Research protocol

eRAPID: Electronic monitoring of patient-reported symptoms in patients with a diagnosis of thoracic cancer managed at Leeds Cancer Centre

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List of abbreviations

ACE	Adult Comorbidity Evaluation
CNS	Clinical Nurse Specialist
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EMR	Electronic medical record
EORTC	European Organisation for Research and Treatment of Cancer
eRAPID	Electronic patient self-reporting of adverse events: patient information and advice
HCP	Healthcare professional
HCRU	Healthcare resource utilisation
HRA	Health Research Authority
HRQoL	Health related quality of life
IRAS	Integrated Research Application System
IRB	Institutional Review Board
LCC	Leeds Cancer Centre
LoT	Line of therapy
LTHT	Leeds Teaching Hospital NHS Trust
MDT	Multi-disciplinary team
NCI	National Cancer Institute
NHS	National Health Service
NSCLC	Non-small cell lung cancer
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI	Principal investigator
PPE	Palmar-Plantar Erythrodysesthesia
PPM	Patient pathway manager
PRAE	Patient reported adverse event adaptation
PROM	Patient reported outcome measure
PS	Performance status
QoL	Quality of life
RCT	Randomised controlled trial
REAL-Oncology	Real world Evidence Alliance in Leeds
SACT	Systemic anti-cancer treatment
SCLC	Small cell lung cancer
SoC	Standard of care
TKI	Tyrosine kinase inhibitors

1. Background

Thoracic cancer prevalence, subtypes and prognosis

Lung cancer is a leading cause of cancer-related morbidity and mortality, accounting for 11.6% of all cancer-related diagnoses and 18.4% of all cancer-related deaths worldwide [1]. Mortality from lung cancer, both in men and in women, is projected to double worldwide within the next two decades, increasing from an estimated 1.6 million in 2012 to 3 million in 2035 [2].

Lung cancer can be divided into two main categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of lung cancer diagnoses and tobacco smoking remains the most established cause. With fewer smokers in Western countries, lung cancer has become more prevalent in former than current smokers. Almost 70% of NSCLC cases are diagnosed in the advanced/metastatic stages (IIIB-IV) of the disease [3] [4]. SCLC is similarly linked to tobacco smoking and the majority of cases are diagnosed in metastatic stages; SCLC is characterised by its rapid growth [5]. Patients with lung cancer have a poor prognosis. The National Lung Cancer Audit of patients diagnosed in the UK in 2015 found a 1-year survival of 38% [6]. Pleural mesothelioma is a rare form of lung cancer, which is predominantly attributed to asbestos exposure. The average incidence across European countries is 20 cases per million people [7].

Treatment

Historically, all patients with NSCLC were treated with the same algorithm, without consideration of their histological sub-type or their molecular profile [9]. More recently, with increasing recognition of the role of histology and mutation status on treatment response, personalised therapies based on histology and/or molecular pathology have become the standard of care [10]. The stage of NSCLC determines treatment options, with surgery being the mainstay of treatment for patients in early stages of the disease (stages I-IIIA). Additionally, those with localised disease spread (stages II and IIIA) may receive adjuvant therapy [11]. In patients with advanced/metastatic disease (stages IIIB-IV) and a performance status (PS) score of 0-2, the first line treatment options include chemotherapy regimens with or without immunotherapy or targeted biological therapy; in those with a PS of >2 and without documented evidence of active EFGR mutation or ALK rearrangement, best supportive care is advised [10].

Patient-reported outcome measures (PROMs)

PROMs encompass data self-reported by patients about how they feel and function such as symptoms, physical function, emotional distress and health-related quality of life (HRQoL). PROMs are becoming important for patient care, as they provide the means of recording the experience of the patient in a structured format readily available to relevant clinical staff [12]. Using PROMs in oncology practice can support doctor-patient communication, improve symptom control and patient HRQoL [13].

Systematically and repeatedly assessing symptoms with electronic methods during treatment of advanced cancers improved HRQoL, enhanced treatment tolerance, reduced the number of emergency room visits and lengthened survival [14]. Recently a randomised controlled trial (RCT) in advanced lung cancer using web-mediated follow-up showed overall survival benefit of 7-9 months compared to usual care, whilst maintaining cost-effectiveness. The relapses were detected earlier in patients in the intervention arm facilitating earlier and appropriate treatment initiation compared to patients in the control arm [15].

2. Study aim and objectives

The purpose of this study is to systematically capture patient reported disease-related symptoms, treatment-related side effects and HRQoL in a cohort of patients treated with systemic anti-cancer therapy (SACT) for thoracic cancer in a real world setting. The aim of this study is to benefit patient care by detecting disease progression and treatment toxicity both more accurately and timely than conventional follow up.

The objectives of the study are:

1. To compare disease-related symptoms and HRQoL across groups of patients with a diagnosis of thoracic cancer stratified by patient and clinical characteristics.
2. To compare treatment-related side effects of patients with a diagnosis of thoracic cancer prescribed chemotherapy, tyrosine kinase inhibitors (TKIs) or checkpoint inhibitors.
3. To compare outcomes, such as healthcare resource utilisation (HCRU), in a cohort of patients with a diagnosis of thoracic cancer systematically self-reporting symptoms.
4. To examine the patient acceptance and feasibility of this approach. To determine optimal means to engage patients with a diagnosis of thoracic cancer in the systematic reporting of PROMs in a real world setting.
5. To assess the utility to of PROMs reported by patients with a diagnosis of thoracic cancer to their treating healthcare professionals (HCPs).

3. Method

3.1. Study design overview and setting

This is an interventional, prospective real world study conducted at a single cancer centre in England. Leeds Cancer Centre (LCC) is a major regional NHS cancer centre in northern England serving a metropolitan catchment area of 750,000 people for secondary care and over 5 million for tertiary care.

Patients with a diagnosis of thoracic cancer prescribed SACT (chemotherapy, TKIs or checkpoint inhibitors) will be enrolled in the study at oncology clinic visits at LCC. The intervention will be an electronic patient self-report of disease-related symptoms, treatment-related side effects and HRQoL. The responses will be provided immediately to treating HCPs during the study period. The study project manager/research nurse will provide training to the treating HCPs on how to use the software capturing PROMs and how to view the results. At each clinic scheduled as standard care the research team will make the treating HCP aware that the patient is taking part in clinical research and self-reporting symptoms electronically. This design allows the assessment of the utility to HCPs of PROMs reporting in the real world setting and provides an opportunity to study customised patient interventions based on PROMs reporting.

There will be two cohorts of patients. Cohort inclusion is not random; it is dependent on patient choice. The two cohorts will be:

1. Cohort 1 (Online access cohort): Patients with online access who will report PROMs away from LCC clinic visits at a location of their choice, using their own devices (laptop, tablet, smart phone). They will be requested to reported symptoms and side effects once a week, and additionally at any time when they feel unwell.
2. Cohort 2 (In clinic access cohort): Patients without online access who will complete PROMs on a tablet at LCC in a private space prior to clinic visits. The frequency of reporting will be determined by routine clinical care (clinic visits are approximately every 3-4 weeks during treatment.)

This is a proof of concept study to develop the capability to capture PROMs in routine clinical care at LCC in terms of hardware, software and staff knowledge. The analysis of PROMs will be descriptive, and the number of patients to recruit in the study will not be stipulated. To determine the optimal means to engage patients in the systematic reporting of PROMs, the recruitment and compliance rate will be recorded overall and will be compared between the two cohorts (Cohort 1 Online access cohort to Cohort 2 In clinic access cohort).

To assess the utility of captured PROMs to HCPs, there will be interim review, semi-structured interviews and feedback sessions during the study period.

3.2. Patients

3.2.1. Selection criteria

Patients must meet all of the following criteria in order to be enrolled:

- Diagnosis of thoracic cancer:
  - Non-small cell lung cancer (NSCLC), or
  - Small cell lung cancer (SCLC), or
  - Pleural mesothelioma
- Age ≥18 years
- Initiation of a SACT LoT (listed in Table 1) with a clinic visit at LCC during the recruitment period
- Willing and able to provide written informed consent
- Fluency in English

Patients meeting any of the following criteria are not eligible for participation:

- Cognitive impairment
- Receiving best-supportive care only

The aim is to include a representative real world cohort of patients with a diagnosis of thoracic cancer prescribed SACT. Disease stage and time since diagnosis are not included in selection criteria; however, these details will be captured for analysis purposes (see variable list in section 3.4). Patients enrolled in clinical trials will not be excluded from this study; however the possibility that enrolment in this study might reduce compliance or interfere with results of other trials will need to be considered and approved by the principal investigator (PI) of the trial before patients are approached. Patients receiving best supportive care will not be enrolled in the study; however patients who initiate SACT and are enrolled in the study then complete SACT will be followed until death or the end of the study period.

Table 1: SACT prescribed for enrollment in the study

Diagnosis	Treatment description
NSCLC	Platinum-based chemotherapy: • Carboplatin-based • Cisplatin-based Non-platinum-based chemotherapy • Pemetrexed TKIs Immune-checkpoint inhibitors (inc. anti-PDL1)
SCLC	Platinum-based chemotherapy: • Carboplatin-based • Cisplatin-based Non-platinum-based chemotherapy
Pleural mesothelioma	Platinum-based chemotherapy: • Carboplatin-based • Cisplatin-based Non-platinum-based chemotherapy • Pemetrexed

3.2.2. Number of patients

The number of consecutive patients to be enrolled in this study, and the number of patients belonging to each cohort, will not be stipulated. All patients meeting patient selection criteria during the recruitment period will be invited to participate. Approximately 100 patients are expected to be enrolled (70 patients with a diagnosis of NSCLC, 20 patients with a diagnosis of SCLC, and 10 patients with a diagnosis of pleural mesothelioma). The sample sizes are estimates and maximum numbers and has been based on an estimate that 150 thoracic cancer patients per year start a course of systemic anti-cancer therapy (SACT) at Leeds Cancer Centre. This includes patients starting a first line, second line or even third line of SACT and who are followed up by oncology consultants. This estimate is from a survey of routine clinical practice in lung oncology clinics at Leeds Cancer Centre (Snee et al 2018). The rate of 70-75% was based on the recruitment experience over

10 years of Patient Centred Outcome Research studies of electronic patient reported outcomes with cancer patients at Leeds.

3.2.3. Patient withdrawal

Patients from both cohorts may withdraw consent and discontinue participation in the study at any time, with no effect on their care. If a patient is withdrawn prior to completing the study follow up period, any known reason for withdrawal will be documented. Information already collected as part of the study will be retained for analysis (patients will be asked if they consent to this in the consent form).

3.3. Intervention

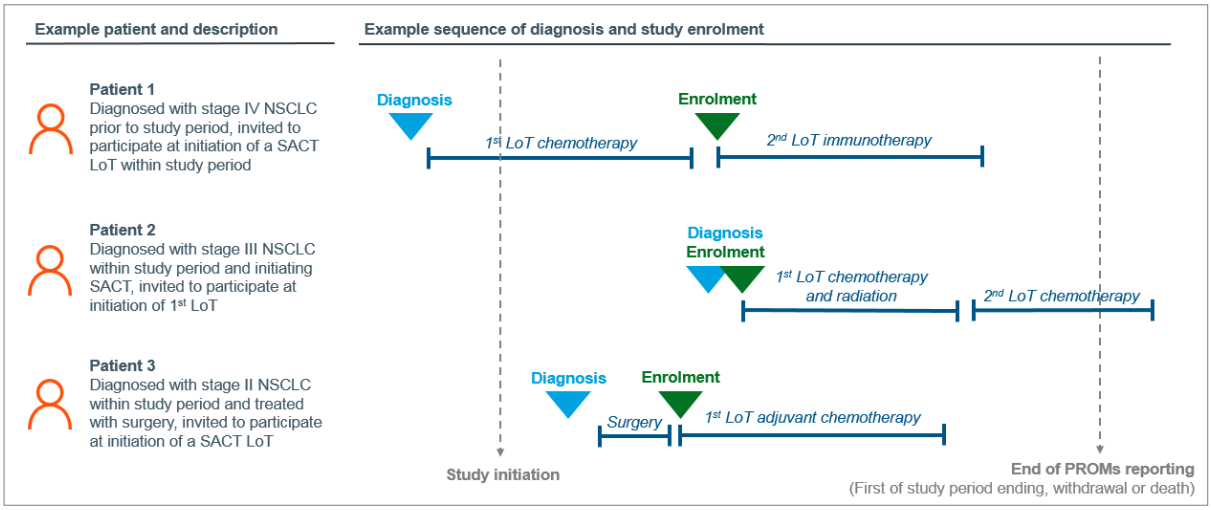
3.3.1. Recruitment and study duration

Index date is defined in both cohorts as the initiation of a line of SACT within the study period. For patients newly diagnosed within the study period, this will be the initiation of their 1st line of therapy (LoT). For patients diagnosed prior to the study period, the index date will be initiation of 1st or subsequent LoT. Collecting baseline PROMs at the start of a LoT (rather than index date being at any time during a SACT LoT) allows the analysis of change from baseline in disease- and treatment-related side effects with each new LoT. See Figure 1 for the sequence of diagnosis, treatment initiation and study enrolment for three example patients. Patients will continue to report PROMs until end of study period (irrespective of whether they continue or discontinue SACT), withdrawal of consent or death.

The project manager will work closely with the thoracic cancer multi-disciplinary team (MDT) at LCC during the study period to review the treatment plan of newly diagnosed and previously diagnosed patients to assess eligibility for the study. Eligible patients will be identified by the clinical team at a routine clinic visit. They will be first approached by a member of the clinical team to ask if they would agree to consider the study and speak to the project manager (or a trained researcher). The project manager will explain the study, provide a patient information leaflet. Patients will be given sufficient time to consider the information and ask any questions. If the patient wishes to be enrolled, they will be set up on the software (provided with a username and password), and trained how to use the system. The formal consent will be completed electronically, at the beginning the training session. Afterwards the participant will be invited to complete the baseline questionnaires on the electronic platform.

Following ethics board approval of the study, recruitment will occur at LCC only over a 12-month period with a subsequent 12-month follow up period. This duration means patients recruited in the first month have a 24-month follow up opportunity. There will be an interim study review (estimated September 2020, 12 months from ethics board application) to assess the number of patients enrolled, description of patients enrolled, systematic PROMs reporting compliance, and interim HCP feedback.

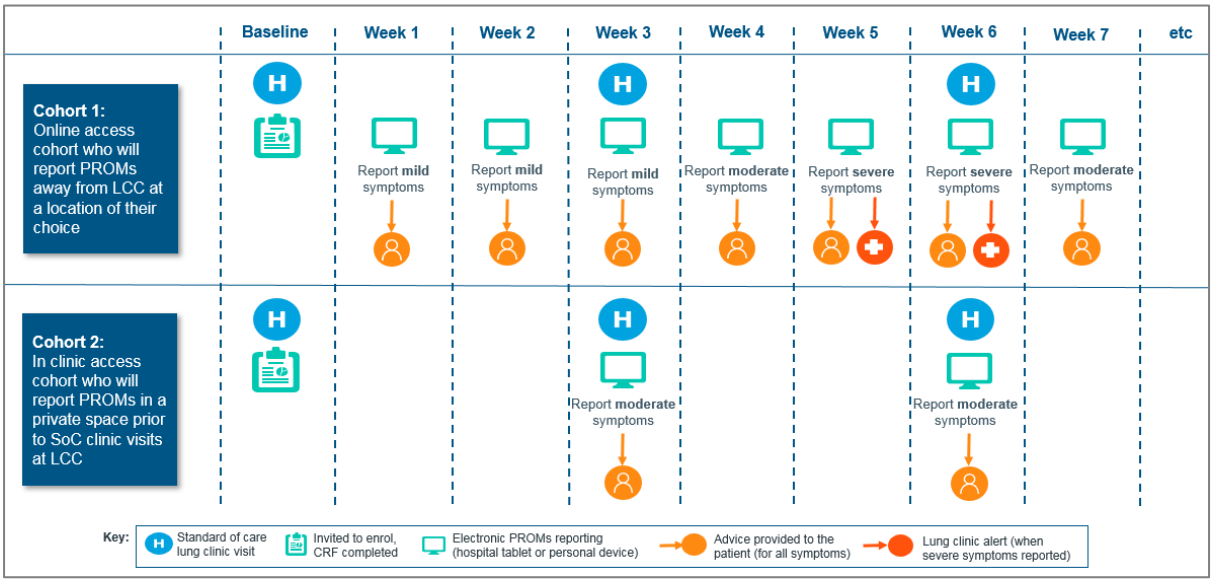
Figure 1: Study design visual: Sequence of diagnosis, treatment initiation and enrolment



3.3.2. Changes to standard of care

Patients' clinic frequency will be determined by routine clinical care; there are no protocol mandated study visits (see S 3.3.3.3 for detail of the frequency of clinic visits for the different treatment groups). For Cohort 1 (Online access cohort), all reporting of PROMs will occur away from Leeds Cancer Centre clinic visits at a location of the patient's choice. If the patient has not completed the online questions recently, they will be invited to do this in clinic before seeing the oncologist. For Cohort 2 (In clinic access cohort), all reporting of PROMs will occur in a private space at Leeds Cancer Centre prior to clinic visits. When an enrolled patient completes a questionnaire they can view their results in a graphic format and receive immediate online bespoke advice on self-management strategies for mild symptoms or side effects. For moderate or severe problems patients will be advised to contact the hospital, and the system generates notifications via email for predetermined severe adverse events to the relevant clinical team. See Figure 2 for an example patient pathway by cohort.

Figure 2: Study design visual: Example patient pathway by cohort



3.3.3. Patient reported outcome measures

3.3.3.1. Items to report

There are two types of PROMs to capture: disease-related symptoms and treatment-related side effects. Disease-related symptoms are symptoms that can be caused by thoracic cancer (their appearance may indicate recurrence) and treatment-related side effects are symptoms that could be caused by the SACT prescribed for the treatment of thoracic cancer. Some symptoms, such as breathlessness, can be caused by disease or treatment. There will be a maximum of eight disease-related symptoms asked of a patient at any one time, whereas the number of treatment-related side effects will vary by type of SACT. Treatment-related side effects have been categorized as more prevalent for certain treatment types (chemotherapy, TKIs or checkpoint inhibitors) and these will be prioritized for response when a patient is prescribed those treatments. All patients will have access to their recorded symptoms and side effects.

The selection of items for the symptoms and side effects questionnaire involved three steps. Oncologists working at LTHT identified disease-related symptoms and treatment side-effects that are important to measure for patient care based on their clinical experience. The IQVIA Patient Centered Endpoints team conducted a literature review of disease related symptoms and treatment side effects on NSCLC only, which affects the majority of patients. The list of symptoms/side effects were the generalized to apply to SCLC and pleural mesothelioma patients. Finally, both parties reviewed the symptoms and side effects identified by the two methods.

The oncologists conducted three consensus exercises to select items for the symptom and side effects questionnaire, which were facilitated by the research team. The reviews were led by Dr. Katy Clarke, consulted other members of the LTHT Lung MDT, and involved a representative from the Clinical Nurse Specialist team and clinical specialists from the research team (oncologist and research sister) and IQVIA (clinical adviser in oncology). The outcomes of these exercises identified

six disease related symptoms: pain, cough (dry and productive and including haemoptysis although this is considered rare), shortness of breath/breathlessness, appetite loss, fatigue, depression/low mood and weakness/numbness. IQVIA's literature review identified five of these symptoms as clinically important: appetite loss, cough, fatigue, pain, breathlessness. Two items identified by the review as salient to patients, haemoptysis and jaundice were de-prioritised by clinicians because they are now rare. Haemoptysis could be identified by the questionnaire because of the inclusion of both dry and productive cough. See Table 2: Disease related symptoms and effects.

The oncologist's identified three effects of disease: impact on daily activities, depression and physical activity/performance status. Physical activity/performance status was found to be highly salient to patients, alongside insomnia and weight loss. The three impacts selected are two of those identified by patients (performance status and insomnia). Depression/low mood was selected as relevant to effects of disease and treatment. HRQoL will be measured using the EQ-5D-5L which also incorporates questions on daily activities and depression.

The review by the oncologist's identified 15 treatment side-effects, 12 were different to the disease related symptoms above and three were in both categories. Severe abdominal, muscle and joint pains have been included in the pain item, a core disease related symptom, similarly shortness of breath/breathlessness is included as a core disease related symptom. See Table 3: Treatment-related side-effects.

Four of the treatment-related symptoms were identified as salient to patients in IQVIA's literature review: fever/shivering/chills, nausea/vomiting, mucositis/stomatitis, and diarrhoea. Additional treatment-related symptoms identified through the literature review as salient to patients (and different to the identified disease-related symptoms) were alopecia and injection-site reactions for patients prescribed chemotherapy. Injection site reactions (extraversion i.e. pain, swelling or redness at injection site and phlebitis which is pain along the veins of the arm) was included because of their clinical salience, while alopecia was de-prioritized from the final list of treatment-related symptoms because it was seen as less important for clinical care. Further review by clinicians indicated there is a high degree of overlap in the side effects of the three different treatments (Table 3).

The final list of symptoms and side effects required in the full Lung Cancer PRAE-CTCAE questionnaire are documented Table 8: PRAE CTCAE symptom questionnaire.

Item	**Decision**
Pain (including pain in chest, and treatment related pain in abdomen, muscles or joints)	Important clinically & salient to patients
Cough (dry and/or productive, haemoptysis would be identified in this item)	
Breathlessness/shortness of breath	
Appetite loss	
Fatigue	
Limb weakness/numbness	Important clinically
Haemoptysis	De-prioritised as rare.
Jaundice	
Voice changes	
Facial swelling	
Effects	**Decision**
Insomnia/difficulty sleeping	Salient to patients
Depression/low mood	Salient to patients
Performance status/physical activity	Important clinically and salient to patients.
Health related quality of life (HRQoL)	Including instruments: QLQ-C30 & EQ-5D-5L

Table 2: Disease related symptoms and effects

Item	Treatment types			Decision
	Chemo-therapy	TKI	Checkpoint inhibitors anti-PDL1	
Fever, shivering, chills	+	+	+	Important clinically and salient to patients
Nausea	+	+		
Vomiting	+	+		
Mucositis/stomatitis (sore mouth/tongue)	+	+	+	Prioritised as important clinically, salient to patients and prevalent across 3 treatment types
Diarrhoea	+	+	+	
Constipation	+			
Indigestion/heartburn	+			
Severe abdominal pain (already included as pain, a core disease related symptom)	+	+	+	
Neuropathy	+		+	
Skin rash	+	+		
Itching		+	+	
Palmar-Plantar Erythrodysesthesia (PPE) (sore hands/feet)	+	+	+	
Eye irritation	+	+	+	
Muscle, joint aches and pains (already included as pain, a core disease related symptom)	+		+	
Breathlessness/SOB (already included as a core disease related symptom)	+	+	+	

Table 3: Treatment-related side effects

3.3.3.2. Instruments

Three instruments will be used in this study:

1. Patient Reported Adverse Event (PRAE) adaptation of the clinician reporting system Common Terminology Criteria for Adverse Events (CTCAE);
2. European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire of Cancer patients (QLQ-C30)
3. EQ-5D-5L a standardized instrument for measuring generic health status

Reporting frequency by cohort and instrument is described in Table 4 above. When patients are requested to complete more than one instrument in a session, the PRAE CTCAE will always come first, the EORTC QLQC30 will come second (if requested that session) and the EQ-5D-5L will come last (if requested that session). Patients can submit a questionnaire without responding to all questions.

PRAE CTCAE questionnaire in lung cancer

The primary instrument will be the PRAE CTCAE. The responses to each PRAE CTCAE question are allocated a score from 0-3 which correspond to the severity grades used by clinicians in the Common Terminology Criteria for Adverse Events (CTCAE). This is an international clinical tool providing descriptive terminology which can be used to report Adverse Events:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

The full list of symptoms and their grading from mild (1), moderate (2) to serious (3) are listed in Table 8: PRAE CTCAE symptoms and side effects questionnaire, in the study protocol. This questionnaire is the basis of the online symptom questionnaire completed by patients.

The PRAE CTCAE was developed by the Patient Reported Outcomes Group at the Leeds Institute of Cancer Research [19]. Selected PRAE CTCAE items were tested with 60 patients undergoing treatment (chemotherapy or biological) for breast, gynecological, colorectal, lung or renal cancers. The testing involved patients self-reporting symptoms most common in these five types of cancer using the PRAE CTCAE on a touch-screen computer followed by cognitive interviews over a 6-month period. As a result, changes were made to facilitate patient understanding, adding additional descriptors or images [20].

The PRAE CTCAE will be used to measure all of the disease-related symptoms, treatment-related side effects, insomnia and performance status. The PRAE CTCAE has the substantial benefit that the responses reported by patients will correspond to adverse event severity grading's already familiar to clinicians, and can be combined with bespoke advice for each particular symptom or side effect. Twenty three items have been selected for the study by clinicians. Eighteen of these are existing PRAE CTCAE items with questions and responses. Five of the items (limb weakness/numbness; skin rash, cough (including dry and productive), itching and eye irritation) do not have existing PRAE CTCAE questions. Questions for these items have been drawn up as part of the consultation exercise with clinicians described in the section 3.3.3.1 above using the PRAE CTCAE approach. Table 8 lists the selected symptom and side effects items in the questionnaire and the potential responses to each question.

Pilot study: PRAE CTCAE further item development
Draft questions have been drawn up for these items by oncologists and following a similar method used to develop the existing PRAE CTCAE questions [19]. The project manager will coordinate the Patient Reported Outcomes Group at the Leeds Institute of Medical Research at St James's to further develop questions, responses, advice and alerts which will be reviewed by clinicians managing patients with thoracic cancer and subsequently tested with a convenience sample of patients receiving SACT at Leeds Cancer Centre. Patients will be asked in an interview setting to provide feedback on their comprehension of the questions. Once changes recommended by clinicians and patients have been implemented, the questions will be uploaded into questionnaire software for use by patients enrolled in the study.

EORTC QLQ-C30
The EORTC QLQ-C30 (see **Error! Reference source not found.**) has 30 questions to assess the quality of life of cancer patients. This instrument was selected so that the responses of patients in this study can be compared to the responses of patients taking part in clinical trials and other studies. The EORTC QLQ-C30 covers 4 of the selected disease-related symptoms (pain, shortness of breath, appetite loss, fatigue), 3 of the selected treatment-relate side effects (diarrhoea, nausea, constipation) and all 3 of the selected outcomes (insomnia, performance status, quality of life).

EQ-5D-5L
The EQ-5D-5L (see **Error! Reference source not found.**), commonly used to measure health status, will be used to measure HRQoL. The five questions in the EQ-5D-5L relate to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition, there is a visual analogue scale used for patient-reported overall health.

3.3.3.3. Reporting frequency

Reporting frequency

The online questionnaire will be pre-programmed with the eRAPID PRAE CTCAE, EORTC QLQ-C30 and EQ5D-5L instruments at the required intervals by the project manager. The frequency of patient self-reported symptoms and side effects will differ depending on cohort inclusion (patients in Cohort 1 or Cohort 2) and frequency of routine clinics (for Cohort 2 In clinic access cohort).

Patients in Cohort 1 (Online access cohort) will be asked to log onto the software and complete the questionnaire weekly. The prescribed SACT and schedule of their routine clinics at LCC will not determine the frequency of completion of the questionnaire. The questionnaire will include the PRAE CTCAE every time, the EORTC QLQ-C30 and the EQ5D-5L at baseline then quarterly over the year, Electronic reminders will be sent to patients when questionnaire is due irrespective of whether it has been completed or not, and patients will be asked to additionally complete the questionnaires at any time when they feel unwell. If patients don't complete the EORTC QLQ-C30 or EQ5D-5L in the intended week, the questionnaires will be available for an additional 4 weeks either side to provide more time to complete (i.e. EQ5D-5L will be available to complete in weeks 8-10 from enrolment, weeks 16-18 from enrolment, etc). Table 4; describes the reporting frequency by cohort and instrument.

Patients in Cohort 2 (In clinic access cohort) will self-report symptoms and side effects on a tablet prior to routine clinic visits at LCC because they don't have online access or don't feel confident completing the questionnaires remotely. Therefore the treatment they're receiving and frequency of their routine clinics at LCC determines the frequency with which they complete the questionnaire.

Treatment pathways are complex and depend on type of treatment and rates of cancer response/progression. Making the assumption that patients who start first treatment do not progress for 12 months, then broadly,

- Patients on TKIs or Immunotherapy will have 8-9 planned treatment visits
- Patients on chemo-immunotherapy-therapy or chemo for adenocarcinomas will have 17 planned visits
- Patients on chemo-therapy for SCLC, NSCLC or others will have 10 planned visits (4 for chemo and 6 follow-up)

If patient progress within the first 12 months, they are likely to need more visits if suitable for 2nd line treatment or less visits, if for best supportive care.

Table 4 describes the average treatment pathways for 12 months. Symptoms and side effects will be duplicated across instruments in weeks where the questionnaire includes multiple instruments.

Table 4: Reporting frequency by cohort and instrument

Cohort	**Treatment type**	**Frequency of use of each instrument**		
		PRAE CTCAE	**EORTC QLQ-C30**	**EQ5D-5L**
Cohort 1 (Online access cohort)	All treatment types	Weekly	Baseline + 3 monthly. Total = 5	Baseline + 3 monthly. Total = 5
Cohort 2 (In clinic access cohort)	All treatment types	Every clinic visit	Baseline + 3 monthly. Total = 5	Baseline + 3 monthly. Total = 5

*If not completed in intended week, the questionnaires will be available for an additional 4 weeks either side.

Table 5: Lung cancer pathways for 12 months, assuming the patients do not progress

Treatment type	Planned treatment pathway	Follow-up	Max. Number of planned clinic visits for 12 months from start of treatment
TKI	Induction Two weeklyx2 (1 month) 4 weekly x 4 (4 months) 3 monthly until progression (7 months left =2-3 visits)	2 monthly	8-9 visits
Chemo adenocarcinoma	3 weekly until progression	-	17 planned visits
Chemo SCLC NSCLC	3 weekly x4 (3 months)	2 monthly (6 visits)	10 planned visits
Immuno-therapy only	6 weekly until progression	-	8-9 visits
Chemo-immuno-therapy	3 weekly for 2 years	-	17 planned visits

3.3.4. Software

ERAPID uses an online system utilizing a web-based questionnaire builder system, called QTool, to support the collection and clinical integration of patients' symptom and adverse event reports during and after cancer treatment. eRAPID was developed between 2010 and 2013, (funded by a National Institute of Health Research Programme Development Grant RP-DG-1209-10,031). The system enables patients to self-report symptoms online, receive tailored advice, and see their responses as graphs over time. Patient self-reports are almost immediately displayed in the electronic patient records for clinicians to view. This data can then be used in routine clinic visits to support clinician decision-making and focus on the most prevalent symptoms of thoracic cancer as well as the common and or most serious side effects of SACT. Since, 2013, the eRAPID approach has been extensively studied in a definitive RCT during chemotherapy for breast, gynaecological and colorectal cancer (n=508), a pilot two-centre RCT during pelvic radiotherapy (n=167) and a pilot study after upper gastro-intestinal surgery.

Since 2018, a new software system PROMPT was introduced that also allows:

- Allocation of patients to clinical pathways;
- Scheduling of PROMs online completion with patient reminders
- Display of results to clinicians in tabular and graphic formats, both in the electronic patient records (PPM+) or via separate PROMPT login.

The eRAPID system can be accessed remotely by patients or set up on a tablet so that patients without online access can report PROMs in LCC. There is no option to provide PROMs by paper in this study.

Algorithmic questionnaire scoring to generate severity-dependent management advice to patients and staff is incorporated in the eRAPID software when patients self-report symptoms and side effects using the PRAE CTCAE. The eRAPID reporting and intervention consists of the following components:

- Patients will login to QTool using a unique username and password and complete the questionnaire loaded in eRAPID remotely on computers/mobile phones/tablets or on a tablet provided in clinic at LCC.
- Immediate, tailored advice derived from a series of algorithms is generated in response to reported symptoms and toxicities.
- If severe symptoms are reported, patients are advised to contact the hospital immediately and an alert is sent to a member of the clinical team.
- For mild/moderate complications, information about self-managing these issues are provided in QTool and hyperlinks to more detailed advice on the eRAPID patient websites.
- The PROMs are immediately available for patients to view in the eRAPID system and for HCPs to review in the individuals' medical record patient pathway manager (PPM+) in LCC.
- The EORTC QLQ-C30 and EQ5D-5L instruments with a question about number of GP contacts with GP will be loaded into the same software.

3.3.5. Feedback about using eRAPID system from healthcare professionals and patients

Interviews will be conducted with a sub-set of participants from healthcare professionals and patients about their views of using the eRAPID system.
Healthcare professional interviews: Interviews will be conducted five members of staff (n=3 oncologists, n=2 CNSs). Interviews will be conducted twice during the study period: interim feedback at 4- 6 months into the study and at the end of the study. The aim of the interviews will be to gain feedback on the usefulness of the electronically reported PROMS. The topic guide will seek views about the usability of the eRAPID software and the perceived value and use of patient reported data within their clinical practice.
Patient interviews: Interviews will be conducted with patients during the study period about their experience of using eRAPID. Approximately 12 patients will be interviewed at different stages of using the system, including patients from both cohorts. Six patients will be interviewed early in the study between 2-3 months of using eRAPID and six patients with 6 months or longer experience of using eRAPID. Participants will be asked about their perceptions of the relevance and burden of completing the measures routinely, if they felt the system has had an impact on their care or self-care and their views of usefulness of eRAPID.
Observations: Research staff will keep field notes which record healthcare staff and patient's comments, questions or problems with the eRAPID system during the study period. Notes will be written up each week after clinic visits.
Analysis: The qualitative interview and field data will be analysed thematically using framework analysis. Example topic guides have been drawn up to indicate the kinds of questions that will be asked to assess acceptability and usability of the reporting system.

3.4. Variables

In addition to the outputs that the eRAPID/QTool software will capture (such as questionnaire completed, date of completion, response to questions, and compliance) the following patient characteristics, clinical characteristics, treatment (listed in Table 6 and 7) and outcome variables (listed in Table 8, 9 and 10) will be captured. These variables will be captured by one of two methods: prospectively in a study specific case report form (CRF), retrospectively by extracting the data from PPM or Chemocare (PPM is the EMR used at LCC, Chemocare is used to prescribe anti-cancer treatment at LCC), If the variable is in a structured format in PPM or Chemocare with high completeness, it will be extracted and linked to the patient's self-reported symptoms and side effects from eRAPID/QTool software. Some of the treatment variables will be algorithmically derived using methods IQVIA have established working with LTHT clinicians. If the variable is in an unstructured format, has low completeness or the information is not captured in PPM or Chemocare then it'll be captured in the CRF.

The data entered by the project manager or research nurse in the CRF may be patient reported (such as smoking status), HCP reported (such as reason for SACT dose modification) or manually extracted from the notes section in PPM (such as date of imaging showing progression on CT scan). The frequency of data capture column in Table 6 and Table 7 indicates whether the variable is expected to be captured once or multiple times. Variables captured once at baseline by CRF will be entered when the patient enrolls in the study. The analyst extracting the dataset from PPM or Chemocare for analysis will extract the data point entered as part of standard care closest to the date of primary thoracic cancer diagnosis (if frequency of capture is 'one data point closest to diagnosis' in Table 7) or all of the entries entered as part of standard care for that variable from baseline to end of study period (if frequency of capture is 'follow up' in Table 7).
The data set described in Table 6 will be collected by University of Leeds, and held in a de-identified form on the university secure servers and transferred in de-identified form to LTHT server. Most of the variables in Table 7 will be extracted by LTHT analysts and held on LTHT servers. Linking of clinical patient data and eRAPID PROMS data sets will occur by use of PPM Patient Identifier in order to enable analysis by LTHT analysts.

Two variables in this list (marked with an *) are collected by eRAPID/QTool by the University of Leeds and transferred to LTHT server

Table 6: Variables to capture prospectively by eCRF

Variable category	Variable	Frequency of capture	Method of capture	Variable detail
Patient characteristics	Patient identifier (study ID)	One data point	Project manager/research nurse	The unique patient identifier in the CRF will allow linkage to the patient's clinical record in PPM
Patient characteristics	Smoking status	One data point at baseline	Patient reported	Categorised as current smoker, former smoker, or never smoker
Patient characteristics	Number of pack years if patient is current or ex-smoker	One data point at baseline	Patient reported	
Clinical characteristics	Comorbidities	One data point at baseline	Clinician reported	Adult Comorbidity Evaluation (ACE-27) instrument
Treatment	Current medication	One data point at baseline	Patient reported	Not including thoracic cancer treatment
Treatment	Line of therapy	One data point at baseline	Clinician reported	Details of the cancer treatment that made the patient eligible for enrolment
Treatment	Start date of line of therapy	One data point at baseline	Clinician reported	
Treatment	Name of the SACT regimen administered	One data point at baseline	Clinician reported	Regimen name lists both single agent and combination therapies used.
Treatment	Reason for SACT dose modification	Follow up, per dose modification	Clinician reported	
Treatment	Reason for SACT discontinuation	Follow up, per treatment discontinuation	Clinician reported	
Outcomes	Date of imaging showing progression on CT scan	Follow up	Project manager/research nurse manually extracting from PPM (in free text notes)	Used to create progression-free survival (PFS) variable: date of initiation of a subsequent SACT LoT or date of imaging showing progression on CT scan. Assessment of response will be clinician reported; RECIST criteria will not be used.

Table 7: Variables to extract retrospectively from PPM, Chemocare

Variable category	Variable	Frequency of capture	Method of capture	Variable detail
Patient characteristics	Date of birth	One data point	PPM	
Patient characteristics	Gender	One data point closest to diagnosis	PPM	
Clinical characteristics	Date of diagnosis	One data point	PPM	Initial diagnosis of thoracic cancer
Clinical characteristics	Primary diagnosis code	One data point closest to diagnosis	PPM	Initial diagnosis of thoracic cancer (ICD-10)
Clinical characteristics	Morphology code	One data point closest to diagnosis	PPM	Initial diagnosis of thoracic cancer (ICD-O-3)
Clinical characteristics	TNM stage	One data point closest to diagnosis	PPM	Closest to date of initial thoracic cancer diagnosis (UICC/AJCC 7th edition)
Clinical characteristics	Date of evaluation of TNM stage	One data point closest to diagnosis	PPM	
Treatment	Date of SACT initiation	One data point	Chemocare	Date of first SACT, date may be prior to study initiation
Treatment	Line of therapy	Follow up, per SACT LoT	Chemocare (algorithm)	LoT initiated during the study period
Treatment	Start date of line of therapy	Follow up, per SACT LoT	Chemocare (algorithm)	LoT initiated during the study period
Treatment	Name of the SACT regimen administered	Follow up, per regimen	Chemocare	Regimen describes the systemic therapies used in a single LoT. Regimen name lists both single agent and combination therapies used.
Treatment	End date of line of therapy	Follow up, per SACT LoT	Chemocare (algorithm)	LoT initiated during the study period
Treatment	Number of planned cycles of chemotherapy	Follow up, per LoT	Chemocare (algorithm)	
Treatment	Number of current cycle of chemotherapy	Follow up, per cycle	Chemocare (algorithm)	

Variable category	Variable	Frequency of capture	Method of capture	Variable detail
Treatment	Start date of treatment cycle	Follow up, per cycle	Chemocare	
Treatment	Treatment dose	Follow up, per SACT LoT	Chemocare	Actual treatment dose per administration
Treatment	Date of SACT dose modification	Follow up, per dose modification	Chemocare (algorithm)	
Treatment	Date of SACT discontinuation	Follow up, per treatment discontinuation	Chemocare	
Treatment	Date of surgical procedure	Follow up, per surgical procedure	PPM	Related to diagnosis of thoracic cancer
Treatment	Surgical procedure type	Follow up, per surgical procedure	PPM	Such as lung transplantation, pneumonectomy, lobectomy, segmentectomy, sleeve resection, wedge resection, bilobectomy, pleurectomy/ decortication (P/D), extra pleural pneumonectomy (EPP)
Treatment	Date of radiotherapy	Follow up, per radiotherapy	PPM	
Treatment	Radiotherapy type	Follow up, per radiotherapy	PPM	Such as external beam radiation therapy, brachytherapy, stereotactic body radiotherapy (SBRT), radioisotopes, stereotactic radiosurgery
Treatment	Clinical trial recruitment date	Follow up	PPM	During study period
Treatment	Clinical trial name	Follow up	PPM	During study period
Outcomes	Date of death	One data point	PPM	
Outcomes*	Number of severe symptom alerts	Follow up	eRAPID/QTool software	Number of alerts generated by eRAPID due to severe symptom reports

Variable category	Variable	Frequency of capture	Method of capture	Variable detail
Outcomes*	Severity of symptoms and side effects	Follow up	eRAPID/QTool software	Severity of each symptom and side effects will be analysed by treatment and over time
Outcomes	Number of acute oncology admissions	Follow up	PPM	During study period
Outcomes	Number of scheduled appointments with oncology unit or contacts with lung nurse	Follow up	PPM	During study period

3.5. Data management

Patients are provided with a QTool username and password when they are enrolled to the study which they use to log into QTool and electronically complete the online questionnaire. Patient's responses are stored in the QTool database (hosted by ITechoHealth within University of Leeds' Azure tenancy)) under the patient's unique username. Every 5 minutes, responses are downloaded to the PROMPT database which is within the NHS firewall on LTHT servers. Once within the NHS firewall, the questionnaire responses can be linked to confidential and identifiable patient medical data for clinicians to see patient's self-reported symptoms within their electronic medical records. All data outside the NHS firewall will be de-identified.

Data collected via the eCRFs, which contain only patient study ID, will be by stored on University of Leeds servers- PCOR Data Management System.

The quantitative data will be analysed by analysts, who have honorary contracts with LTHT and work on site at Leeds Institute for Data Analytics (LIDA). The analysts work on a de-identified dataset, removed of patient identifiable information by University of Leeds researchers, on secure computers within the NHS firewall.

Routine data collection will be monitored for quality and completeness by the project manager from University of Leeds, using verification, validation and checking processes. Missing data, except individual data items collected from weekly symptom questionnaires, will be chased until they are received or confirmed as not available.

3.6. Monitoring and reporting of symptoms and side effects

If the disease-related symptoms and treatment-related side effects reported by patients using the online questionnaires are severe, patients are advised to contact the hospital immediately, and an alert is sent to a member of the clinical team with details of the symptom reported.

The overall clinical responsibility and welfare of the patients involved in the study, including any pharmacovigilance requirements to report adverse events relating to specific products, will remain with the individual treating clinicians at LCC.

3.7. Data analysis

Baseline demographic and clinical data will be tabulated using frequencies and summary by age, gender, cancer pathology type, stage and treatments.

The feasibility of the recruitment strategy will be evaluated by summarising the eligibility and consent processes. The proportion of patients who meet the eligibility criteria in terms of cancer site, treatment type and timescale will be reported using information from the PPM system. The number of patients completing the AE online (cohort 1) vs those in clinic (cohort 2) will be summarised. Where available, reasons for ineligibility and non-participation in the study will be summarised. Retention during the study, including the number of participants withdrawing from the study and the timing of and reasons for withdrawal will also be presented. The number of participants involved at each stage will be summarised (patients identified, approached, consented, completed symptoms and side effects).

The integrity of systems used for registering patients and reporting symptoms and side effects using the online system and the tablets in clinic will be assessed by exploring any technical issues encountered during the study, summarising the rates of questionnaires not being fully completed (assessed by incomplete calls or time-outs depending on the system used). Reasons for patients completing symptoms and side effects in clinic rather than from home will be presented. Time taken to complete the questionnaires will be summarised using timestamps of start and end of calls / online sessions.

The numbers of expected and additional AE reports and severe AE alerts generated will be summarised overall, by cancer type, treatment and completion modality (online vs clinic).

The number of telephone calls to hospital staff (via the UKONS Acute triage or to CNS and nurses on pre-assessment, chemotherapy day unit), acute admissions, ward stays, contacts with GP and/or community services (where available) and number of deaths will be summarised overall and by

treatment modality. Changes to supportive medication, treatment (chemotherapy, immunotherapy, targeted therapies) doses and treatment plans and the percentage of planned therapy received will be summarised overall and by treatment modalities. Differences between treatments may be explored using logistic or linear regression (as appropriate) adjusted for stratification factors.

Clinician/staff acceptability will be explored by framework analysis of the interviews and field notes.

In view of recently published results (Denis et al., 2019) suggesting that regular monitoring may improve survival of lung cancer patients, we will perform exploratory analysis of participants' survival overall, and by cancer type and compare with historical data.

4. Ethical and regulatory obligations

4.1. IRB process and informed consent

An application will be submitted to the Integrated Research Application System (IRAS) seeking Health Research Authority (HRA) approval. The application will include the following documents: application form, study protocol, patient information sheet, and patient informed consent form. University of Leeds will be responsible for submitting the application and all study documents for study approval. The study will be initiated only after approval is granted, and subject recruitment materials will be approved by the IRB prior to being used.

The study will be performed in accordance with the recommendations guiding clinicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, and (October 2008).

Informed written consent will be obtained from the patients prior to enrollment in the study. We want to pilot two innovative approaches to patient consent procedures:

- Online confirmation of consent instead of paper and ink signatures. Patient information will be provided in the traditional way printed on paper. Patients will be given as much time as they need to review the information. Afterwards, we will pilot online consent after patients are given enough time to review the PIS on paper
- To include as part of the procedure a consent to share their medical information, including results from scans, blood tests and biopsies).

The right of a patient to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

The research team:

- Have received GCP training; honorary NHS contracts and adhere to NHS confidentiality guidelines and codes of conduct.
- Have access to a number of private rooms in the outpatients and clinic areas in which to consent patients and carry out the study processes.

4.2. Potential benefits and risks

Potential benefits to participants of taking part in this study include:

- The ability to track their symptoms over time and quantify changes in symptoms using the tabulated view of their responses in the QTool patient interface
- Improved patient-clinician communication
- The tailored, immediate feedback on how to manage their symptoms and alerts sent to the clinical team at the hospital (for severe symptoms) may result in more timely action in response to worsening condition
- A feeling of satisfaction that their unique perspective may lead to improved use of patient-reported data in clinical practice in the future

There are no expected risks to participants as a result of involvement in this study. The patient self-reporting of symptoms and side effects will occur in addition to routine care. The risks of the natural evolution of thoracic cancer are not modified by this study.

There may be non-physical risks associated with enrolling in this study, such as:

- The risk of accidental disclosure of personally identifiable medical information
- By reporting symptoms and side effects at regular intervals, patients may become increasingly aware of their condition which may affect mental health

4.3. Protection of subjects and confidentiality

All the information collected during the study concerning individual participants will be treated in the strictest confidence. As a minimum the data will be held in accordance with GDPR (Regulation EU 2016/679 Regulation of the European Parliament and the Council on the Protection of individuals with regard to the processing of personal data and on the free movement of such data). This will include every participant being assigned a unique identifier to be used in study documentation, and sensitive study information will be stored within locked cabinets or electronically on secure servers. A Master Collaboration Agreement (MCA) and Data Protection Contract (DPC) signed between IQVIA and LTHT that covers all aspects of data sharing.

4.4. Intended use of the data

The data will be used to:

- Improve the understanding of the experience of patients living with thoracic cancer, and the treatment-related side effects associated with SACT, analysed according to the objectives in section 2
- Create research abstract(s) and/or publication(s) for submission to conferences and/or peer-reviewed journals to disseminate findings

The data is additionally intended to be used:

- By patients to track their symptoms and side effects over time and use the tailored feedback to manage their symptoms
- By clinicians to review their patients' self-reported symptoms and side effects and make modifications to care as required

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