# Study Protocol

**Study Title:**

SORT: **S**urgery **O**r **R**adio**T**herapy for early-stage cancer

**Version 1.1**

**11 December 2024**

**Study sponsor:** The London School of Hygiene & Tropical Medicine

**Funder:** This study is funded by the National Institute for Health and Care Research – Health and Social Care Delivery Research (NIHR HSDR). Award ID: NIHR153580. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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# 1. SORT: Surgery Or RadioTherapy for early-stage cancer

## 1.1 List of Investigators

Prof Richard Grieve (PI) – London School of Hygiene & Tropical Medicine
Dr David Lugo-Palacios (Co-PI) – London School of Hygiene & Tropical Medicine
Eva Kagenaar – London School of Hygiene & Tropical Medicine
Prof Bernard Rachet – London School of Hygiene & Tropical Medicine
Andrew Hutchings – London School of Hygiene & Tropical Medicine
Prof Ajay Aggarwal – London School of Hygiene & Tropical Medicine
Prof Corinne Faivre-Finn – The University of Manchester
Prof Ananya Choudhury – The University of Manchester
Jo Cresswell – South Tees Hospitals NHS Foundation Trust
John Edwards – Sheffield Teaching Hospitals NHS Foundation Trust
Ravinder Vohra – Nottingham University Hospitals NHS Trust
Prof Ellen Nolte – London School of Hygiene & Tropical Medicine
Dr Stephen O'Neill – London School of Hygiene & Tropical Medicine
Katja Gravenhorst – London School of Hygiene & Tropical Medicine
Yuki Alencar – London School of Hygiene & Tropical Medicine
Paul Charlton – PPI Representative
David Chuter – PPI Representative

## 2. Summary of Research

### *2.1 Summary, aims and objectives of the study*

For people with common solid tumour cancers, survival in England is worse than in comparable countries (1), with wide inequalities in outcomes across sociodemographic groups (2). For three major tumour types, non-small cell lung cancer (NSCLC), oesophageal squamous cell carcinoma (OSCC), and muscle-invasive bladder cancer (MIBC), all-stage five-year survival rates remains low at 16%, 17%, and 53%, respectively (3). For early stages of these cancers, surgical resection has been the mainstay of curative treatment. While clinical guidelines recommend radical radiotherapy (RT) as an alternative (4-6), there is limited evidence from randomised controlled trials (RCTs) to guide which of the two interventions is more effective or cost-effective (7-12). This uncertainty about the effectiveness of surgical resection or curative RT for these three major types of cancer is associated with unexplained variation across areas in England, and over time, in rates of these curative interventions (7,13).

The COVID-19 pandemic reduced surgical capacity and disrupted cancer pathways, which may have increased variations in the use of curative treatments (14). For people with early-stage NSCLC, OSCC or MIBC, these variations raise three important issues. First, underserved sociodemographic population groups may be less likely to receive *either* curative intervention, and during the COVID-19 period these inequalities may have grown (14-17). Second, the lack of surgical capacity may have increased the substitution of curative RT for surgery even though for these early-stage cancers the relative effectiveness is unknown (7,13). Third, the backlog of patients waiting for curative cancer treatments has grown, and generating evidence on the relative cost-effectiveness of curative RT versus surgical strategies could help improve patient outcomes while managing the backlog (14).

We will address these urgent interlinked issues for each of these three major tumour types. The aims of this 36-month study are: to assess inequalities across sociodemographic groups in the use of curative versus non-curative interventions, and to estimate the relative effectiveness and cost-effectiveness of curative RT versus surgical strategies for patients with early-stage NSCLC, OSCC, or MIBC.

For patients with these early-stage cancers, the objectives are

1. To describe the influence of patient and organisational factors on the use of curative RT, curative surgery or non-curative strategies
2. To assess inequalities in the receipt of curative versus non-curative interventions
3. To assess the effectiveness of curative RT versus curative surgical strategies
4. To assess the cost-effectiveness of curative RT versus curative surgical strategies

The study design has followed recommendations for achieving impact by engaging with a broad stakeholder group from the outset (18). The relevant stakeholders include multidisciplinary cancer clinicians, patients, NICE guidelines developers and NHS commissioners. The engagement of these groups will help the study provide the NHS with useful recommendations on the provision of curative RT and surgery. The research methods -are in line with guidance from the Goldacre review, and NICE requirements for the generation of real-world evidence (19, 20). These approaches will exemplify best use of NHS routine data for generating evidence that can improve service provision, the accessibility of patient information and reduce health inequalities. The research will be of international interest.

### *2.2 Overview of Methods*

The study will have four interlinked work packages (WPs). The overall design combines linked routine cancer data with insights from clinical panels, and patient interviews. The proposal has been shaped by the clinical and Patient and Public Involvement and Engagement (PPIE) co-applicants, who have emphasised the importance of the topic and the need for the views of clinicians, patients and members of the wider public to inform the study design. The Study Steering Committee will help monitor project progress and ensure the PPIE voice is heard throughout the project. It will include representatives from national charities, people with lived experience of the three tumours, and those from underserved groups.

*WP 1* provides the foundation for WPs 2-4. For each of these three cancers, we will use linked cancer registry data to describe patient populations, organisational characteristics and their influence on use of curative and non-curative treatments. This information will be presented in workshops to 8-10 clinical panellists involved in the choice of curative treatment for each of these three tumour types. The clinical panellists will help refine the definitions of the populations and comparator groups that will be used in subsequent WPs. The clinical panellists will also discuss local organisational factors likely to influence treatment choice, beyond those available from the routine data. We will convene a PPIE panel who will be asked to guide aspects of the protocols for the subsequent research, in particular the strategy for inviting patients to participate in the interview study, and the proposed strategy for ensuring the research findings are accessible to underserved groups.

We will interview 10-15 people with lived experience of each of these cancers to better understand people's experiences of decision-making about curative treatment. We will include participants from underserved groups. The findings from the interviews will provide new insights into the informational needs of patients about the curative treatment decision.

We will draw insights from these descriptive analyses, clinical panels, PPIE panels and patient interviews in shaping the protocols for the subsequent research packages.

In *WP 2*, we will assess inequalities according to patient characteristics (e.g. age, sex, ethnicity) in the receipt of curative versus non-curative interventions for each of these three early stage cancers. The final choice of subgroups will be informed by the advice of the PPIE panels in WP 1. We will consider inequalities in the period before COVID-19, and then the impact of the pandemic on these inequalities.

In *WP 3,* we will use the target trial framework to assess the relative effectiveness of curative RT versus surgical strategies for each early-stage cancer. A target trial is a hypothetical pragmatic RCT for assessing comparative effectiveness from observational data that is designed to minimise prognostic differences between the comparison groups (21). The target trial framework requires clinicians to help define the main elements of the target trial's protocol, including eligibility criteria, and the respective treatment strategies. Target trials have been shown to replicate effectiveness estimates from corresponding RCTs (22,23). Our target trials will apply appropriate eligibility criteria to identify patients of similar case-mix who receive curative RT versus surgical strategies, and will compare their three-year survival.

In *WP 4,* we will assess the relative cost-effectiveness of curative RT versus surgical strategies for each early-stage cancer. Within a value of implementation analysis, for each sociodemographic subgroup, we will consider the value of increasing the uptake of the curative intervention that is on average most cost-effective.

We will synthesise findings across the WPs drawing on insights from the patient interviews, and the clinical panels to contextualise the quantitative findings. We will convene a translation workshop with all stakeholder including PPIE representatives, clinicians, and service commissioners. We will consider how the findings can feed directly into clinical guidelines. We will work with representatives from underserved communities to help ensure the findings are widely accessible to people with these three major cancers.

## 3. Background and Rationale

### *3.1 Background*

These three major cancers, NSCLC, OSCC or MIBC, have been chosen as they represent nearly a third of annual cancer deaths in England (24), cancer incidence and mortality is higher for underserved groups (16,25), and there is no clear evidence as to whether curative RT or surgery is more effective (25,26). Curative RT is a non-invasive, organ-preserving intervention with the potential to reduce morbidity, mortality and hospitalisations compared to surgery (7-13). However, evidence is required on the effectiveness and cost-effectiveness of curative RT versus surgical strategies (26). A major concern is that underserved groups are less likely to receive *either* curative intervention, and these inequalities may have increased during the COVID-19 period.

### *3.2 Brief Literature review*

Previous research has reported wide inequalities in the receipt of cancer treatment across the NHS in England according to sociodemographic characteristics (15-17), and older patients with these three cancers are less likely to have surgery (27). As curative pathways for cancer patients become increasingly complex to navigate, this may increase inequalities in uptake of curative interventions across sociodemographic groups, and contribute to wide variations in practice and outcomes. Sociodemographic inequalities in receipt of curative treatment may contribute to differential survival (28,29), particularly for lung cancer (29,30). However, previous studies have not considered the impact of the COVID-19 period on inequalities in rates of curative treatments for these three major tumour types.

RCTs have aimed to compare curative RT versus surgery for patients at early stages of these three cancers, but these stopped early due to low recruitment (10,31-34), had small numbers of patients (35), or will not report timely results (9). Observational studies of RT versus surgery are subject to residual confounding and have had small sample sizes (8,11, 36). Hence, there is uncertainty about the relative effectiveness of curative RT versus surgery for people with these three early-stage cancers who are eligible for either modality.

In the UK, this uncertainty in the clinical evidence is reflected in national audits and Getting It Right First Time (GIRFT) reports, which documented wide practice variations across NHS

trusts in the proportion of patients receiving curative treatments for these three tumour types (37-40). Insights from other tumour types suggest that the patient's travel time to their nearest provider may influence the choice of curative treatment (41). However, there is a lack of research about local organisational factors, and patient preferences that may influence whether patients have curative RT, surgery or non-curative treatment. Studies that have investigated the views of early-stage NSCLC patients on surgery or SBRT, focused on treatment experience (42,43), advocating understanding amongst clinicians about patients' values, expectations, and preferences to inform treatment decisions (44,45).

### *3.3 Why this research is needed now*

Patients with lung, oesophageal and bladder cancer continue to have low survival. Improving treatment strategies while addressing inequalities in access to treatment, is a major priority to help improve patient outcomes. Cancer services are under severe pressure, with waiting lists for elective treatments predicted to reach 12 million by March 2025 (46), which is likely to lead to higher mortality, and greater inequalities (16,26).

The National Inquiry into cancer services recognised the potential for curative RT as a replacement for surgery stating that:

"*Faster, smarter and effective radiotherapy, supported by greater networking of specialised expertise, will mean more patients are offered curative treatment, with fewer side effects and shorter treatment times.*" (14, p60)

However, there is little evidence on relative effectiveness and cost-effectiveness to inform national guidelines. For example, for patients with NSCLC NICE guidelines identified a high priority research question as:

*"What is the effectiveness and cost-effectiveness of stereotactic ablative radiotherapy (SABR) compared with surgery for people with non-small-cell lung cancer (stage I and IIA) in whom surgery is suitable?"* (6, p.26)

The proposed research will assess the relative effectiveness and cost-effectiveness of curative RT compared to surgery for each early-stage cancer. The importance of these research questions has been emphasised by PPIE advisors. We convened two panel meetings with PPIE advisors in May 2022 to discuss the proposed research, and 11/12 participants stated that they felt the research questions were 'very relevant' for the NHS.

### *3.4 Building on existing work*

Prior to COVID-19, while there was natural variation across NHS regions in the use of either of these curative interventions, fitness for surgery was a key factor and observational studies comparing these interventions were subject to confounding by indication (8,9,11). During the COVID-19 period, the use of RT increased for these three cancers (7), but uptake of RT differed across regions (47). Hence, the periods before, and during the different waves of the pandemic offer the opportunity to conduct natural experiments to assess the relative effectiveness of curative RT versus surgery for each tumour type. The study will use the target trial framework to improve the comparability of patients who have curative RT versus surgery. Our analytical approach will reduce the risk of residual confounding from unmeasured differences between the comparison groups, pertaining to the local context and the individual's preferences.

Our team has experience of combining analysis of routine datasets with qualitative approaches in reporting: inequalities in access to cancer care (Aggarwal, 48,49) and outcomes

(Rachet, 17), association of the COVID-19 pandemic with cancer mortality (Rachet & Aggarwal, 50), and the impact of centralisation and travel time on patient choice (Aggarwal, 41). Complementary NIHR-funded research is evaluating RT regimens for lung cancer from electronic health records (Faivre-Finn, 51).

Our overarching approach to combine insights from clinical and patient groups with advanced analytical methods used successfully in the NIHR-funded ESORT study evaluating emergency surgery (Grieve, Lugo-Palacios, Hutchings & O'Neill, 52-54). The ESORT study showed the importance of input from clinicians and patients in defining the main elements of the target trial's protocol, including eligibility criteria, and the treatment strategy protocols. For the assessment of the effectiveness of curative RT versus surgery, we will adjust for differences between the comparison groups in measured patient and organisational factors. However, we recognise that there is a risk of residual confounding from unmeasured differences between the comparison groups. We will address this risk of residual confounding in an instrumental variable analysis. An instrumental variable encourages receipt of the intervention, but does not have a direct effect on the outcome. The ESORT study showed how an instrumental variable analysis could reduce the risk of confounding when comparing outcomes from routine data (53,54). The proposed research draws on work by co-applicant Aggarwal (41), who found that as curative RT requires more outpatient visits than surgery, patients who have to travel further may be less likely to receive curative RT. We will use the patient's travel time to the nearest RT centre, as an instrumental variable to minimise residual confounding after adjusting for all measured organisational and patient factors (see also WP 3).

## 4. Aims and objectives

The aims are to evaluate the impact of the COVID-19 period on inequalities in the use of curative interventions, and to assess the relative effectiveness and cost-effectiveness of RT versus surgery for patients with early-stage NSCLC, OSCC and MIBC.

For patients with these early-stage cancers, the objectives are:

1. To describe the influence of patient and organisational factors on the use of curative RT, curative surgery or non-curative strategies
2. To assess inequalities in the receipt of curative versus non-curative interventions
3. To assess the effectiveness of curative RT versus curative surgical strategies
4. To assess the cost-effectiveness of curative RT versus curative surgical strategies

Each of these objectives will be considered for time periods before and during the different waves of the COVID-19 pandemic. The cancer service provision during the first wave of COVID-19 in England (1st February 2020 to 30 June 2020) is likely to reflect the immediate response to the pandemic. By contrast, service provision during the subsequent waves of COVID-19 may provide more useful context for other settings when the NHS and care sectors are under prolonged pressures. Hence the analytical models and the interpretation of the results will reflect how relevant the context is to future decision-making. The overall findings across the four objectives will be synthesised and discussed with stakeholders who will help ensure the study provides information that is broadly accessible to service providers, and patients including those from underserved communities.

## 5. Research Plan / Methods

This study will use linked National Cancer Registration and Analysis Service (NCRAS) data which includes all cancer patients diagnosed in England (55), and links data from the Cancer Registry, Systemic Anti-Cancer Therapy (SACT) data, Radiotherapy Dataset (RTDS), Hospital Episodes Statistics (HES), and Cancer Waiting times data (Table 1). The research

design, proposed analyses and interpretation draws on insights from three tumour-specific clinical panels, and interviews with patients, through four interlinked WP.

### *WP 1: influence of patient and organisational factors on curative RT, surgical or non-curative strategies*
**(leads Lugo-Palacios, Hutchings)**

#### *Overview*

*WP 1* will provide the foundation for the study. In WP 1.1 we will acquire and prepare the linked data and address issues concerning missing data and coding. We will develop 'working definitions' of the populations and comparators of interest. In WP 1.2 we will describe the influence of organisational and patient factors on the receipt of curative or non-curative interventions. In WP 1.3 we will present this information to three tumour-specific clinical panels each comprising of 8-10 clinicians involved in curative treatment decisions. The panels will refine the definitions of the populations, the treatment comparators, and offer insights on additional local factors that may influence the choice of curative or non-curative interventions for time periods prior to and during the COVID-19 pandemic. In WP 1.4 we will discuss the preliminary study protocol with the PPIE panel, who will provide advice on the study design and translation strategies. In WP 1.5 we will interview 10-15 patients with each early-stage cancer to find out about their experiences of the treatment pathways, and how we can provide information to improve the patient experience. We will draw on the insights from the clinical panels, the PPIE panel and the patient interviews for the final descriptive analyses (WP 1.6) and study protocols (WP 1.7).

#### *WP 1.1 Initial data preparation and definition of study cohorts (Hutchings, Lugo-Palacios)*

On notification of funding, we will access pilot data (Table 1) held in LSHTM's secure data environment according to pre-existing permissions for related research. The datasets will be checked for completeness and quality of linkage. We will create initial cohorts of patients aged 18 or older diagnosed with a first primary NSCLC or OSCC in England from 1.1.2015 to 31.12.2022 defined by ICD-10 (diagnosis) and ICD-O (morphology) codes for the primary diagnosis using detailed tumour stage information. The MIBC cohort will include diagnoses from 1.1.2012 to 31.12.2022 as no new recommended RT therapy regimen emerged during this period for this type of cancer. These criteria will yield sample sizes of about 35,000 (NSCLC), 5,000 (OSCC) and 18,000 (MIBC). Eligible cohorts will have treatment categorised as curative RT, curative surgery or non-curative (WP2), and curative RT or curative surgery (WP3 and 4)

#### *WP 1.2 Descriptive analysis of patterns of treatment and organisation of services (Hutchings, advisor Lewis on use of GIS software)*

We will use the linked datasets to define treatment pathways focussing on the period from diagnosis to curative and non-curative intervention for each tumour type. We will describe patients' sociodemographic, clinical and pre-diagnosis (e.g. time from referral) characteristics. At the organisation level (cancer alliance, NHS trust and hospital) we will recognise regional and temporal differences in how services have been centralised within the 'hub and spoke system'. We will describe the inter-relationships between treatment pathways, patient characteristics and the organisation of services. For example, we will report the numbers of NHS trusts that directly provide either curative RT or surgical services, provide neither, or offer both modalities. The way services are organised can influence care coordination, time to treatment, the patients' travel time, and access to curative RT, surgery or non-curative interventions. We will derive travel time data between each patient's area of residence, and the nearest centre providing each of the curative treatments using Geographic Information System (GIS) software (41). We will also consider the influence of the availability and volumes

of each service on the choice of curative intervention. For each cancer alliance we will describe relationships between organisations at different levels in providing curative RT, curative surgery and other oncology services, and if they have changed over time.

These descriptive findings will be presented to the clinical panels and will provide context for the synthesising the findings from WPs 2-4 (see dissemination and translation section).

**Table 1: Data sources, and data categories that will be accessed from the linked NCRAS data ('the linked data')**

| Source | Key data categories |
|---|---|
| Cancer registration data | Demographics, diagnosis, tumour characteristics, travel time to centre |
| HES admitted patient-care, outpatient data | Comorbidities, frailty, surgical procedures, Resource use |
| RTDS | Radiotherapy, dose and fractionation, duration, and date |
| SACT | Chemotherapy and systemic therapy received, doses, duration and date |
| National audit data for NSCLC and OSCC | Performance status, organisational audit data. |
| Diagnostic and Imaging dataset | Resource use |
| Office of National Statistics (ONS) Mortality | All-cause death |

HES: Hospital Episode Statistics, RTDS: National Radiotherapy Dataset, SACT: Systemic Anti-cancer Therapy Dataset

***WP 1.3 Clinical panels to refine the target trial protocols, and understanding of local organisational factors (Faivre-Finn, Choudhury, Cresswell, Vohra, Aggarwal)***

The target trial protocols require definitions of the study cohorts and treatment strategies, and recognition of local organisational factors. We will convene clinical panels from multidisciplinary teams across the UK who are involved with the curative treatment decision. The panels will be presented with 'working definitions' of the study populations, treatment groups, and descriptions of the influence of patient and organisational factors on the receipt of curative and non-curative treatment strategies. The panels will be asked to refine the study eligibility criteria, the definition of the treatment groups, and to propose additional organisational factors that may influence the choice of curative treatment, beyond those measured in the linked data.

We will establish three tumour-specific clinical panels. Each panel will comprise 8-12 clinicians (oncologists and surgeons) involved in decision-making about curative treatments. Online meetings will allow involvement of panellists from different regions in England, who will meet for a three-hour facilitated discussion, led by the clinical co-applicants. Prior to the meetings, panellists will be provided with information packs including summaries of above descriptive analyses, and the provisional eligibility and treatment strategies for the target trials (see below). Panellists will be asked to complete surveys that improve these definitions, before and after the facilitated discussions.

*Eligibility criteria*

The provisional eligibility criteria and treatment strategies for the target trials (WP3), will be extracted from the cohorts with a first primary cancer diagnosis for each tumour type between 1.1.2012 and 31.12.2022 (MIBC) and 1.1.2015 and 31.12.2022 (NSCLC and OSCC) using the working criteria in Table 2. Inclusion of patients between these dates will ensure survival data are available for a minimum of three-years for all patients. Basic eligibility criteria for each cancer requires: (i) the appropriate tumour size (T), no cancer in lymph nodes (N0), cancer is

not metastatic (M0), and (ii) curative RT or surgery received within six months of diagnosis to ensure similarity of patient groups and curative intent.

The following *exclusion criteria* will be applied to help ensure that the comparison of patients curative RT versus a surgical strategy only includes those of similar baseline prognosis.

a) Previous radiotherapy or previous malignancy within five years prior to diagnosis for the tumour type in question (all three tumour types)
b) Pregnancy or lactation (all three tumour types)
c) Carcinoid histology or synchronous lung cancer (NSCLC)
d) Metastasis to solid visceral organs (OSCC)
e) Simultaneous upper tract transitional cancer (MIBC)

The clinical panel will consider additional exclusion criteria including the presence of specific comorbidities, with a final list established by panel consensus [52-54].

**Table 2: For each target trial, cancer stage, and comparison groups according to recommended or common practice in the NHS in England 2018-2022**

| Cancer | Stage | Intervention | Comparator |
|---|---|---|---|
| **NSCLC** (35) | T1 and N0 or M0<br>or<br>T2 and N0 or Mo | SBRT | VAT or open lobectomy +/- MLND<br>Segmentectomy +/- MLND<br>Wedge resection +/- MLND |
| **OSCC (**34) | T1bN and M0<br>or<br>T2-4 and N0-2 and M0 | External beam radiotherapy + chemotherapy | Standard oesophagectomy +/- Neoadjuvant chemotherapy |
| **MIBC** (10) | T2 and N0 or M0<br>T3 and N0 and M0 | External beam radiotherapy, +/- radiosensitiser +/-neoadjuvant chemotherapy | Radical cystectomy +/- neoadjuvant chemotherapy |

T-tumour size, N-number of nearby lymph nodes, M- metastases, SBRT- stereotactic body radiotherapy, VAT-video-assisted thoracic, MLND- mediastinal lymph dissection

*Definition of comparator strategies*

The clinical panels will help select treatment pathways for inclusion within the broad definitions of the ‘intervention’ and ‘comparator’ strategies, recognising that in practice some treatment pathways will differ to those recommended within clinical guidelines.

*Curative RT strategies*

The preliminary datasets from linked RTDS and SACT data will include forms of curative RT recommended by clinical guidelines (Table 2). We will extract information on the dose, fractionation and duration of therapy, and will allow for divergences from recommended practice to reflect commonly observed clinical practice. For example, for MIBC with localised small tumours, guidelines recommend neoadjuvant chemotherapy combined with external beam radiotherapy. However, the regimens included will recognise that during the COVID-19 pandemic some local oncology teams recommended that patients did not have neoadjuvant chemotherapy because of risks associated with immunosuppression.

*Surgical strategies*

The surgical strategies will be based on tumour-specific guidelines, but will also include common surgical procedures used in routine clinical practice. For example, for NSCLC the recommended strategy is video-assisted thoracic or open lobectomy, but we will also include segmentectomy with or without MLND, and wedge resection with or without MLND. Information on each surgical procedure will be extracted from the linked HES data according to Operating Procedure Codes (OPCS) (56).

*Organisational factors not measured in the linked data*

The clinical panels will also offer insights into those local organisational factors that may influence the choice of RT versus surgery, but that are not measured within the linked data. For example, the local capacity for surgery and RT at different timepoints, the location of services, multi-disciplinary team (MDT) composition and experience, whether or not centres adopt enhanced recovery after surgery (ERAS) protocols may all influence choice of curative treatment.

### *WP 1.4 PPIE (see separate PPIE section) (Alencar)*

We will follow the ESORT study in establishing a general PPIE panel early in the study, and work with panel members throughout the project. The PPIE panel will help ensure that a broad set of PPIE views including those from underserved groups are reflected in the final study protocol. For example, the PPIE group will discuss the definition of sociodemographic groups that will be used within the inequalities WP, and the proposed strategy for translation of key results to a broad patient and public audience (see dissemination).

We will work with collaborators, such as the Roy Castle Lung Cancer Charity, the Oesophageal Patients Association, and Fight Bladder Cancer who are undertaking research in collaboration with workers unions, with B'Me Against Cancer and the Centre for Ethnic Health Research to reach, involve, listen, and respond to recruit panel members who represent the voices of relevant communities, including those from ethnic minority groups. The PPIE panels will be advisory rather than research participants and will therefore complement the role of the patient interviews. The PPIE panel will have three main purposes: first, to advise on our strategy and materials for the patient interviews, in particular those for patients from underserved communities; second, to advise on relevant aspects of the research design, for example the definitions of subgroups for the inequalities research; third, to help ensure that our proposed translation strategy will be broadly accessible.

### *WP 1.5 Patient interviews (Nolte, Aggarwal)*

Our PPIE advisors emphasised that to better understand the context within which decision making about curative treatment takes place, the project should directly interview patients. This approach was also encouraged by the funding committee's comments on the first-stage application. Cancer treatment decisions are complex and influenced by a wide range of factors, including sociodemographic background, perceptions of the decision-making process, decisional control and conceptions about cancer, including cancer fatalism (57). All these complexities need to be navigated by patients when embarking on what may be a complex treatment pathway following a cancer diagnosis (57). The issues involved in the treatment decisions from the patient's perspective may be compounded by wider contextual factors such as the availability of a caregiver, geographical access to treatment and financial concerns. A few studies have investigated the views of early-stage NSCLC patients on surgery or stereotactic body radiotherapy (SBRT), but these have focused on the treatment experience (42,43). Studies have highlighted the need for better understanding among practitioners of patients' values, expectations, and preferences to inform treatment decisions (44,45).

This work package will explore the views, understanding and experiences of people who have received curative RT or surgery for the three early-stage cancers. We will use in-depth, semi-structured interviews to elicit people's accounts of their experiences to help understand how the context (home, family, work) affects the major treatment decision following a new cancer diagnosis.

***Recruitment:*** For each tumour type, we will recruit a group of 15-20 patients, who have received either curative RT or surgery. Our sampling will ensure inclusion of people from the different NHS commissioning regions, as well as underserved groups including older people and those from lower socioeconomic groups. This purposive sampling criteria draws from the literature, and our PPIE advisors' views, by including those groups whose experience about the curative treatment pathway is especially important to understand. Patients will be recruited from support groups or networks hosted or run by our collaborative partners including: the Centre for Ethnic Health Research, and national charities for each cancer (see support letters). Where patient participants express a preference for a care-giver to be involved in interviews, opportunities will be provided to include carers either in joint or separate interviews (58).

***Interview data collection:*** Interviews will be carried out in person, by phone or via secure video conferencing, depending on the participant's preference. All interviews will follow a topic guide, and will cover: patient living situation and treatment; initial response to diagnosis and possible treatment options; experience of treatment decision-making process; views on the use and usefulness of information about treatment modalities. Interviews, lasting up to 60 minutes, will be undertaken by an experienced qualitative researcher, audio recorded upon consent, and transcribed verbatim.

***Interview analysis:*** We will use a framework method to guide the analysis (59). A coding frame will be developed and applied across all transcripts, making modifications as required and seeking negative cases while highlighting tumour-specific aspects. We will use NVivo software to assist with data management. This research will provide insights into patients experiences of the curative treatment pathway, including those from underserved groups. The findings will be reported in a research paper. These results will provide useful context for interpreting the findings of the subsequent WP. For example, providing insights into patients' experiences, including those from underserved groups, will help understanding about the barriers that some patients experience in accessing alternative curative treatments which may be appropriate for them.

The overall interpretation of the implications of the study for patients will also draw from these findings, for example when making recommendations for future service delivery including improving the accessibility of information. The implications of the findings for patients will be discussed with our PPIE panels as part of the translation strategy (see dissemination).

### *WP 1.6 Final descriptive analyses (Hutchings, Lugo-Palacios)*

Following the advice from the clinical and PPI panels, and the insights from the patient interviews, we will undertake final descriptive analyses that report the influence of organisational and patient characteristics on the use of the different treatment strategies. These descriptive analyses will inform subsequent WPs, and help contextualise the findings when disseminating the results.

### *WP 1.7 Outputs*

**WP 1 provides the foundation for later WPs. The outputs will be: descriptions of the influence of organisational and patient factors for each cancer on receipt of curative and non-curative treatments, variation across NHS regions and over time periods before and during the COVID-19 pandemic. Summary report from each clinical panel, protocols for WP2 (inequalities) and WP3 (effectiveness) informed by the clinical and PPIE panels, completed data management and access plan, and papers summarising the key insights from the patient interviews, and the descriptive analyses.**

## *WP 2: To assess inequalities in receipt of curative versus non-curative interventions (Objective 2)*
## *(lead Rachet)*

### *Overview*

*WP2* will build directly from the descriptive analyses in *WP1*, to assess inequalities in the receipt of curative versus non-curative treatments. The WP will consider these inequalities for time periods before the COVID-19 pandemic. We will then consider the impact of time periods during the pandemic on these inequalities. This WP will use insights from the clinical and PPIE panels with respect to the important organisational factors and equity subgroups to consider.

### *WP 2.1 Factors and comparators of interest for assessing inequalities*

We will extract information from the linked data on patient characteristics including: age, sex, ethnicity, index of multiple deprivation (IMD) (quintiles), number and types of comorbidities, frailty level (60), date of primary cancer diagnosis, NHS trust hospital in which the patient is diagnosed, whether that NHS trust is a surgical and radiotherapy centre, patient's travel time to the nearest centre providing each curative intervention, the respective cancer alliance, and place of residence, including NHS region. The Charlson comorbidity index (61), the Cambridge Multimorbidity Score (62) and secondary care administrative records frailty (SCARF) index scores will be defined from HES diagnosis data (60).

We will identify surgical procedures and RT regimens with curative intent (56), and non-curative interventions, from the linked data. The definition of a 'curative intervention' strategy will require that either curative RT or surgery is received within six months of the diagnosis date. For RT to be defined as 'with curative intent' the dose and fractionation must also meet the criteria specified by guidelines for the time period in question. We will describe the variation in time to receiving either curative intervention, overall and across sociodemographic subgroups.

All interventions that do not meet the 'curative intent' criteria will be categorised as 'non-curative' interventions

We will define those patients diagnosed in the 'post COVID-19 period' as from the start of the first national lockdown in England (March 11$^{th}$ 2020), and those in the preceding period as 'pre-COVID-19'. We will calculate the proportions of patients who received either 'curative intervention' for periods before and after the onset of COVID-19. The interpretation of the results will consider the specific time-period and context; for example, recognising that the provision of cancer services may reflect different organisational factors and pressures, such as those arising from the COVID-19 pandemic.

### *WP 2.2 Analysis*

We will describe baseline characteristics of the study populations during the 'pre COVID-19' and 'COVID-19' periods, overall, and stratified by sociodemographic characteristics. We will report the total numbers of patients per quarter with each early-stage tumour during the 'pre' and 'COVID-19' periods, and the proportions who had curative RT and surgical treatments. We will report these proportions overall, and according to sociodemographic characteristics (e.g. age, sex, deprivation, ethnicity). We will address missing data with multiple imputation approaches, apart from for missing ethnicity data, for which we will define an 'unknown' category recognising that these data may be 'missing not at random'.

We will develop mixed-effect multivariable, multinomial logistic regression models to assess first, the proportions receiving curative RT and surgical strategies versus no curative intervention according to sociodemographic characteristics prior to COVID-19. Second, we will assess whether these inequalities changed during COVID-19 compared to previous periods.

Each model will adjust for other patient characteristics (e.g., comorbidity, frailty levels, performance status and cancer stage, distance to centre), time period, seasonality and allow for clustering within NHS trust hospitals and cancer alliances (random effects). In sensitivity analyses we will assess the robustness of results to, alternative standpoints, for example alternative approaches to handling the missing data, and exclusion of the first wave of COVID-19 (1st February to 30 June 2020) given the atypical nature of the care provided during this period.

### *WP 2.3 Outputs*

**For each tumour type, we will report the association of sociodemographic characteristics on the use of either curative intervention versus non-curative interventions prior to the onset of the pandemic. We will report the impact of COVID versus pre-COVID periods on the corresponding probability of receiving either curative modality, overall and according to sociodemographic characteristics.**

**We will draw from the findings of WP1 to contextualise these findings, recognising that curative treatment is within a complex care pathway, and may also reflect local organisational and patient factors beyond those measured in the routine data.**

### *WP 3: To assess the effectiveness of curative RT versus surgery (Objective 3) (lead Lugo-Palacios, unless stated)*

The third WP will assess the effectiveness of curative RT versus surgery using a target trial design to ensure comparability of the treatment groups (21). We will conduct a separate target trial of curative RT versus surgical strategies for each tumour type. The provisional definitions of target populations, and comparison groups are listed in Table 2. These definitions will be finalised by the clinical panels in WP1. We will address the risk of residual confounding, with an instrumental variable analysis, as this can provide consistent estimates of treatment effectiveness when comparing outcomes across treatment groups from routine data (53,54). This section describes the target trial outcomes and analysis.

### *WP 3.1 Definition of time zero, primary and secondary outcomes and sample sizes*

The target trial protocols require the definition of time zero, the analogue to randomisation in an RCT. For each of these target trials, we will define time zero as the treatment start date. At

this timepoint the eligibility criteria are met, and the patients included are 'assigned' to either the curative RT or surgical strategies. This time zero choice also minimises immortal time bias.

We will extract information on patients' vital status up to seven years after cancer diagnosis and all patients will have three-year mortality data available. The primary outcome measure will be all-cause mortality at three years from the treatment start date (time zero). This choice of endpoint was supported by the study's PPIE advisors. The target trials will have three-year mortality data for between 3,000 (OSCC) and 20,000 (NSCLC) patients. Table 3 reports the sample sizes required to detect differences in the absolute risk of death at three years of 5% and 10%, with power of at least 80%. The target of a 5% difference in the mortality relative risk is equivalent to the lower bound of a Grade A benefit in the Magnitude of Clinical Benefit Scale from the European Society for Medical Oncology (63).

The sample sizes presented are for early stage OSCC as this has the smallest sample size across the three conditions. We follow methodological recommendations for sample size calculations with IV designs recognising that while the proposed IV is reasonably strong (F-statistic >20), it will not perfectly predict the treatment received (64). We present different scenarios for the 'compliance rate' that is the proportion of patients for whom the variation in the IV changes the treatment assignment. We also present the proportion of eligible patients anticipated to receive curative RT, and the standard deviation of the 3-year mortality risk in the population. The assumed levels of these parameters were informed by insights from the 2014-2017 pilot data described in Box 1, but we anticipate that these values may change in the full data. In particular, the compliance rates are likely to be higher.

Under the plausible assumption that the standard deviation of the risk of three-year mortality is 0.3 or lower or the IV compliance rate is at least 0.7 in the full population, the study will have at least 80% power to detect a 10% difference in the absolute risk of three-year mortality of 5% or more. This level of compliance can be ensured by combining the IV which was already found to be strong in the pilot data, with confounding adjustment and matching methods. These are approaches that we have undertaken in our previous research (65).

Secondary outcomes will include: all-cause and cancer-specific mortality at 30 days, 90 days, 12 months, and 24 months, time to death, and the number of days in hospital prior to 12 months, as this may be associated with grade three or four adverse events. We will use life tables in England according to calendar year, region, age, gender, deprivation and ethnicity to calculate rates of net cancer survival, which recognise the excess risks of death following a cancer diagnosis, versus those for the general population [66].

**Table 3: Required sample size (N) for the IV design according to instrument strength (level of compliance) and magnitude of effect size at 80% power**

| Effect size (three-year mortality difference in level of absolute risk) | Standard deviation of the outcome in the population | Proportion of patients receiving RT | Levels of compliance (IV strength): | | |
|---|---|---|---|---|---|
| | | | 0.5 | 0.6 | 0.7 |
| 5% | 0.3 | 0.5 | 4,521 | 3,140 | 2,307 |
| 5% | 0.4 | 0.5 | 8,037 | 5,581 | 4,101 |
| 5% | 0.4 | 0.6 | 8,372 | 5,814 | 4,271 |
| 10% | 0.3 | 0.5 | 1,130 | 785 | 577 |
| 10% | 0.4 | 0.5 | 2,009 | 1,395 | 1,025 |
| 10% | 0.4 | 0.6 | 2,093 | 1,453 | 1,068 |

### *WP 3.2 Quantitative analysis of the target trials (leads Lugo-Palacios, O'Neill, advisor Prof Anirban Basu developer of the local instrumental variable method)*

The analysis will recognise that even after applying the target trial inclusion criteria, and adjusting for measured covariates, the choice of curative RT versus surgical treatment will reflect some organisational (e.g. MDT composition) or patient factors (e.g. patient preference) that are not available within the linked data. We will use the instrumental variable approach taken in the ESORT study to address this form of confounding by indication due to unmeasured factors that commonly arises with routine data (52-54,64).

The instrumental variable approach will be set out in a Statistical Analysis Plan. In brief, we will draw from previous research that has used distance or travel time, as an instrumental variable for treatment choice (67). Recent work by co-applicant Aggarwal found that travel time to the nearest RT centre from a patient's area of residence predicted whether they had curative RT or surgery (41). Our PPI colleagues have emphasised that increased travel time may discourage patients from having curative RT versus surgery as this requires more outpatient visits. We will calculate a continuous measure of travel time from the patient's area of residence to the nearest NHS trust that provides curative RT (see WP1). We will use this measure of travel time as an instrumental variable for the receipt of curative RT versus surgery. This instrumental variable will be combined with adjustment for measured covariates to minimise bias from unobserved confounding in comparing 3-year mortality following curative RT versus surgery, for eligible patients with each of these three early-stage cancers.

**Box 1: Results from Pilot work supporting the Instrumental Variable approach**

We undertook *preparatory work* using the 2014-17 national linked cancer data for early stage OSCC which has the smallest sample size across the 3 conditions, and hence presents a greater challenge for the instrumental variable approach. We found that the essential assumptions for travel time to be an instrumental variable were realistic. *First*, the travel time from the patients' area of residence to the nearest NHS trust providing curative RT was associated with receipt of curative RT versus surgery (F statistics >20 versus the recommended cut-off of >10). *Second,* travel time balanced prognostic measures such as the patients' cancer stage. We will repeat these assessments on the final linked data for all three conditions, which given the larger sample sizes would be anticipated to yield a stronger instrument. The assumption that travel time is independent of unmeasured confounders cannot be assessed empirically, but is likely to be justified, since after accounting for measured baseline variables (geographical place of residence, deprivation level, time period, 'centre' and other quality of care variables), it is unlikely that travel time direct predicts all-cause mortality. This assumption will also be discussed with the clinical panels (W1) (see also sensitivity analyses).

### *WP 3.3 Estimating effectiveness of curative RT versus surgery for each tumour type*

The three target trials will report differences between the comparison groups according to absolute risk differences for three-year mortality (primary endpoint) and other binary measures, and difference in means for continuous measures (secondary endpoints). We will use a local instrumental variable approach to estimate the relative effectiveness of RT versus surgery for each individual, as this approach can fully account for confounding and heterogeneity across patient subgroups (54). We will report relative effectiveness across all patients included in each target trial, and for each pre-specified subgroup of interest: tumour size and spread to nearby lymph nodes and/or to distant sites, age (years), performance status, smoking status, Charlson comorbidity index, and year of diagnosis. This analysis will

be conducted according to the intention-to-treat principle, recognising that patients may experience delays in the receipt of either curative intervention, may not complete their allocated treatment or may switch from one treatment option to the other. Following this principle, we will include all patients from the time they meet the inclusion criteria, and adjust for covariates anticipated to predict the assigned treatment and the outcome, according to their observed level at baseline (time zero).

The local instrumental variable approach comprises two stages. In the first stage, Probit regression models will be used to estimate the initial propensity score as a function of covariates and the IV. In the second stage, this predicted propensity score will be included alongside covariates in Generalised Linear Models with appropriate link functions for continuous or binary outcomes. Models at both stages will adjust for case-mix, organisational- and temporal factors described above including time period, proxies for care quality, defined by rates of 30-day and 1-year mortality for each NHS hospital trust for the early-stage cancers in question, for the year prior to the individual's diagnosis. The estimates will be reported with bootstrapped confidence intervals that allow for the clustering of individuals within NHS trusts and cancer alliances, and with multiple imputation to allow for missing covariate information.

***WP 3.4 Sensitivity analyses***

Sensitivity analyses will be undertaken to assess whether the results are robust to alternative definitions and assumptions. First, alternative inclusion criteria with respect to the time to curative treatment will be applied, including stricter (within three months of diagnosis), and looser (within nine month) cut-offs. Second, we will consider as an alternative instrumental variable, the percentage of eligible patients receiving RT versus surgery in each NHS trust in the year preceding the individual patient's diagnosis. Third, rather than using an instrumental variable analysis, the study will instead undertake conventional risk adjustment assuming that all relevant confounders have been measured, while assessing the impact of plausible levels of unobserved confounding on the results. Fourth, as in WP2, we will exclude data from the first wave of COVID-19 in England to assess the extent to which the results are sensitive to the inclusion of this period that is anticipated to be atypical for the provision of cancer services.

***WP 3.5 Output and Interpretation of results (leads Faivre-Finn, Choudhury, Cresswell, Vohra, Aggarwal, Lugo-Palacios)***

**We will report the relative effectiveness of RT versus surgery according to differences in absolute risk of 3-year mortality for each cancer. In interpreting the results, we will draw on insights from the clinical panels, and patient interviews, about the influence of local organisational factors and patient preferences on curative treatment decisions. The interpretation of the results will be according to the specific time-period. This will be important to provide recommendations for periods when the NHS is under exceptional pressures, such as during the first wave of COVID-19, and under prolonged pressures; for example, the increasing waiting lists for cancer care during the subsequent waves of COVID-19.**

***WP 4: Cost-effectiveness (Objective 4)***
***(lead Lugo-Palacios and Griffin advisor on combining inequality and cost-effectiveness)***

The cost-effectiveness analyses (CEA) will take the NHS and Personal Social Services perspective recommended by NICE. For each early-stage cancer we will report the relative cost-effectiveness of curative RT versus surgery strategies, over a lifetime time horizon. The choice of comparators will not include a 'no curative treatment alternative' as this is not a recommended treatment alternative for people with these early-stage cancers. The study will

incorporate patient-level resource use and mortality data from the linked dataset, combined with unit costs and health-related quality of life (HRQoL) estimates from the literature (68-73). The CEA will follow the assessment of effectiveness, in using travel time as an instrumental variable to address confounding. The value of implementation analysis will incorporate the findings about inequalities (WP1), to report the value of increasing the uptake of the most cost-effective curative intervention for each cancer, within sociodemographic groups (e.g. according to deprivation-level).

### *WP 4.1 Resource use and unit costs*

The linked datasets will identify resource use data for those categories anticipated to drive incremental costs, including the delivery of radiotherapy, surgical treatments, systemic care, hospital inpatient stays, and outpatient visits. Data for all types of external beam radiotherapy, doses, and fractions delivered to eligible patients will be extracted. We will identify the OPCS code of all surgeries and operative procedures performed on each eligible patient. We will obtain the drug administered, dose, number of cycles, and route of administration for patients undergoing chemotherapy including pre- or perioperative therapies, as well as those with curative and palliative intent. Information from the linked dataset on all hospitalisations since the date of cancer diagnosis will be extracted. We will distinguish between the time spent in critical care and on general wards, and all outpatient visits and accompanying medical procedures (e.g. imaging),

Unit costs, including those for RT and surgical strategies, will be taken from the NHS National Costs Collection (74) and the PSSRU Unit Cost databases (75). We will combine resource use with unit costs to report total costs per patient for the maximum duration of follow-up.

*Outcomes*

We will use ONS data for vital status which will be available for between three and seven years from date of diagnosis. We will calculate the number of life year years from the date of diagnosis up to three years, and for the maximum observation period available. We will use the maximum available survival data in extrapolations to lifetime survival, recognising that for these three tumour types 5-year survival is relatively low. These extrapolations will follow recent recommendations (76), and in choosing the more appropriate parametric models will differentiate between mortality that is ‘cancer-specific’ (see WP3), versus ‘background’ all-cause death for which general population death rates will be more appropriate.

We have undertaken a literature review of published studies that used a recommended, generic instrument to estimate HRQoL for these early-stage cancer patients (68-73). HRQoL estimates for each cancer, and according to disease stage, performance status, age, and number of comorbidities will be extracted from the sources selected. We will use the ‘area under the curve’ approach, to combine survival time with HRQoL estimates from the literature review, to report lifetime quality-adjusted life years (QALYs) for each cancer.

### *WP 4.2 Evaluating relative cost-effectiveness of RT versus surgery*

We will extend the previous instrumental variable analyses to report the incremental net monetary benefit (INB) of curative RT versus surgical strategies overall and for those subgroups for whom there is a clinical and decision-making rationale (e.g. cancer stage, performance status)

### *WP 4.3 Sensitivity analyses*

We will re-consider the previous scenarios (WP3) for the CEA. In addition, we will consider alternative time horizons (five years versus lifetime), different parametric models for the extrapolations, and alternative sources of HRQoL data. Finally, we will adopt a societal perspective by incorporating patient costs e.g. travel time, or time away from usual activities while receiving or recovering from either curation intervention.

### *WP 4.3 Evaluating the value of implementation (advisor Prof Susan Griffin, York)*

The study will combine the findings from the inequalities research (WP2) with those of the CEA (WP4). While we considered using a distributional cost-effectiveness framework, it was judged impractical to apply within this study. In particular, the requisite weights to address any 'efficiency versus equity trade-offs' were not available, and eliciting appropriate weights within the proposed research was judged infeasible. Instead, we will apply a value of implementation framework (77) to combine the inequalities (WP2) with the CEA results. For each underserved subgroup, we will estimate the value and costs of increasing the uptake of the more cost-effective intervention, from current levels to 100%. We will identify the number of patients in each sociodemographic subgroup who either receive no curative treatment or the less cost-effective treatment and multiply it by the incremental net monetary benefit of the more cost-effective intervention. We will consider the expected effectiveness and costs of specific implementation strategies. We will draw on insights from the clinical panels and patient interviews in considering barriers that subgroups may experience in accessing curative treatments within complex cancer pathways.

**WP 4.4 Output: we will provide evidence about which curative intervention is most cost-effective for each early-stage cancer. We will provide evidence to help service providers improve uptake of the curative intervention that is more cost-effective overall, with a focus on those sociodemographic subgroups for whom uptake is relatively low.**

## 6. Dissemination, knowledge mobilisation and pathways to impact

### *6.1 Dissemination*

We will use findings from all four WPs to develop recommendations for each cancer about:

- the major organisational barriers that need to be addressed to improve access to either curative intervention

- the curative treatment strategy that is more effective, and more cost-effective

-the sociodemographic groups that have low uptake of the curative intervention that is more cost-effective

--improving patient experiences of the curative treatment pathway, for example in the provision of accessible information to underserved groups.

We will publish seven open access peer-review journal articles (patient interviews, descriptive analysis of the receipt of curative and non-curative treatments, inequalities, impact of COVID on inequalities, effectiveness, cost-effectiveness, overall recommendations for policy and patients). The target journals will include clinical, social science, policy and health economics journals. We will work with our PPIE co-applicants, the Centre for Ethnic Health Research, the National Cancer Research Institute (NCRI) Consumer forum, and with representatives from national charities to co-produce accessible, culturally sensitive and appropriate easy read documents, videos, infographics and lay summaries. We will co-produce recommendations for implementation of our findings with professional bodies and

PPIE co-applicants which will be made available on our own project website (e.g. sort.lshtm.ac.uk), and those hosted by national cancer charities, and the NCRI.

### *6.2 Knowledge mobilisation*

The study will generate outputs and evaluation methods that are highly relevant for a broad stakeholder group including multidisciplinary cancer clinicians (surgeons, oncologists, burse specialists); patients; professional bodies (e.g. Royal College of Surgeons, Royal College of Radiologists, British Association of Urological surgeons (BAUS) British Thoracic Oncology Group), NICE guidelines developers and NHS commissioners. Many of these groups will also be represented within our project steering committee. We recognise the importance of bringing together all the above stakeholders and will do so within a stakeholder translation workshop in month 33 of the project. We will work with these groups to inform future clinical practice and the provision of accessible information for patients.

*All stakeholder translation workshop*

For each cancer we will convene translation workshops to consider how the study findings can improve clinical practice, and the information available to patients. We will discuss the priorities for future research provoked by this study's findings. The workshop will be co-led by our PPIE co-applicants, clinical co-applicants, and the study PI/co-PI. The workshop participants will include:

a) *PPIE members,* including patients with these three tumour types, carers, members of the public including underserved communities, and representatives of national, local charities and NCRI clinical subgroups (lung, bladder, upper gastrointestinal).

b) *Multidisciplinary clinical teams, cancer alliances,* including clinical and medical oncologists, surgeons, radiotherapists, cancer nurse specialists representing all 21 cancer alliances.

c) *National and international guideline committees,* including those involved in national and international guideline committees, European Society of Radiation Oncology and the Royal College of Surgeons of England.

d) *NHS England, cancer alliances and Integrated Care Systems (ICS)*. Including leads of cancer alliances, and relevant clinical leads at NHS England.

### *6.3 Pathways to impact*

**The results and their implications for the provision of future cancer services and the information available to patients will be discussed with the following groups:**

*National and international cancer guidelines and networks:* clinical co-applicants and advisors will ensure timely results are available to inform future guidelines and guidance. Faivre-Finn and Choudhury have led guideline development and work closely with the British Uro-oncology Group (BUG) and the British thoracic oncology group (BTOG), Cresswell is President of the British Association of Urological Surgeons Advisors, and McGrath (advisor) is GIRFT lead for urology.

*NHS England:* advisors include those leading workforce planning at NHS England, and will consider the implications of the findings for investments in workforce, capital infrastructure, and changes to the national tariff to incentivise provision of cost-effective interventions.

*Parliamentary health select committees:* results will be discussed with colleagues on parliamentary select committees including: the All parliamentary group for Radiotherapy (lead, Tim Farron) with a view to informing updates to the National Inquiry for cancer services.

*Civil society and charity groups:* the provision of information to patients will be discussed with representatives of national charities including the Roy Castle Lung Cancer Charity, Fight Bladder Cancer and the Oesophageal Patients Association.

*National and international groups of oncologists, surgeons, health service managers and researchers:* findings will be presented at conferences such as the European Society of Radiation Oncology, the National Cancer Research Institute (oncological, surgical), the Health Services Research network, and Health Economist study group meetings in the UK and USA.

## 7. Project/research timetable

**Grant Start date: June 2023**

On funding notification, we will prepare study protocols and ethics applications.

| **Months** | **Activities** |
|---|---|
| -6 to 0 | Prepare initial study protocols<br>University ethics application and approval<br>Access already available NCRAS data. |
| 0 to 3 | WP1, Data extraction, provisional definition of cohorts, construction of care pathways, prepare data for clinical panels. |
| 3 to 6 | WP1. Convene clinical and PPIE panels, |
| 6 to 18 | WP1. Undertake patient interviews. Finalise and publish study protocols, and update ethics application. |
| 6 to 18 | WP2. Undertake inequalities analysis, prepare peer-review papers |
| 18 to 24 | WP3. Prepare analysis code for the three target trials |
| 21 to 27 | WP4. Prepare analysis code for CEA and extract additional parameters required from literature review. Apply for NCRAS data refresh |
| 28 to 33 | WP3 and 4. Final assessments of effectiveness and cost-effectiveness |
| 33 to 36 | Translation workshops, conference presentations, peer review papers |
| | |
| 33 to 36 | Final draft report to NIHR |

## 8. Project management

Prof Richard Grieve (PI) will take overall responsibility for project delivery (20% WTE); he will guide the team, ensure close collaboration between the methodological and clinical inputs, and monitor progress against timelines. The study management group will include leaders of each WP, and the research fellows working on the project and will meet bi-weekly. We will discuss progress quarterly with all co-applicants, and will report annually to the Study Steering Committee. The costs requested include those for an experienced research manager (20% WTE) to co-ordinate this complex project.

The Study Steering committee will meet annually to guide the delivery of the project with particular attention to ensuring the translation strategy reaches underserved communities. The committee will be chaired by Prof Jane Blazeby, a leading health services research and Consultant Surgeon, University of Bristol. Other members will include: John McGrath (GiRFT national joint lead, urology), Prof Ramani Moonesinghe (NHS England), Prof Matt Sutton (University of Manchester), Prof Andrew Briggs (LSHTM), Michael Chapman, Research Director, NHS digital, Paul Charlton (PPIE, ex cancer carer) and David Chuter (PPIE, lived

experience of oesophageal cancer), Lydia Makaroff (chief executive, Fight Bladder cancer), representatives from the Centre for Ethnic Health Research, and from other national charities for these three cancers.

## 9. Ethics approval

The project uses routinely allocated anonymous administrative data, discussions with PPI and clinical representatives and interviews with patients recruited by the respective charities. The project will not require approval by NHS ethics committees, but we will apply for approval from the LSHTM Research Ethics committee in advance of the project start date, and for amendments to the ethics approvals once the study protocols have been finalised.

## 10. Project/research expertise (LSHTM unless stated, see also costing section)

Prof Richard Grieve (PI) is a health economist/methodologist with over 25 years of experience, and a specialist in designing, analysing and interpreting comparative effectiveness and cost-effectiveness studies used to inform service delivery.

Dr David Lugo-Palacios (Co-PI) is an experienced health economist/econometrician with expertise in addressing the methodological issues that arise with analysing routine health data. He will lead major aspects of WP1, WP3 and WP4.

Prof Bernard Rachet is an eminent cancer epidemiologist who leads a programme of work examining cancer inequalities using cancer registry data. He will lead WP2.

Prof Ellen Nolte is a leading health services researcher with expertise in qualitative research methods and their integration within mixed methods studies. She will oversee the patient interviews, and how the overall study draws on insights from the qualitative research.

Andrew Hutchings has expertise in the use of linked routine data for health services research, and will co-lead the descriptive analyses for defining the complex care pathways, and provision of information for the clinical panels in WP1.

Dr Stephen O'Neill is an econometrician with experience of instrumental variable methods in particular their application to routine NHS data. He will advise on the analyses for WP3 and 4.

Dr Ajay Aggarwal (Guy's & St Thomas' NHS Trust and LSHTM) is a consultant clinical oncologist specialising in the delivery of radiation therapies. He holds an NIHR advanced fellowship studying integrated care systems for specialist cancer treatments using routinely collected data. He will provide clinical expertise on the care pathways from an oncologist perspective, and co-lead the patient interviews.

Prof Corinne Faivre-Finn (The Christie NHS Foundation Trust and University of Manchester), is a consultant clinical oncologist with a specialist interest in radiation therapies for lung cancer, Radiotherapy Chair of the European Organisation for Research and Treatment of Cancer Lung group and member of the European Society for Radiotherapy and Oncology Clinical Committee . She will lead the clinical panels and translation activities for early stage lung cancer.

Prof Ananya Choudhury (The Christie NHS Foundation Trust and University of Manchester), is a consultant clinical oncologist with a specialist interest in radiation therapies for bladder

cancer, and was on the NICE bladder cancer guideline development group. She will lead the clinical panels and translation activities for early stage bladder cancer.

Ravinder Vohra (Nottingham University hospitals) is a consultant surgeon with specialist interests in oesophago-Gastric cancer surgery, he will lead the clinical panels and translation activities for early-stage oesophageal cancer.

Jo Cresswell (South-Tees hospital) is a consultant urological surgeon and president of the British Association of Urological Surgeons. She will lead the translation activities relating to bladder cancer.

**PPIE leads**

Yuki Alencar is manager of the inequalities in cancer outcomes network, and has extensive experience in leading PPIE activity with cancer patients, she will lead the PPIE aspects of the project. Yuki will also coordinate the input from the PPIE partner organisations, the National Consumer Research Form at Cancer Research UK, the Centre for Ethnic Health research, and the charities Fight Bladder Cancer; the Roy Castle Lung Cancer Foundation, the Oesophageal Patients Association (OPA), The VOCAL PPIE group in Manchester, and B'ME Against Cancer

Paul Charlton (PPIE) is an NIHR patient ambassador, previously PPIE member of NIHR commissioning committee, and lived experience as a carer for people with cancer. Paul has extensive experience in leading PPIE activities for NIHR funded projects including the ESORT study, and has guided the PPIE strategy for the proposed research. He will advise on all PPIE aspects helping ensure that patient information sheets, and workshop preparatory materials are accessible to underserved groups, will facilitate active participation from these groups on PPIE panels and in patient interviews, and will co-lead the PPIE workshops.

David Chuter (PPIE) is an oesophageal cancer survivor and ex-chair (2017-2020) of the Oesophageal Patients Association, with continued links to the charity and currently Vice Chair of the Board and Chair of the Patient Advisory Committee of Digestive Cancers Europe.

**Named Researcher**

Katja Gravenhorst has extensive experience of designing theoretically informed interview studies involving underserved groups and of conducting and analysing in-depth interviews exploring patient experiences. She will conduct the patient interviews, analyse the results, and draft the peer-review paper reporting these findings (WP1).

## 11. Success criteria, barriers/risks and mitigation strategies

| Success criteria | Barriers/Risks | Mitigation |
|---|---|---|
| Accessing NCRAS data approved for this purpose | Data access delayed while all approvals are granted | Approval process will be initiated on notification of funding. Research team already have access to linked data |
| Final selection of subpopulations, intervention and comparator strategies | Complex curative treatment pathways that differ across settings | Team experienced in defining treatment strategies from routine data. Clinical panel will ensure populations and strategies relevant to NHS |
| Strategy to missing data makes clear assumptions | Some case-mix data will be missing | We will draw on our experience of methods for handling missing data. |
| Instrumental variable analysis is judged to address confounding | Patients who receive curative RT may be sicker than those have surgery | The target trial will only include patients who have similar prognosis, and the instrumental variable analysis will minimise residual confounding. |
| The study's results help inform changes to service provision and patient choice | Clinical and health service decision-makers are reluctant to use evidence from an observational design. | Key clinical opinion leaders have shaped the research, and insights from patient interviews will help ensure information is communicated appropriately |

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