chapter 6. Although this motivating factor is specific to the research context of the screening study, it could continue to be relevant to participation in future studies of lung cancer screening, until such time as it was adopted as standard practice.

Qualitative enquiry in chapters 2 and 6 found that the facilitators of participation in lung cancer screening largely relate to the previous experience that HL survivors have of navigating healthcare pathways, due to their previous experience of cancer and often, cancer screening. For example, perceptions of CT scans and the potential anxiety whilst waiting for results were informed by their previous experiences which led participants to consider the process to be acceptable. The ease with which people could manage practical aspects relating to attending screening, such as travel to the hospital and taking time away from work or other responsibilities, was another important facilitating factor. In chapter 3, self-efficacy was the only one of the LCSHBS to be associated with screening hesitancy (a lower level of self-efficacy being associated with hesitancy). The self-efficacy scale includes items relating to traveling and finding time to attend screening, as well as items relating to coping with uncertainty and anxiety about the procedure and results. Therefore, the items within the self-efficacy scale are reflected in the qualitative data, which helps us to understand how the previous health-related experiences of HL survivors can facilitate

participation in lung cancer screening. These motivating and facilitating factors and factors underpinning them are shown in figure 7.1.

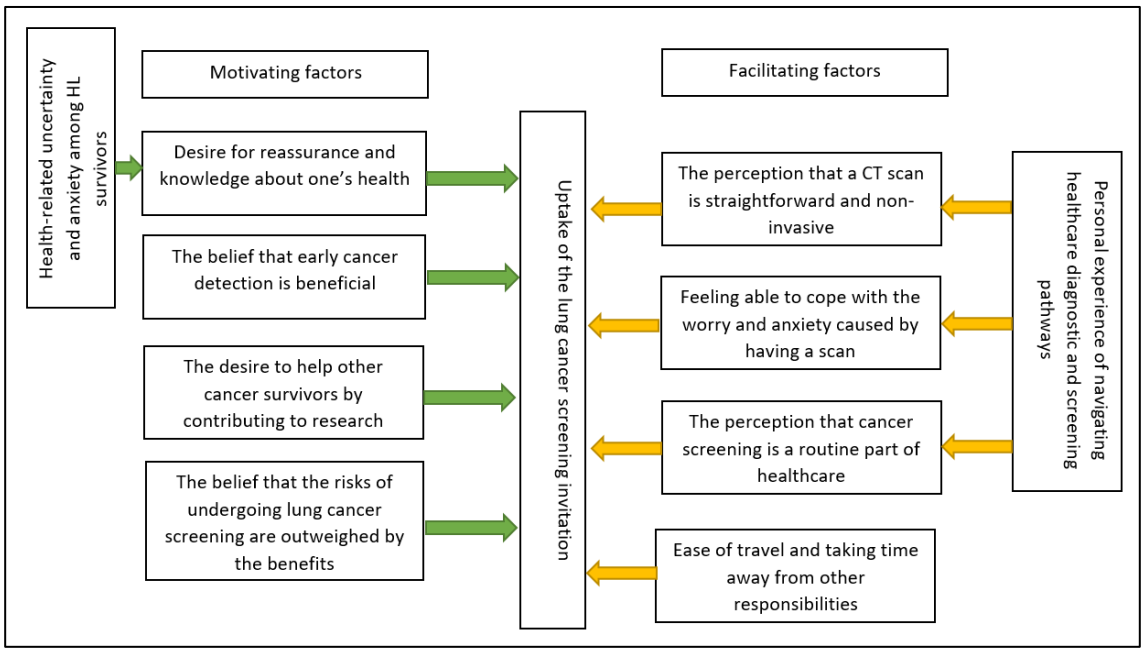

Figure 7.1: Motivating and facilitating factors underpinning uptake of lung cancer screening

The interviews with two HL survivors who declined lung cancer screening (chapter 6) demonstrated that affective and experiential risk perceptions of developing a radiation-induced cancer because of the LDCT scan were key factors in decision making. One of the decliners interviewed also cited her negative experiences undergoing breast cancer screening as a factor which influenced her decision. In experiencing false positive breast cancer screening results, leading to painful biopsies, she had personal experience of the potential harms of screening. In my view, the factors leading these two people to decline lung cancer screening are not suitable targets for interventions – such as targeted messaging – designed to increase screening uptake. Firstly because the interviews did not reveal any barriers to participation that related to the processes and practicalities of undergoing screening within the study. Screening decliner 1 reported that she did not have the time or energy to participate, but this was due to extraneous factors rather than the study design. Secondly, both appeared to understand the rationale for the study, the absolute risks of lung cancer and radiation-induced cancers because of LDCT scans, the potential scan outcomes and what participation in the study would have involved. Therefore, informational needs appeared to be met with one exception - screening-

decliner 1 wanted to know the absolute risk reduction for lung cancer mortality through screening. Thirdly, it is probably impossible and unethical to try to change someone's decision about a screening test by disputing their emotional response or gut feelings regarding the risks of a procedure.

In chapters 3 and 5 I explored the association between the sociodemographic characteristics of HL survivors and willingness to undergo (or actually participate in) lung cancer screening. Despite the finding that being male was associated with screening hesitancy (chapter 3) and the perception that current age could influence participation decisions (chapter 4), there was no statistically significant difference in age or gender between participants and non-participants in chapter 5. However, these findings should not discourage further exploration of the impact of sociodemographic characteristics of HL survivors on lung cancer screening uptake in larger studies. To date, there has not been conclusive evidence for the association between gender and lung cancer screening uptake.[3,4] However, since male HL survivors are at higher risk of lung cancer compared to women due to patterns of smoking,[5] aiming for optimal uptake by men is one way to ensure lung cancer screening participation by those at highest risk. In addition, low socioeconomic status has consistently proven to be associated with non-participation in lung cancer screening trials.[6] Even considering the specific motivating factors affecting HL survivors, which might somewhat mitigate the effects of lower socioeconomic status, future studies should also aim to minimise barriers associated with being of lower socioeconomic status.

7.2 DECISION MAKING BY HL SURVIVORS INVITED TO UNDERGO LUNG CANCER SCREENING

Chapters 4 and 5 in this thesis describe the development and evaluation of a novel decision aid tool designed specifically for HL survivors participating in the lung cancer screening pilot. At the outset of this research, it was anticipated that the lung cancer screening pilot would involve randomising participants to receive either a standard invitation letter or an enhanced invitation package (the content of which was to be decided). Our hypothesis was

that an enhanced invitation package may improve uptake rates. After careful discussion with my supervisors, an alternative approach was decided upon for the following reasons.

The study described in chapter 2 had not revealed any clear barriers to participation which could be targeted in an 'intervention' and compared to a control, although it was clear that there were informational needs relating to lung cancer risks, risk factors and as expected, the pros and cons of lung cancer screening. A review of the literature around decision aids, led me to decide that a decision aid could address the informational needs identified in chapter 2. Upon reviewing published randomised studies which compared decision aids to standard approaches, I noted that the authors had calculated sample sizes of at least 190 participants in each arm to detect statistically significant differences in decision making outcomes, and even higher sample sizes to detect a different in uptake rates.[7–10] We were aware that we would not be able to recruit such numbers to a lung cancer screening pilot using the ADAPT database. Finally, it would be challenging to determine the true impact of a decision aid in a randomised study because it would be ethically imperative to provide all potential participants with the information required to make an informed decision - the NHS cervical, breast and bowel cancer screening programmes provide very similar information to the requirements for a decision aid.

I will now describe the evidence in this thesis regarding the information and support provided to HL survivors considering lung cancer screening. There was evidence across chapters 4 and 5 that the decision aid improved lung cancer risk and screening related knowledge. In chapter 4, decisional conflict scores improved after viewing the decision aid and in chapter 5, median decisional conflict scores recording after viewing the decision aid were zero or close to zero, suggesting minimal decisional conflict for a majority who received the decision aid. In chapter 5, the median score on the preparation for decision making scale was 80 out of a possible 100. Furthermore, participants in chapter 6 perceived that the decision aid helped them make an informed decision and perceived that they were being presented with a choice. Taken together, these findings support the effectiveness of the decision aid in improving the quality of the decision-making process, by helping people recognise that a decision needs to be made, helping people feel informed, be clear about what matters most to them relating to the decision. These are core attributes described by Sepucha *et al*[11] which are required to measure quality of the

decision-making process. Sepucha *et al* also list the following core attributes relating to quality of decision-making: that patients feel able to "discuss goals, concerns, and preferences with their health care providers (e.g., as measured by items in the Perceived Involvement in Care Scale" and help patients feel able to "be involved in decision making (e.g., as measured by the Control Preferences Scale".[11] These latter two core attributes are less well demonstrated as I did not make use of these scales. However, measuring these attributes within the lung cancer screening pilot was of limited relevance because the decision aid aimed to provide invitees with sufficient written information to decide on participation without the input of a healthcare professional. Reflecting this, it was universally the case that those who attended the study visit, where written informed consent was taken, had decided to take part in the study.

The protocol for lung cancer screening pilots running in England specifies that information provided should facilitate informed-decision making[12], whereas in the United States, the US Preventive Services Taskforce stipulate a shared-decision making (SDM) process in lung cancer screening.[13] SDM has been defined as "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences".[14] By focussing on informed-decision making, my approach reflects that used in the NHS cancer screening programmes. However, there is evidence in chapters 4 and 5 in this thesis to suggest that my approach - the decision aid with little no input from a healthcare professional during decision-making – may not suit everyone. In chapter 4, I found that around a third of survey participants would seek out more information after reading the decision aid, potentially from more than one source, and that a third would decide about lung cancer screening after consulting their doctor (an option that was not mandated and not widely taken up in the pilot). In chapter 5, the median PDMS score was relatively high (80) but there was a wide range of scores both overall (35-100) and as demonstrated by the large interquartile range of 18.5. Furthermore, the focus groups in chapter 4 showed that some participants sought more tailored information about their personal risk – which might be better provided through a discussion with a clinician than in the decision aid - and screening-decliner 1 (chapter 6) expressed positive view about the opportunity to discuss her lung cancer risk with a clinician. Taken together, these examples suggest that HL

survivors invited to lung cancer screening in the future may benefit from having access to different sources of information and opportunities to discuss lung cancer screening, which are discussed in the next section.

7.3 IMPLICATIONS OF THE FINDINGS IN THIS THESIS

The findings I have presented above are important because they can inform the development of a larger study of lung cancer screening for HL survivors. A larger study is required to address the feasibility of identifying and contacting HL survivors discharged from follow-up, and to report the prevalence, stages and types of lung cancer detected by LDCT in a larger sample.

Optimising uptake in a future study

The factors impacting lung cancer screening uptake in this study can inform the recruitment methods used in a larger study, with the aim of optimising uptake. Higher uptake should not come at the expense of facilitating informed decision making, however it is appropriate to consider interventions that would allow larger proportions of those wishing to be screened to attend.

In chapter 6, I used the Capabilities, Opportunities, Motivations-Behaviour (COM-B) model[15] as a framework for the interview schedule and categorised motivating and facilitating factors and barriers identified during the process of thematic analysis according to the domains of the Theoretical Domains Framework (TDF). TDF domains can be mapped on to the COM-B components (Physical capability, psychological capability, physical opportunity, social opportunity, reflective motivation, automatic motivation). I decided on this method with the aim of identifying factors which could be targeted using the intervention functions of the behaviour change wheel to potentially optimise lung cancer screening uptake in a future larger study. I believe that some of the motivating and facilitating factors identified are potential targets for intervention. Here I discuss three potential targets for intervention according to the intervention functions of the behaviour change wheel [15] which is illustrated in figure 7.2.

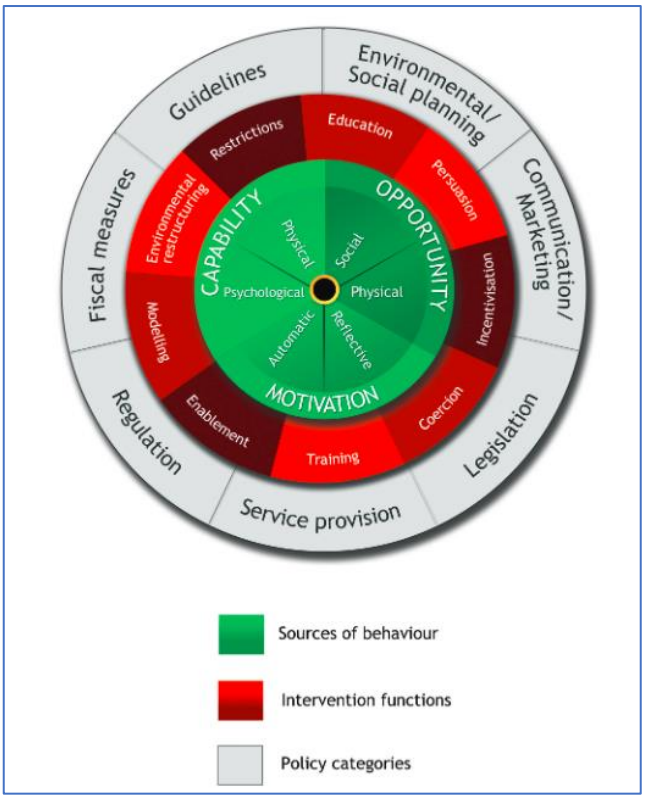

Figure 7.2: The Behaviour Change Wheel (image taken from 'The Behaviour Change Wheel A Guide to Designing Interventions)[16]

Targets for intervention: ***Motivating factors: Getting a check-up on lung health; Seeking reassurance through follow-up. (Intervention function: Incentivisation)***

HL survivors have a desire for knowledge about lung health and general desire for surveillance, so a lung cancer screening test offered as part of a tailored general health check could be appealing. This might include a review of cardiovascular health and risk factors for other late effects alongside lung cancer screening. So long as the associated invitation and information material did not disguise the purpose of undergoing a LDCT scan and every effort was made to obtain informed consent, the 'incentivisation' itself should not pose an ethical dilemma. Lung cancer screening for ever smokers in the general population have been framed as 'Lung Health Checks', with the aim of addressing the fear of lung cancer as a barrier to participation. Presuming that some HL survivors would not attend lung cancer screening due to fear of lung cancer, similar framing of the health check

proposed above for HL survivors might produce a similar collateral effect and increase uptake. It would be wise to prospectively explore whether this option is preferred by HL survivors, as the additional time taken to perform a general health check might in fact be a barrier to participation.

Targets for intervention: Facilitating factors: Being able to take time off work. (Intervention function: Enablement)

Many HL survivors eligible for lung cancer screening will be of working age. Being able to take time off work easily – either through sympathetic employers or being self-employed - was identified as a facilitating factor in chapter 5. Providing flexibility in the days and times at which lung cancer screening appointment are offered, and making appointments available outside of normal working hours, should minimise work-related barriers to participation. However, this could be expensive, and before setting up an out-of-hours service it would be useful to know what the demand would be.

Target for intervention: Potential for early diagnosis; Awareness of increased risk of subsequent cancers; Belief that pros outweigh cons. (Intervention function: Education)

Although some HL survivors may already be aware of their lung cancer risk, evidence from this thesis suggests many are not. Providing the decision aid upfront at the point of invitation to lung cancer screening might prompt people to participate by providing information about lung cancer risk, potentially making it harder to ignore the invitation. However, this may only be effective for people who would be swayed towards participating in screening but require a prompt, as was the case for one of the participants interviewed in chapter 5. This approach would reflect the method of invitation to established cancer screening programmes for the general population, in which information (or a means of accessing the information) is sent at the point of invitation. We were unable to take this approach for the lung cancer screening pilot because the sponsor stipulated that a brief invitation letter should be sent first to avoid provoking anxiety. The pilot study is collecting data on health-related quality of life, cancer worry, and anxiety measured before and after receipt of the decision aid. This data alongside qualitative exploration within focus groups for example, could inform the acceptability of providing the decision aid upfront.

Employing alternative methods to identify barriers to participation

In the design of future studies, researchers should consider alternative methods to investigate barriers to participation than those used in this thesis. Every effort should be made to record the smoking histories and ethnicities of those invited to lung cancer screening, so that the impact of these factors on participation can be explored. This information is most likely to be held by GPs so engagement with primary care would be required. An application to the Confidentiality Advisory Group would be needed for this approach because information on non-participants would be collected without their consent. Researchers should also develop methods to enable the collection of data on barriers to participation among lung cancer screening non-participants. The findings of my thesis suggest that efforts should focus on collecting this data from people who engage the least in the study. This might involve sending non-participant questionnaires (NPQ) and making return of the NPQ as easy as possible, for example by offering an online response option. Providing monetary incentives for NPQ return or interview participation may increase participation in these aspects but would be at the discretion of the research ethics committee.

Supporting decision making in a future study

As highlighted earlier, there is evidence in this thesis that the approach to information provision used in the lung cancer screening pilot could be improved upon to meet the needs of a larger proportion of HL survivors invited to lung cancer screening. Whilst there is evidence to support the further use of the decision aid, the information contained within it could be made more widely accessible using other supplementary formats such as videos. This may improve decisional conflict – and therefore potentially improve uptake - among HL survivors with lower levels of health literacy.[17] The informational needs of those with high and low literacy were not explored in this thesis but there is evidence that those with high and low literacy interpret information differently within cancer screening decision aids[18] and this is an area worthy of further exploration.

Introducing a SDM process in a future study could be beneficial in that the opportunity to discuss evidence with a healthcare professional during the decision-making process could help those invitees whose informational needs are not fully met by the decision aid. A SDM consultation might also mitigate concerns that those heavily in favour of screening are not

engaging with written information about the pros and cons of screening before deciding, as highlighted in chapters 4 and 6. The timing of the SDM aspect would be important in that one would want to offer the SDM consultation to both those inclined towards and against screening, without reducing uptake by making participation more burdensome. A possible avenue for exploring information provision and decision-making approaches would be a randomised controlled trial, comparing the approach taken in the pilot described in chapter 5, versus the decision aid provided alongside a SDM consultation. This approach has been investigated in a trial of prostate cancer screening (using prostate-specific antigen)[19], which is a particularly preference-sensitive decision. Important outcomes to measure would include the impact on uptake and invitees and clinicians' satisfaction with the decision-making process.

7.4 STRENGTHS AND LIMITATIONS OF THE THESIS

Strengths

I believe the main strength of this thesis is the use of mixed qualitative and quantitative methods. The benefits of using mixed methodology are well described. Curry and Nunez-Smith describe three main reasons for using mixed methods.[20] Firstly, the use of mixed methods can minimise the limitations of the single qualitative or quantitative approach. Secondly, the initial use of one method can enhance the development or design of a study or instrument using the alternative method, for example a qualitative study might inform the development of a quantitative instrument. Thirdly, using mixed methods can generate data which provides a richer, more complete answer to a research question.

This thesis includes mixed methods within a study (chapter 4) and qualitative and quantitative methods alone to answer discrete but related research questions (chapters 2, 3, 5 and 6). According to the agreed definition, only the study presented in chapter 4 qualifies as a mixed methods study, as qualitative and quantitative methods were used within the study.[21] Although chapters 2 and 3 were not mixed methods studies, in this discussion section I have used triangulation[21] in reporting the data from these chapters, whereby data produced using different methods allowed me to corroborate the results of each study. For example, the interview data from chapter 2 describes how HL survivors feel

able to navigate the physical aspects and psychological consequences of undergoing lung cancer screening because of their experiences resulting from a previous cancer diagnosis. This data explains why scores on the self-efficacy scale within the LCSHBS described in chapter 3 were high and corroborates the finding that self-efficacy is associated with willingness to be screened through the exploration of personal narratives.

In chapter 4, focus groups and interviews followed the survey. Whilst a survey was better suited than qualitative methods to determine whether the decision aid improved lung cancer risk and screening related knowledge, the focus groups were an opportunity to identify and explore specific areas of confusion or need for greater clarity regarding the information in the decision aid. In chapter 6, interviews followed participation or non-participation in the pilot and receipt of the decision aid. Here, data from the interviews enhanced the questionnaire data from chapter 5 with regards to evaluating the decision aid. For example, the interviews identified that in some cases, the decision aid helped people feel informed after a decision about participation had already been made. In addition, the interviews demonstrated that concerns about radiation, a barrier to participation, stemmed from a sense of high susceptibility to radiation induced cancers. This discovery was possible because the qualitative methods used allowed the participants to express their beliefs and explain how they relate to their lived experience. These examples demonstrate how qualitative and quantitative methods were complementary. The use of qualitative methodology mitigated the limitations of the quantitative methods, which could not have provided information about the perspectives and experiences which informed participation decisions or the chronology of informed decision making. Furthermore, they demonstrate how using different methods to examine differing aspects of the research question allowed me to give a more complete answer to the research questions. Complementarity and expansion are well-described benefits of using mixed methods.[21] I believe that my use of qualitative and quantitative methods across the thesis has enabled me to answer my research questions in greater depth, enabling me to draw more robust conclusions and provide evidence-based suggestions for how the research could influence the development of a larger study of lung cancer screening.

Limitations: Exploring barriers to participation

One of the objectives of the thesis was to explore barriers to undergoing lung cancer screening, which I hoped to address in chapters 2, 3 and 6. Due to response bias in chapters 2 and 3 and methodological challenges and restrictions affecting data collection in chapter 5, this objective has been less well met. I will firstly address the issue of response bias. Of the 30 HL survivors interviewed in chapter 2 (who were enthusiastic about lung cancer screening), 21 were later invited to the lung cancer screening pilot and 20/21 participated. This demonstrates that chapter 2 is affected by a response bias, in that the views presented are reflective of HL survivors who hold positive views towards lung cancer screening and who were not later prevented from participating by psychological or practical barriers. A very large majority of the responders in chapter 3 indicated willingness to undergo lung cancer screening. Given that the response rate to the questionnaire was 58%, it may be that the 42% who did not return the questionnaire are those HL survivors who are less engaged with their health and their risk of late effects, or, who are currently experiencing barriers to participating in research - such as older age, belonging to an ethnic minority or comorbid conditions[22] - that would also impact their ability to undergo lung cancer screening. Therefore, the findings of chapter 3 are likely to have been similarly affected by response bias and the characteristics of participants in these chapters limits my ability to extrapolate the findings to the wider population of HL survivors.

The lung cancer screening pilot was a further opportunity to explore the barriers to undergoing lung cancer screening, however as I acknowledge in the chapter 6 discussion section, my ability to explore the barriers to participation was limited by the very small number of people invited to the study who decided against participation after reading the decision aid and who agreed to be interviewed about their decision (it was deemed unethical to collect data on reasons for non-participation from those not wishing to engage with the study, ie. those who did not request a participant information sheet). One way of navigating this issue would have been to send a NPQ to all invitees, allowing people to provide their reasons for non-participation and to provide written consent to allow me to use this information for research. However, rates of return of NPQs in cancer screening studies are typically low [23–25]. For this reason, and because I felt that a qualitative approach would yield richer data, I decided against this approach. Therefore, I was limited to

approaching people who had requested the study participant information sheet – 'decliners', few of whom agreed to interview.

Intended collaboration with The Centre for Childhood Cancer Survivor Studies

The intention at the outset of this research was to collaborate with researchers at The Centre for Childhood Cancer Survivor Studies based at The University of Birmingham. The centre, directed by Professor Mike Hawkins, holds a database – created through the Teenage and Young Adult Cancer Survivor Study (TYACSS) - containing the details of over 300,000 individuals diagnosed with cancer at the age of 15-39 years in England and Wales between 1971 and 2006, including nearly 17,000 survivors of HL. Our intention was to seek approvals from a research ethics committee and the Confidentiality Advisory Group to contact HL survivors whose details were held in the database to invite them to participate in a questionnaire study (akin to the study described in chapter 3 in this thesis). We hoped to send out 1000 questionnaires, to receive around 300 returned questionnaires and to subsequently recruit responders to a later interview study. Since the TYACSS database was created with permission from the Confidentiality Advisory Group, the persons whose details are contained in the database did not consent to their data being held, shared with other researchers, or to being contacted by other research groups. This meant we needed to seek permission from the Confidentiality Advisory Group to run the study and that we would need to engage the individuals' GPs as gatekeepers, prior to contacting them. Although we were granted permission from a research ethics committee, it became clear that it would not be feasible to complete the study in the remaining time available for this thesis. This was largely due to the volume of work that our collaborators at the CCCSS would have needed to do to facilitate the study in the context of the additional workload and pressures they were experiencing during the COVID-19 pandemic. My supervisors and I decided that the best option was to recruit HL survivors whose details were contained in the ADAPT database to the proposed interview and questionnaire studies.

Repeated sampling of HL survivors in the ADAPT database

The ADAPT database was an invaluable resource for this thesis. Using the database, alongside electronic medical records, I was able to identify a cohort of HL survivors treated up to 45 years ago who I knew to be at excess risk of lung cancer as I could source details of their treatment from medical records. Crucially, because they remained under the care

of The Christie, I was able to contact them directly for recruitment to the studies in chapters 2, 3, 5 and 6. To our knowledge, there are no other databases in the UK going back as far and containing the range and completeness of data which are maintained by a single treating centre.

However, the repeated sampling of HL survivors listed in the database could potentially bias the data presented in this thesis. During the period in which I collected data for this thesis, there were slightly over 400 HL survivors registered in the ADAPT database. Broadly speaking, the same group of HL survivors were eligible for the two studies described in chapters 2 and 3 due the overlapping eligibility criteria. To obtain as many responses to the questionnaire study as possible, people who participated in the study described in chapter 2 (or who were invited to participate), were not excluded from participation in the questionnaire study (chapter 3). Responses to the questionnaire study by those who had been invited to, or participated in the first study, could have been biased by the study information they had already received, which mentioned their excess of risk of lung cancer. Recruitment to the questionnaire study (chapter 3) and the lung cancer screening pilot (chapter 5) took place in 2021, so it is likely that nearly all of the 218 HL survivors invited to the lung cancer screening pilot would have received the questionnaire and the associated participant study information. Therefore, some of the participants in the questionnaire study and the lung cancer screening pilot had some prior awareness of lung cancer risk and the of prospect of lung cancer screening, potentially impacting their willingness to be screened and differentiating them from the national HL survivor population who may be approached for screening in future.

Limitations: The potential influence of my role as a doctor in the qualitative studies

The people invited to participate in the studies described in chapters 2 and 6 had been under the care of lymphoma physicians at The Christie Hospital and in the recruitment documents, I was identified as a doctor and research working within the lymphoma team at The Christie. Therefore, despite the fact I had not been involved in their care before, participants and potential participants would have related to me as a doctor. The extent to which this, in isolation, introduced a power imbalance would have depended on the potential participants' perceptions of doctors, but there were other ways in which my role introduced a power imbalance. Firstly, people invited to participate in the interview study

(chapter 2), were sent an invitation letter by post without prior contact, and in this sense, there was a power imbalance in the recruitment process since I had been able to access their details and contact them without their permission. It is important to consider impact of the 'knowledge gap' that became evident during the research process in chapter 2 - I had an understanding of HL survivors' lung cancer risk and of lung cancer screening, whilst the participants (and presumably those who didn't participate, did not). In hindsight, I expect that this imbalance may have impacted the resulting research data, since the people who participated probably felt confident in their ability to discuss a healthcare intervention (which they had no prior knowledge of) with a doctor, whilst a lack of confidence in this matter - perhaps due to lower levels of health literacy - might have been a barrier to participating in the study.

The potential for my role to introduce bias, was perhaps greater in the study described in chapter 6, due to my role in running the lung cancer screening pilot. Those eligible to be invited to the chapter 6 interview study were the HL survivors who had been invited to the lung cancer screening pilot (by a letter signed by me), who had requested further information on the study, and who had returned a questionnaire (after receiving the decision aid) indicating that they were happy to be contacted to be interviewed about "the decision they made" at a later date. There were six people who returned this questionnaire, who had declined to take part, but only two of them agreed to contacted to be interviewed about their decision. My role and my proximity to the lung cancer screening pilot could have discouraged the other screening decliners from discussing their decision with me, perhaps for fear of my judgement about their decision, considering that I was a doctor within their treating team and was offering them an intervention.

These potential biases introduced by my role are a reminder of the importance of 'reflexivity' ("the researchers' engagement of continuous examination and explanation of how they have influenced a research project"[26]), which is a key concept in evaluating the trustworthiness of qualitative research. I have tried to demonstrate the trustworthiness of the qualitative research studies I conducted in this thesis through the inclusion of 'reflexivity statements'.

7.5 CHALLENGES FACING THE DEVELOPMENT OF LUNG CANCER SCREENING FOR HL SURVIVORS

A major challenge facing the development of a larger study of lung cancer screening for HL survivors is the method of identifying and contacting survivors at risk. Having ready access to the ADAPT database meant we could identify survivors who are risk of lung cancer due to their treatment and who were treated up to 45 years ago. However, follow-up programmes like ADAPT are rare and alternative methods of identifying at-risk HL survivors who have been discharged from follow-up must be explored. We do not know the extent to which other UK cancer centres who have treated HL patients over the past four decades are able to provide details of such patients and the treatments they received. Our research group is actively looking to seek this information by approaching large treating centres via the National Cancer Research Institute (NCRI) HL Study Group. However, we expect that many at-risk HL survivors will not be identified through medical records held by treating centres due to missing or incomplete historical records. Whilst it may be tempting to focus future lung cancer screening efforts on centres who are able to identify large numbers of at-risk survivors, doing so would be a disservice to the many HL survivors who were treated elsewhere, who are unable to access lung cancer screening services. As discussed in chapter 5, a potential solution to this challenge is a hybrid approach, whereby an exhaustive list of living HL survivors is sought from the National Cancer Registration and Analysis Service (NCRAS) and their treatment details are sought from NCRAS where available, or their treating centres. We do not know the extent to which NCRAS holds treatment data for HL patients treated decades ago - the NCRAS linked national radiotherapy dataset (RTDS) holds data since 2009 and the Systemic Anti-Cancer Therapy dataset holds data since 2014 - but we hypothesise that between NCRAS and treating centres which hold historic treatment data, we could create a national database of HL survivors potentially eligible for a larger lung cancer screening trial. Our research group are in the early stages of developing a protocol for a study to examine the feasibility of creating a national register of living HL survivors at risk of lung cancer. In this study we will seek to link identifiable data from several national databases hosted by NHS Digital (NCRAS, RTDS, SACT), to create the basis of a national risk register, and subsequently determine the extent to which a number of selected treating cancer centres can collect

missing lung cancer risk factor data from hospital records to update the national risk register. We have submitted a study protocol for review at the National Cancer Research Institutes' Living With and Beyond Cancer proposal guidance meeting, taking place in February 2023.

This feasibility exercise is crucial because the challenges involved in identifying HL survivors at risk of lung cancer could hinder recruitment to a larger screening study, potentially leading to a failure to demonstrate that lung cancer screening for HL survivors is feasible on a large scale. However, the successful creation of a national risk register would provide a large cohort to invite to a larger national lung cancer screening study, were it deemed ethical.

The creation of a national register of HL survivors at risk of lung cancer using the methods described above, would require significant amounts of time, funding, and engagement by cancer centres. However, a similar approach has been used in the creation of the Breast Cancer After Radiotherapy Dataset (BARD)[27], whereby around 8000 women treated with radiotherapy under the age of 30 and at risk of breast cancer have been retrospectively identified using a combination of methods – a national recall exercise, cancer registries, radiotherapy treatment centres and the national radiotherapy dataset (RTDS) – and referred for annual breast cancer screening. The success of the BARD programme demonstrates that it is possible to retrospectively identify HL survivors at risk of a subsequent malignancy due to treatment. In exploring the feasibility of developing a targeted lung cancer screening programme for HL survivors, we can learn from the successes and difficulties experienced during the creation of BARD.

A particular strength of lung cancer screening pilots aimed at the ever smoking general population in the UK is their ability to offer screening to those who are most at risk – and to avoid exposing those least at risk to the potential harms of screening – by using validated lung cancer risk calculators to determine eligibility. A large study of lung cancer screening for HL survivors may provide the granular demographic, treatment, and smoking data to create such a calculator, but in its absence, researchers will need to reach a consensus on the risk threshold for eligibility for lung cancer screening. To illustrate the issue, HL survivors who received an alkylating agent but have never smoked are at much lower risk that those who received an alkylating agent, thoracic radiation and who have

smoked.[28] Additionally, the risk of lung cancer also increases with time since treatment and the threshold at which screening should commence is not clear. Future lung cancer screening studies for HL survivors should aim to address the question of the risk threshold for lung cancer screening eligibility.

7.6 CONCLUSION

Despite the numerous challenges, it is my view that there is a degree of urgency to offer lung cancer screening opportunities to HL survivors. Delaying the development of a targeted lung cancer screening programme in the hope of creating the optimal methodologies for recruitment and risk stratification would be an injustice to those survivors who meanwhile develop lung cancer and miss the opportunity for early diagnosis.

The studies undertaken for this thesis have provided novel data supporting the further development of lung cancer screening for HL survivors. I would argue that the evidence is also timely, firstly because of the recent successes of lung cancer screening pilots for the ever smokers in the general population and secondly because the risk of lung cancer continues to increase for the many thousands of at-risk HL survivors, most of whom would not be eligible for lung cancer screening pilots aimed at ever smokers. In relation to participation in lung cancer screening by HL survivors, I have demonstrated that upon first invitation, approximately half of HL survivors will attend for lung cancer screening. Although this participation rate is modest, it suggests recruitment to a larger study is feasible and can inform recruitment targets as sample size will be important to answer certain research questions. By exploring the motivating and facilitating factors and barriers to screening, I have identified potential targets for intervention with the aim of optimising participation rates and identified areas for further research and proposed appropriate methods. In relation to methods used to inform and invite HL survivors to lung cancer screening, I have developed a novel decision aid and demonstrated its utility in facilitating informed decision making by HL survivors, supporting its use in further studies as well as identifying ways in which further studies might improve the quality of the decision-making process. Crucially, I have demonstrated that the scanning and reporting protocols used to screen ever smokers in the general population for lung cancer are appropriate for use in the HL survivor population. Specifically, I have demonstrated that prior treatment for HL does not lead to high rates of pulmonary nodule detection requiring surveillance or

invasive investigations, nor does it lead to an unacceptably high rate of clinically significant incidental findings. Therefore, the evidence provided by this thesis, even considering the limitations of the findings, supports the further development of lung cancer screening for HL survivors.

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APPENDICES

CHAPTER 3 STUDY QUESTIONNAIRE

The Christie NHS
NHS Foundation Trust

A survey exploring health and screening tests in people treated for Hodgkin lymphoma

Study ID:

Thank you for taking part in this study.

The study asks for your views on attending various cancer screening tests. It also covers topics such as your health and your lifestyle. It also asks for some information about you.

How to fill in this questionnaire

- Please read the instructions and questions carefully.
- To answer the questions, tick the box ☐, write on the dotted line or in the box provided
- Fill in the answer which best describes how you feel.
- Please try to answer all the questions. If you do not wish to answer a question, please leave it blank.
- Do not spend too long on each question – the first answer which comes to you is probably the best one.
- There are no right or wrong answers. If you are unsure about how to answer a question please put the best answer you can.
- You may wish to take breaks while completing the questionnaire
- The information you provide will remain **strictly confidential.**
- Please return your questionnaire for free in the envelope provided
- If you wish to complete the questionnaire online you can do this by emailing (redacted) and we will send you a link

Part 1: About you and your health

These questions help us to know more about you and your health and help us to better understand the results of this survey. You may have been asked about these issues before in other surveys, but please respond to all the questions if you can.

1) How would you describe yourself? Choose ONE section from A to E then tick ONE box which best describes your ethnic group or background

A) White

☐ English/Welsh/Scottish/Northern Irish/ British
☐ Irish
☐ Gypsy or Irish traveller
☐ Any other white background please specify:

.....
.....

B) Black / African / Caribbean / Black British

☐ African
☐ Caribbean
☐ Any other Black / African / Caribbean background please specify:

.....
.....

C) Asian / Asian British

☐ Indian
☐ Pakistani
☐ Bangladesh
☐ Chinese
☐ Any other Asian background please specify:

.....
.....

D) Mixed / multiple ethnic groups

☐ White and Black Caribbean
☐ White and Black African
☐ White and Asian
☐ Any other mixed / multiple ethnic background please specify:

.....
.....

E) Other ethnic group

☐ Arab

☐ Any other ethnic background please specify:

.....
.....

2) Which of the following best describes your education? Tick one box

- ☐ I left school with no qualifications
- ☐ I have GCSEs (previously CSEs) or equivalent
- ☐ I have A levels or O-levels
- ☐ I did some further education (beyond college) but not a degree
- ☐ I have an undergraduate university degree
- ☐ I have a postgraduate degree
- ☐ Prefer not to say

3) Which of the following best describes your current employment? Tick one box.

Employed full-time

- ☐ Employed part-time
- ☐ Self-employed
- ☐ On sick-leave
- ☐ Looking after home or family
- ☐ Voluntary work
- ☐ Disabled or long-term sick
- ☐ Unemployed
- ☐ Retired
- ☐ In full-time education/training
- ☐ In part-time education/training

Other please specify: .....

4) For someone your age, how would you rate your health overall? : Tick one box.

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

5) Have you ever been diagnosed with COPD or emphysema or bronchitis?

- ☐ Yes
- ☐ No

6) Which of the following best describes you?

- ☐ I have **never smoked** (go to question 9)
- ☐ I am an **ex-smoker**
  If you are an ex-smokers, how many years ago did you quit smoking? ..... years
- ☐ I **currently smoke**

7) How many years have you/did you smoke for? (Include cigarettes, pipes and cigars).

..... years

8) How many cigarettes did/do you smoke on an average day? .....

9) a) What is your height?..... cm OR ..... feet ..... inches

b) What is your weight? ..... kg OR ..... Stones.....pounds

10) *In the last 4 weeks*, how often were you bothered by thoughts or worry about your chances of getting cancer again in the future? Tick one box.

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

11) Please read the statements below carefully and rate how much you agree or disagree with the statement by ticking a box to the right.

In uncertain times I usually expect the best	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
It's easy for me to relax	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
If something can go wrong for me, it will	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I'm always optimistic about my future	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I enjoy my friends a lot	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
It's important for me to keep busy	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I hardly ever expect things to go my way	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I don't get upset too easily	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I rarely count on good things happening to me	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Overall, I expect more good things to happen to me than bad	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

Health problems after treatment for Hodgkin lymphoma

12) Cancer treatments can cause health problems later in life. Below is a list of health problems. Please tell us which ones you think **can** be caused by treatment for Hodgkin lymphoma based on your personal knowledge by ticking the box next to the problem.

- ☐ High blood pressure
- ☐ Breast cancer
- ☐ Problems with vision
- ☐ Bowel (colorectal) cancer
- ☐ Leukaemia
- ☐ Weak heart muscles
- ☐ Heart attacks
- ☐ An underactive thyroid
- ☐ Difficulties getting pregnant
- ☐ Diabetes
- ☐ Lung cancer
- ☐ Eczema
- ☐ An overactive thyroid
- ☐ Asthma or bronchitis
- ☐ Arthritis
- ☐ Early menopause in women
- ☐ Low testosterone levels in men
- ☐ Problems with hearing

Going for cancer screening tests

The NHS runs cancer screening programs for breast cancer, bowel cancer and cervical cancer. In the future there may be a lung cancer screening program for people at risk.

We would like to know how you feel about your risk of developing cancer in the future and your views on going for cancer screening test for breast, bowel and lung cancer.

13) Compared to the average person of your age and sex, how likely is it in your opinion that you will develop the following types of cancer? Circle your answer.

1.	Breast cancer (women only)	Much less likely	A bit less likely	About the same	A bit more likely	Much more likely	I don't know
2.	Bowel cancer (men and women)	Much less likely	A bit less likely	About the same	A bit more likely	Much more likely	I don't know
3.	Lung cancer (men and women)	Much less likely	A bit less likely	About the same	A bit more likely	Much more likely	I don't know

14) Have you ever *been invited* to do a **bowel cancer** screening home test kit?

- ☐ Yes
- ☐ No

If the answer was yes, have you *ever had* a **bowel cancer** screening test?

- ☐ Yes
- ☐ No

15) Women only: Have you ever *been invited* to go for a **breast cancer** screening test (mammogram or MRI scan)?

- ☐ Yes
- ☐ No

If the answer was yes, have you *ever had* a **breast cancer** screening test (mammogram or MRI scan)?

- ☐ Yes
- ☐ No

16) A lung cancer screening programme may become available on the NHS in the future. The test used for lung cancer screening is a CT scan of the chest. The scan takes 20 seconds and does not require an injection. Please respond to the following statements about having a lung cancer screening test. Circle your answer.

It is likely that I will get lung cancer sometime in my lifetime	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
It is likely that I will get lung cancer in the next ten years	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
It is likely that I will get lung cancer in the next five years	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
Having a lung scan would help find lung cancer early	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
Having a lung scan would lower my chances of dying from lung cancer	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
Having a lung scan would help me not worry as much about lung cancer	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
Having a lung scan would help me plan for the future	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree

Having a lung scan would help my family not worry as much	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
Having a lung scan would give me peace of mind	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I worry about finding something wrong	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I don't have the time	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off a lung scan because no one in my family had lung cancer	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I don't have any lung problems or symptoms	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because transportation would be a problem	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I am afraid the lung scan will damage my lungs	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I have had a bad experience with a hospital or healthcare provider	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree

I might put off having a lung scan because I don't know enough about the test	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I think I am too old to benefit from screening for lung cancer	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I would rather **not** know if I have any lung problems	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because it is not worth the effort	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might put off having a lung scan because I do not trust the healthcare system	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree

Only answer the next 3 statements if you have ever smoked tobacco:

I might be put off having a lung scan because I currently smoke or used to smoke	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might be put off having a lung scan because I feel like a social outcast for smoking	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree
I might be put off having a lung scan because I worry about being blamed for having smoked	Strongly Agree	Agree	Neither agree not disagree	Disagree	Strongly disagree

Please read the statements below carefully and rate your confidence level by ticking a box to the right

How confident are you that you could find the time to have a lung scan?	Very confident	Somewhat confident	Slightly confident	Not at all confident
How confident are you that you could find transportation to get to and from the clinic/hospital to have a lung scan?	Very confident	Somewhat confident	Slightly confident	Not at all confident
How confident are you that you could get enough information about having a lung scan?	Very confident	Somewhat confident	Slightly confident	Not at all confident
How confident are you that you could get a lung scan even if you were worried about the results?	Very confident	Somewhat confident	Slightly confident	Not at all confident
How confident are you that you could get a lung scan even if you didn't know what to expect about the procedure?	Very confident	Somewhat confident	Slightly confident	Not at all confident
How confident are you that you could get a lung scan even if you were anxious **about the process**?	Very confident	Somewhat confident	Slightly confident	Not at all confident
How confident are you that you could get a lung scan even if you were **anxious about the results**?	Very confident	Somewhat confident	Slightly confident	Not at all confident

17) Has anyone you know been diagnosed with lung cancer?

- ☐ Yes, one of my parents or siblings
- ☐ Yes, another family member
- ☐ Yes, someone I know but am not related to
- ☐ No

18) If you were invited to go for a lung cancer screening test, would you go? Tick one box.

- ☐ Yes definitely
- ☐ Yes probably
- ☐ Probably not
- ☐ Definitely not

In the UK the NHS runs a bowel cancer screening programme for men and women aged 60 to 74. The test used in the screening programme is a kit you use at home to collect a small sample of poo, known as the FIT kit.

19) Please answer the following statements about the bowel cancer screening home test kit. Circle your answer.

It is extremely likely that I will get colorectal cancer in my lifetime	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
The bowel screening test can find bowel cancer early	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
When bowel cancer is found early it can be cured	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Regular bowel screening helps you live longer	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

Regular bowel screening helps you to worry less	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Bowel screening gives you peace of mind	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Bowel screening gives you a sense of control over your health	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off bowel screening because it is embarrassing	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off bowel screening because it is uncomfortable	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off bowel screening because it is inconvenient	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off bowel screening because I don't want to know if I have bowel cancer	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off bowel screening because it is a cause for worry	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I am confident that I could manage to do the bowel screening home test kit	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

20) Has your doctor ever recommended that you should do the bowel screening test when you are invited?

- ☐ Yes
- ☐ No
- ☐ Unsure

21) Has anyone you know been diagnosed with bowel cancer?

- ☐ Yes, one of my parents or siblings
- ☐ Yes, another family member
- ☐ Yes, someone I know but am not related to
- ☐ No

22) When you are next invited to do a bowel screening test, will you do it?

- ☐ Yes definitely
- ☐ Yes probably
- ☐ Probably not
- ☐ Definitely not

Only women should answer this next section. For men this is the end of the survey – go to page 18.

In the UK women aged 50-71 are invited to have a breast cancer screening test (a mammogram).

Women who had radiotherapy to the chest area before the age of 36 are invited to have a breast cancer screening test (either a mammogram or MRI depending on their current age) earlier than the general population.

23) Please answer the following statements about breast cancer screening. Circle your answer.

It is likely that I will get breast cancer	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
My chances of getting breast cancer in the next few years are great	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

I feel I will get breast cancer sometime during my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
If I get a breast screening test and nothing is found, I do not worry as much about breast cancer	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Having a breast screening test will help me find breast lumps early	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
If a lump is found on my breast screening test, my treatment may not be as bad	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Having a breast screening test is the best way for me to find a very small lump	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Having a breast screening test will decrease my chance of dying from breast cancer	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because I might find out something is wrong	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because I don't understand what will be done	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

I might be put off a breast screening test because it is embarrassing	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because it takes too much time	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because it is too painful	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because the people who do it are rude to women	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because it exposes me to unnecessary radiation	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because I have other problems that are more important	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I might be put off a breast screening test because I am too old to benefit	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
I am confident that I can go for a breast screening test when invited	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

Has your doctor ever recommended that you should go for the breast screening test when you are invited?

- ☐ Yes
- ☐ No
- ☐ Unsure

Has anyone you know been diagnosed with breast cancer?

- ☐ Yes, one of my parents or siblings
- ☐ Yes, another family member
- ☐ Yes, someone I know but am not related to
- ☐ No

When you are next invited to go for a breast screening test, will you have it?

- ☐ Yes definitely
- ☐ Yes probably
- ☐ Probably not
- ☐ Definitely not

End of survey

What to do if you want more information or have concerns:

If you have any concerns, or would like more information on the late effects of cancer treatment, you can:

- Speak to a lymphoma clinical nurse specialist at The Christie: (telephone number)

- Seek advice and support from Lymphoma Action- they are aware of this study
  - via their website http://lymphoma-action.org.uk
  - or their free helpline 0808 808 5555 Monday to Friday 10am-3pm
  - a live chat option is available via the 'Contact Us' section of the website

If you would like to discuss any aspect of the questionnaire survey you can contact our research team:
By email:
By phone:

By post:

To obtain a summary of the results of this survey, contact Dr Rachel Broadbent using any of the contact methods above.

Please post your survey back to us using the envelope we have provided.

Thank you for your participation.

Screening to find the early signs of lung cancer after treatment for Hodgkin lymphoma: Helping you decide

A lung scan can detect the early signs of lung cancer before symptoms have developed

Decision aid v1 dated 23.3.21

This leaflet has been written to help you decide whether or not to have a lung cancer screening test (a lung scan). It is entirely your choice whether to have the test. Please read the information carefully. You may want to discuss it with your family, friends or doctor before deciding. You can also contact a specialist nurse who will be able to provide more information and help you with any questions you may have. Their contact number is provided on page 14.

Contents

Why should I think about lung cancer screening?

People treated for Hodgkin lymphoma have a higher chance of getting lung cancer than people in the general population who have not had Hodgkin lymphoma. This is because cancer treatments like radiotherapy and chemotherapy cause damage to cells in the lung.
Specifically, the treatments that increase the chance of getting lung cancer are:

- Radiotherapy to the chest area
- A chemotherapy drug called Procarbazine which is found in chemotherapy treatments such as MOPP, MVPP, ChlVPP and BEACOPP.

At what time in my life do I have a higher chance of getting lung cancer?

People treated for Hodgkin lymphoma have a higher chance of getting lung cancer for at least 40 years after their diagnosis. The chance of getting lung cancer also gets higher as you get older.

Do I still have a higher chance of getting lung cancer if I don't smoke?

Yes, you have a higher chance of getting lung cancer even if you have never smoked or have given up. This is because of the cancer treatment you were given.

If you **have smoked**, this adds to your chance of getting lung cancer.

How likely is it that I will develop lung cancer?

A study of more than 16,000 people treated for Hodgkin lymphoma when they were aged 15-39 in the UK found that:

5 out 100 men treated for Hodgkin lymphoma develop lung cancer in the 35 years after treatment

4 out 100 women treated for Hodgkin lymphoma develop lung cancer in the 35 years after treatment.

Other things to know about your chance of getting lung cancer:

If a close family member has had lung cancer, you have a higher chance of getting lung cancer.

If you had radiotherapy *and* chemotherapy, you are at higher chance than if you only had chemotherapy.
This is shown is the picture below.

Out of 100 people treated with chemotherapy and chest radio-therapy, we would expect 5 to develop lung cancer

Out of 100 people treated with chemotherapy alone, we would expect 1 to develop lung cancer

How many people in the general population get lung cancer?

In the general population in the UK, which includes smokers, ex-smokers and people who have never smoked:

- 8 out of every 100 men will get lung cancer in their lifetime
- 7 out of every 100 women will get lung cancer in their lifetime

What does lung cancer screening involve?

Lung cancer screening involves having a CT scan of your chest. The CT scan is looking for spots on your lung (called nodules). During the scan you will usually lie on your back on a flatbed that passes into the CT scanner. The scanner has a ring that rotates around a small bit of your body as you pass through it. During the scan you will need to lie still and follow simple breathing instructions for less than 10 seconds to make sure that the pictures are not blurred.

- The scan takes around 20 seconds to complete.
- You do **not** need to have an injection.
- You do **not** need to take your clothes off but you should avoid wearing clothes with metal such as zips, or jewellery, as these will need to be removed.
- After the scan you can eat, drink and drive as usual.
- You cannot have a CT scan if you are pregnant.

When will I get the results?

You will be told the scan results by phone within 2 weeks. You will also get a letter with the results and a copy will be sent to your GP.

What could the scan show?

The scan could be normal, or it could show a spot (a nodule) that needs further investigation.

What are the chances of having a clear scan?
Around 90 out of 100 people will have a normal scan

What are the chances of a spot (nodule) being found?
Around 10 in every 100 people will have a spot on their lung seen on their scan. Of these 10 people, most will **not** have lung cancer. They will need another scan in 3 months to check on the spot. It is possible that some of these 10 people will need more tests straightaway to find out if a spot is lung cancer or not.

We think that 90 out of every 100 people screened will have a normal scan

We think that 10 out of every 100 people screened will need more tests to rule out lung cancer

Because lung screening has not been tested in people treated for Hodgkin lymphoma, we cannot be certain of these numbers. They are our best guess.

What happens if the scan is clear?

If the scan is clear, you do not need another lung scan at this time. If you smoke you will be offered support to give up should you wish.

What happens if the scan result is uncertain?

Sometimes it is not clear whether a small spot on the lung is cancer or not. In this case, another CT scan is advised 3 or 12 months later to check on the spot. We can arrange these scans for you.

What happens if a possible lung cancer is seen?

If a possible lung cancer is seen, you will be referred to a lung clinic at your local hospital. You should be seen in the clinic within 2 weeks of the referral being made. The lung clinic will arrange more tests.

What else might the scan show?

The CT scan can also find problems that are not cancer. Chest radiotherapy and some kinds of chemotherapy can cause problems like weakness of the heart muscle or lung scarring. If the scan showed a problem that needed tests or treatment, we would write to you and your GP.

How often can I have a lung scan?

In this study you can have the first lung scan and another lung scan in 3 and / or 12 months if it is needed. After this, you will not be offered any more lung scans within this study.

What are the benefits of having a lung scan?

A lung scan can find lung cancer early, before it causes symptoms. Early stage lung cancer is smaller and has not spread to other areas of the body. When lung cancer is found at an early stage, it can be cured.

Early stage lung cancer is often treated with an operation where a section of lung containing the cancer is removed. Sometimes, radiotherapy is used instead of surgery. Occasionally, chemotherapy is used after surgery.

Around 7 out of every 10 lung cancers **found through screening** are early stage.

A very large study found that people who had lung cancer screening tests were between 20% and 26% less likely to die of lung cancer compared to people who did not have the test. The people in this study were current or ex-smokers who had not had Hodgkin lymphoma.

We think that people who were treated for Hodgkin lymphoma could also benefit from lung cancer screening, but there has not been a large study to prove this yet.

What are the disadvantages of having a lung scan?

Radiation

A CT scan exposes you to a small amount of radiation. The CT scan used for lung cancer screening uses less radiation than a standard scan. In fact, the amount of radiation used in a screening lung scan is about the same as the radiation you are exposed to naturally in 1 year in the UK.
The chance of getting cancer *because of the low-dose CT scan* is very low (between 1 in every 10,000 and 1 in every 100,000 people who have the scan).
You can find more information about radiation by visiting:

- www.xrayrisk.com/calculator/calculator-normal-studies.php and select CT scan, then Chest CT (Low dose Screening)
- www.radiologyinfo.org and select 'Safety'

Extra scans and false positives (false alarms)

Around 10 out of 100 people who have a lung scan need another CT scan to monitor an abnormality that turns out not to be cancer. Some people could be told they have cancer on their scan, but it turns out not to be cancer after extra tests. This is known as a false positive.

We understand that needing extra scans or having a false positive scan can make people feeling anxious or worried. If you feel this way at any point, there are a number of ways you can access support listed later in this booklet, including talking to our lymphoma clinical nurse specialist.

False negatives
Sometimes, tiny cancers are not seen on the scan. This can mean that a person is given a clear scan result but goes onto to develop lung cancer. This is uncommon (around 1 in every 250 people who have the scan.)

Overdiagnosis
Some lung cancers that are found on a lung scan would never have caused problems. This means people could have unnecessary treatment such as surgery, chemotherapy and radiotherapy.

Can having a lung cancer screening test stop me getting lung cancer?
No, a lung scan cannot stop you getting lung cancer.
If you smoke, the best way to decrease your risk of lung cancer is to stop smoking.
For help to stop smoking, speak to your GP or visit:
www.nhs.uk/live-well/quit-smoking/nhs-stop-smoking-services-help-you-quit/

What are the benefits and disadvantages of not having the lung scan?

If you do not have the lung scan, you will not be exposed to the risks associated with it.

If you do not have the lung scan and you have an early stage lung cancer that is not causing you symptoms, the cancer could become advanced before it is diagnosed. 7 out of every 10 lung cancers that are diagnosed **without screening** are diagnosed at an advanced stage when they cannot usually be cured.

What are the common symptoms of lung cancer?

- having a cough most of the time
- having a change in a cough you have had for a long time - it may sound different or be painful when you cough
- getting out of breath doing the things you used to do without a problem
- coughing up phlegm (sputum) with blood in it
- having an ache or pain in the chest or shoulder
- chest infections that keep coming back or a chest infection that doesn't get better
- losing your appetite
- feeling tired all the time (fatigue)
- losing weight

If you have any of these symptoms it is important for you to speak to your GP.

Making a decision

To help you decide whether to have a lung cancer screening test, you should think about which of the benefits and disadvantages matter most to you.

Pros of having a lung cancer screening test	Cons of having a lung cancer screening test
Lung cancer could be found at an early stage before symptoms develop	You might need more CT scans or a biopsy for a spot that turns out not to be cancer
If lung cancer is found early, treatment is more successful	False alarms or extra scans could cause anxiety
You are less likely to die from lung cancer	A lung cancer could be diagnosed that was never going to cause you any problems
If advanced stage lung cancer is diagnosed, you can access treatments and support	Exposure to a small amount of radiation

We understand that a lot of information has been given to you. You might find it helpful to follow these steps to help you make a decision about having a lung cancer screening test:

- Read the information in this booklet as many times as you need to
- Speak to your family or friends
- Contact the doctors and nurses who are running this study. **You do not need to have made a decision before contacting us. We would be happy to have a discussion with you to help you decide.** (provide contact details)
- Speak to your GP or a specialist lymphoma nurse or doctor

- We have provided a worksheet on the last page of this booklet where you can write down the pros and cons that are important to you. You can also write down any questions that could would like to discuss.

How do I contact you?

If you have made a decision about the screening test or wish to discuss it, you can contact us by:

Phone: xxxxxx (times)

Email: .....

If you email or leave us a message we will get back to you within 48 hours (excluding weekends).

Information and Support

Where to find more information about the issues discussed in this booklet:
For more information about lung cancer:
https://www.cancerresearchuk.org/about-cancer/lung-cancer

For more information about lung cancer screening:
The Roy Castle Lung Cancer Foundation have produced a video about lung cancer screening. You can find it by going to YouTube and searching 'Roy Castle Lung Cancer Screening'. Because it is designed for people who have smoked, some of the figures are different to those in this leaflet.

To find out more about the late effects of treatment for Hodgkin lymphoma:
Lymphoma Action have produced a section on their website:
www.lymphoma-action.org.uk/about-lymphoma-side-effects-treatment/late-effects-lymphoma-treatment

We understand that thinking about cancer can upset people and cause anxiety. If you are feeling worried or anxious after reading this booklet, you can access support and counselling by:
Speaking to a lymphoma clinical nurse specialist who is helping run this study (details)

Contacting Lymphoma Action:
via their website http://lymphoma-action.org.uk
or their free helpline 0808 808 5555 Monday to Friday 10am-3pm
a live chat option is available via the 'Contact Us' section of the website
Speaking to your GP, or a specialist lymphoma nurse or doctor

Worksheet

Write down the pros of having a lung cancer screening test that are most important to you:

Write down the cons of having a lung cancer screening test that are most important to you:

Use the space to write down any questions you have about lung cancer screening

LUNG CANCER SCREENING PILOT (CHAPTER 5) STUDY PROTOCOL

Lung screening for Hodgkin lymphoma survivors: a feasibility study

Protocol version 2 dated 4/5/2021

IRAS number: 294837

Sponsors number: CFTSp204.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

Name: (please print):

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Sponsor	The Christie NHS Foundation Trust
Funder(s)	The Christie Charitable Fund: £168,833 The NIHR PSTRC Greater Manchester: £53,685 The NIHR Manchester Biomedical Research Centre: £9000 The Roy Castle Lung Cancer Foundation: £78327

Study summary

Long title	Lung screening for Hodgkin lymphoma survivors: a feasibility study
Short title	Lung screening in people cured of Hodgkin lymphoma
Design	A single arm study where Hodgkin lymphoma (HL) survivors are invited to have a lung cancer screening test (a low dose CT scan).
Participants	Survivors of HL who are in a long-term follow up programme at The Christie NHS Foundation Trust
Key Eligibility	5 year + survivors of Hodgkin lymphoma who have not had a diagnosis of lung cancer Current age 18-80 Received radiotherapy to the chest and / or an alkylating agent containing chemotherapy regimen known to increase lung cancer risk Living within approximately 40 miles of The Christie Hospital Do not have a current advanced cancer diagnosis or previous lung cancer diagnosis
Intervention	A lung cancer screening test (low dose CT scan)
Primary and secondary outcomes	Primary outcome To test the feasibility of inviting HL survivors to lung cancer screening Secondary outcomes To report the quality of the decision-making process and the decision

<table>
<tr><td></td><td>quality in HL survivors invited to screening
To report the proportions of those deemed to have made an informed decision about screening
To report the impact of information materials and undergoing screening on cancer worry, anxiety and health-related quality of life
To report intention to quit smoking rates in current smokers following lung cancer screening
The acceptability of undergoing lung cancer screening
To report the clinical findings in HL survivors who undergo lung cancer screening
The barriers and motivators to undergoing lung cancer screening

-</td></tr>
<tr><td>Sample size</td><td>All HL survivors meeting key eligibility criteria within the ADAPT database (estimated to be 217)</td></tr>
<tr><td>Study duration</td><td>20 months</td></tr>
<tr><td>Funding</td><td><table>
<tr><td>The Christie Lymphoma Research Fund</td><td>£168,833</td></tr>
<tr><td>The NIHR PSTRC Greater Manchester</td><td>£53,685</td></tr>
<tr><td>The NIHR Manchester BRC
The Roy Castle Lung Cancer Foundation</td><td>£2,880
£78,327</td></tr>
</table></td></tr>
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Background

Survival after Hodgkin lymphoma

Hodgkin lymphoma (HL) is a lymphoid malignancy of clonal B cells which has a bimodal incidence, with incidence peaks at the ages of 20-24 years and 80-84 in women and 25-29 and 75-79 in men.[1] Lymphomas are the commonest type of cancer diagnosed in young people and HL accounts for 68% of lymphomas in 15-24 year olds.[2] In the past 5 decades, advances in the treatment of HL have improved survival rates such that 5-year overall survival has increased from 86% in those treated in the 1970s, to 96% in those treated in the 2000s.[3] 10 year survival is around 90% in those diagnosed with HL between the aged of 15 and 34 and 76-85% for those diagnosed aged 35-59.[4] Late relapses are rare.

Key point: HL is a cancer with favourable survival rates meaning the majority of those diagnosed live to experience the late effects of treatment

Treatment for HL

Radiotherapy and chemotherapy, alone or in combination, are the key treatment modalities in HL. In around 2007, it became standard practice to deliver radiotherapy to involved nodes only (the involved field).[5,6] Prior to this, radiotherapy was delivered to large anatomical areas (the extended field) resulting in significant doses of radiation to the lungs when delivered above the diaphragm.[7,8] Multi-agent chemotherapy regimens containing alkylating agents are key treatment for HL. Table 1 below lists the alkylating agents commonly used to treat HL and the chemotherapy regimens containing them.[9]

Table 1

Alkylating agent[9]	Chemotherapy regimens (Acronyms)
Chlorambucil	ChlVPP ChlVPP-EVA
Dacarbazine	ABVD, MOPP-ABVD hybrid
Procarbazine	BEACOPP, MOPP, MVPP, MOPP-ABVD hybrid, ChlVPP, ChlVPP-EVA
Mechlorethamine	MOPP, MVPP, MOPP-ABVD hybrid
Lomustine	LOPP
Cyclophosphamide	BEACOPP, VAPEC-B
Cisplatin	EHAP, DHAP
Carmustine	BCNU

Melphalan	BEAM

Key point: Radiotherapy and alkylating-agent containing chemotherapy regimens have been standard of care treatments for HL for the last 5 decades. Both are known to increase lung cancer risk.

Second cancer risk after treatment for HL

Survivors of HL are at excess risk of developing a number of different second cancers and second cancers are the commonest cause of mortality in survivors.[10–12] Cancers of the respiratory tract, along with gastrointestinal cancers, are the commonest cause of death due to a second cancer (RR 8.8 for respiratory malignancy).[10] Studies have found a cumulative incidence of lung cancer in HL survivors of 5.1-8.1% in men and 3.8-4.3% in women, with the absolute excess risk of lung cancer increasing with time since treatment. [13,14]

Key point: Cancers of the respiratory tract are an important cause of long-term mortality in HL survivors

The impact of treatment and patient characteristics on lung cancer risk

Radiotherapy

Radiotherapy to the chest increases the risk of lung cancer and smaller radiation fields do not reduce this risk according to a meta-analysis. .[15]

A case control study, in which the majority of radiotherapy treatment was given to the extended field, found that radiotherapy alone at a dose of ≥5 Gy (to the lung tissue) was associated with a statistically significant increase of lung cancer in analyses that adjusted for smoking history. The relative risk of developing lung cancer increased with radiotherapy dose to the lung with statistical significance above 30 Gy. [16]

Chemotherapy

Alkylating-agent containing chemotherapy significantly increases the risk of lung cancer, in particular the regimens MOPP, MVPP and ChlVPP . There is no consensus as to whether Dacarbazine, the alkylating agent contained in the contemporary regimen 'ABVD', increases lung cancer risk.[16,17]

Radiotherapy alone, chemotherapy alone or combined modality

A meta-analysis of lung cancer risk in HL survivors has found that the relative risk of lung cancer increases incrementally according to treatment: chemotherapy alone (RR = 2.39, 95 %CI 1.60–3.55, radiotherapy alone (RR 4.88, 95 % CI, 3.14–7.60) and combined chemotherapy and radiotherapy (RR = 5.15 [95 % CI, 4.08–6.50).[18]

Smoking

Smoking is the most important risk factor for developing lung cancer in the general population. In HL survivors, a history of moderate-heavy smoking has a multiplicative effect on treatment related risk of lung cancer, demonstrated in Table 2, but light or never smokers are also at excess risk due to their treatment alone

Table 2 (adapted from [16])

Treatment for HL		Relative risk by smoking category (all p values <0.05)	
Radiation ≥ 5Gy	Alkylating agent	Non-smoker/light/other	Moderate/heavy smoker
No	No	1	6
Yes	No	7.2	20.2
No	Yes	4.3	16.8
Yes	Yes	7.2	49.1

Age at HL diagnosis and time since HL treatment

The median age for developing lung cancer after treatment for HL is 45 and the median time between completion of treatment and development of lung cancer is 11 years. [18] The

relative risk of developing lung cancer is highest for those treated age 15-24 and lowest in those treated over the age 55. Another systematic review found that with increasing age at treatment for HL, most studies show the SIR decreases but the AER increases, with the highest AER in those treated at age 45 years or older. [19] Other studies support this association between a higher risk of developing lung cancer in those treated for HL over the age of 45. [20,21]

The aforementioned meta-analysis found that relative risk for lung cancer increases with duration of follow-up, peaking at 10-14 years (RR 4.17). However, even 5-9 years after treatment relative risk is increased (RR 3.0).[18] In a population-based study, lung cancer cases in HL survivors who were 5-9 years out of treatment represented 15% and 22% of the total AER (of any second cancer at that time period) in male and female survivors respectively. This study found that AER increased with time since follow-up such that the AER for lung cancer at ≥30 years follow-up was 26 and 50 in female and male survivors respectively.[14]

Key points:

- Lung cancer risk is increased with chemotherapy and radiotherapy alone, but is increased when combined treatment modalities are used
- Whilst moderate-heavy smoking has a multiplicative effect on treatment related risk, there is an excess risk of lung cancer in light or never smokers.
- AER for lung cancer increases with time elapsed since treatment, but there is an excess risk as early as 5-9 years after treatment.

Lung cancer screening in ever smokers

In former or current smokers, screening for lung cancer with a thoracic low dose CT (LDCT) scan saves lives by diagnosing lung cancer at an early stage when asymptomatic. The first study to report a lung cancer mortality reduction was the National Lung Screening Trial in the United States which found a 20% reduction in lung cancer mortality.[22] Subsequent European studies have found that screening reduced lung cancer mortality by up to 39%.[23–25]

A number of lung cancer screening pilots are being rolled out in England. Former or current smokers are eligible for a LDCT scan if they meet risk thresholds determined by a lung cancer risk calculator.[26] Unfortunately, most HL survivors at risk of lung cancer will not be

eligible for screening in these pilots, because they are unlikely to meet the eligibility threshold as calculated by the risk calculators based on age, smoking history and other factors known to increase smoking risk in the general population. The majority of HL survivors are therefore unable to access lung cancer screening since there is no programme specifically targeting this group.

Rationale for this study

There is growing interest internationally in trialling lung cancer screening in HL survivors, with two small trials of LDCT underway in the US and Canada, as yet unreported.[27,28] Both trials are recruiting 5+ year survivors of Hodgkin lymphoma currently aged 18-80 who were treated with mediastinal irradiation and / or alkylating agent containing chemotherapy, and have a ≥10 pack year history of smoking to undergo lung cancer screening with a LDCT scan. There are multiple unanswered questions pertaining to the feasibility and impact of lung cancer screening in this group.

Interest and uptake rates

Of those who are eligible, it is not known what proportion of survivors will be interested in undergoing lung cancer screening or what the uptake rates will be. The uptake rates in lung cancer screening pilots to date has been suboptimal; in the Manchester Lung Health check pilot, 26% of those invited attending for the lung health check.[29] Data on uptake of cancer screening tests by HL survivors is scanty. Two studies have reported the percentage of survivors who had not undergone screening for breast cancer (44% and 32%), cervical cancer (32% and 19%) and colorectal cancer (77% and 62%).[30,31] This study will investigate uptake rates in order to inform the feasibility and methods used in future lung cancer screening studies for HL survivors.

Provision of information to allow HL survivors to make an informed choice about lung cancer screening

Since lung cancer screening is not widely available to the general population, or indeed HL survivors, it is expected that HL survivors lack awareness of the processes and issues - including risks and benefits – associated with a lung cancer screening test. We have found in a prior study (as yet unpublished as forms part of Dr Rachel Broadbents' ongoing PhD

programme), that HL survivors often perceive themselves to be at low risk of lung cancer and lack knowledge about the lung cancer risk associated with chemotherapy and radiotherapy. Furthermore, in this study some survivors believed that all cancer screening was beneficial. A lung cancer screening programme involves exposing an asymptomatic population to significant risks. Namely, risks associated with the screening test (radiation), exposure to invasive investigations required to rule out cancer after a false positive result, additional radiation from further LDCT scans for nodule surveillance, surgery and toxic treatments which may not have been required in the case of over-diagnosis and the psychological impact of the screening process. Providing individuals with the information required to make an informed choice regarding a screening test is considered ethically imperative. This is particularly important in the context of screening because screening programmes (as opposed to trials of cancer screening) do not require participants to provide written consent.[32] To address HL survivors' knowledge gap and explain the rationale for a lung cancer screening invitation, we have developed a decision aid for HL survivors who are invited to undergo a lung cancer screening test which will be tested in this study. In this study, decision making outcomes will be tested using validated scales.

Clinical findings

A low dose CT scan detects pulmonary nodules which may require further assessment to rule out lung cancer, but there is a significant risk of a false positive result. Lung cancer screening pilots for ever smokers have reported false positive rates of 14-25%. [33,34] The majority of false positive results require one or more LDCT scans to monitor nodules, but a small number of individuals may require a biopsy to rule out lung cancer. As a result of their prior cancer treatment, particularly radiotherapy, HL survivors could have clinically significant incidental findings on LDCT such as coronary calcification, pulmonary scarring and thyroid nodules.[35,36] In this study we will report on the proportion of positive, indeterminate and negative scans as well as clinically significant incidental findings requiring further investigation or referral.

Psychological impact

Several studies have identified HL survivors as being more likely to experience significant psychological symptoms compared to their peers without a prior cancer diagnosis.[37–39] An

invitation to undergo cancer screening is likely to provoke short-term anxiety based on studies of the psychological impact of cancer screening.[40–42] It is important to understand the psychological impact of an invitation to lung cancer screening and undergoing the screening test in HL survivors who were unlikely to be aware of their excess risk of lung cancer.

Impact on smoking cessation

In lung cancer screening trials for ever smokers, a lung cancer screening test has been identified as a teachable moment and an important opportunity to offer advice and help with smoking cessation.[43] There is scant evidence on the proportion of HL survivors who are current smokers but it is important to understand the impact of a screening invitation on rates of smoking cessation in these individuals.

Acceptability of undergoing lung cancer screening

According to criteria for appraising screening programmes published by Public Health England, each aspect of a screening programme 'should be acceptable to the target population'. [44] A Theoretical Framework of Acceptability has recently been developed, providing a framework of the theoretical constructs which should be investigated in those undergoing a healthcare intervention.[45]

Barriers and facilitators to undergoing lung cancer screening

The factors influencing uptake of cancer screening tests have been investigated across many cancer screening tests, although to a lesser degree in lung cancer screening due to its recent development and never in HL survivors. Sociodemographic factors such as age, gender, ethnicity and socioeconomic status influence uptake of cancer screening tests. In particular, non-white ethnicity and lower socioeconomic status are associated with lower uptake across a number of different cancer screening programmes. [46] In addition, there are both intrapersonal and interpersonal factors which affect uptake. Intrapersonal factors shown to be associated with higher uptake rates of cancer screening tests include better knowledge (of cancer risk and the benefits of screening) and positive attitudes towards screening. On the other hand, those with more fatalistic attitudes towards cancer are less likely to attend for screening.[46] Risk perception, whether deliberative, affective or intuitive, has been shown

to be associated with greater uptake of cancer screening tests, although there is contradictory evidence with regards to its' effect on lung cancer screening uptake.[47,48] Interpersonal factors shown to impact uptake include perceived norms, a recommendation from a healthcare professional and environmental resources (or constraints).[46] A number of health behavioural theories have been shown to predict and explain cancer screening uptake by analysing the factors described above, but resulting behaviour change interventions have often been unsuccessful. The behaviour change wheel (BCW) was developed to address this challenge. The BCW incorporates the constructs from multiple health behavioural theories in a hub of conditions (capability, opportunity, motivation) around which are positioned interventions to address deficits in these conditions.[49] The BCW can therefore be used to investigate the barriers and motivations to performing a behaviour such as undergoing a cancer screening test and develop interventions to change that behaviour (ie. improve uptake)

Study aim, outcome and objectives

The aim of this study is to test the feasibility of lung cancer screening in HL survivors.

Table 3 below shows the study outcomes and linked objectives.

Table 3

Primary outcome	Linked objectives
To test the feasibility of inviting HL survivors to lung cancer screening	The proportion of those invited who are interested in undergoing a screening test and actual lung cancer screening test uptake

Secondary outcomes	
To report the quality of the decision-making process and the decision quality in HL survivors invited to screening	Responses to scales measuring quality of decision-making quality and decision quality (Decisional Conflict Scale, Knowledge Scale, Preparedness for Informed Decision Making).
To report the proportions of those deemed to have made an informed decision about screening	The proportion who have made an informed decision as measured by the Multidimensional Measure of Informed Choice
To report the impact of information materials and undergoing screening on cancer worry, anxiety and health-related quality of life	Responses to scales measuring anxiety, cancer worry and health related quality of life measured at several timepoints
To report intention to quit smoking rates in current smokers following lung cancer screening	Proportion of current smokers reporting intention to quit smoking before and after receipt of the invitation materials +/- undergoing screening
The acceptability of undergoing lung cancer screening	Responses to questionnaire items informed by the Theoretical Framework of Acceptability
To report the clinical findings in HL survivors who undergo lung cancer screening	• The proportion with negative, indeterminate or positive screening scans • The proportion requiring further LDCT for nodule surveillance and clinical outcome

	• The number and type of lung cancer diagnosed and subsequent treatments received • Clinically significant incidental findings : proportion affected and degree of a) coronary artery calcification or valvular calcification and b) any other clinically significant incidental findings
The barriers and facilitators to undergoing lung cancer screening	• The barriers and facilitators associated with uptake, or non-uptake, of the lung cancer screening test
To use saliva samples to analyse the prevalence of single nucleotide polymorphisms associated with lung or radiation induced cancers	• Prevalence of single nucleotide polymorphisms which may be associated with lung cancer risk

Study design

A single arm feasibility study in which HL survivors registered in a long term distanced follow up programme – known as ADAPT- at The Christie NHS Foundation Trust are invited to undergo lung cancer screening with low-dose CT scan/s. The invitation they receive upon expression of interest contains a decision aid which has been developed by a steering group of clinical experts and HL survivors and has been tested for usability and acceptability by HL survivors.

Eligibility

Inclusion criteria:

1. Aged 18-80
2. 5 year or more survivor of HL

3. Any of: a) treated with radiotherapy for HL with radiation dose to the lung b) an alkylating agent containing chemotherapy regimen known to increase lung cancer risk
4. Living within approximately 40 miles of The Christie Hospital

Exclusion criteria

1. Previous diagnoses of malignant neoplasm of trachea, bronchus, lung, thymus or pleura
2. A current diagnosis of metastatic cancer
3. Residents in nursing homes or housebound
4. Had a CT scan of the thorax within the last 12 months
5. Pregnant women
6. Unable to provide consent

Recruitment

Identification of potential participants:

Potential participants are identified from the ADAPT database. This is a prospectively maintained database of lymphoma patients treated at The Christie Hospital who have not relapsed in the 5 years since completion of treatment.

The inclusion criteria reflect the need to select HL survivors who:

a) are at excess risk for lung cancer due to their prior treatment (as not all the HL survivors in the database have received chest radiotherapy or an alkylating agent known to increase lung cancer risk)

b) have reached a time since completion of treatment where excess risk of lung cancer has been demonstrated

c) could reasonably travel to the Christie for the screening scan (as this is a long-term follow-up database, some individuals in the database no longer live in Greater Manchester or surrounding areas.)

Inclusion criteria are checked against hospital medical records. Vital status, contact details and GP details are checked through NHS Spine no longer than 6 weeks before the invitation letter is sent. Individuals who appear to meet the eligibility criteria are sent a

letter of invitation to the study. Those who respond and indicate they are interested in participating in the study are sent the Participant Information Sheet and Decision aid. Individuals who do not respond to the initial invitation are telephoned 2 weeks after the study invitation was sent.

Potential participants who were sent the PIS and decision aid who are interested in taking part in the study are invited to an appointment with the study team at The Christie Hospital.

Study visit

At the study visit, there will be:

A full eligibility check

- Opportunity to ask questions about the study
- Eligible participants who wish to be screened will sign a written consent form
- A questionnaire to collect data on lung cancer risk factors and respiratory symptoms[a]
- Current smokers will be offered a referral to a smoking cessation service at The Christie or local to them
- The option of providing a saliva sample for the genomic study
- Following the meeting with the study team, consented patients will undergo a low dose CT scan of the thorax on the same day where possible. This will have been provisionally booked in advance.

[a]If the individual presents to their meeting with the trial team with symptoms of advanced cancer then they would not be recruited to the study but would be managed via a standard clinical diagnostic pathway which would be initiated by trial team member to avoid delay.

- Patients with a negative scan do not require any additional LDCT scans but remain in the study until 14 months following their baseline scan
- A finding of an indeterminate pulmonary nodule will trigger a request for a further LDCT for surveillance in 3 months, which is incorporated in this study protocol. Patients who require additional scans for surveillance of pulmonary nodules will be referred back to an NHS clinical service where surveillance would be considered a standard of care for a patient with a pulmonary nodule.
- Patients with a positive scan are referred urgently to an NHS lung cancer service.

Table 4 below details the management and associated communications for possible scan findings.

Table 4: Scan findings, action and associated communication

Scan Outcome: Definition	Action: *Reason*	Communication
Negative: No nodules OR Nodule/s <80mm3 or <5mm max. diameter	No further LDCT scan arranged. *No action required*	Phone call to participant which is followed by a letter GP letter communicating result with copy of the CT report
Indeterminate: 1st scan: Nodule/s ≥80 to <300mm3 OR	Nodule surveillance: *indeterminate nodule requiring surveillance** *this protocol covers 3 month interval	Indeterminate nodules requiring a second opinion will be referred through the thoracic radiology MDT at Wythenshawe Hospital

≥6mm and <8mm max. Diam. (if volumetry not possible) OR ≥300mm3 or ≥8mm max. diam. and Brock risk <10%	scans only, for further surveillance a referral is made to local NHS chest clinic **for any further interval scans a referral is made to local NHS chest clinic	Phone call to participant which is followed by a letter: • Letter explains presence of nodule(s), need for surveillance, date (approx.) of repeat scan, who will be organising the repeat scan • If participant is current smoker, letter includes smoking cessation advice and signposting • Information leaflet about pulmonary nodules included GP letter communicating result and explaining presence of nodule(s), need for surveillance, approximate date of repeat scan and how the scan is to be organised and with copy of the CT report
Positive: 1st scan: ≥300mm3 or	Suspected lung cancer: CI makes referral to Fast Track Lung Cancer Clinic at patients local hospital	Participant invited to face to face appointment at The Christie where they will be

<table>
<tr>
<td>≥8mm max. diam. and Brock risk ≥10%

New nodule seen on an interval scan: ≥300mm3 or ≥8mm max. diam.</td>
<td>within 5 days of scan report

Abnormality requiring immediate further investigation for possible lung cancer</td>
<td>given the results

Follow-up telephone call by clinical nurse specialist within 5 days to offer support

GP informed of the outcome and action plan by letter (urgent) with copy of the CT report</td>
</tr>
<tr>
<td>Incidental finding:

Life-threatening; mandating urgent referral; findings indicative of cancer at another site; non-cancer findings requiring referral to secondary care; other non-urgent assessment</td>
<td>
<table>
<tr><th>Category</th><th>Action</th></tr>
<tr><td>Life-threatening</td><td>Radiographer/radiologist contacts on-call registrar to arrange hospital admission</td></tr>
<tr><td>Mandating urgent referral</td><td>Radiographer/radiologist contacts CI on same day, CI arranges urgent referral</td></tr>
<tr><td>Findings indicative of cancer at another site</td><td>CI makes referral to appropriate Fast Track Cancer Clinic at patients local hospital</td></tr>
<tr><td>Non-cancer requiring secondary care</td><td>Appropriate referral/request made to GP by CI</td></tr>
</table>
</td>
<td>Urgent referrals will be made by telephone by the chief investigator which will concurrently be discussed with the participant by phone. The GP will be informed by letter.

Fast track cancer referrals: Participant invited to face to face appointment at The Christie where they will be given the results .
Follow-up telephone call by clinical nurse specialist within 5 days to offer support
GP informed of the outcome and action plan by letter (urgent) with copy of the CT</td>
</tr>
</table>

<table>
<tr>
<td>needed; non clinically significant.</td>
<td>
<table>
<tr><td>referral</td><td rowspan="2"></td></tr>
<tr><td>Other non-urgent assessment required</td></tr>
<tr><td>Non clinically significant</td><td>Should not be recorded or reported to participant/GP</td></tr>
</table>
</td>
<td>report

Non-urgent secondary care referrals: Participant informed by letter, GP informed by letter with copy of the CT report

Other non-urgent assessments: GP and patient informed by letter with copy of the CT report</td>
</tr>
</table>

Study questionnaires and follow-up

Study questionnaires:

Questionnaires are administered throughout the study to measure a variety of patient reported outcomes relating to the decision aid and the experience of being screened. The timing of the questionnaires and the measures within them are described in the schedule of events table (Table 5).

Questionnaires administered prior to study visit:

1. The baseline questionnaire is sent to the potential participant with the study invitation letter, with a request that if they are interested receiving more information about the study, they complete the baseline questionnaire prior to being sent the decision aid and participant information sheet. If the potential participant does not wish to receive further information about the study they may ignore the questionnaire enclosed in the invitation letter

2. A further questionnaire is sent with the participant information sheet and decision aid, which the individual is asked to complete regardless of their decision to undergo screening or not.

The potential participant provides written consent for the researchers to keep these questionnaire data for the purposes of the study, regardless of their future decision about participating in the screening aspect of the study. The rationale for delivering the questionnaires prior to the study visit is to:

- compare lung cancer screening related knowledge pre and post exposure to the decision aid
- Gather baseline data on anxiety, cancer worry and health related quality of life prior to the receipt of any lung cancer screening informational material
- Gather information on measures relating to decision making in those who do and do not wish to undergo screening.

Subsequent questionnaires:

- Study visit questionnaire: Individuals who attend the study visit are asked to complete a questionnaire with measures relating to cancer worry and anxiety.
- Postal questionnaires at 2, 6 and 12 months following baseline LDCT scan

Follow up

For clinical management of scan findings see 'Management following baseline CT scan'. In addition to study questionnaires, participants are followed up at 6 and 14 months by telephone to gather information on any investigations and resulting diagnoses that took place outside of the study protocol but as a result of having the baseline or 3 month study scan.

In addition, researchers will access regional PACS systems to access reports of additional surveillance scans that the patient received as a result of their study scan but outside of the study protocol (through referral to an NHS clinical service for standard of care management).

Provision of information and support to those invited to the study

This study examines the impact of the decision aid on levels of anxiety and cancer worry and on lung cancer screening related knowledge. Whilst we endeavour to provide information and support to those who seek it via our trial team and lymphoma clinical nurse specialists, we aim to minimise variation in levels of information provided, whilst psychological support will be tailored to the individuals need. To minimise the impact of additional information or support on study outcomes:

1) We will, at any stage of the study where participants seek information, reiterate the information that is provided within the decision aid or refer them to the additional sources of information which are listed in the decision aid.
2) Our clinical nurse specialists will refer to the information provided in the decision aid to answer participants queries about lung cancer risk, or the risks or benefits of screening. Appropriate psychological support tailored to individuals needs will be provided to those who seek it.
3) It is mandated within the protocol that participants who have a positive scan showing a possible lung cancer are contacted by our clinical nurse specialists by phone within 5 days of being told the scan result. Other than this, participants may request information/support from the clinical nurse specialists or trial team at any time.

Interviews

This is a qualitative interview component to explore barriers and facilitators to lung cancer screening in people who decided to be screened as well as those who opted not to be screened after reading the decision aid. The findings will inform a future approach to lung screening in this population.

Eligibility

Inclusion criteria:

Individuals who received the decision aid and consented to be contacted about the interview component

Exclusion criteria:

Individuals who responded after receiving the decision aid but indicated that they did not wish to be contacted further for this research

Individuals who did not respond to the initial study invitation, or following receipt of the decision aid

Sampling and sample size

We will purposively sample two groups of individuals who agreed to be sent the study information: 1) those who responded wishing to be screened 2) those who responded not wishing to be screened.

Within each group we stratify as follows to select a cohort to invite to interview:

1) Gender: Male: female 50:50
2) Current age: 20-50: 51-80, 50:50

The maximum sample size is 34 (17 individuals in each group). This is in keeping with research showing that between 10 and 17 interviews are required to reach data saturation in theory based interviews.[52] We anticipate that fewer individuals who did *not* wish to be screened will respond to the invitation to interview, compared to those who did wish to be screened. Therefore we will invite 34 individuals who wished to be screened to interview, and 51 individuals who did not wish to be screened to interview. If there are fewer than 51 who did not wish to be screened, we will invite approximately 50% more individuals who did not wish to be screened, than those who did wish to be screened. The invitation to participate in this sub-study will be sent around 4 weeks after the study information pack was sent, since we anticipate having had a response from the majority by this point.

Consent

Participants will provide written consent prior to the interview. There will be the option of completing this consent form on paper and posting it back to the researcher in a pre-paid envelope, or completing the same form online using a survey tool (the online consent form will mirror the content of the paper consent form)

Study activity

A semi-structured interview will take place either over the phone or using Zoom teleconferencing with the participant. The interview schedule will be informed by the capability, opportunity and motivation components of the behaviour change wheel.[53] The interview will last approximately 20 minutes.

Compensation

Participants will be provided with a high-street store £30 voucher following participation.

Data analysis

The interview will be audio-recorded and transcribed by Dr Rachel Broadbent or by an external transcribing company (1st class transcriptions). The first 10 interviews in each group will be analysed using inductive thematic analysis.[54] The themes that are identified will subsequently be deductively analysed using the Theoretical Domains Framework components. [55] If data saturation has not been reached after 10 interviews, a further 3 interviews will take place. If data saturation is reached, no further interviews will take place. If it has not, a maximum of 17 interviews in each group will take place.

Table 5: Schedule of events

Timepoint / Activity	Study invitation	Study documents to interested individuals	Study visit	2 months after baseline LDCT scan	6 months after baseline LDCT scan	12 months after baseline LDCT scan	14 months after baseline LDCT scan
SF-12 scale	X				X	X	
Knowledge scale	X	X					
Attitude to lung cancer screening measure		X					
DCS		X					
PDMS items		X					
Cancer worry measure	X		X	X	X	X	
STAI-6 Anxiety scale	X		X	X	X	X	

Acceptability items				X			
Intention to quit smoking measure					X	X	
PIS		X					
Decision aid		X					
Eligibility check			X				
Consent			X				
Lung cancer risk factors assessment			X				
Low dose CT scan			X				
3 month surveillance LDCT scan	For participants with an indeterminate nodule on their baseline LDCT scan a 3 month LDCT scan will be arranged.						
Provision of saliva sample (optional)			X				

Telephone follow up					X		X
Invitation to interview (selected individuals only)	Invitation to interview for selected individuals sent within 3 months of decision regarding screening. Consent and interview may take place at any time within the 3 months following invitation to interview.						
Consent (interview)							
Interview							

PIS: Participant information sheet, DCS: decisional conflict scale, PDMS: items from the preparation for decision making scale

Consent

Consent for baseline questionnaire data to be used in the study prior to full written consent:

As discussed in the 'Study Questionnaires' section, potential participants who are interested in the study are asked to complete the baseline questionnaire upon invitation to the study. They will be asked to consent to the researchers keeping this information for the study regardless of future participation.

2nd stage: At the study visit, written informed consent is obtained covering all other study activities.

Interviews

Potential participants who are sent the decision aid and PIS are given the option to consent **to being contacted** about the interview component of the study. They may provide this consent by completing statement in the questionnaire, or verbally over the phone or by email. Individuals who agree to be interviewed will provide written consent on a separate consent form covering only this aspect of the study.

Low dose CT scan

Following the appointment, the participant will have a LDCT of the thorax at The Christie NHS Foundation Trust.

CT Image Acquisition Protocol

Preparation: No cannula required

Scan

- Positioning- supine, feet towards scanner
- Centring point-chin
- PA Topogram
- Care kV is on

- Quality Reference mAs is set at 20
- SAFIRE is set at 3 for all reconstructions

Table 5: Protocol for LDCT

Region	Slice th.	Slice int.	Detectors	Pitch	Ref kV	Reconstructions (to GE PACS unless otherwise stated)
Thorax Lung apex to lung bases to	3mm	3mm	0.6mm	1.2	120	1. 3mm/3mm I30 med.smooth/ mediastinall windows 2. 3mm/3mm I70f/ very sharp/ lung windows 3. 1mm/0.7mm I70f/very sharp/ lung windows 4. MIPs 5mm/2mm axial I70fu sharp AS, lung windows 5. 3mm/3mm sagittal and coronal I30 mediastinal

						windows

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

Methodology for CT scan reading and reporting

Volumetry software

Volumetric software will be used for assessment of pulmonary nodules and should remain constant to allow accurate comparison of volumes. Software updates will be recorded. Volumetric software will be directly or indirectly integrated into PACS systems, capable of automated image retrieval of historical imaging.

Reporting

The CT scans will be reported by a consultant radiologists with experience in thoracic imaging. Reporting radiologists will access the scan through PACS systems to generate a protocolled report. Findings on CT scans relating to lung nodules will be categorised according to one of the 4 categories detailed below:

- Negative = normal scan, or abnormal scan but does not require any further investigation or intervention.
- Indeterminate = indeterminate pulmonary nodule(s) needing surveillance.
- Positive = finding(s) concerning for lung cancer - requires immediate investigation.
- Incidental = other finding(s) that requires clinical review.

Reporting of pulmonary nodules will follow the British Thoracic Society Guidelines.[50]

Pulmonary nodule definitions

Pulmonary nodules are defined as: Focal, rounded opacity ≤3 cm diameter, mostly surrounded by aerated lung, including contact with pleura, but without potentially related abnormalities in the thorax. Nodules are categorised according to the following definitions:

- Solid nodule
- Sub-solid nodule (SSN)
    - Pure ground glass opacification (pGGO): A focal ground-glass opacity ≤3 cm diameter that does not obscure vascular pattern.
    - Part solid nodule (PSN): A focal opacity that has both solid and ground-glass component ≤3 cm diameter.

        - The solid component is defined as: the part of a nodule that obscures the underlying bronchovascular structure.
        - Ground glass component is defined as opacification that is greater than that of the background but through which the underlying vascular structure is visible. All nodules will be measured using volumetry.

Reporting coronary artery, aortic valve and other calcification

Presence of coronary artery calcification and valvular calcification will be recorded by the reporting radiologist in accordance with guidelines produced by the British Society of Cardiovascular Imaging/British Society of Cardiac Computed Tomography and British Society of Thoracic Imaging.[51]

- Coronary artery calcification should be reported using simple visual quantification if present as none, mild, moderate or severe.
    - Its presence should prompt the following text in the report: "Mild/Moderate/Severe coronary artery calcification, indicating the presence of coronary artery disease. If the patient has associated symptoms recommend management as per chest pain guidelines (eg. NICE CG95, SIGN 151). If the patient is asymptomatic consider

reviewing modifiable cardiovascular risk factors and managing as per guidelines for primary prevention (eg NICE CG 181).

- Aortic valve calcification should be reported using simple visual quantification if present as moderate or severe.
    - If aortic valve calcification is identified, the diameter of the aortic root and ascending thoracic aorta should also be reviewed
    - Presence of moderate or severe aortic stenosis should prompt the following in the text report: “Moderate/Severe aortic valve calcification. This may indicate the presence of aortic valve stenosis. Consider echocardiography if clinically appropriate.”
- Mitral or annular calcification, or myocardial or pericardial calcifications should be identified and reported.

Genomic sub-study

Aim

To explore the prevalence of single nucleotide polymorphisms associated with lung cancer in HL survivors invited to a lung cancer screening study

Methodology

Sample collection and storage

Saliva samples will be collected from consenting individuals during their study visit. The samples will be stored temporarily in the MCRC (Manchester Cancer Research Centre) Biobank until approximately April 2022, when they will be transferred to a laboratory at St. Mary’s Hospital for genomic analysis. If there is saliva remaining after analysis which could be suitable for further research, samples will be transferred back to the MCRC Biobank for storage for future research.

Analysis

DNA will be extracted from saliva samples and analysed for the presence of single-nucleotide polymorphisms which are associated with lung cancer in the general population and radiation induced cancers in the general population. An agnostic polygenic risk score (PRS) will be generated by multiplying the per allele odds ratios normalised around 1.0. The PRS will be assessed for its predictive value of developing lung cancer.

Consent

Participants will consent to the storage and analysis of their saliva samples for this study as well as future ethically approved research projects. This consent process is incorporated into the main study consent form as an optional component.

Safety

A pragmatic approach to safety evaluation and reporting will be adopted. LDCT scanning is a well-established technology, and established risk-management procedures for scans will be followed. There are no expected adverse events relating to the scan.

The other study investigations do not have the potential to cause physical harm.

Untoward events that may occur later in the patient pathway if a nodule is discovered (e.g. bleeding following a biopsy) will NOT be considered an AE or SAE, and will be dealt with according to local practice in the treating centre.

Adverse event surveillance, evaluation and reporting in this study is limited **only** to adverse events meeting the criteria for 'seriousness' detailed below, which occur while the patient is at the pre-scan appointment and/or which occur as a result of scanning. The following definitions will be used:

Adverse Event: Any untoward medical occurrence in a participant who has undergone a
research procedure, including occurrences which are not necessarily caused by or related to
that procedure.

Serious Adverse Event: an adverse event which:

• Results in death

• Is life-threatening* (subject at immediate risk of death)

• Requires in-patient hospitalisation or prolongation of existing hospitalisation**

• Results in persistent or significant disability or incapacity, or

• Consists of a congenital anomaly or birth defect

• Other important medical events***

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

All SAEs noted by study personnel, or self-reported to study personnel by participants during their time in the hospital (appointment and/or scan) or immediately after, should be reported to the Chief Investigator within 24 hours of becoming aware of the event. Events should also be reported to the Sponsor within 24 hours of becoming aware using the following email address: the-christie.safety@nhs.net

Reported SAEs will be reviewed within 24 hours of being received and clinical causality will be completed.

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.

Oversight of safety

Safety will be managed in accordance with the Sponsor's SOP SPON 011.000 Safety Reporting in Non-CTIMPs.

Information on all SAEs will be summarised for trial oversight committee, the Annual Progress Reports to the REC and for other progress reports (e.g. funder), as required.

Statistical considerations

Sample size

This is a pilot study and our sample size reflects the cohort in follow-up at our centre who fulfil the eligibility criteria. As such power calculations to achieve the study outcomes are not appropriate. Having applied the inclusion criteria to our ADAPT database, we estimate that approximately 217 HL survivors will be invited to take part in the study.

Analysis

Simple descriptive analyses will be used to present:

- The proportion and characteristics of our survivor cohort who were eligible for the study
- The proportion and characteristics of those who express interest in participating, decline participation or do not respond (or are not contactable)
- The proportion and characteristics of those who are screened
- Clinical scan findings
- The reasons given for non-participation

- Results of the decisional conflict scale and preparedness for decision making scale items
- The proportions considered to have made an informed or uninformed decision

Statistical tests

1) To assess the impact of receiving the decision aid on anxiety levels and cancer worry, results of the anxiety scale and cancer worry scale will be analysed using the paired t-test:
    - Baseline compared to the study visit
2) To assess the impact of undergoing screening on anxiety levels and cancer worry, results of the anxiety scale and cancer worry scale will be analysed using the paired t-test in all participants who underwent screening
    - Baseline, compared to 2 months, 6 months and 12 months
3) To assess the impact of the decision aid on knowledge, the results of the knowledge scale will be analysed using the paired t-test
    - Baseline and approximately 4 weeks after receiving it (or study visit)

Ethical and regulatory considerations

Recruitment

In order to test the impact of the decision aid intervention, which is embedded within study information material, it is important not to provide information about lung cancer screening upon initial invitation that could bias the study results. However, we have taken into account that some individuals may not wish to participate in the study even before reading the materials. The purpose of the initial study invitation, is to ensure that we do not send the information to individuals who do not wish to consider participating.

Consent

The main study consent form completed at the study visit covers all the study activities from the study visit onwards. Some individuals may decide not to undergo screening after reading the decision aid in which case they would not

attend the hospital for the study visit and will not sign the main consent form. However, they may complete the baseline questionnaire and questionnaire delivered with the decision aid and PIS. They are asked to provide consent to the questionnaire data being used for the study by signing a consent statement incorporated within the questionnaire to cover this aspect only.

A separate written consent is obtained for the interview study as described above.

Assessment and management of risk

Risks and benefits

Taking part in a lung cancer screening is associated with potential benefits and harms. The potential benefits to patients taking part in this study are the potential for an early diagnosis of lung cancer making a cure more likely and the potential for reassurance through a clear screening result. The potential harms (radiation, interventions to rule out or diagnose lung cancer, worry/anxiety) are listed in the decision aid and participants will be given an opportunity to discuss risks and benefits prior to being screened. Thus at the point of consent, every effort will be made to ensure that participants are fully informed of the risks and benefits.

Potential for psychological distress

An invitation to be tested for a serious illness such as lung cancer has the potential to distress HL survivors who are invited to participate in the study. The decision aid to be used in the study has been developed in collaboration with HL survivors and tested for acceptability and usability by HL survivors in a separate research study. All individuals invited to this study are under long-term follow up with the clinical team at the Christie Hospital and have access to psychological support from trained clinical nurse specialists who are aware of the nature of this study. This ongoing relationship should help mitigate potential distress through the relationships that have already been established.

Furthermore, individuals who opt to participate will be regularly signposted to ways of accessing psychological support during the study. At the study visit, they will have the opportunity to discuss any concerns with a lymphoma speciality doctor, a clinical trial nurse and clinical nurse specialist.

Throughout the study, the principles outlined in the UK framework for health and social care research will be followed. In particular: the safety of participants, respect for the autonomy of potential and actual research participants, the study will be guided by scientifically sound and ethically sound principles.

Research Ethics Committee (REC)

- Before the start of the study, a favourable opinion will be sought from a REC for the study protocol and associated study documents.
- Any substantial amendments will only by implemented following NHS REC review

The Chief investigator will notify the REC when the study ends and take responsibility for submitted the Annual Progress Reports and Clinical Study Report (final report) within the required timeframes

Radiation Assurance

Prior to a submission to the REC, radiation assurance will be sought.

Regulatory Review & Compliance

Amendments

Any changes in research activity will be reviewed and approved by the Chief Investigator and Sponsor and submitted in writing to the appropriate REC, the Health Research Authority and local R&D for approval prior to enrolment into an amended protocol.

Protocol compliance

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 patient. 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 CI 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.

Peer review and PPI involvement

Peer review

- The design of the larger research project was given an overall favourable review at the NIHR Lung CSG meeting in 2019.
- The study was developed with the support and endorsement of the NIHR Screening, Prevention and Early Detection (SPED) advisory group (chaired by David Baldwin) and the NCRI Lymphoma Clinical Studies Group
- This study has received a grant award from The Roy Castle Lung Cancer Foundation through a competitive application process which incorporated expert peer review.

Public and patient involvement in the study materials

- The decision aid was reviewed by a steering group consisting of HL survivors, clinicians and other experts. Feedback from the steering group informed the decision aid content. The decision aid is currently undergoing testing for acceptability and usability in HL survivors in a study sponsored by the University of Manchester(Ref: 2021-10619-17592)

Data management

All databases will be electronic and password protected and stored on NHS computers which require and username and password to access.

A database of potentially eligible participants and their details obtained through the NHS Spine check will be maintained and stored on password protected NHS computers.

Data collected following initial invitation will be stored as follows:

- For individuals not wishing to take part, their gender and age will be recorded against any reasons given for not wishing to participate and stored anonymously, and separate to any further study data.
- A separate database will be maintained containing study data for participating individuals who consent to the study

Consent forms and paper questionnaires will be stored securely on hospital premises.

Access to study data will only be made available to study personnel who require it.

Data protection and patient confidentiality

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC.

Any personal data recorded will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain including in resulting publications.

The sponsor and investigators will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. The Investigator and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.

Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

All Investigators and trial site staff involved with the trial must comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The paper questionnaires will be stored securely. Computers used to collate the data will have limited access measures via user names and passwords.

Access to the final study dataset

The chief investigator and co-investigators will have access to the final dataset.

Withdrawal of data or consent

Consented patients wishing to withdraw from the study will be able to do so at any time. If a participant asks to withdraw from the study, either before or after the LDCT screen, researchers will ask if the participant is willing to share their reason for withdrawing, although it will be made clear to the participant that they are not required to share this information if they do not wish. If a participant withdraws from the study, their data which has already been collected will no longer be used and no further data will be collected from their medical notes for the purposes of the study.

Mental Capacity

A person may lose mental capacity from the point of their initial consent to the study. This may be identified through participant or participants representative contacting the study team. Any participant who loses mental capacity will be withdrawn from the study from the time at which the incapacity is identified.

Indemnity

The sponsor, The Christie NHS Foundation Trust, takes full responsibility for insurance and indemnity. As the sponsor is an NHS organisation the NHS indemnity scheme will apply.

Dissemination policy

The main trial results will be published in a peer-reviewed journal on behalf of all collaborators. The PhD student and Chief Investigator, Dr Rachel Broadbent, will prepare the manuscript as first author. All contributing parties and funders will be acknowledged in the publication.

In keeping with the policy of the NIHR PSTRC, any publications resulting from the study, which is part of a PhD project, will be published in open-access journals.

Those who have made contributions to the study design or made significant contributions to the manuscript will be eligible for authorship on any resulting manuscripts.

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

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LUNG CANCER SCREENING PILOT (CHAPTER 5) LETTER OF INVITATION

The Christie NHS
NHS Foundation Trust

Manchester Lymphoma Group

Department of Medical Oncology

The Christie NHS Foundation Trust

Wilmslow Road

Withington

Manchester

M20 4BX

Date

Patient name

Patient address

Dear Mr/Mrs/Ms

We invite you to take part in a study:

Lung screening in people cured of Hodgkin lymphoma

We are writing to you because people treated for Hodgkin lymphoma are at increased risk of getting lung cancer. This is because of the chemotherapy and radiotherapy used to treat Hodgkin lymphoma.

We invite you to consider having a lung cancer screening test as part of a study we are running at The Christie. This study is being done as part of a PhD project.

The screening test is a CT scan (CAT scan) of your chest. A CT scan involves lying on a bed which slides through the scanner (which looks like a thick ring).

To take part in the study you **must:**

- Be aged 18-80 years old
- Be able to travel to The Christie Hospital for the study

You **cannot** take part if:

- You have ever been diagnosed with lung cancer

- You have had a CT scan of your chest within the last 12 months
- Live in a nursing home
- You are pregnant
- You have a current diagnosis of cancer (if your cancer has been fully removed with surgery or another treatment you may be able to take part)

What to do if you are interested in taking part in the study:

If you think you are eligible and are interested in taking part in the study, please contact us using the details at the end of this letter.

After you contact us we will send you a Participant Information Sheet and a booklet to help you decide whether to have the test. After reading the information, you can contact us to tell us whether you wish to take part in the study.

Enclosed study questionnaire

If you are interested in taking part, please complete the enclosed questionnaire and return it to us in the envelope provided. The questionnaire is part of the study. Completing the questionnaire does not mean you must take part in the rest of the study (the part involving a CT scan), but for those who do want to take part *it must be completed before we send you the information booklet*. If you return the questionnaire, we will use the information in it for the study, even if you later decide not to have the screening test.

What to do if you are NOT interested in taking part in the study:

If you do not want to hear more about the study, your care will not be affected in any way. If you tell us you are not interested in the study we will not contact you again about the study.

If we have not heard from you within 2 weeks of this letter, we will contact you by phone.

To contact us about the study:

Research nurses:

Email:

Telephone:

What to do if you are worried about your risk of lung cancer:

If you are concerned and wish to speak to someone, there are several options:

1) Call our lymphoma clinical nurse specialists on: 0161 446 8573

2) Seek advice and support from Lymphoma Action- they are aware of this study:

- via their website http://lymphoma-action.org.uk
- or their free helpline 0808 808 5555 Monday to Friday 10am-3pm
- a live chat option is available via the 'Contact Us' section of the website

With kind regards,

Dr Rachel Broadbent

Clinical Research Fellow

The Manchester Lymphoma Group

Participant Information Sheet: 294837

The Christie NHS
NHS Foundation Trust

Lung screening in people cured of Hodgkin lymphoma

Lung screening for Hodgkin lymphoma survivors: a feasibility study

We invite you to take part in a research study.

Joining the study is entirely up to you. Before you decide whether to take part, we would like you to understand why the research is being done and what it will involve for you.

Please take time to read the following information carefully. Discuss it with friends and relatives if you wish.

Ask us if there is anything that is not clear or if you would like more information.

Important things that you need to know

People treated for Hodgkin lymphoma are at risk of getting lung cancer later in life. We want to find out if it is possible to screen people cured of Hodgkin lymphoma for lung cancer using a 'low-dose CT scan'.

If you choose to take part, you can stop taking part in the study at any time.

If you choose not to take part this will not impact the standard of care you are receiving now or in the future.

In this research study we will use information from you and your medical records. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study we will save some of the data in case we need to check it or use it for future research.

We will make sure no-one can work out who you are from the reports we write. The full information sheet will tell you more about this.

Contents

Participant Information Sheet: 294837

The Christie NHS
NHS Foundation Trust

10 Additional information

How to contact us

If you have any questions about this study, please talk to the doctors who organise it: Dr Rachel Broadbent on rachel.broadbent1@nhs.net or 0161 918 7963 / 7964

1 Why are we doing this study?

People treated for Hodgkin lymphoma have a higher chance of getting lung cancer than the average person in the general population. This is because of the cancer treatment they were given for Hodgkin lymphoma. Research in people who have smoked has shown that screening for lung cancer saves lives by diagnosing lung cancer at an early stage, when it is not causing symptoms. The screening test for lung cancer is a 'low-dose CT scan' of the chest (thorax). In this study, we want to test lung cancer screening in people cured of Hodgkin lymphoma.

We want to find out whether people cured of Hodgkin lymphoma would attend for a lung screening test (low dose CT scan). We also want to:

- Find out if an information booklet we have written about lung screening helps people to make an informed decision about having the test
- Find out what effect lung screening has on how anxious people are and how much they worry about getting cancer
- Find out if lung screening is acceptable to people cured of Hodgkin lymphoma
- Find out the reasons why people have the test, or do not have it
- Find out whether a low dose CT scan is a good method of lung screening in people cured of Hodgkin lymphoma

Lung screening is only available to a small number of people in the UK and most people cured of Hodgkin lymphoma will not be able to access the service. So if a person cured of Hodgkin lymphoma wanted to have a lung screening test, it is unlikely they would be able to have the test outside of this study.

To be able to take part in this study, you must:

- Have been cured of Hodgkin lymphoma (with no evidence of a return of the lymphoma within at least 5 years)
- Be aged 18-80

- Be able to travel to the Christie hospital for the low dose CT scan (if you want it). You can still take part in some parts of the study if you do not want the scan).

You **cannot** take part in the study if:

- You have ever been diagnosed with lung cancer
- You have another diagnosis of advanced cancer
- You had a CT scan of your chest within the last 12 months
- You are pregnant
- You live in a nursing home or are unable to leave the house

If you take part you will remain in the study until 14 months after your low dose CT scan.

2 Why have I been invited to take part?

You have been invited to take part because you have been diagnosed with Hodgkin lymphoma that has not relapsed for at least 5 years. Our hospital records show that you were given a treatment for Hodgkin lymphoma that increases your chance of getting lung cancer.

3 What will happen if I take part?

You will be invited to an appointment at The Christie hospital. At the appointment, you will firstly be asked to sign a consent form. Then you will complete a questionnaire about your risk factors for lung cancer. This will be followed by a low dose CT scan of your chest at The Christie on the same day. The CT scan itself takes around 20 seconds to complete, but you should expect to be in the radiology department for up to 20 minutes.

For the scan, you do not need to have an injection of contrast, so you do not need a cannula. You do not need to take your clothes off, but you should avoid wearing metal such as zips, or jewellery, as these will need to be taken off. After the CT scan you can eat, drink and drive as usual.

You will be contacted by phone within 2 weeks of the scan. We will give you the scan results over the phone. You may need to come to an appointment at the hospital to get your results. We will also send you and your GP a letter with the scan results. Some people may need another scan/s in 3 and/or 12 months to check on a lung nodule. If you need a scan in 3 months from the first, we will arrange this for you at The Christie as part of the study. If you need any further scans to check on a lung nodule after the 3-month study scan, these can either be arranged at your local hospital or at The Christie. If you need to have any other tests, or if you need a referral to another specialty because of your scan, we will arrange those tests, or referrals, or if appropriate, ask your GP to arrange them.

There are a number of questionnaires for you to complete during the study. These questionnaires will ask you about your decision making, your knowledge about lung cancer screening, how worried you are about cancer and how anxious you are feeling. If you take part in the study, you will complete four questionnaires over the course of 14 months. Three of them will be sent in the post and one will be completed at your study visit. If, after reading this information you do **not** wish to have a lung screening scan (ie. You do not wish to participate in the study), we would be very grateful if you would return the questionnaire that we have already sent to you. After that, we will not send you any more questionnaires.

If you take part in the study, we will telephone you 6 and 14 months after your first low dose CT scan, to find out how you have been since the scan and whether the scan led to any diagnosis, change in medications, or any other change.

The low dose CT scans which are offered in this study are 'extra' to what you would usually be offered. Taking part in this study does not affect the care that The Christie, or other NHS services would offer you.

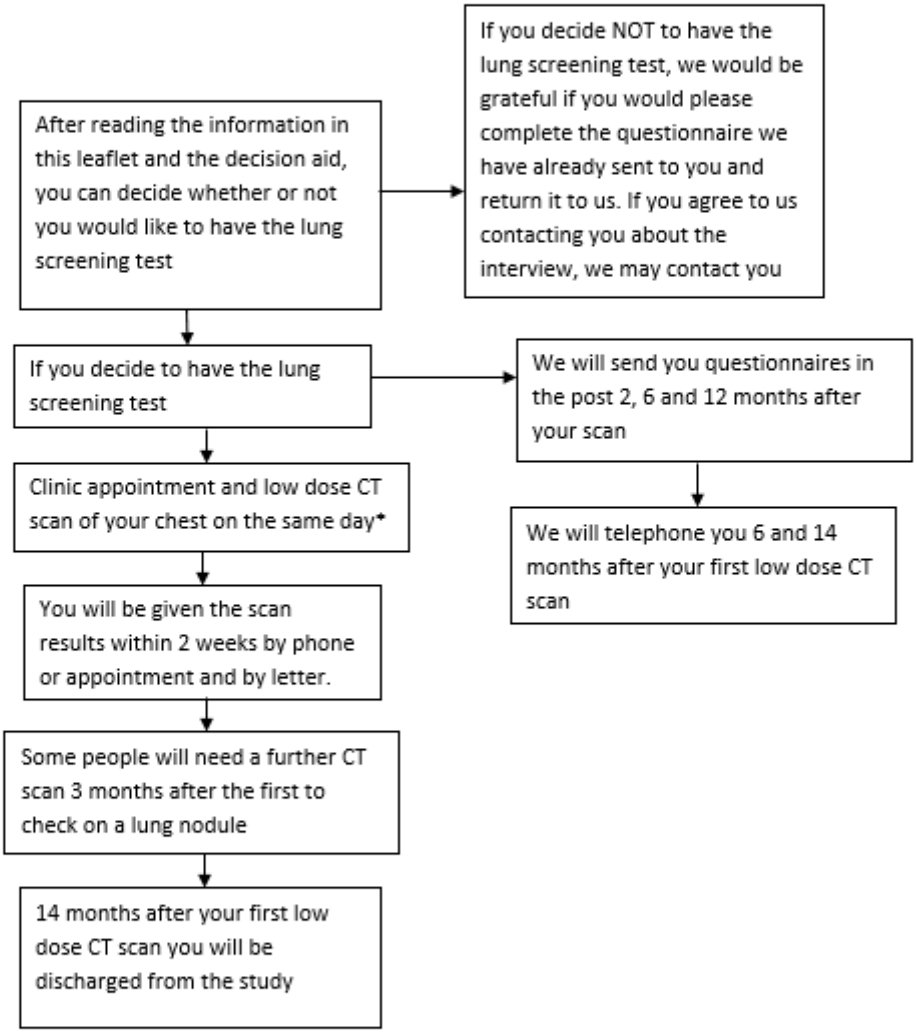
Optional extras

1. Providing saliva for genetic research

At the appointment before your scan, you will have the option of providing a small sample of saliva which will be stored at the Manchester Cancer Research Biobank, before being transferred to a laboratory. In the laboratory, researchers will check your saliva for changes in the DNA which might affect lung cancer risk. The checks performed on your saliva cannot diagnose you with lung cancer or any other cancer, or accurately predict your risk of cancer in the future. Participation in this part of the study is entirely optional and does not affect your participation in the other parts of the study. We will store your saliva sample for use in future ethically approved research studies.

2. Interview study

Some people invited to this study will also be invited to be interviewed about the reasons why they decided to have the lung screening scan, or not have it. You can take part in the interview study even if you do not undergo screening. If we invite you to interview, we will send you a **separate information sheet** about that part of the study and a **separate consent form**. You can opt out of being contacted for interview by ticking the appropriate box in the questionnaire which we have sent to you with this information sheet.



*If you provide a saliva sample, this is analysed in a lab at a later date

4 What are the possible benefits of taking part?

Lung screening in people cured of Hodgkin lymphoma has not been tested before, so we cannot be sure whether you will benefit from having the low dose CT scan. The possible benefits are:

- Diagnosis of lung cancer at an early stage
    - In people who have smoked and who do **not** have any symptoms of lung cancer, a low dose CT scan has been shown to find lung cancers at an early stage when they can be cured. This means that fewer people who have smoked die of lung cancer.
- Diagnosis of another health issue
    - The scan could find another health issue that you didn't know about such as a narrowed heart value. If this was found, you could be monitored or treated.
- Reassurance
    - If you have a normal scan, this could give you reassurance
- Contributing to research
    - The findings of this study will help us develop larger studies of lung screening for people cured of Hodgkin lymphoma

5 What are the possible disadvantage and risks of taking part?

Lung screening has some possible risks.

Radiation

If you take part in this study you will have one or more low dose CT scans of your chest. All of these will be extra to those that you would have if you did not take part in the trial. These procedures use ionising radiation to form images of your body. Ionising radiation may cause cancer many years or decades after the exposure.

We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study will increase the chances of this happening to you to about 50.03%.

Extra scans and false positives (false alarms)

Some people could be told they have a possible cancer on their scan, but it turns out not to be cancer after extra tests. This is known as a false positive and means you could be exposed to extra scans, biopsies or an operation unnecessarily. We estimate that around 1 in 10 people who have a lung scan will need another CT scan to monitor an abnormality that turns out not to be cancer. Around 2% of smokers who had a lung screening scan had surgery for an abnormality which turned out not to be cancer. To minimise the risk of this happening, our radiologists will measure any lung nodules on your scan using tried and tested protocols

which help us to decide how to manage the nodule.

False negatives

Sometimes, tiny cancers are not seen on the scan. This can mean that a person is given a clear scan result but goes onto to develop lung cancer. This is uncommon (around 1 in every 250 people who have the scan.)

Overdiagnosis

Some lung cancers that are found on a lung scan would never have caused problems. This means people could have unnecessary treatment such as surgery, chemotherapy and radiotherapy.

Worry and anxiety

Having a lung screening test could make you more worried or anxious. If you feel this way at any point in the study, we can offer you support. Our lymphoma clinical nurse specialists, research nurses and study doctors are available to talk through any worries you may have. Their details are provided later in this information sheet.

6 What if there is a problem?

If you have a concern about any aspect of this study, you should speak with any of the research staff or the Chief Investigator, Dr Kim Linton at 0161 4463753.

If you remain unhappy and wish to complain formally, the normal NHS complaints mechanism will be available to you. You can contact the Patient Advice and Liaison Service on this email:

the-christie.pals@nhs.net

7 How will we use information about you?

We will need to use information from you and your medical records for this research project.

This information will include your:

- Name
- Date of birth
- Address
- Phone number
- NHS number and hospital number

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason. If you tell us you no longer wish to be part of the study, we will not use your data for this study.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. If you opted to provide a saliva sample to be stored in the Manchester Cancer Research Centre, we will use your data from this study in the future research.

You can find out more about how we use your information:

- At www.hra.nhs.uk/information-about-patients
- Our leaflet available from one of your research team
- By asking one of the research team
- By sending an email to the-christie.dpo@nhs.net

8 What will happen to the results of the study?

At the end of the study, the results will be analysed and published in medical journal and/or presented at scientific meetings.

All data will be anonymised and no personal details such as name or address will ever be included in any publications or presentations.

If you would like to obtain a summary of the results of this study, please tick the box on your consent form and we will send you a summary when it is available.

9 What will happen if I do not want to carry on with the study?

You can withdraw from the study at any time. If you consent to the study but subsequently become unable to give consent then you will be withdrawn from the study and no further information scan data will be collected. Previously obtained data and scan images will still be used in the study.

10 Additional information

Will I be paid?

We will reimburse you for reasonable travel expenses for the clinic appointment and low-dose CT scan appointments that are required in the study.

If we interview you for the study, you will receive a £30 voucher which can be spent at UK high street stores.

Who has organised this study?
The Christie NHS Foundation Trust is legally responsible for the study. The study forms part of work being undertaken by Dr Broadbent for a PhD qualification.

Who is funding the study?

The study is funded by:

The Christie Charity (Lymphoma Research Fund)

National Institute for Health Research Patient Safety and Translational Research Centre Greater Manchester (NIHR PSTRC GM)

National Institute for Health Research Biomedical Research Centre (NIHR BRC) Manchester

The Roy Castle Lung Cancer Foundation

Who has reviewed this study?

All research in the NHS is reviewed and approved by an independent group of people, called a Research Ethics Committee. It has also been reviewed by Research and Development department at The Christie. This is to make sure that your safety and rights are respected throughout the study. This study has been approved by <insert name of Ethics Committee, reference number and date>

Further information about cancer, including how to find support:

Cancer Research UK www.cancerresearchuk.org

Macmillian Cancer Support
www.macmillian.org.uk

Thank you for considering entry into this study. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

LETTERS OF PERMISSION FROM CO-AUTHORS

The Division of Cancer Sciences
School of Medical Sciences

Faculty of Biology, Medicine and Health

The University of Manchester

Oxford Road

Manchester

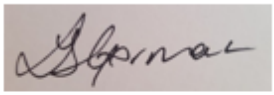
M1 9TG

Paper titles:

1. The perspectives of survivors of Hodgkin lymphoma on lung cancer screening: A qualitative study, published in the journal Health Expectations (Chapter 2 in the candidates' thesis)

I hereby give permission for Rachel S. Broadbent to include the above paper in her thesis, titled 'Lung Cancer Screening for Survivors of Hodgkin Lymphoma'.

Louise Gorman



Dated: 25th September 2022

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School of Medical Sciences

Faculty of Biology, Medicine and Health

The University of Manchester

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3. The development of a decision aid to support Hodgkin lymphoma survivors considering lung cancer screening, published in the journal BMC Medical Informatics and Decision Making (Chapter 4 in the candidates' thesis)

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Kim Linton

Dated: 26/09/2022

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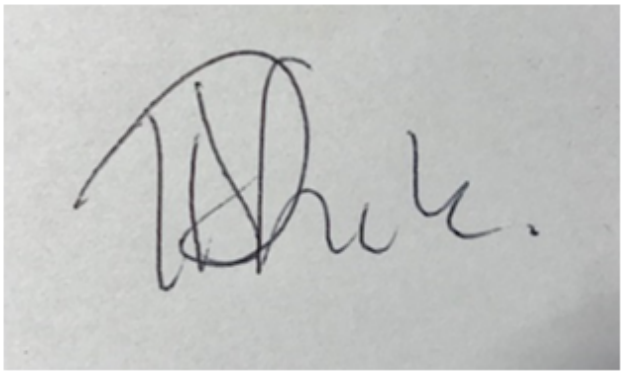
Tania Seale



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Christopher J. Armitage

Dated: 26/9/22

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John Radford

Dated: 25 September 2022

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Philip Crosbie

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