Multi-modality local consolidative treatment *versus* conventional care of advanced lung cancer after first line systemic anti-cancer treatment: a multi-centre randomised controlled trial with an internal pilot.

RAdical Management Of Advanced Non-small cell lung cancer

The RAMON Study

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Glossary / abbreviations

AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AKI	Acute kidney injury - an acute increase in serum creatinine > 26.4 µmol/l or a percentage increase in serum creatinine of more than or equal to 50%
ALI	Acute lung injury
ALK	Anaplastic lymphoma kinase
ALT	Alanine Aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate transaminase
BTC	Bristol Trials Centre
CECT	Contrast-enhanced computed tomography
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case report form
CT	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
DI	Deprivation Index
DMSC	Data monitoring and safety committee
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation For Research and Treatment of Cancer's Quality of Life Questionnaire-C30
EORTC QLQ-LC13	European Organisation For Research and Treatment of Cancer's Quality of Life Questionnaire-LC13
EQ-5D-5L	EuroQol EQ-5D-5L questionnaire
GCP	Good Clinical Practice
GI	Gastrointestinal
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HSG	Health and safety guidance
ICER	Incremental cost-effectiveness ratio
ICH-GCP	International conference for harmonisation of good clinical practice
IEP	Image Exchange Portal
LCT	Local Consolidative Treatment'
MDT	Multidisciplinary Team
MCC	My Cancer Companion
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PACS	Primary and Acute Care Systems
PaO2/FiO2 ratio	Ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2)
PET	Positron Emission Tomography scan
PFS	(disease) Progression free survival

PI	Principal investigator
PIL	Patient information leaflet
PPI	Patient and public involvement
QALY	Quality adjusted life year
QRI	QuinteT Recruitment Intervention
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RECIST	Response evaluation criteria in solid tumours
SABR	Stereotactic Ablative Radiotherapy
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SACT	Systemic anti-cancer treatment
SMS	Short messaging service
SOP	Standard operating procedure
SPC	Summary of product characteristics
SRS	Stereotactic radiosurgery
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TMG	Trial management group
TSC	Trial steering committee (study steering committee)
VATS	Video-assisted thoracoscopic surgery
VTE	Venous thromboembolism

1. Study summary

Lung cancer is the most common cause of cancer death worldwide, and the majority of patients in the UK present with advanced disease. One-year survival is improving but remains low at 37% despite new treatments which now form the current standard of care for advanced lung cancer.

Although these new therapies are very good, residual cancer persists in most patients after treatment and little is known on how best to deal with it. As such the management of residual advanced lung cancer is highly variable across the UK, with some patients receiving only symptom management treatment whilst others may receive local consolidative treatment (LCT), alongside symptom management treatment, with the intention to prolong survival. LCT is a combination of surgery, radiotherapy and/or ablation (an image-guided technique that uses heat to destroy cancer cells) to remove all remaining cancer within the lung and throughout the body. LCT is intensive, impacts quality of life and is expensive but most importantly, we do not know if it results in a better outcome for patients.

The RAMON study will find out whether LCT is worthwhile (or not) for patients with residual advanced lung cancer. Patients who agree to join the study will be divided into two equal sized groups. One group will receive LCT and the other group will not. Everything else will be the same for all patients (all patients will have treatment for symptoms as necessary).

Over 3 years we will aim to recruit 244 patients who have completed initial treatment of their cancer with medicines. An economic evaluation will be undertaken and experts in trial recruitment will be working closely with the study team to optimise recruitment and informed consent.

This study will be carried out by an experienced multi-disciplinary team of oncologists, surgeons, researchers and patient representatives with experience of lung cancer treatments. It is expected to take 6 years to complete.

The RAMON study also includes an optional sub-study that participants may choose to take part in. The sub-study, AQUA lung, involves participants using a mobile phone application (app) to record their quality of life and physical activity throughout the study. The information collected *via* the app will be compared to data collected through questionnaires as part of the main study, to see if the app could be used in place of questionnaires in future studies.

2. Background

Lung cancer is still the most common cause of cancer death worldwide and the majority (57%) of patients in the UK present with advanced disease (defined as stage IIIB or IV). One-year survival is improving but remains low at 37% (1).

A number of Phase II Randomised Controlled Trials (RCTs) have focused on the prospect of radically (*i.e.* with the intent of improving survival) treating patients with advanced lung cancer and oligometastatic (defined as less than 5 sites (2)) disease at presentation with systemic anti-cancer treatment followed by radiotherapy to all remaining sites, a pathway known as LCT. Two trials reported improvements with radiotherapy as LCT for overall survival and progression free survival respectively. (3, 4)

For a minority of patients with oligometastatic disease at presentation, further RCTs are underway evaluating radiotherapy alone as LCT, with the SARON trial (NCT02417662)(5) in the UK, and the ROLE (NCT01796288) and CORE (NCT02759783)(6) trials internationally. Based on published data, the inclusion criteria are widening from (arbitrarily defined) oligometastatic disease to extensive (polymetastatic) disease at presentation; the SABR-COMET-10 trial (NCT03721341)(7) is investigating radiotherapy as LCT for patients with up to 10 sites of disease. However, there are no trials for the majority of patients who present with extensive disease that becomes oligometastatic disease (*i.e.* all residual sites amenable to radical treatment) after systemic anti-cancer treatment (more recently defined as "induced" oligometastatic (8) disease).

In the UK, LCT is multi-modal including radiotherapy, surgery, and local ablation, tailored to each patient's specific disease site. A multi-modality approach has the advantage of reducing total radiation dosage. Inclusion of surgery has additional advantages of providing tissue (to evaluate treatment response), refine staging (*e.g.* lymph node status) and may achieve complete cancer clearance in a single episode of care.

To date only one trial has included surgery as an option alongside radiotherapy for LCT (9). The trial was stopped early for efficacy after 49 patients had been enrolled (9).

Currently the most efficacious systemic anti-cancer treatment includes molecular targeted treatment and immunotherapy, but most previous trials were undertaken when chemotherapy was the standard of care with few receiving immunotherapy or molecular targeted treatments.

3. Rationale

LCT is intensive, impacts health related quality of life (HRQoL) and is expensive. Whilst there are trials of radiotherapy LCT for patients with lung cancer with LCT eligible metastases receiving standard chemotherapy (*e.g*. SARON (5)) in the UK, these trials are not addressing the question of the clinical and cost effectiveness of multi-modality LCT in patients with the more common presentation of extensive disease, reduced to LCT eligible disease (see section 5.5 for details) after highly efficacious contemporary systemic anti-cancer treatment such as immunotherapy and molecular targeted agents.

4. Aims and objectives

To evaluate the clinical and cost effectiveness of multi-modality LCT in patients with advanced lung cancer, rendered LCT eligible metastatic disease (see section 5.5), after contemporary standard-of-care systemic anti-cancer treatment in comparison to symptom management treatment alone.

Specific objectives are to estimate:

A) the difference between groups in overall survival
B) the difference between groups in secondary outcomes that include HRQoL, progression free survival, adverse health events
C) the cost-effectiveness of LCT compared to symptom management treatment alone.

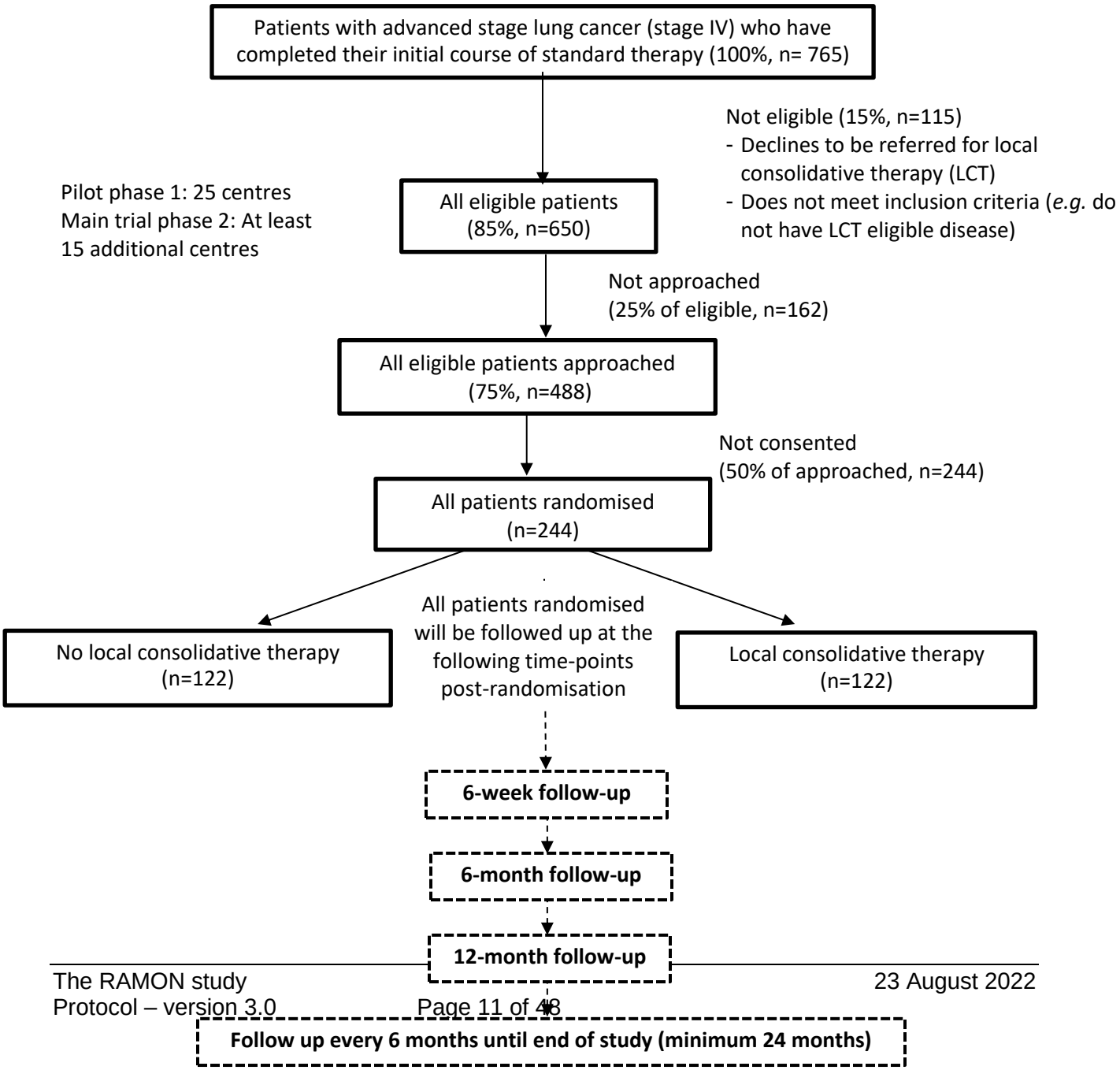
The objectives for the AQUA lung sub-study are as follows:

D) To compare participants self-reporting of HRQoL outcomes via a purpose-designed mobile phone app ('My Cancer Companion') to completion of HRQoL scales at pre-specified time points within the RAMON study

5. Plan of Investigation

5.1 Study schema

Figure 1 Study schema



5.2 Study design

RAMON is a pragmatic open multi-centre, parallel group, superiority RCT in NHS hospitals with an internal pilot phase and active follow-up for a minimum of 2 years. The full RCT will evaluate the acceptability, effectiveness, and cost effectiveness of LCT *versus* no LCT after first line systemic treatment for advanced lung cancer.

Recruiting centres will be supported with an integrated QuinteT Recruitment Intervention (QRI) and patients will be followed up for quality of life and resource use outcomes at various time points over a two-year period.

5.3 Setting

Recruitment to the study will take place in NHS secondary and tertiary care centres treating patients with advanced lung cancer. LCT may take place within the recruiting hospital or the participant may attend another hospital for some or all of their treatment (*e.g*. treatment of brain metastases). Some hospitals may provide LCT but not recruit participants. These hospitals will also be opened as study centres in order that data on the LCT treatment may be collected.

5.4 Key design features to minimise bias

(a) Selection bias (systematic differences between baseline characteristics of the groups that are compared) will be prevented by allocation concealment. The allocation will not be revealed until sufficient information to uniquely identify the participant has been entered into the randomisation database.

(b) **Performance bias** (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest) will be minimised by i) defining the interventions; ii) defining procedures for follow-up; iii) monitoring adherence to the protocol. The patient information leaflet (PIL) and the process of obtaining informed consent will describe the uncertainty about the benefits of LCT versus no LCT in terms of quality and quantity of life. Patient-reported outcomes will be susceptible to bias although we believe that expectations about the alternative care pathways are likely to wane with follow-up.

(c) **Detection bias** (systematic differences between groups in how outcomes are determined) will be minimised by using an objective primary outcome measure (survival) (see section 6.6), and by providing clear unambiguous definitions for each of the secondary outcome measures (see section 5.7).

(d) **Attrition bias** (systematic differences between groups in withdrawals from a study) will be minimised by using established methods developed in the Bristol Trials Centre (BTC) to maximise the quality and completeness of the data, for example regular monitoring of data, detailed querying of data inbuilt into the study database, offering alternative methods for participating in follow-up (e.g. postal, online or telephone if unable to attend in person). Instances of non-adherence will be documented and reviewed at study meetings and an action plan for maximising compliance drawn up as appropriate. Data will be analysed by intention to treat irrespective of future management and events and every effort will be made to include all randomised patients.

(e) **Reporting bias** will be minimised by having pre-specified outcomes (see section 5.7) and following a detailed analysis plan which will be prepared in advance of any comparative analyses.

5.5 Study population

The target population is adults (18 years or older) with advanced stage non-small cell lung cancer (stage IV) and who have undergone an initial course of systemic anti-cancer treatment (SACT), defined as one of:

- At least four cycles of platinum doublet chemotherapy or
- At least three months of approved first-line molecular targeted treatment
  a) epidermal growth factor receptor (EGFR) inhibitor in patients with EGFR mutant tumours or
  b) anaplastic lymphoma kinase (ALK) inhibitor for patients with ALK rearranged tumours or
- At least three months of approved first line immunotherapy or combination immuno-chemotherapy.

Patients will be screened and approached after initial therapy, (as above), and local re-staging (as per that of the local policy/standard of care) to identify 'LCT eligible disease' (as defined in section 5.5.1 below). It is recommended that the staging investigations are planned on the last cycle of SACT (or at 3 months if SACT treatment ongoing), to ensure that randomisation is not delayed and to facilitate LCT treatment commencing within 4 weeks of randomisation.

5.5.1 Inclusion criteria

Participant may enter study if ALL of the following apply[1]

1. 18 years of age or over
2. Tissue confirmed non-small cell lung cancer pre-treatment clinical stage IV
3. Lung cancer treatment naïve prior to initial study systemic anti-cancer treatment
4. Completed standard of care systemic anti-cancer treatment (see section 5.5)
5. Performance status 0 (*i.e*. asymptomatic) or performance status 1 (*i.e.* symptomatic but completely ambulatory) as per Eastern Cooperative Oncology Group (ECOG) definitions

6. LCT eligible disease, defined as all disease sites amenable to radical treatment (*e.g.* surgery, radiotherapy or ablation)

[1]All participants eligible for RAMON are eligible to take part in the sub-study.

5.5.2 Exclusion criteria

Participant may not enter study if ANY of the following apply

1. Serious concomitant disorder that would compromise patient safety during LCT
2. Complications from initial SACT that precludes maintenance SACT
3. Patient unable/unwilling to adhere to study procedures
4. Patient unable to give written informed consent
5. Women who are pregnant or breast feeding
6. Currently enrolled in another trial if either: interventional trial that aims to improve survival, not permitted by other trial, would result in too much patient burden[2]

[2]See section 10.5 for information on co-enrolment

5.6 Study interventions

5.6.1 Experimental group

The experimental intervention is LCT in the form of surgical resection, radiotherapy* and / or ablation with radical intent (aim to improve survival) to all sites of residual disease, after the completion of initial systemic anti-cancer treatment.

The MDT caring for the participant will decide on the most appropriate type and sequence of LCT (*e.g.* symptomatic metastatic sites first, followed by surgery for the primary lesion and then maintenance systemic anti-cancer treatment or an alternative sequence). Depending on the residual sites of disease the treatment options are as follows:

- Lung – surgery or stereotactic radiotherapy or ablation
- Brain – stereotactic radiosurgery (SRS) or neurosurgery
- Adrenal glands – stereotactic radiotherapy or surgery or ablation
- Bone – stereotactic radiotherapy or (less commonly) surgery
- Liver – surgery, ablation or stereotactic radiotherapy
- Other sites of disease that are suitable for surgery, ablation or stereotactic radiotherapy may also be considered for local consolidative treatment, if considered appropriate at MDT

This is undertaken in sequence or conjunction with maintenance systemic anti-cancer treatment and/or supportive care (where appropriate).

****Note:*** *If administering Stereotactic Ablative Radiotherapy (SABR) please follow the SABR UK Consortium guidelines (10).*

5.6.2 Comparator group

The control intervention is treatment with the intention to improve symptoms (palliative care) without surgery, radiotherapy, or ablation to any residual site of disease (unless for palliation of symptoms).

The group allocated to no LCT will receive maintenance systemic anti-cancer treatment and/or supportive care. No restriction will be placed on the management of the primary or secondary sites of disease for the purposes of palliation of symptoms.

For all participants, the treatment plan will be documented as part of the study (including reasons for treatment). Adherence to the allocation and to the proposed treatment plan will be monitored. Reasons of deviations from the allocation and the proposed treatment plan will be captured.

5.7 Primary and secondary outcomes

5.7.1 Primary outcome

The primary outcome is overall survival defined as date of randomisation to death from any cause (minimum follow-up 2 years after randomisation).

5.7.2 Secondary outcomes

Secondary outcomes include:

- Disease progression free survival (PFS) defined as the time from randomisation to documented disease progression, as evaluated by local site radiologist from CT or PET/CT scan (e.g. CT of the head, chest, abdomen, pelvis and other anatomical sites); bone scan or MRI, carried out as part of the patients' standard care (minimum follow-up 2 years after randomisation) or death from any cause
- Serious adverse health events from randomisation to the end of the study (minimum of 2 years)
- Patient reported HRQoL measured using the European Organisation For Research and Treatment of Cancer's Quality of Life Questionnaire-C30 (EORTC QLQ-C30) from randomisation to the end of the study (minimum of 2 years)
- European Organisation For Research and Treatment of Cancer's Quality of Life Questionnaire-LC13 (EORTC QLQ-LC13) to the end of the study (minimum of 2 years)
- EQ-5D-5L questionnaire (EuroQol EQ-5D-5L) to the end of the study (minimum of 2 years)

5.7.3 Exploratory endpoints/outcomes

The following outcomes will be collected for the sub-study

- Pedometer data collected *via* the 'My Cancer Companion' app
- Physical health and mental wellbeing scores collected *via* the 'My Cancer Companion' app.

5.8 Sample size calculation

The study hypothesis is that LCT in addition to maintenance systemic anti-cancer treatment and/or supportive care (conventional care) improves overall survival by an absolute 20% at 2-years compared to conventional care alone.

The primary outcome is overall survival. The minimum clinically important difference, namely an absolute survival improvement of the order of 20% at 2 years, was chosen by the study's patient and public involvement (PPI) group, which includes those who have lived in experience of lung cancer or are carers of someone with lung cancer and agreed by the trial management group (TMG) during the study design phase in 2019. The possibility that survival could be worse with LCT was also discussed and therefore a two-tailed test was agreed.

Two-year survival in patients with advanced lung cancer eligible for immunotherapy was estimated to be 52%, based on the KEYNOTE-024 trial (11). The total sample size has been set at 244 participants (122 per group). This is sufficient to detect an 18% improvement in survival (hazard ratio 0.55) with 90% power and a 15% improvement in survival (hazard ratio 0.6) with 80% power, both of which are lower than the target 20% recommended by our PPI group. They are also consistent with the target effect size (hazard ratio 0.57 for progression free survival) of the phase II trial reported by Gomez and colleagues (9). Additionally, these calculations assume that all participants are followed-up for survival to the end of the study (minimum 2 years, maximum 5 years) and allow for up to 5% cross-over. Allowance for drop-out has not been included as participant consent will be sought for study centres to determine the survival status for all participants, including any who choose to withdraw from active follow-up, at the end of the study, using summary care records.

The target recruitment for phase 1 of the study is 45 participants, the remainder recruited by the end of Phase 2.

6. Study methods

6.1 Description of randomisation and code breaking

Randomisation will be carried out by a member of the research team after initial systemic anti-cancer treatment, confirmation of eligibility and consent given, using a secure internet-based randomisation system ensuring allocation concealment. Participants will be randomised in a 1:1 ratio to either LCT or symptom management treatment after collection of baseline data. Randomisation will be stratified by centre and type of initial systemic anti-cancer treatment received (molecular targeted treatment, immunotherapy or chemotherapy).

6.2 Blinding

It is not possible to blind participants or the clinical care team to the randomised allocation so the study will be at risk of measurement outcome bias, however the study has been designed to protect against bias as outlined in section 5.4.

6.3 Research procedures

6.3.1 All participants

Patients with stage IV advanced lung cancer who have undergone a course of initial systemic anticancer treatment at a participating centre, will be screened for eligibility and sent or given the study information if potentially eligible. Potential participants will have an opportunity to discuss the study with a member of the study team before deciding if they wish to take part.

Apart from reading the information leaflet and providing informed written consent, study participants will be required to:

a) Complete questionnaires at baseline prior to randomisation.

b) Undergo follow-up for primary and secondary outcomes at around 6 weeks, and then every 6 months until the end of the study (or death). Participants receiving LCT will also be followed postoperatively for each modality to discharge.

Participants will be followed up by telephone or video call (local research team will contact patients at mutually agreed times, unless patients will be attending hospital anyway, in which case face to face follow up can be completed) to ascertain treatments received, serious adverse events, progression or new cancer, resource use and participation in any other studies up until the end of the study (or death) for a minimum of 2 years. To maximise efficiency HRQoL questionnaires will be completed online or by post according to the participant's preference. Reminders will be sent by email, post, and/or SMS as appropriate. Participants who fail to respond to reminders will be contacted by the local research team and invited to complete the questionnaires by telephone.

6.3.2 RAMON sub-study participants

Participants may also opt to take part in the sub-study. This is optional.

Participants who consent to take part in the sub-study will be asked to download the freely available 'My cancer companion' app. They will be encouraged to record their physical health and mental wellbeing status using the app throughout their participation in RAMON. The frequency of using the app will not be mandated. When using the app responses to questions on physical and mental function are required, other questions are optional. Participants will be identified by the trial acronym and their unique study ID.

6.3.3 The QuinteT Recruitment Intervention (QRI)

To facilitate this recruitment process we have embedded the recruitment intervention (QRI) into the study (12). This is optional for participants and participants can take part in the QRI study even if they do not consent to the main part of the study.

There are several issues that have potential to compromise recruitment:

1) Patients receive care from multidisciplinary staff and the initial care pathway and systemic treatment is variable between patients and centres. Eligible patients are more likely to 'slip through the net' when there is heterogeneity in clinical care pathways with multiple clinical specialties.

2) Patients may decline study participation based on preferences for LCT or not.

3) Clinician ingrained practices and preferences for LCT (or not) could undermine recruitment (*i.e.* equipoise issues).

Optimising recruitment – QRI

Some of the issues highlighted above will be addressed pre-emptively and monitored throughout recruitment. Others are difficult to address without knowing if/how they play out in practice (*e.g.* equipoise issues and patient preferences). The QRI aims to understand the root causes of recruitment issues as a study is underway, to inform specifically designed interventions to address these. The QRI will begin with pre-emptive training and discussion of anticipated challenges before centres open for recruitment. This will encourage centres to consider the logistical and organisational issues (*e.g.* the role of different professionals throughout the recruitment pathway). The training will also disseminate general recruitment strategies, informed by QRI findings from previous studies (*e.g*. approaches to explain randomisation). Once recruitment begins, the QRI will investigate and address recruitment issues in 'real-time' through two iterative phases:

Phase 1: understanding recruitment issues

Mixed-methods will be used to identify and understand actual (rather than anticipated) issues impacting on recruitment (13). A flexible approach will be taken using one or more of the following:

a. Semi-structured interviews with i) members of the TMG, ii) staff involved in study recruitment ('recruiters'), and iii) eligible patients who have been approached to consider the study. Interviews with TMG members and recruiters will explore their perceptions of equipoise, local (or national) challenges encountered, and how recruitment is organised in individual centres. Interviews with patients may also take place if further information is needed to elucidate the reasons underpinning recruitment issues.

b. Audio-recording recruitment discussions: Recruiters' discussions with eligible patients will be audio-recorded (with consent) to provide direct insight into how the study is being presented. We will pay particular attention to whether the study interventions are described in a clear, accurate and balanced way (*i.e.* equipoise issues); ways in which recruiters manage patients' expectations and preferences, and approaches to explaining study processes such as randomisation and follow-up.

c. Mapping of recruitment pathways and screening log analyses: this will capture information about each patient screened for RAMON, including whether they were eligible, approached and randomised (with reasons if not). The interviews with recruiters (above) will be used to map out the recruitment pathway for each centre, noting processes for screening and identifying eligible patients, steps taken to confirm eligibility, when/how patients are approached, and the staff involved in these activities. This information will be compared with screening log figures to identify bottlenecks in recruitment pathways.

d. Attendance at TMG and investigator meetings: the QRI researcher will attend TMG and investigator meetings to gain an overview of study conduct and overarching challenges.

e. Review of study documentation to ensure that study documents are unbiased and clear. As the study progresses, the PIL and consent form(s) will be compared with interviews and recorded appointments to identify any disparities or improvements that could be made.

Phase 2: Development and implementation of recruitment intervention strategies

The QRI team will work closely with the TMG to design and implement tailored actions to support recruitment. The types of actions taken will be informed by Phase 1 findings. Cross-centre actions may include disseminating 'tips' documents with suggestions on how to convey equipoise and clearly explain the study design/processes, based on issues arising from the audio-recorded consultations. Changes may also be made to patient-facing materials (*e.g*. PIL). Group discussions between the CI (chief investigator) and recruiters may be organised to address aspects of the eligibility criteria that are problematic or challenge clinicians' perceptions of equipoise. Centre-specific interventions may entail changes to how recruitment is organised and delivered, facilitated by sharing examples of 'good practice' from other centres that have more efficient recruitment models.

Supportive feedback on recruiters' communication is likely to be delivered *via* multiple routes. Group feedback sessions will use anonymised extracts from audio-recorded consultations to illustrate how recruiters' communication can influence patients' responses to invitations of study participation. These may be organised through centre or investigator meetings. Individual confidential feedback will also be offered, particularly where recruiters experience specific difficulties or where there is a need to discuss sensitive issues.

Iterative nature of QRI phases

Both QRI phases will run iteratively. New avenues of enquiry will emerge throughout the conduct of the QRI and thus both phases will run cyclically throughout the period of opening centres. Lessons learnt from the first centres to open will be shared up-front with subsequent centres opening later in the study's timeline.

6.4 Duration of treatment period

6.4.1 Patients randomised to LCT

For participants randomised into LCT, the treatment duration is the time required to treat each site. As new sites of disease develop, it is expected that all new sites are treated (when feasible). At the time point for which the disease site exceeds the threshold for continuing radical treatment (as decided by the multidisciplinary team (MDT), then the participant will be considered to be in a palliative pathway and the date for this decision will be recorded.

6.4.2 Patients randomised to no LCT

Participants randomised to no LCT will have their treatments (best supportive care) as appropriate to their clinical management during the course of the study.

6.5 Definition of end of study

The end of the study as a whole is when all participants have been followed up to at least 2 years (or death if before 2 years), all data entry has been completed, all data queries cleared and the database has been locked and analyses completed.

The end of study for the participant is when they have completed all follow up visits/questionnaires or they have either been lost to follow up, withdrawn from the study or died.

6.6 Data collection

Recruitment data (*e.g.* numbers screened, sent/given study information, eligible, approached and consented) will be collected on a study screening log.

As part of the screening process, deprivation index (DI) and ethnicity will be collected for both consented and non-consented patients. To calculate DI, post code will be collected and entered onto the study database where the postcode will automatically be converted to DI. Postcode will therefore not be stored on the electronic screening logs.

Participant demography, past history, and clinical outcome data will be collected using purpose-designed case report forms (CRFs), which will be completed by a member of the research team, at baseline, and at the follow-up time points. The primary data sources will be the participant's hospital records and participant-completed questionnaires.

Table 1 Schedule of data collection for primary and secondary outcomes

Data item	Baseline	LCT treatments*	Post randomisation						
			6 w	6 m	12 m	18 m	24 m	Every 6 m to end of trial	End of trial
Demography, medical history, initial systemic treatment	✓								
HRQoL questionnaires	✓		✓	✓	✓	✓	✓		
LCT treatment and in-hospital post-operative data **		✓	✓	✓	✓	✓	✓		
Serious adverse events		✓	✓	✓	✓	✓	✓	✓	✓
Patient-reported resource use			✓	✓	✓	✓	✓	✓	
Disease progression/new cancer			✓	✓	✓	✓	✓	✓	
Survival ***			✓	✓	✓	✓	✓	✓	✓
HRQoL app****	✓	✓	✓	✓	✓	✓	✓	✓	✓

* Patients allocated to LCT and/or receiving surgery only
** Including resource use
***All participants will be checked for survival at the end of the trial using summary care records
**** Participants encouraged to complete it regularly throughout the trial, but frequency and time points are not mandated

6.7 Source data

Source data will be the patient's medical records and patient-reported questionnaires. Where information is not recorded anywhere else, the CRFs (paper or electronic) are the source data.

6.8 Planned recruitment rate

The aim is to randomise 244 participants over 34 months from around 40 NHS hospitals. To inform the recruitment projections, HES data were analysed and approximately 2,600 patients per year were identified as undergoing LCT, with a mean of 20 cases and median of 13 cases per centre per year.

6.8.1 Phase 1

Set-up and recruit across initial centres for 12 months with integrated monitoring and feedback to maximise adherence. There will be a review of the progression criteria after 12 months.

6.8.2 Phase 2

If progression criteria are met, increased number of centres opened and continued recruitment using the optimum methods of recruitment and adherence established in Phase 1 for an additional 22 months, following all participants to the end of the study (minimum 2 years).

6.8.3 Continuation/stopping rules to proceed to Phase 2

The study will continue into Phase 2 if it is possible to demonstrate that the criteria for progression from Phase 1 to 2 have been met: 25 centres open, 45 participants randomised, and at least 95% of randomised participants adhere to the allocated treatment pathway (see Table 2). This will be reviewed after 12 months of recruitment. If one or more of these criteria is not met we will a) suggest adaptions to address the short fall (if in amber zone) or b) discuss with the Trial Steering Committee (TSC) if the study is feasible (if in red zone).

Table 2 Progression criteria (after 12 months of active recruitment)

Criterion	Target	Red	Amber	Green
Trial recruitment	45	<34	34-44	>44
Centres open	25	<19	19-24	25
Randomisation rate/centre/month	0.32	<0.24	0.24-0.31	≥0.32
Adherence to allocated intervention	100%	<90%	90-94%	≥95%

The Data Monitoring & Safety Committee (DMSC) may recommend stopping the study if the accrued data suggest that the study is unsafe for one or both groups of participants.

6.9 Participant recruitment

At the earliest opportunity in the patient pathway, potential participants will be given a PIL (approved by the Research Ethics Committee (REC)) describing the study. The patient will have time to read the PIL and to discuss their participation with others outside the research team (*e.g.* relatives or friends) if they wish. Participants will be given a minimum of 24 hours post receipt of the PIL to consider taking part.

If the patient consents to recording of consultations (QRI component), all discussions about study participation will be recorded until the patient has reached a decision. It is beneficial if as many

consultations during the patient pathway as possible can be recorded, therefore consent to recording will be requested at the earliest possible opportunity. This may be verbal consent (recorded in the patient's medical notes) in the first instance, with a view to obtaining written informed consent subsequently. This will be on the understanding that the data will not be uploaded/submitted or used until written consent has been obtained.

As part of the QRI component of the study, patients may also be asked if they would like to take part in an interview with one of the study qualitative researchers. Patients will be asked if they agree to be contacted by a qualitative researcher when they consent to the recording. Patients who do not consent to recording, may agree verbally to be contacted about an interview (and this will be documented on the study CRFs). One of the study qualitative researchers will contact the patient to explain more about the interview and if the patient wishes to proceed with an interview over the phone, the researcher will capture their verbal consent for the interview to go ahead. A consent form will then be posted for the participant to complete and return, and data from the interview will not be used until written consent has been received. Where relatives/carers are present and wish to participate in the interview, verbal consent for their data to be used will be sought.

Potential participants will be seen or contacted by a member of the local research team who will answer any questions and take informed consent if the patient decides to participate. Consent will be obtained either by face to face at a clinic appointment or remotely by telephone/video call or electronically using a purposed designed electronic database. The consent process will be described in detail in the study manual.

Details of all patients approached for the study and reason(s) for non-participation (*e.g.* reason for being ineligible or patient refusal) will be documented.

6.10 Discontinuation of participants

There are no specific criteria for discontinuation. Participants can discontinue from certain aspects of the study and not others if they wish (*e.g*. stop the completion of study questionnaires but continue with allocated treatment; stop participating in the sub-study but continue with allocated treatment *etc*) or discontinue with the study as a whole.

Non-adherence to the allocated intervention (for any reason) will not constitute discontinuation in the study. However, a participant may request to discontinue at any time (without giving a reason). In addition, the investigator may opt to discontinue the participant from their allocated treatment group for clinical reasons. Participants withdrawn from their allocated intervention but willing to continue completing follow-up schedules will be encouraged to do so. All discontinuations will be documented. If a participant wishes to discontinue, data collected up until that point will be included in the analyses, unless the participant expresses a wish for their data to not be used. Participant consent will be sought to determine the survival status for all participants, including any who choose to discontinue from active follow-up, at the end of the study, using summary care records.

6.11 Frequency and duration of follow up

Participants will be followed up for primary and secondary outcomes at 6 weeks post-randomisation, and then every 6 months until the end of the study (minimum 24 months). Participants will receive treatment throughout their participation in the trial. For participants in the LCT group follow up may take place pre- and post-surgery. Participants receiving LCT will also be followed postoperatively for each modality to discharge.

Standard of care imaging for participants may not coincide with study follow-up timepoints. Data will be collected for standard of care imaging at the next study follow-up.

Up until 24 months, participants will be followed up by telephone or video call by the local research team, as outlined in section 6.3.1.

6.1 Expenses

Participants can claim travel costs of up to £30 per LCT treatment visit, this is covered in the per-patient fee provided to participating sites.

7. Statistical analyses

7.1 Primary and secondary outcomes

The primary analyses will be by intention-to-treat and will be directed by a pre-specified statistical analysis plan (SAP). Results will be reported in accordance with the CONSORT reporting guidelines.

Primary and secondary survival outcomes will be compared using Cox regression, and adjusted for type of initial systemic anti-cancer treatment. Any participants who withdraw consent for ongoing access to medical records will be censored at the point of withdrawal. HRQoL outcomes will be analysed using mixed regression adjusting for baseline values and initial systemic anti-cancer treatment as fixed effects, and participant and centre as random effects. Mixed models allow all participants with baseline and follow up data to be included in the analysis, i.e. partial missing follow up data (assumed missing at random) is valid. Interactions between treatment and time will be examined and if significant at the 10% level, results will be reported separately for each post-baseline time point; otherwise, overall treatment effects will be reported. Deaths will be accounted for by modelling HRQoL and survival jointly. Full details of the proposed model will be specified in the SAP. Model fit will be assessed using standard methods and alternative models and/or transformations for the scores will be explored as appropriate (*e.g*. log transformations to induce normality or mixed-effects mixed-distribution models). The strategy for choosing the most appropriate model will be provided in the SAP. Treatment differences will be reported with 95% confidence intervals.

Adverse events will be graded using CTCAE criteria and reported using the Medical Dictionary for Regulatory Activities (MedDRA) classification system, with events grouped by system organ class and the preferred term to describe events. Safety outcomes will be described and the occurrence of one or more serious adverse events will be compared using a generalised linear model.

Subgroups will be compared by including a sub-group-by-treatment interaction in the models.

Secondary instrumental variable analyses will be used to account for non-adherence with the treatment allocation. Non-adherence will be defined as no LCT in the LCT group and any LCT in the no LCT group.

Findings will be reported as effect sizes with 95% confidence intervals.

7.2 Sub study outcomes

Bland and Altman plots will be used to estimate the limits of agreement between the physical and mental scores derived from scores collected via the app and the scores derived from data collected through the RAMON questionnaire booklet. The app scores obtained closest in time to the completion of the RAMON questionnaire booklet will be used. The two methods will be considered to be in agreement if the 95% limits of agreement are less than 0.2 SD for the measure (e.g. +/- 5 for physical function, +/- 6 for mental wellbeing)(14).

Other exploratory analyses will include:

- Correlation between pedometry data and EORTC physical function
- Average number of data points reported per year through the app (e.g. the EORTC QLQ C-30 questionnaire included 30 items, completion in full on 4 occasions would provide 120 data points)
- Agreement between not selecting the optional items in the app and reporting 0 values for in the RAMON questionnaires as measured by the kappa statistic
- Descriptive analysis of quality of life measures added by participants in the app that are not captured in the RAMON questionnaire booklet

7.3 QRI data analyses

Interviews and recruitment consultations will be recorded, transcribed in full or parts and, along with recruitment screening logs and observations, subject to simple counts, content, thematic and targeted conversation analyses. Preliminary analysis will be used to inform training and further data collection. Members of the qualitative team will independently analyse a proportion of transcripts to assess the dependability of coding and will meet regularly to review coding and descriptive findings, agree further sampling and training strategies, and discuss theoretical development – all in close collaboration with the CI.

7.4 Subgroup analyses

Three subgroup analyses for the primary outcome are planned. The first will be by initial systemic anti-cancer treatment (molecular targeted treatment, immunotherapy or chemotherapy); the second by number of disease sites; and third by location site of residual disease (brain, visceral, bone, other).

7.5 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants, or all recruited participants have died. Safety data will be reported to the DMSC at a frequency to be

agreed, together with any additional analyses the committee requests. In these reports the data will be presented by group but the allocation will remain masked, where possible.

A preliminary analyses of data collected via the app for the Aqua lung sub-study will be carried out when 50 participants have joined the sub-study and have been followed-up for at least 12 months. A final analysis will take place at the end of the study.

7.6 Criteria for the termination of the study

The study may be stopped early on the advice of the DMSC or if the results of another study supersede the necessity for completion of this study.

7.7 Economic Evaluation

The aim of the economic evaluation is to evaluate whether LCT represents good value for money for the NHS. The economic evaluation will follow established guidelines as set out by the National Institute for Health and Care Excellence (NICE) (15). A within-trial cost-utility analysis will estimate the cost effectiveness of LCT compared to conventional care from an NHS and personal social services perspective with a time horizon from randomisation to 2 years, as it is anticipated that most major resource use will occur within this timeframe. The primary outcome for the economic evaluation will be quality adjusted life years (QALYs), estimated using the EQ-5D-5L (16-18), which will be administered at baseline (pre-randomisation), 6 weeks, and 6, 12, 18 and 24 months follow-up via post or online. Responses will be assigned valuations according to NICE guidance at the time of analysis and combined with survival to calculate QALYs gained per participant. Resource use data collection will be integrated into the study CRFs for systemic treatment and surgery, and collected at each follow-up from patients on treatments, hospital admissions and further contact with health professionals in primary or secondary care. Unit costs will be derived from nationally published sources such as NHS Reference Costs and attached to the resource use data (19).

Missing resource use and EQ-5D data will be handled using multiple imputation methods (20). From average costs and QALYs associated with each group, the incremental cost-effectiveness ratio (ICER) will be derived, producing the incremental cost per QALY gained with LCT compared to conventional care. LCT will be considered cost-effective if the ICER falls below £20,000, the level below which NICE generally recommends interventions to the NHS (21). Uncertainty around the ICER will be represented graphically on the cost-effectiveness plane by the bootstrap replicates of the mean difference in costs and QALYs between the groups. If there are differences in mortality between groups, then costs and outcomes will be extrapolated to a longer time horizon. Results will be expressed in terms of a cost-effectiveness acceptability curve, (which indicates the likelihood that LCT is cost-effective for different levels of willingness to pay for health gain) to help decision makers assess whether LCT is likely to represent value for money for the NHS.

8. Study management

The Royal Brompton and Harefield Hospitals, part of Guy's and St Thomas' NHS Foundation Trust will act as Sponsor. Responsibility for running the RCT will be established *via* agreement

with the University of Bristol. Agreements between the Sponsor and participating centres will be required, as well as standard site-initiation documents, before recruitment commences. The study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines, the Data Protection legislation, and the UK Policy Framework for Health and Social Care Research. The study will be registered on an open access clinical trial database (ISRCTN). Clinical study documents will be archived and held by the Sponsor for 5 years after study closure in accordance with the standard operating procedures of the Sponsor and in compliance with the principles of GCP.

8.1 Study Oversight

The study will be managed by a Trial Management Group (TMG), which will meet face-to-face or by teleconference as agreed with the chief investigator (CI). The TMG will be chaired by the CI and will include members of the named research team, including a patient representative. (see Chief Investigators & Research Team Contact Details).

The TMG will be supported by the BTC which is a UK Clinical Research Collaboration registered Clinical Trials Unit. The BTC will prepare all the study documentation and data collection forms, develop and maintain the study database, check data quality as the study progresses, monitor recruitment and carry out study analyses in collaboration with the clinical investigators.

The BTC study manager will be the contact point to provide support and guidance to the participating centres/specialties throughout the study.

8.2 Day-to-day management

An appropriately qualified person by training will be responsible for identifying potential study participants, seeking informed participant consent, randomising participants, collecting study data and ensuring the study protocol is adhered to.

8.3 Monitoring of sites

8.3.1 Site Initiation

Before this protocol is implemented training session(s) will be organised by the BTC. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

8.3.2 Site monitoring

The BTC will carry out regular remote monitoring and audit of compliance of centres with GCP and data collection procedures described in section 6.6. On site monitoring may take place by the study sponsor should issues be identified.

8.4 Trial Steering Committee and Data Monitoring and Safety Committee

8.4.1 Trial Steering Committee

An independent TSC will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the lead investigators, an independent chair and at least two additional independent members, at least one of whom will be a patient/public representative. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet before recruitment begins and regularly (at intervals to be agreed with the Committee) during the study.

8.4.2 Data Monitoring and Safety Committee

An independent DMSC will be established to review safety data during the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet (before or jointly with the TSC) before the study begins and they will meet regularly thereafter (at intervals to be agreed with the Committee). Stopping rules for the study will be discussed at the first DMSC meeting, and decisions documented in the DMSC Charter.

9. Safety reporting

9.1 Overview

Adverse events that meet the serious criteria will be recorded and reported in accordance with GCP guidelines and BTC Study Conduct Standard Operating Procedure (BTC-SOP-TM-002, Section 5.4 Recording, Managing and Reporting Adverse Events), (see Figure 2).

An **Adverse Event** (AE) is any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with the study treatment or procedure (*e.g.* abnormal laboratory findings, unfavourable symptoms or diseases).

A **Serious Adverse Event** (SAE) is an adverse event, adverse reaction, or unexpected adverse reaction that meets the following criteria:

- Requires hospitalisation or prolongation of existing hospitalisation
- Is Life threatening
- Results in persistent or significant disability or incapacity
- Results in death
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant.

Adverse Events (AEs) will be recorded using the event names of and graded in severity in accordance with the **Common Terminology Criteria for Adverse Events v5.0 (CTCAE),** which is a set of criteria for the standardised classification of adverse events in cancer studies:

- **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

- **Grade 3** - Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.
- **Grade 4** - Life-threatening consequences; urgent intervention indicated.
  Grade 5 - Death related to AE.

The Principal Investigator, or delegated clinician, will assess whether an event is expected of the specific treatment which the individual participant has received. Participants may receive a variety of treatments, including the study intervention(s), therefore guidance lists of expected events will be provided for guidance only (see appendix) and these lists are not exhaustive.

The PI, or delegated clinician will assess relatedness to the study intervention(s). Related events are those judged as possibly, probably or definitely related to the study intervention(s) received (LCT).

All SAEs will be collected on the study CRFs. Only those deemed **unexpected and related to the study intervention(s)** will require onward reporting to the sponsor. The coordinating centre will report all SAEs to the DMSC as part of the scheduled reporting of the study.

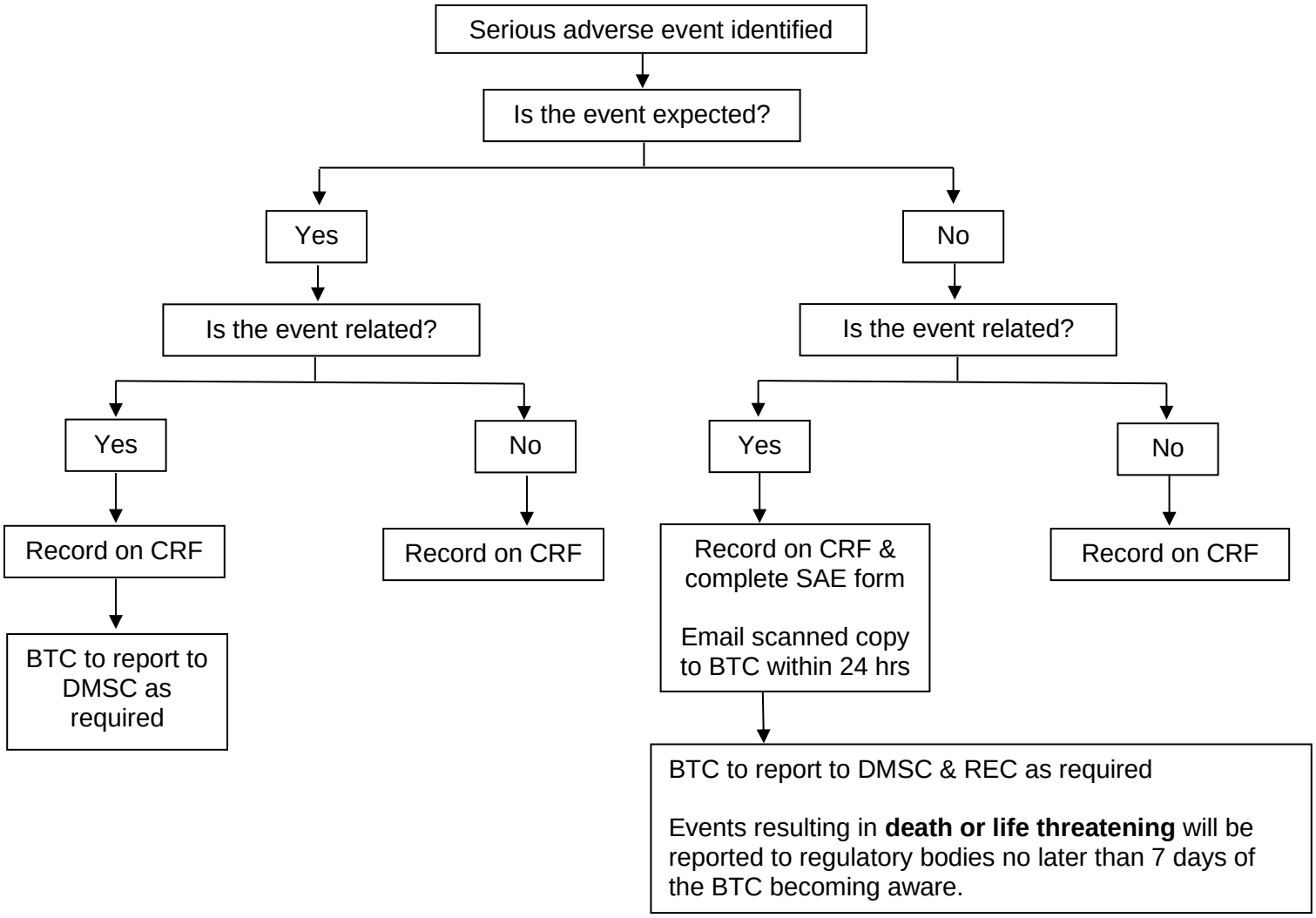
All **unexpected** SAEs **related** to the study intervention should be reported to the coordinating centre within 24 hours of the local site staff becoming aware of the event, even if sections of the forms are incomplete. Scanned copies of the SAE forms should be emailed to ramon-study@bristol.ac.uk and entered onto the RAMON study database as soon as possible. The co-ordinating centre will report all 'unexpected' and 'related' SAEs to the REC and DMSC within 15 days of becoming aware of the event and copy all reports to the Study Sponsor. The DMSC will review all SAEs at their regular meetings.

For SAE events that are deemed as 'ongoing' at the point of initial report, the co-ordinating centre should be updated within 5 days of the initial report. If the event is still ongoing after this, updates should be provided on new safety follow-up forms when new information becomes available about the event, until resolved or agreed with the sponsor that reporting can end. Updated information can be provided by scanned copies of the form and emailed to ramon-study@bristol.ac.uk. These should be entered onto the RAMON database as soon as possible.

Death as a result of disease progression is expected in the study population. All deaths should be recorded using inpatient records and the study CRFs. Deaths will only be onward reported *to the sponsor* if the cause of death is deemed to be unexpected and related to the study intervention.

Any pre-existing condition(s) that result in an SAE do not need to be reported unless they worsen during study participation.

Figure 2 Serious adverse event reporting flow chart



Note: Only deaths where the cause is both RELATED to the study intervention and UNEXPECTED require reporting on an SAE form to the study sponsor. All other deaths will be captured on the CRFs.

9.2 Period for recording adverse events and serious adverse events

Data on serious adverse events will be collected from date of randomisation until the end of the patient's participation in the study.

10. Ethical considerations

10.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the study and other study related essential documents (*e.g*. PIL and consent form) will be carried out by a UK REC.

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC and Health Research Authority (HRA) for approval prior to implementation. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving REC/HRA approval. However, in this case, approval must be obtained as soon as possible after implementation. All participating sites will need to confirm capability and capacity to deliver the protocol.

10.2 Risks and anticipated benefits

There should be no additional risks to participants when taking part in this study as neither LCT nor the symptom management treatment are new or experimental, however there may be side effects associated with the treatments received (see section 9.1). At present there is a lack of evidence to suggest that one treatment option is superior to the other; this forms the rationale for this study and will be the main benefit to society. Such evidence will inform NHS policy and patient and clinician decision-making.

10.3 Informing potential study participants of possible benefits and known risks

All potential participants will be sent or given the study PIL, approved by the REC, describing the study. The PIL will outline the risks and benefits of taking part. Patients will have adequate time to consider participation and will only be consented if the patient feels that further deliberation will not change their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given.

10.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the study given to patients in advance of recruitment, is described above in section 6.9.

The principal investigator (PI) or members of the team delegated by them will be responsible for obtaining informed consent. Research personnel authorised to obtain consent will be recorded on the Delegation of Responsibilities Log. All individuals obtaining informed consent will have

received GCP training. The consent process will be described in detail in the study working instructions.

10.5 Co-enrolment

Participants cannot be co-enrolled into other interventional studies influencing survival during their participation in RAMON but can do so after. Interventional studies that do not influence survival will be reviewed on a case-by-case basis. Participants can be co-enrolled into observational studies if this does not pose too much of a burden to the participant.

11. Research governance

This study will be conducted in accordance with:

- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care Research

The CI and BTC team will work with the co-applicants to prepare the final protocol, submitting applications to the Sponsor, HRA and REC for approval, preparing study manuals, providing the randomisation service and designing and implementing the data management system. The CI, BTC team and project Sponsor will ensure that the study runs according to the pre-agreed timetable, recruitment targets are met, the purpose-designed CRFs are completed accurately, complies with relevant ethical and other regulatory standards, and that all aspects of the study are performed to the highest quality. Clinical applicants and BTC team members will also train investigators at participating centres, check that centres are ready to start, issue the “green light” to start and monitor their progress during the study.

11.1 Sponsor approval

Any amendments to the study documents must be approved by the sponsor prior to submission to the REC.

11.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the study.

Any amendments to the study documents approved by the REC will be submitted to the Trust for information or approval as required.

11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual

and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved by the REC that they receive and ensure that the changes are complied with.

11.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All study related documents will be made available on request for monitoring and audit by the sponsor, BTC, the relevant REC and for inspection by other licensing bodies.

11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research Health and Safety Guidance (HSG) (96)48 reference no. 2 refers. If there is negligent harm during the clinical study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.6 Clinical Trial Authorisation

Local consolidative treatment is not classed as an investigational medicinal product and a Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) is not required.

12. Data protection and participant confidentiality

12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

12.2 Data handling and storage for participant electronic consent (e-consent) data

Electronic consent will be available through a Research Electronic Data Capture (REDCap) e-consent module for participants who choose to use this method of consent. Access to the REDCap e-consent module will be granted to authorised members of the local research team and coordinating centre. Participant email addresses and completed consent forms will be stored in the REDCap e-consent module on a University of Bristol server. A log of all email invitations will be retained in the REDCap system which can only be accessed by BTC staff. No

data will be transferred out of the REDCap e-consent module. Data will be archived for 5 years after the end of the study. A copy of the final PDF detailing the patient's consent and member of the local research team's confirmation of obtaining consent will be uploaded to the main study database held on the NHS server, where all other participant study data will be held (see section 12.3).

12.3 Data handling, storage and sharing

12.3.1 Data handling

All participant data (with the exception of e-consent data as outlined above 12.2) will be entered into a purpose-designed server database hosted on the NHS network. Information capable of identifying participants and the nature of treatment received will be held in the database with passwords restricted to RAMON study staff at the participating site and the co-ordinating centre.

The database and randomisation system will be designed to protect patient information in line with data protection legislation. Study staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at participating sites and in accordance with ethics approval. All documents will be stored securely and only accessible by study staff and authorised personnel. Data will be collected and retained in accordance with data protection legislation.

Access to the database will be via a secure password-protected web-interface. Study data transferred electronically to the University of Bristol network for statistical analyses will contain the participant's unique study identifier only and will not include any personal identifiable information. Participants will be identified using their name and unique study identifier on the secure NHS hosted database. Other personal identifiers (address, postcode, contact number, email address, NHS number) will be held in order that study patients may be contacted during follow-up and provided with a summary of the results at the end of the study. These identifiers will be held securely in the database. Data will be entered promptly, and data validation and cleaning will be carried out throughout the study. Where electronic patient medical notes are used, local Trust policies will be followed.

Each recruiting centres will have access to the study manual, which will cover database use, data validation and data cleaning. The BTC will maintain and update the study manual as required.

Data transferred from the Coordinating Centre to the Health Economics team will also be transferred by secure means.

12.3.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where study related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the study in accordance to BTC policy. In compliance with the MRC Policy on Data Sharing, relevant 'meta'-data about the study and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key'

with a unique participant identifier, and key personal identifiers (*e.g*. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

Data generated from the QRI will be stored indefinitely at the University of Bristol for teaching and training purposes. Transcripts will be labelled with a study-assigned participant number, edited to ensure anonymity of respondents and stored securely adhering to the University of Bristol's data storage policies. Anonymised quotations and parts of voice modified recordings may be used for training, teaching, research and publication purposes for this and future studies. Anonymised transcripts may be made available to other researchers (including those outside of the University) by controlled access if they secure the necessary approvals for purposes not related to this study, subject to individual written informed consent from participants.

12.3.3 Data sharing

Trial data will not be made available for sharing until after publication of the main results of the study, unless agreed by the CI/TMG on a case by case basis. Anonymised consultation data collected through the QRI may be used for training and for cross-trial synthesis may be used once trial recruitment is complete and the report on this element of the research is completed. Following publication of the main results of the study, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the medical research council (MRC) Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available prespecified protocol describing the purpose, methods and analysis of the secondary research, *e.g.* a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

13. Dissemination of findings

The findings will be disseminated by usual academic channels, *i.e*. presentation at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR-HTA programme) and through patient organisations, newsletters to patients and social media where available.

14. References

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15. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)

16. Appendix

16.1 Anticipated & Expected adverse events guidance

Adverse events that might be expected for patients with stage IV advanced lung cancer or after initial systemic anti-cancer treatment, as well as events that might be expected after LCT treatments and symptom management are listed below. Please note that these lists are not exhaustive and it will be the responsibility of the treating clinician to determine if an event is related to the standard of care treatment a patient is receiving or the study intervention.

16.1.1 Adverse events considered as expected for participants with the condition

- New primary and secondary cancers
- Disease progression
- Death from disease progression.

16.1.2 Adverse events considered as 'anticipated' for participants undergoing chemotherapy

Note: Additional adverse events may also be considered expected if identified on the product summary of product characteristics (SPC).

Blood & lymphatic complications:
- Anaemia
- Thrombocytopenia
- Neutropenia (Febrile Neutropenia)
- Myelosuppression

Gastrointestinal complications:
- Nausea
- Vomiting
- Diarrhoea
- Constipation

Infectious complications:
- Infections

Nervous system complications:
Peripheral sensory neuropathy
Peripheral motor neuropathy
Headaches
Insomnia

Immune system complications:
Anaphylaxis / Hypersensitivity reaction
Muscular complications
Arthralgia
- Myalgia

Abnormal laboratory results:
- Leukopenia
- Elevated AST / ALTs
- Elevated alkaline phosphatase

16.1.3 Adverse events considered as expected for participants undergoing immunotherapy

Blood & lymphatic complications:
- Anaemia
- Thrombocytopenia
- Leukopenia
- Immune thrombocytopenia

Gastrointestinal complications:
- Nausea, Vomiting
- Diarrhoea
- Colitis
- Pancreatitis

Nervous system complications:
Peripheral neuropathy
Headaches
Insomnia
Seizures
Guillain-Barre syndrome
Myaesthenia Gravis
Encephalitis, Myelitis

Immune system complications:
Anaphylaxis / Hypersensitivity reaction

- Gastritis
- Dry mouth

Infectious complications:
- Pneumonia

Endocrine complications:
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

Eye complications:
- Uveitis
- Dry eyes

Cardiac complications:
- Arrhythmias including atrial fibrillation
- Myocarditis, pericarditis

Musculoskeletal complications:
- Myalgia, arthralgia
- Arthritis
- Sjogren's syndrome

Renal and urinary complications:
- Nephritis
- Acute kidney injury

Abnormal laboratory results:
- Elevated AST / ALTs
  - Elevated alkaline phosphatase
  - Hypercalcaemia
  - Elevated bilirubin

Metabolic and nutrition complications:
- Anorexia
- Hyponatraemia, hypokalaemia
- Type 1 diabetes mellitus

Respiratory complications:
- Pneumonitis
- Dyspnoea, cough

Hepatobiliary complications:
- Hepatitis
- Sclerosing cholangitis

Skin complications:
- Rash, pruritis
- Eczema
- Alopecia
- Psoriasis
- Toxic epidermal necrolysis
- Stevens-Johnson Syndrome
- Erythema Nodosum
- Vitiligo

16.1.4 Adverse events considered as expected for participants undergoing molecular targeted treatment

Blood & lymphatic complications:
- Anaemia
- Thrombocytopenia
- Leukopenia

Gastrointestinal complications:
- Nausea
- Vomiting
- Constipation
- Diarrhoea
- Stomatitis

Infectious complications:
- Pneumonia

Eye complications:

Nervous system complications:
Peripheral neuropathy
Headaches
Insomnia

Abnormal laboratory results:
- Elevated AST / ALTs
- Elevated alkaline phosphatase
- Hypercalcaemia
- Elevated bilirubin

Metabolic and nutrition complications:
- Anorexia
- Taste change
- Hyponatraemia, hypokalaemia
- Hypophosphataemia

- Keratitis
- Conjunctivitis
- Dry eyes

Cardiac complications:
- QTc prolongation
- Reduction in LV function
- Bradycardia
- Tachycardia
- Hypertension

Musculoskeletal complications:
- Myalgia, arthralgia

Renal and urinary complications:
- Acute kidney injury

Respiratory complications:
- Interstitial lung disease / pneumonitis
- Epistaxis
- Dyspnoea, cough
- Hypomagnasaemia
- Hyperglycaemia
- Elevated amylase
- Elevated lipase
- Hyperlipdaemia

Skin complications:
- Oedema
- Rash
- Pruritis
- Paronychia
- Palmar-plantar erythrodyaesthesia syndrome
- Alopecia
- Urticaria
- Stevens-Johnson Syndrome
- Erythema multiforme

Hepatobiliary complications:
- Pancreatitis

16.1.5 Adverse events considered as expected <u>for patients undergoing radiotherapy</u>

Thoracic:
- *Cardiac Toxicities:*
  - Pericardial abnormalities
  - Heart failure
  - Congestive heart failure
  - Angina pectoris
  - Pericarditis
  - Cardiac tamponade
  - Myocardial infarction
  - Radiation-induced brachial plexopathy
- *ECG changes*
  - Non-specified ECG changes
  - T wave inversion
  - ST changes
  - Sinus tachycardia
- *Oesophageal Toxicities:*
  - Dyspepsia
  - Oesophagitis
  - Oesophageal perforation
  - Oesophageal candidiasis
  - Oesophageal fistula
  - Oesophageal fibrosis
  - Oesophageal necrosis
  - Late oesophageal stricture

Pelvic:
- Bladder & Renal Toxicities:
- Radiation cystitis
- Increased urinary frequency
- Nocturia
- Urinary urgency
- Haematuria
- Bladder obstruction
- Dysuria
- Epithelial atrophy (bladder)
- Telangiectasia (bladder)
- Haematuria
- Bladder necrosis
- Urinary Incontinence
- Renal impairment/reduced creatinine clearance

Brain:
- *Symptoms*
- Headache
- Nausea
- Vomiting
- Worsening of original brain met symptom

- *Lung Toxicities:*
  - Dyspnoea
  - Lung fibrosis
  - Respiratory insufficiency
  - Dry cough
  - Pneumonitis
  - Haemoptysis = Pulmonary haemorrhage
  - Lung infection
  - Bronchial or pulmonary fistula
  - Lung abscess* = pulmonary abscess
  - Altered Lung Function:
    - Carbon monoxide diffusing capacity decreased
    - Forced Expiratory Volume decreased
    - Vital Capacity abnormal
  - Chest wall pain
  - Rib fractures
  - Pulmonary embolism
  - Pulmonary Haemorrhage
  - Bronchial Stenosis
  - Bronchial Stricture
  - Atelectasis

Abdominal:

- *Liver toxicities:*
  - Radiation hepatitis
  - Abnormal liver function
  - Abdominal oedema or ascites
  - Encephalopathy
- *Gastro-intestinal toxicities:*
  - *Oesophageal:*
    - Dyspepsia
    - Oesophagitis
    - Oesophageal perforation
    - Oesophageal necrosis
    - Oesophageal fistula
    - Oesophageal fibrosis
    - Oesophageal candidiasis
    - Late oesophageal stricture
  - *Gastric:*
    - Gastritis
    - Haemorrhagic gastritis
    - Gastric ulcer
    - GI bleed
  - Could include progressive focal neurological deficit, dysphasia or cerebellar ataxia
- Fits/seizures
- Dizziness
- Otitis
- Tinnitus
- *Radiological Findings:*
  - Radiation necrosis
  - Brain swelling
- *Physical Findings:*
  - Paresis = Limb weakness = Paralysis = Mono/para/quadriplegia
  - Loss of power/CNS dysfunction
  - Coma
  - L Hermitte's Syndrome
  - Sensory neuropathy
- *Eye/Optic toxicities:*
  - Conjunctivitis
  - Reduced vision
  - Cataract
  - Corneal ulceration
  - Keratitis
  - Retinopathy
  - Glaucoma
  - Blindness
  - Panopthalmitis

Bone:

- *Bone toxicities*
  - Bony pain = Back pain
  - Bony fracture = Compression fracture
  - Bone marrow suppression
  - Osteoradionecrosis
  - Reduced bone density
  - Irregular bone sclerosis
  - Necrosis
- *Joint toxicities*
  - Joint stiffness and limited movement
  - Joint pain
  - Joint fixation
- *Nerve toxicities*
  - Nerve root pain
  - Injury to spinal cord

- *Small Bowel:*
  - Duodenal ulcer
  - Duodenal bleed
  - Small bowel obstruction
  - Bowel perforation
  - Bowel necrosis
- *Large Bowel:*
  - Colonic ulcer
  - Rectal bleeding
  - Bowel obstruction
  - Bowel perforation
  - Bowel necrosis

- *Symptoms:*
  - Dyspepsia
  - Loss of appetite
  - Abdominal pain
  - Vomiting
  - Nausea
  - Bowel cramping
  - Lassitude= fatigue
  - Asthenia = Loss of energy
  - Rectal discharge
  - Diarrhoea
  - Constipation
- *Other:*
  - Radiation enteritis
  - Neuritis
  - Rib fracture
  - Adrenal Insufficiency
  - Nerve damage* = Peripheral neuropathy/neuritis

Skin Toxicity:
- Erythema/radiation dermatitis
- Desquamation
- Decreased sweating
- Hair Loss
- Skin atrophy
- Skin pigmentation change
- Skin ulceration
- Fibrosis of subcutaneous tissue
- Loss of subcutaneous tissue
- Skin tissue breakdown
- Mucositis

Haematological Toxicity:
- Anaemia (Haemaglobin)
- Thrombocytopenia (platelets)
- Neutropenia (Neutrophils)
- Reduced Haematocrit

All Sites:
- Anorexia
- Weight loss
- Nausea
- Dry mouth
- Altered taste
- Hoarse voice
- Lethargy/fatigue

16.1.6 Adverse events considered as expected <u>for patients undergoing ablation</u>

Liver ablation (RFA, MWA and IRE)
- Bleeding
- Haematoma
- portal vein thrombosis
- pleural effusions
- pneumothorax
- ascites
- infections and fever
- bile duct injury
- bile leak
- adjacent organ injury (bowel perforation)

Lung ablation (RFA, MWA and CRYO)
- Self-limiting pneumothorax
- pneumothorax with drainage requirement
- haemoptysis
- lesion cavitation
- bronchopleural fistula
- adjacent organ thermal injury

- intercostal nerve thermal injury
- abscess formation
- cutaneous fistula
- atrial fibrillation (for IRE)

Adrenal ablation (RFA, MWA and CRYO)

- Hypertensive crisis
- Pneumothorax
- Haemorrhage
- vascular thrombosis
- visceral perforation
- pain
- adjacent organ thermal injury

Musculoskeletal (MSK) ablation (RFA, MWA and CRYO)

- adjacent organ thermal injury
- skin frost injury
- fracture, infection
- nerve injury
- Abscess formation

16.1.7 Adverse events considered as 'expected' from the time of surgery to post-operative discharge

Procedural complications:

Pulmonary:

- Acute respiratory failure
- Atelectasis/ Pulmonary collapse
- Pneumonia / Chest Infection (defined by the administration of antibiotics)
- Empyema (defined as the requirement for antibiotics or drainage)
- Surgical emphysema (requiring intervention)
- Bronchopleural fistula
- Prolonged Air leak (≥ 7 days)
- Post-drain pneumothorax requiring intervention
- Chylothorax
- ARDS (acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO2/FiO2 ratio ≤200 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic oedema).
- Acute Lung Injury (ALI), defined as above but by a 200 < PaO2/FiO2 ≤300 mmHg)
- Pleural effusion

Cardiovascular:

Renal complications:

- New haemofiltration/dialysis
- Acute Kidney injury (rise in serum creatinine >50% preoperative value to any rise above the reference range in previously normal values)

Infective complications:

- Sepsis (defined as antibiotic treatment for suspected infection)
- Wound infection
- Respiratory infection
- Other infection

Neurological complications:

- Transient ischaemic attack
- Stroke
- Acute psychosis

Other:

- Re-operation (due to any reason, including bleeding, or other cause)
- Excess bleeding, (whether or not it requires reoperation)
- Wound dehiscence requiring treatment
- Insertion of a mini-tracheostomy tube
- Tissue biopsy

- Serious arrhythmia (defined by the requirement of intervention)
- Myocardial infarction (defined by elevated Troponin)
- Bleeding (in or around the operation site)
- Blood clots
- Haematoma
    - Open & close thoracotomy in the event of inoperable lung cancer or extensive malignancy
    - Laryngeal nerve damage
    - Bronchoscopy for any cause

Thromboembolic complications:
- Deep vein thrombosis
- Pulmonary embolus
- Venous thromboembolism (VTE)

GI complications, including:
- Peptic ulcer/Gastrointestinal (GI) bleed/perforation
- Pancreatitis (amylase >1500iu)
- Other (e.g., laparotomy, obstruction)

16.2 App based QUality of life Assessment in Lung Cancer – The AQUA lung study

16.2.1 Background

The effectiveness of many clinical interventions is measured in terms of quality and length of life. Quality of life is an important patient orientated outcome that matters, but the meaning and quantification is abstract, ranging from the broadest definition of “whatever is important to the patient” to rigid (validated) scales such as EORTC QLQ-C30 and LC-13 for lung cancer.
In clinical trials, patient reported quality of life outcomes at pre-specified time points using validated scales are standard. However, there are numerous challenges that include:
- administrative burden of contacting and ensuring patients complete questionnaires on time
- time required with each patient to explain how to complete the questionnaire correctly
- patient fatigue from answering so many questions at one specific point in time
- significant number of questions that may not be applicable or important to the individual
- information only available at specific time points with “blindness” between the survey intervals
- recording measures of perceived outcomes (e.g. reported physical function) rather than actual measure of the outcome of interest (e.g. pedometry)

There is an increasing drive towards the use of technology to augment healthcare with innate potential to improve efficiency and reduce costs.
The use of the smartphone in the UK is increasing annually (figure 1). In 2012 less than 5% of people over 65 were using smart phone, and by 2020 the usage had increased to over 65% in the same age group. Correspondingly, the age range between 45 to 70 years old accounts for just under half of the patients with lung cancer in the UK (figure 2).
The AQUA lung study seeks to evaluate the use of a mobile phone-based healthcare app (My Cancer Companion) to determine agreement between patients self-reporting of quality-of-life outcomes compared to completion of quality-of-life scales at pre-specified time points within the

RAMON study which will evaluate the clinical and cost effectiveness of Local Consolidative Treatment (LCT) for advanced lung cancer.

16.2.2 Methods

The AQUA lung study is based on the following hypothesis for app-based monitoring of quality-of-life outcomes:

1. In 2022, more than 33% of patients with advanced lung cancer will be able to use app reporting
2. There is acceptable agreement between app and form reporting
3. Participants will complete more time points for app reporting
4. It is possible to use a reduce set of questions to achieve comparable information
5. Absence of specific outcomes reporting is due to the lack of symptoms [participants can save time]
6. App reporting can increase efficacy for physical function reporting [we can measure direct outcomes of interest and save time]
7. Perceived physical function is comparable to actual performance measured by pedometer [we can reduce the number of questions]
8. Participants will prefer app based to form reporting [participants will report more willingly]
9. Participants will report more outcomes using app reporting compared to that listed in EORTC QLQ-C30 and LC-13 [participants will report more than conventional questions asked]
10. App reporting will be cost-effective

My Cancer Companion (MCC) is a mobile phone application that is currently being developed in collaboration with healthcare professionals and patients. Discussions on clinical utility and usage have been undertaken with professional societies and patient groups. The first round of prototype testing was undertaken with patients and healthcare providers in August 2021 with a focus on user experience and interface regarding the presentation and recording of quality-of-life outcomes. Based on patient and healthcare professional feedback, a second round of modification and testing was undertaken in September 2021 to facilitate a key set of data elements that could be easily understood by patients with lung cancer and mesothelioma. The product launch is planned for 22 August 2022.
All participants in the RAMON study will be offered an opportunity to participate in AQUA lung with signed informed consent, and the app (My Cancer Companion) will be available to download freely. AQUA lung participants will be asked to enter the clinical trial code “RAMON” into the app and their trial ID which allows us to identify the participants. They will be then asked to record their physical health and mental wellbeing status using the app [physical and mental function is mandatory, and the rest optional]. In addition, they will be asked to complete the EORTC-QLQ C30, LC-13 and EQ-5D quality of life questionnaires at pre-specified time points as part of the RAMON study.

16.2.3 Analyses

During the study we will compare agreement between the data elements in common between the MCC v1.0 data set versus common elements within the EORTC-QLQ C30, LC-13 and EQ-5D quality of life questionnaires.

Agreement in common elements
Bland and Altman plots will be used to estimate agreements on common measures between the last patient recorded MCC data item with the timed RAMON reporting. An important difference would be considered present if the mean difference were to exceed the published acceptable values (14) (e.g. if the difference exceed -15.8 to +3.1 on the pain scale). Where published minimally important differences do not exist, then an expression of the difference as a percentage will be reported with an arbitrarily defined difference of (less than 10, 11-20, 21-30 and more than 31) to indicate minimal, small, medium and large difference.

Exploratory analysis
Pre-specified exploratory analyses would include:

- Correlation between pedometry data and EORTC physical function (correlation coefficient)
- Average number of data points reported per year for MCC (e.g. EORTC QLQ C-30 at 4 time point is 120 data points)
- Agreement between patients not selected optional items for reporting and reporting of 0 values for EORTC scales (kappa)
- Additional quality of life measures added by participants (not otherwise covered)

Figure 1. Smartphone usage by age

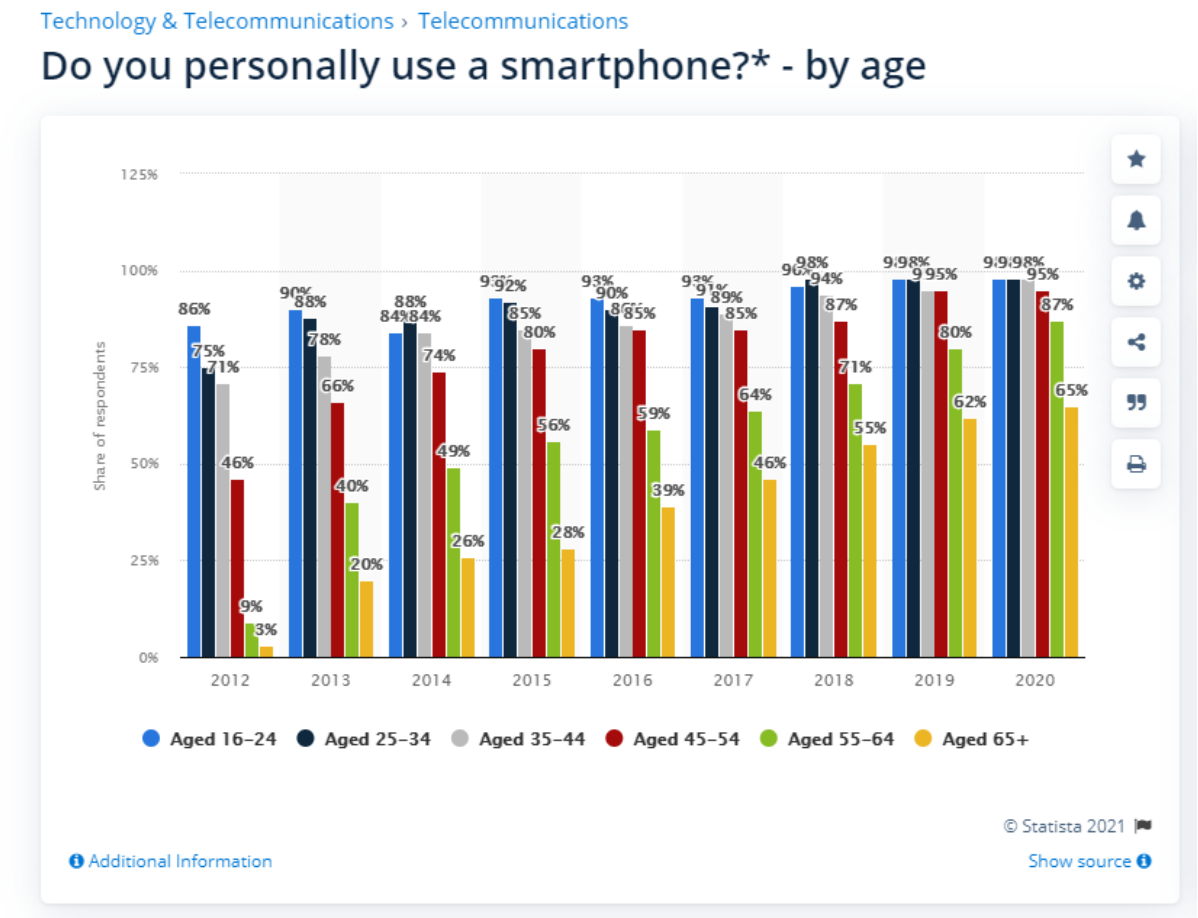

Figure 2. Age incidence of lung cancer in the UK

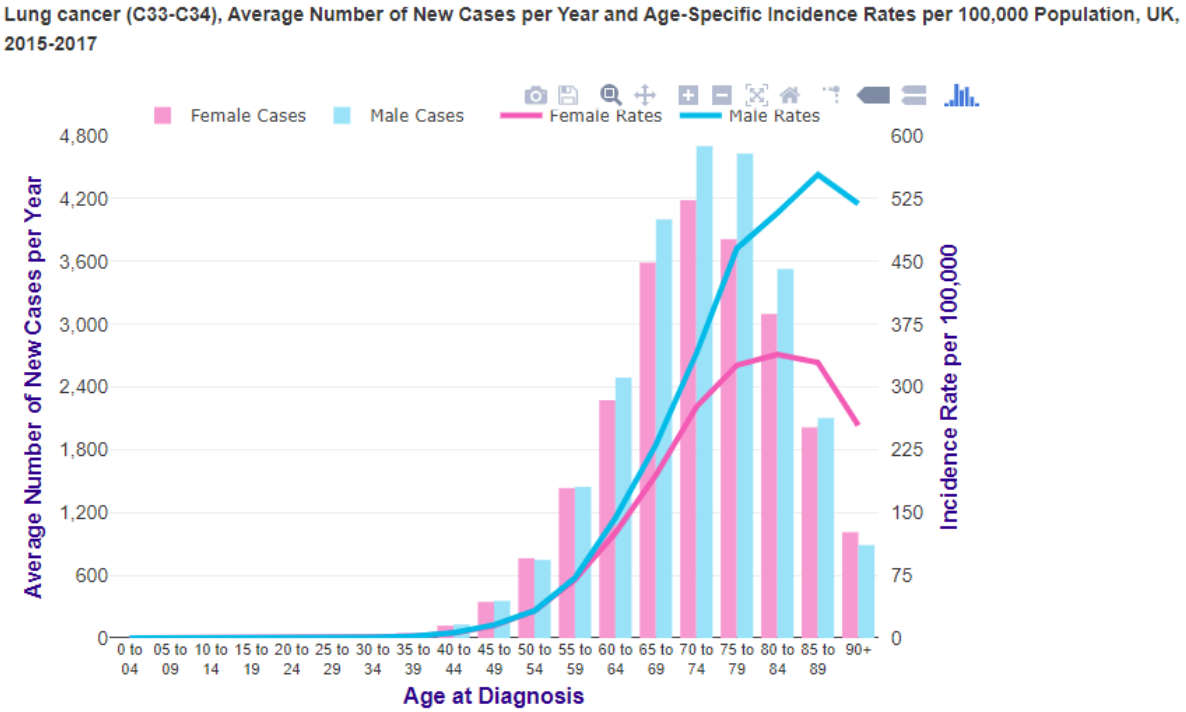

Table 1. MCC data items versus EORTC QLQ C30 and LC13

MCC item	Name	EORTC QLQ C-30 and LC-13	Composite
1	Overall health	29,30	Global health status
2	Mental wellness	N/A	
3	Shortness of breath	8,33,34,35	Dyspnoea
4	Concentration or memory difficulty	20,25	Cognitive functioning
5	Constipation	16	
6	Cough	31	
7	Diarrhoea	17	
8	Family or social life interference	26,27	Social functioning
9	Financial difficulties	28	
10	Hair loss	39	
11	Impact on daily work or leisure	6,7	Role functioning
12	Loss of appetite	13	
13	Mobility trouble	1,2,3,4,5	Physical functioning
14	Nausea or vomiting	14,15	Nausea and vomiting
15	Pain	9,19,40,41,42,43	Pain
16	Sore mouth	36	
17	Tension, worry, anxiety or sadness	21,22,23,24	Emotional functioning
18	Tingling in hands/feet	38	
19	Tiredness	10,12,18	Fatigue
20	Trouble swallowing	37	
21	Trouble sleeping	11	