PulMiCC

International

A Randomised Phase III, Multi-centre International Trial of Pulmonary Metastasectomy in Colorectal Cancer

Version 18

Sponsor: University College London (Reference No: 08/0390)

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List of Abbreviations

Adverse Event	Adverse event
BMJ	British Medical Journal
BTS	British Thoracic Society
CBCT	Cone beam computed tomography
CEA	Carcinoembryonic antigen
CI	Chief Investigator
CONSORT	CONsolidated Standards Of Reporting Trials
CRF	Case report form
CRUK	Cancer Research UK
CT	Computed tomography
CtE	Commissioning through Evaluation programme
CTG	Clinical Trials Group
DMC	Data Monitoring Committee
DVD	Digital versatile disc
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol
FACT G-F	Functional Assessment of Cancer Therapy general and fatigue
FBC	Full blood count
FEV1	Forced Expiratory Volume
GP	General Practitioner
GTV	Gross Tumour Volume
IGTA	Image Guided Thermal Ablation
ISRCTN	International Standard Registered Clinical/social sTudy Number
LFT	Liver Function Test
MDT	Multidisciplinary team
MRC CTU	Medical Research Council Clinical Trials Unit

NHS	National Health Service
NICE	National institute of clinical excellence
OAR	Organs at Risk
PET-CT	Positron Emission Tomography-Computed Tomography
PI	Principal Investigator
QALYs	Quality-adjusted life years
RCR	Royal College of Radiologists
RCT	Randomised Controlled Trials
REC	Research Ethics Committee
R&D	Research and development
RTTQA	Radiotherapy Trials Quality Assurance
SABR	Stereotactic Ablative Radiotherapy
SAE	Serious adverse events
SHORE-C	Sussex Health Outcomes Research & Education in Cancer
SITU	Surgical & Interventional Trials Unit (SITU) formerly CTG
SOP	Standard operating procedure
SSI	Specific Site Information
STAI	State/Trait Anxiety Inventory
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospitals
USA	United States of America

1.0 **Background**

Colorectal cancer is one of the three commonest solid tumours. Approximately 100 cases are diagnosed each day in the UK. In 2006, 37,514 cases of colorectal cancer were diagnosed.

The increasing intensity of monitoring including various combinations of CT scans chest radiographs, CEA and liver ultrasound in routine follow up of patients has led to earlier diagnosis of metastases.[1-5] Of particular interest in thoracic surgical practice is the detection of isolated subclinical lung nodules and there has been widespread adoption of pulmonary metastasectomy in selected cases. A survey of practice in Europe showed that pulmonary metastasectomy is very commonly performed but criteria vary widely.[6] An estimated 300 such operations were being carried out annually in the UK when PulMiCC opened as a 'feasibility' study. Increasingly Image Guided Thermal Ablation (IGTA) has been used where available as a less invasive alternative to what was perceived to be an already proven treatment.[7] Recently Stereotactic Ablative Radiotherapy (SABR) has also been proposed. This too is without RCT evidence.[8] SABR has been introduced for ablation of metastases in the Commissioning through Evaluation (CtE) programme[9] but metastases from colorectal cancer have not been included in commissioning.

Pulmonary metastasectomy for treatment of lung metastases

Although well-established in clinical practice there have been no previous randomised controlled trials of the effect of lung metastasectomy on survival and there is doubt as to its clinical effectiveness.[10] The most recent systematic review and meta-analysis[11] concludes that pulmonary metastasectomy is associated with a high likelihood of recurrence, with doubling of the recurrence rate with each of three adverse prognostic factors:

- more than one metastasis
- an interoperative interval (primary resection to lung metastasectomy) less than three years
- elevated CEA.

In a prospective registry capturing more than 60% of Spanish practice for a two year period these limits were commonly exceeded.[12]

In an RCT it has been shown that recurrence can be detected earlier with CT and/or CEA surveillance and as a result more liver and lung metastasectomy operations were performed.[2] However, these operations did not provide any survival benefit, within the RCT. The uncertainty about the practice has been set out in the BMJ in 2014.[13-15] Pulmonary metastasectomy is thus part of a bigger question about effectiveness of surgery for metastases from colorectal cancer.

Surgery, SABR and IGTA have in common that none of them has been shown to be clinically effective in prolonging survival. They have not been shown to be ineffective either. In practices with high rates of treatment for metastasectomy either surgery or ablation may be used, sometimes for different metastases in the same patient depending on anatomical location and other technical considerations.

It is proposed following the roll-out of SABR for lung metastasectomy in the NHS in England, it should be viewed as an alternative or adjunct to surgery for patients randomised to intervention in PulMiCC.

Rationale for trial design

There are known prognostic factors which include the number of metastases, the length of time they take to become evident radiologically and the level of carcino-embryonic antigen (CEA).

- A solitary nodule appearing after a long interval is likely to be removed in most instances.
- Surgery is rarely advocated when there are multiple metastases present at the time of surgery on the primary colorectal cancer or appearing soon after.

These scenarios represent opposite ends of the continuum of favourable to adverse factors for survival after resection of pulmonary metastases [15]. Most patients operated fall between these extremes and it is clear that if there is a "yes" towards one end of the continuum and "no" towards the other then there is a cross-over zone where there is clinical uncertainty. PulMiCC aims to investigate the outcome following pulmonary metastasectomy or ablation in patients to provide evidence to guide practice in the future where there is clinical uncertainty about whether they might benefit.

It has also been shown previously that trials requiring patients to consider randomisation between treatments that appear very different, as in this instance between surgery or no surgery, are hard to recruit to. This is because potential participants may have acquired a strong preference for one of the treatments over the other and they are not willing to accept the possibility of being allocated to the more or the less active of two alternatives [16].

There can also be problems of bias if one treatment is mentioned to the patient before the option of a trial is introduced; the first mentioned treatment may be perceived to be preferred between doctor and patient. This trial has been designed to overcome these potential difficulties and maximise recruitment.

Colorectal cancer patients presenting with pulmonary metastases will first be consented for registration into the study. This consent is to undergo evaluation according to the trial protocol as part of the work up for consideration by the Multidisciplinary Team (MDT). Following evaluation, the MDT will consider how they would normally treat each patient according to their standard local practice. Patients eligible for randomisation will be those for whom there is clinical uncertainty exists as to whether surgery, SABR or IGTA would be of benefit. This trial design was successful in a study of the feasibility of randomising patients in a trial of mesothelioma surgery.[16;17].

The time taken for patients to undergo the full range of tests for evaluation gives them time to think carefully about the possible treatment options and to discuss them with their doctor. In addition to the patient information leaflet, patients will be invited to take home a DVD explaining the trial in detail; there is also a DVD available to clinicians. The links provided below are for both the clinician and patient DVDs, these can be streamed on line.
PulMiCC Training DVD
http://shore-c.sussex.ac.uk/pulmicctrainingdvd.html
PulMiCC Patient DVD
http://shore-c.sussex.ac.uk/pulmiccpatientdvd.html

The DVD can be watched as often as the patient likes. It is hoped that those who are ultimately identified as eligible for randomisation will have fewer anxieties because of their extended opportunity to consider the trial.

Local site research staff involved in recruiting patients will be invited to attend a training session to learn the best method of informing patients about the trial before recruitment commences.

2.0 Overall aim

To determine whether there is a survival benefit from surgical excision or ablation of lung metastases.

2.1 Primary endpoint

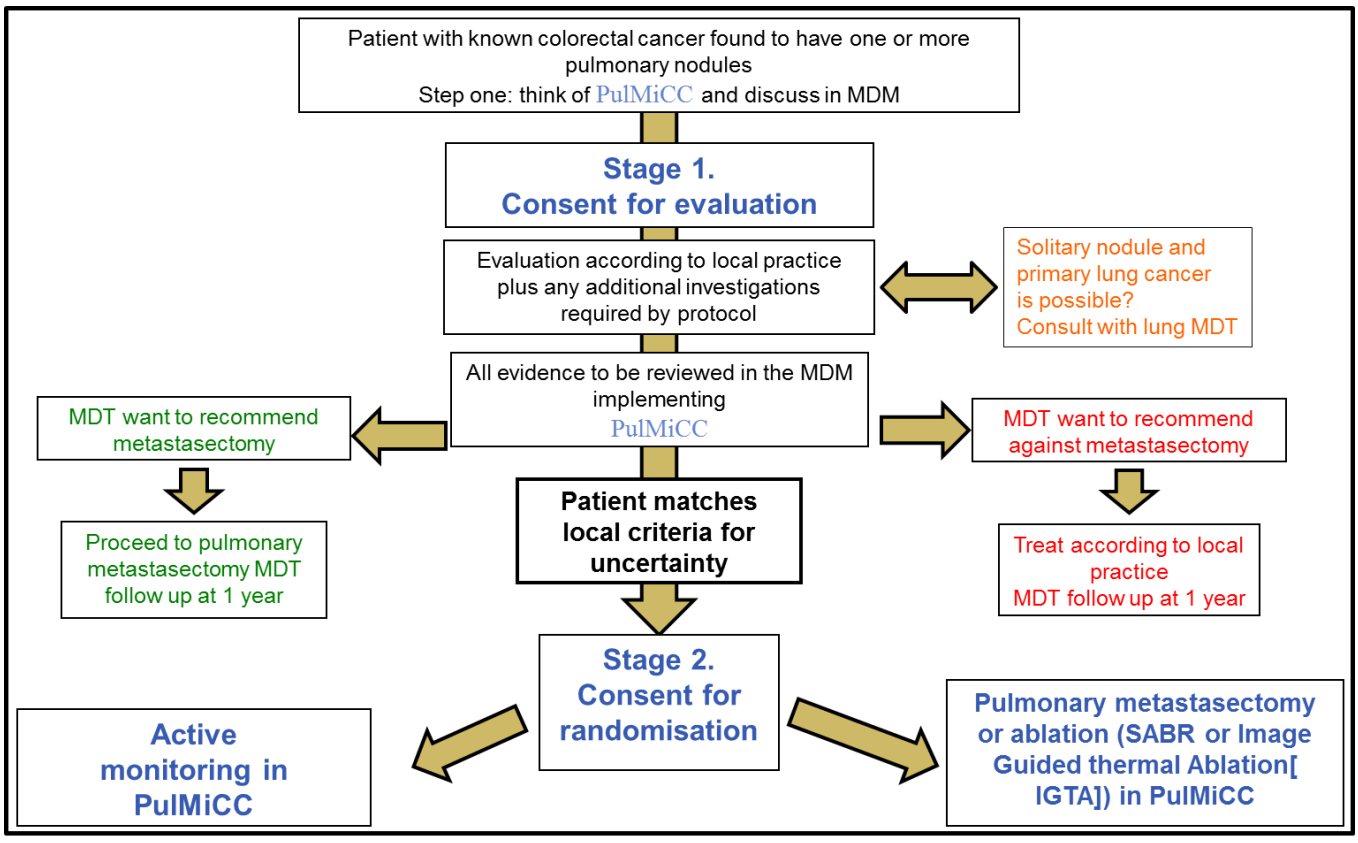
- Overall survival

2.2 Secondary endpoints

- Lung function
- Patient reported quality of life
- Cost effectiveness

3.0 Trial design

This is a two-stage randomised study. Patients will be firstly registered for evaluation (stage 1) and if subsequently eligible, randomised (stage 2) either to active monitoring or to active monitoring with pulmonary metastasectomy.



4.0 Patient selection and informed consent-Registration. Stage1

Patients on routine follow up following resection of primary colorectal cancer may have lung metastases discovered on routine surveillance CT scans or as a result of some specific trigger such as symptoms or a raised CEA.

Note: Where the lung nodule is solitary the possibility that this is primary lung cancer must be considered by the lung cancer MDT.

The results should be discussed in the colorectal MDT meeting where radiological evidence of pulmonary metastases will be first presented by the radiologist.

4.1 **Evaluation for Registration (stage 1)**
Patients fulfilling the following criteria will be eligible for registration for evaluation.

Inclusion criteria for registration

- Patients with primary colorectal cancer who have undergone resection of the primary cancer with prospect of cure
- Local control has been confirmed
- Confirmation of pulmonary metastases at the MDT meeting
- No clinical indications of other active colorectal cancer other than the known lung metastases.

Exclusion criteria

- Previous malignancy likely to interfere with protocol treatment or measurement of endpoints with the exception of early non-melanoma skin cancer and in situ cancer of cervix, any primary cancer more than ten years since treatment without recurrence.
- Any concurrent illness which could interfere with the treatment protocol or confound survival
- Unavailable for follow up and assessment according to protocol
- Lack of mental incapacity that precludes fully informed consent

4.2 Informed consent for registration

The clinical team member designated to inform potentially eligible patients of the MDT findings will explain the situation, indicating explicitly the uncertainty surrounding the management of pulmonary metastases. The trial will be introduced and interested patients will be given a patient information leaflet and DVD to take home explaining the trial in detail, there is also a DVD available to clinicians. The links provided below are for both the clinician and patient DVDs, these can be streamed on line.
PulMiCC Training DVD
http://shore-c.sussex.ac.uk/pulmicctrainingdvd.html
PulMiCC Patient DVD
http://shore-c.sussex.ac.uk/pulmiccpatientdvd.html

The DVD can be watched as often as the patient likes. It is hoped that those who are ultimately identified as eligible for randomisation will have fewer anxieties because of their extended opportunity to consider the trial.

Arrangements will be made for a follow up discussion when patients who express interest in the study will be invited to discuss the trial further and ask questions. Patients who confirm that they are willing to join stage 1 of the trial will be asked to sign a registration for evaluation consent form (Consent Form 1).

4.3 Subject registration

Once site has consented a patient to join stage 1, Registration of all patients will be carried out by the SITU. Site staff will complete the enrolment CRF, which is available on the SITU website (https://www.ucl.ac.uk/surgical-interventional-trials-unit) and submit this either by fax or over the telephone to the SITU (details below), at this point the subject will be issued a registration number which is a unique subject identifier number.

Surgical & Interventional Trials Unit, Division of Surgery, UCL

Tel: +44 (0)20 7679 9280
Fax: +44 (0)20 7679 9290

Office Hours: 9:00am – 5:30pm

4.4 Evaluation following registration

The investigations for PulMiCC are essentially those that are part of standard work up of patients with lung metastasis. Patients should be evaluated according to local practice but investigations should also include the following:

- ECOG performance status assessment (see Appendix)
- PET-CT (whole body)
- Histology/cytology to confirm the nature of the nodules if there is clinical uncertainty concerning their nature (*this is not mandatory)*
- Full blood count, serum biochemistry and liver function tests
- CEA measurement
- Lung spirometry or peak flow
- Further lung function tests if there is uncertainty about fitness for surgery according to BTS guidelines
- Weight

4.5 Schedule of activities: Stage 1

Assessment	Stage 1 Registration for evaluation	12 months	60 months
	According to local practice but should also include the following		
PET-CT scan (whole body)	√		
Histology / cytology	√ *where indicated*		
Clinical examination	√		
Weight	√		
ECOG performance	√		
FBC	√		
Serum biochemistry	√		
LFT	√		
CEA	√		
Lung spirometry/peak flow	√		
Other lung tests *to confirm fitness for surgery*	√		
Adverse Event Recording	√	√	
CRF	√	√	√

5.0 Patient selection and informed consent - Randomisation – Stage2

5.1 Evaluation of randomisation

Following completion of investigations all patients should be evaluated according to local practice guidelines.

In patients for whom uncertainty exists as to whether surgery or SABR or IGTA would improve survival and/or quality of life are eligible for the second stage of the trial.

Patients fulfilling the following criteria will be eligible for randomisation.

Inclusion criteria for randomisation

- One or more nodules histologically/cytologically confirmed as metastases from colorectal cancer **OR** >90% likelihood of being metastases from colorectal cancer
- Pulmonary function adequate to sustain good performance after the largest likely loss of parenchyma *(calculated as the predicted postoperative FEV1 according to BTS guidelines)*
- ECOG performance status 0-1
- Any recommended systemic or other non- surgical treatment has been completed
- The patient is available for trial assessments and follow up
- A consent form has been signed

Exclusion criteria

- Patients with a nodule which is proven or is likely to be lung cancer
- Concurrent disease that may interfere with protocol treatment or measurement of endpoints

5.2 Informed consent for randomisation and 'accept or decline' questionnaire

Following evaluation and any systemic non-surgical treatment, eligible patients will be approached by the oncologist or other designated member of the clinical team and asked if they are willing to consider the second stage of the trial. They will be offered another copy of the patient information leaflet and the chance to ask questions.

All patients eligible for stage 2 of the trial, whether or not they choose to proceed to randomisation, will be invited to complete a questionnaire exploring reasons for accepting or declining trials. Those who agree to complete the questionnaire will be given one to take home and return to Sussex Health Outcomes Research & Education in Cancer SHORE-C) in a stamped addressed envelope.

Patients who confirm that they are willing to be randomised will be asked to sign a second consent form (Consent Form 2) and complete a set of baseline questionnaires.

5.3 Baseline assessment before randomisation

Patients will be asked to complete the following questionnaires prior to randomisation:

- Functional Assessment of Cancer Therapy – general and fatigue sub-scale (FACT-G-F) plus selected items from the Lung Cancer Brief Symptom Index
- Short form of the Spielberger State/Trait Anxiety Inventory (STAI)
- EQ-5D-3Lquestionnaire

5.4 Randomisation

All randomisations will be carried out online centrally at www.sealedenvelope.co.uk. Before site initiation, all site staff who require access to the website for randomisation requests will be set up, and at site initiation they will be give logon credentials and access to the randomisation SOP.

Randomisation will be carried out electronically using a minimisation program with an additional random element (such that each patient will retain a non-zero probability of being randomised to each of the treatment arms). The following variables will be included in the minimisation program:

1. age
2. sex
3. number of metastases
4. CEA level
5. prior liver metastasectomy
6. time since resection of the colorectal primary cancer
7. T stage
8. N stage

Randomisation will also be stratified by local site.

Patients will be allocated equally between the following treatment arms:

Arm 1 – Active monitoring, according to local practice guidelines (control)

Arm 2 – Active monitoring according to local practice guidelines with an intervention which may be pulmonary metastasectomy, ablation by SABR, IGTA or combinations.

6 Treatments

6.1 Active Monitoring

Patients will be managed without metastasectomy, SABR or IGTA according to local practice. (Ablation is not a treatment option within the non-interventional arm of the protocol.) The assessments listed in section 8 (Assessments following treatment) should be carried out at the time points indicated.

Patients in the active monitoring arm should only undergo subsequent metastasectomy, SABR or IGTA in exceptional circumstances, please complete relevant CRF. These patients will remain in the trial and will continue to complete questionnaires and undergo trial follow up assessments at the specified time points from randomisation on the intention to treat principle.

6.2 Pulmonary metastasectomy or ablation (SABR or IGTA).

Pulmonary metastasectomy will be carried out with the objective of an R0 resection. Surgical approach (open thoracotomy or video access) will be at the discretion of the surgeon as to what is most appropriate under the circumstances. The assessments listed in section 8 (Assessments following treatment) should be carried out at the time points indicated.

Pulmonary ablation (SABR or IGTA) will be carried out with the intention of complete ablation the metastasis (see appendix for guidance on trial treatment, planning and dosimetry).

6.3 Assessments following treatment

The following assessments will be carried out at the time points indicated. These time points are counted from date of randomisation - see Summary of assessments chart- Schedule of Activities stage 2 (page 16).

6.4 Clinical assessment

All patients should be reviewed 3 monthly during year 1, 6 monthly during year 2 and then annually up to five years. Investigations will be according to local practice. At each visit patients should undergo the following unless noted otherwise:

- Clinical examination including performance status and weight
- Assessment of morbidity
- Lung function FEV1/peakflow
- Measurement of CEA
- Assessment of response by chest CT scan (at 3 months, 24 Months (year 1), 24 Months (2 years) and 36 Months (3 years)

6.5 Patient reported outcomes

These following assessments will be carried out at baseline, 3, 6, 12, 24 months unless noted otherwise:

- Functional Assessment of cancer Therapy – general and fatigue sub-scale (FACT-G-F) plus selected items from the Lung Cancer Brief Symptom Index
- Short form of the Spielberger State/Trait Anxiety Inventory (STAI)
- EQ5D-3L questionnaire
- All patients eligible for randomisation will be invited to complete a questionnaire which asks about their views on clinical trials and their reasons for accepting or declining to participate (baseline only)

6.6 Schedule of activities stage 2

		Months								
Assessment	**Baseline**	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**	**60**
Clinical examination		√	√	√	√	√	√	√	√	√
Weight		√	√	√	√	√	√	√	√	√
ECOG performance		√	√	√	√	√	√	√	√	√
FBC										
Serum biochemistry										
LFT										
CEA		√	√	√	√	√	√	√	√	√
Lung spirometry/peakflow		√	√	√	√	√	√	√	√	√
FACT + lung symptoms questionnaire	√	√	√		√		√			
STAI questionnaire	√	√	√		√		√			
EQ-5D questionnaire	√	√	√		√		√			
Views on trials questionnaire	√									
Chest CT scan		√			√		√	√		
Adverse Event Recording	√	√	√	√	√	√	√	√	√	√
CRF completion	√	√	√	√	√	√	√	√	√	√

7.0 Treatment following relapse or progression

Suspected recurrence and/or progression should be confirmed according to local practice. Subsequent treatment will be at the discretion of the participating clinician. Data regarding relapse and treatment will be collected on the patient's Case Report Form (CRF). Patients should continue to complete questionnaires and undergo trial follow up assessments at the protocol time points.

8.0 Data management and CRF completion

Screening logs will be completed by each site and copies sent regularly to the co-ordinating centre at the Surgical & Interventional Trials Unit (SITU), UCL. Details of the numbers of patients screened will be required for reporting in accordance with the CONSORT guidelines.

Clinical data will be collected on trial CRFs.

All CRFs, including Adverse Event (AE) reporting should be completed in accordance with guidelines below.

Patient reported outcomes will be collected directly from the patients via questionnaires.

8.1 CRF completion at site

Original CRFs should be sent to the SITU and a copy retained at site. All fields should be completed. Any that are unknown or unavailable should be clearly marked as such. Any corrections should be made by drawing a single line through the incorrect item such that the data are not obscured. The correction should be initialled and dated.

The CRFs received by the SITU will be checked for completeness and accuracy. Queries will be raised for any incomplete, inconsistent or missing data and timelines given for the resolution of these queries.

8.2 Patient reported outcomes

Questionnaires will be accompanied by instructions for completion and will be posted to patients at the correct time points together with an SAE for their return.

If any questionnaires are completed at site during a clinic visit, the researcher should check that all questions have been answered by the patient. Patients should be encouraged to answer all questions. If a patient does not wish to answer a question, this should be annotated by the patient, if possible.

All completed questionnaires should be sent to Sussex Health Outcomes Research & Education in Cancer (SHORE-C). Staff there will check the questionnaires for completeness and will contact patients if necessary to obtain any missing data.

9.0 Withdrawal of patients

During the consent procedure, it will be explained to patients that they are free to withdraw at any time from the trial without giving a reason and without prejudicing their further treatment. If a clinician has concerns about whether continued participation is in the interest of their patient, they will discuss their concerns with the patient and may advise withdrawal.

10.0 Statistical considerations

A 10% difference in overall mortality at 3 years is taken to be the minimally important clinical difference for the design of the PulMiCC trial. Under the assumption of exponential survival curves, and with an expected three year survival rate of 30% in the interventional arm of the trial, then a 20% survival rate for the non- interventional arm would correspond to a relative risk of death for the non- interventional vs the interventional patients of 1.3.

10.1 Sample size

Under the assumptions given of exponential survival and a 30% three year survival rate in the interventional arm, a sample size of 1350 registered patients will be needed to provide 1:1 randomisation of 300 patients. This will provide 78% power to detect an increased relative risk of death of 1.3 for patients in the non- interventional arm, when testing at the one-sided 5% level.

10.2 Planned analyses

The survival, relapse and progression outcomes will be analysed using Cox's relative risk regression model with allowance for correlation between outcomes for patients operated on by the same surgeons. The analysis of quality of life outcomes and other longitudinally measured outcomes will be based on methods for the analysis of longitudinally collected data. Correlation between responses from the same patient will be incorporated either through the use of generalised estimating equations or random effects depending on whether the target of inference is marginal or subject specific effects. The form of the underlying regression model will be chosen in light of the distribution of the outcome of interest. The primary treatment comparison will be based on models that include explanatory variables corresponding to the patient characteristics used in the minimisation algorithm.

An intention-to-treat analysis will be used for the results of the trial. Analysis will not be restricted to this, there may be important information in additional more detailed inspection of longitudinal trial data.

10.3 Health Economics

The health economics analysis will aim to calculate the incremental cost of active monitoring versus active monitoring with pulmonary metastasectomy or ablation and compare this with the incremental benefit in order to assess incremental cost-effectiveness of active monitoring versus pulmonary metastasectomy or IGTA.

Measuring effectiveness:
The effectiveness measures will be:

Primary and secondary outcome measures in the trial
Lifetime quality-adjusted life years (QALYs)

The latter requires extrapolating survival beyond the end of the trial using economic modelling based on published studies. It also requires the use of generic health-related quality of life data (the EQ-5D; www.euroqol.org). This will be collected during the within-trial period. EQ-5D scores will be extrapolated beyond the end of the trial using economic modelling based on published studies.

Measuring costs:
While PulMiCC is a multinational study the perspective in the first instance will be that of the United Kingdom's NHS.
The cost components will include: NHS contacts for receipts for

- pulmonary metastasectomy,
- SABR,
- IGTA,
- active surveillance and
- treating side effects and complications

These data will be collected via study CRFs, and will be combined with unit cost data from standard available sources (*NHS Reference Costs*, *Unit Costs of Health and Social Care*, *British National Formulary*). Data to extrapolate beyond the end of the trial will be estimated using economic modelling based on published studies.

All analyses will be subjected to deterministic and probabilistic sensitivity analysis, and in line with current methodological guidance from the National Institute for Health and Care Excellence.

Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence. available from http://www.nice.org.uk/article/pmg9/chapter/Foreword; accessed on 1st January 2015.

11.0 Additional tests for translational discovery

The PulMiCC team is collaborating with Professor Phil Quirke at Leeds on cancer genome sequencing.

Though not related to the primary outcome of this study, this group of patients presents a unique opportunity to obtain human samples for translational discovery studies. UK participants will have the option to consent to provide tissue. Consent to give these samples is optional and patients do not need to provide this consent to be able to take part in the study

12.0 Long-term data linkage

The group of patients who participate in this study will have the option to consent to long term data linkage.

Patients who specifically consent to longer-term data collection can be flagged and followed-up using the relevant National Databases, for example, the Office for National Statistics and NHS databases (see Consent Form). Linkage to databases such as Hospital Episode Statistics (HES) may give valuable information on further diagnoses, treatments and outcomes beyond the timeframe of the study for future analyses.

Consenting patients may additionally be contacted in future to assess their willingness to respond to questionnaires. This allows the potential for research that would complement the planned long-term follow up in terms of health status, for example assessment of quality of life.

13.0 Serious Adverse Event reporting

13.1 Definitions

Adverse Event (AE)
Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event
An adverse event that:

- Results in death
- Is life threatening
- Requires admission to hospital or prolongation of hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant

13.2 Reporting procedures

Serious Adverse Events (SAE)
Any serious adverse event (SAE) occurring between randomisation and end of protocol follow up (five years) should be recorded in the patient's hospital notes and submitted promptly to the co-ordinating centre at SITU using the SAE form in the CRF.

If an SAE occurs to a research participant that is considered to be **both unexpected and related to the study protocol** then these should be reported to the SITU within 24 hours of the local Principal Investigator becoming aware of the event.

- "Unexpected" is defined as not an expected outcome
- "Related" is defined as resulting from administration of any of the research procedures

The SITU will report any unexpected and related SAEs to the Research Ethics Committee within 15 days of their knowledge of the event. In addition, the Sponsor and local PIs will be notified of any unexpected and related SAEs.

Expected surgical morbidity
Expected morbidity following thoracic surgery can include:

- Pain
- Bleeding
- Pneumothorax
- Infection
- Deep vein thrombosis or embolism
- Renal insufficiency
- Myocardial Infarction
- Stroke

As with all interventions there is also a risk of death. The risk of death with surgical metastasectomy is thought to be less than one in a hundred.

Expected IGTA morbidity
Expected morbidity following IGTA can include:

- Pain
- Bleeding
- Infection
- Deep vein thrombosis or embolism
- Renal insufficiency
- Myocardial Infarction
- Stroke
- Pneumothorax

Expected SABR morbidity

The following is a list of events that are expected as a result of SABR include:-

Lung

- Broncho-pulmonary haemorrhage
- Cough
- Dyspnoea
- Pneumonia
- Pneumonitis
- Pulmonary fibrosis
- Decrease in - carbon monoxide diffusion capacity or forced expiratory volume or vital capacity.

Trachea / proximal bronchial tree: broncho-pulmonary fistula, bronchial stenosis, tracheal stenosis.
Heart: pericarditis, pericardial effusion, myocarditis, myocardial infarction.
Oesophagus: Dysphagia, Oesophagitis, Oesophageal Candidiasis, Oesophageal stricture, Oesophageal fistula.
Spinal cord: myelitis.
Brachial plexus: Brachial plexopathy.
Other : Alopecia, Anaemia, Anorexia, Dyspepsia, Fatigue, Febrile neutropenia, Flu like symptoms, Nausea, Neutropenia, Neutropenic Sepsis, Radiation Dermatitis, Rib fracture, Second radiation induced malignancy, Thrombocytopenia, Vomiting.

For ablation of metastases by SABR or IGTA risk of death is unknown but is likely to be no greater than surgery.

14.0 Discontinuation of trial

Study Discontinuation by the Sponsor
The Sponsor may terminate the study at any time if the following occur, and the investigator is unable to take corrective action in any of these cases:

- The investigator is non-compliant with the protocol
- The investigator is non-compliant with the regulatory requirements
- The investigator is non-compliant with the principles of Good Clinical Practice as outlined in the Declaration of Helsinki and the Research Governance Framework
- The CRF completion is inadequate

Study Discontinuation by the Chief Investigator
If an unwanted effect is considered severe by the Chief Investigator and endangers the health of all patients, the study will be discontinued after agreement with the Sponsor.

Discontinuation of Study for an Individual Patient
The criteria for discontinuing the study in the case on individual patients are:

- **Intercurrent illness**
  - Any illness, which in the judgment of the investigators would affect the assessments of clinical status to a significant degree

- **Request by the patient**
  - It is the patients right to request discontinuation of their participation in the study. If this request is made, it will be respected and will not affect the patient's ability to receive medical care from the investigators now or in the future.

- **Discontinuation of attendance at the investigating site**
  - Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients no longer attend the participating institution.

15.0 Regulatory and ethical considerations

15.1 Sponsorship

University College London will act as the Sponsor for this study. Delegated responsibilities will be assigned to local principal investigators.

Sponsor contact details:

Mr David Wilson
Database and Information Officer & Sponsor Representative
Research Support Centre
1st Floor Maple House
149 Tottenham Court Road
London W1T 7DN
Telephone: 020 3447 5199
Fax: 0207 380 9937

15.2 Indemnity

The Sponsor of this study, University College London (UCL), holds an insurance policy which provides cover for negligent harm arising from the design or management of the research. The NHS indemnity scheme will apply regarding any legal liability arising from harm to participants in the conduct of the research. UCL's insurance policy provides for the payment of compensation for harm to research participants arising from any aspect of the research both where no legal liability arises and where legal liability arises.

15.3 Ethics

This protocol has been developed from the outset with the involvement and advice from Ethicists. The protocol will be submitted to a Research Ethics Committee (REC) for approval before any patients are enrolled. Local sites should submit the Specific Site Information (SSI) forms to their local R&D department. Copies of local approvals will be required by SITU before local site activation.

15.4 Patient confidentiality and Data Protection

SITU will ensure patient confidentiality by using a unique CRF number to identify a patient. SITU will only ever request initials and date of birth and never patient names, addresses or hospital numbers. The CRF pages will be kept in individual patient files (identified by CRF number only) in filing cabinets in locked offices which are accessible only to authorised SITU personnel. Databases will only be accessed by authorised SITU personnel using specific passwords. When SITU request data from sites they will only use the unique CRF number and not patient names.

Sussex Health Outcomes Research & Education in Cancer (SHORE-C) will obtain permission from patients who enter stage 2 of the trial to hold their name, address and telephone number for the duration of their participation in the quality of life part of the study (2 years). This is so that quality of life questionnaires can be posted to participants and in case of query.

SHORE-C will act to preserve patient confidentiality and will not disclose or reproduce any information by which participants could be identified. All questionnaires will be identified by each participant's unique CRF number and will be held separately from their identifiable data. All data will be kept in locked filing cabinets in locked offices. Questionnaire results

will be held electronically in password protected databases and will be linked by unique CRF number only.

The trial will be registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

15.5 Funding

This study has been funded by Cancer Research UK (funding reference: CRUK/14/037).

16.0 Trial management, committees and responsibilities

16.1 Trial Management Group

The Trial Management Group will be responsible for overseeing the trial. The Group will meet regularly to discuss recruitment, safety, data management and local site issues. It will agree protocol amendments prior to submission to the REC. The membership is given on page 1.

16.2 Data Monitoring Committee

The independent Data Monitoring Committee will meet annually to provide independent advice on any recruitment and safety issues. Meetings will also be held as necessary should any urgent issues occur. The DMC will develop a charter which describes the framework within which it will operate. The membership is given in the Appendix.

16.3 Role of Trial Steering Committee

The Trial Steering Committee (TSC) will meet annually (or more frequently if necessary) to monitor and supervise the trial, to ensure it is being conducted according to the protocol and timelines, to review any relevant information from other sources (eg other related trials) and to consider any recommendations from the DMC. The membership is given in the Appendix.

16.4 Role of Expert Advisors

A panel of Expert Advisors has been convened to advice on every aspect of the design of the study. The Expert Advisors will not meet formally but have agreed to assist as required throughout the study. The membership is given in the Appendix.

16.5 Role of the Surgical & Interventional Trials Unit-[SITU] (Formerly Clinical Trials and Evaluation Unit (CTG)

The SITU will be responsible for the day-to-day management of the trial. It will act as custodian of the data except for the patient reported outcome data which will be managed by SHORE-C.

The SITU will be responsible for the following:

- Ensuring trial design has been properly registered and included on appropriate trials portfolios
- Ensuring all necessary authorisations are in place before the study commences at each participating local site
- Administration of any necessary protocol amendments and submission for approval to ethics
- Training study sites in study procedures and to perform the study in accordance with Good Clinical Practice
- Preparation and submission of annual reports to funder, ethics etc.
- Ensuring data management is carried out to high standards and according to data protection, confidentiality and archiving guidelines
- Prompt reporting of unexpected and related SAEs to the REC, Sponsor and local PIs
- Collaborate with the trial statistician and Trial Management Group to prepare results for publication.
- Feedback of results to trial participants

16.6 Role of Sussex Health Outcomes Research & Education in Cancer SHORE-C.

SHORE-C is situated within Brighton & Sussex Medical School at Sussex University. The director, Professor Lesley Fallowfield is known world-wide for her psychosocial oncology research and communication skills training. The central aims of SHORE-C are to evaluate health outcomes of patients, particularly those undergoing treatment for cancer, develop and evaluate supportive intervention programmes and enhance communication between healthcare professionals and patients.

SHORE-C will be responsible for coordinating and managing the patient reported outcomes part of the trial. It will act as custodian for these data on behalf of SITU.

16.7 Responsibilities of the Chief Investigator

The Chief Investigator will be responsible for the following:

- Responsibility for the overall design, management, conduct and reporting of the trial
- Ensuring all local staff involved in the trial are properly trained in protocol procedures
- Ensuring participants, dignity, rights, safety and well-being are respected

16.8 Responsibilities of local Principal Investigators (PIs)

Local PIs will be responsible for the following:

- Ensuring all local authorisations and approvals are in place before the study commences
- Ensuring the R&D department is informed of the study
- Ensuring arrangements are kept in place for the management of financial and other resources provided for the study at the site

- Ensuring each member of the local research team is qualified by education, training and experience to discharge his/her role in the study and their qualifications are documented
- Ensuring each member of the local research team who has direct involvement with research subjects has a full or honorary contract with the NHS trust in which the study is being conducted
- Ensuring that the local site file is kept up to date with the above details of the local research team
- Ensuring that any care professional involved in caring for a participant is informed that their patient is being invited to participate in the study. Each participant's GP should be informed of their patient's participation
- Ensuring trial is conducted according to the protocol
- Maintaining proper version control of study documentation including the protocol
- Ensuring all CRFs, participant questionnaires and other study data are completed in full and returned in a timely manner
- Ensuring any SAEs are reported promptly to SITU and (where required) the R&D department
- Ensuring that appropriate archiving of study documents will be carried out when the research is finished
- Ensuring all data and documentation associated with the study are available at the request of the co-ordinating centre and any auditing authorities

17.0 Publication policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group (TMG). The TMG group will form the basis of the writing committee. Local sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. All publications will quote the Clintrial.gov number (NCT01106261) and will acknowledge the SITU, SHORE-C, the participating investigators, the TSC and DMC, the Sponsor and the Funder.

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Appendix

ECOG performance scale

GRADE
0 - Fully active, able to carry on all pre-disease performance without restriction.
(Karnofsky 90-100).
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. lighthouse work, office work.
(Karnofsky 70-80).
2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
(Karnofsky 50-60).
3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
(Karnofsky 30-40).
4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
(Karnofsky 10-20).

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Appendix 1

Trial Steering Committee

Mr Chris Russell	London	Chair & Surgeon
Prof Brian Davidson	London	Consultant HPB and liver transplant surgeon; Professor of surgery
Dr Fergus Macbeth	Cardiff	Clinical oncologist
Professor Tom Treasure	UCL	Thoracic surgeon & Chief Investigator
Professor Lesley Fallowfield	Brighton	Psycho-oncologist
Professor Vern Farewell	Cambridge	Statistician and Programme Leader
Dr Caroline Dalton	London	Cancer Research UK, Strategy and Research Funding Manager
plus invite observer from host institution (UCL)		

Data Monitoring Committee

Professor Michael Baum	London	Chair & Surgeon
Professor Martyn Evans	Durham	Philosopher
Professor Julian Peto	London	Statistician/trialist
Professor Tim Maughan	Cardiff	Colorectal Oncologist

Expert Advisors

Mr Mark George	Guy's & St Thomas'	Advisor in Coloproctology
Dr George Santis	Kings	Advisor in Respiratory Medicine
Dr Robert Rintoul	Papworth	Advisor in Respiratory Medicine
Mr Ian Hunt	London	Thoracic Surgeon
Dr Rowland Illings	London	Radiologist and expert in RF ablation
Dr Marcus Flather	Norwich Medical School	Trials Advisor & Cardiologist
Richard Stephens	MRC CTU	Trials Advisor & patient reported outcomes
David Gallacher	Guy's & St Thomas'	Consultant Physicist (Radiation Protection Advisor)
Dr Martin Utley	UCL	Clinical Operational Research
Tal Golesworthy	Tewkesbury	Engineer & expert patient
Professor Stephen Morris	UCL	Health Economist
Dr Sally Barrington	Guy's & St Thomas'	Nuclear Medicine Physician
Mr Peter Gibson		Patient and Public Representative

Appendix 2

SABR

1.1 SABR treatment

Patients randomised to SABR will receive a dose and fractionation regimen dependent on the metastatic site and proximity to normal tissues.

Treatment timelines

SABR should commence within 6 weeks following randomisation to allow sufficient time for planning.

Patient position

Patients should be positioned identically for both planning and treatment: supine on the couch with arms supported above the head or a 5 point fixation shell for upper lobe tumour with arms by side. Head and knee supports should also be used and a foot stop. Set up should be by reference to tattoos on stable areas of skin and bony anatomical landmarks. Other patient set-ups such as arms by sides will be considered on a centre by centre basis (Please contact RTTQA for advice).

Radiotherapy planning

Radiotherapy planning and outlining should be carried out in accordance with the guidelines in the current version of the radiotherapy planning and delivery guidelines document, available on request from SITU (SITU@pulmicc@ucl.ac.uk or via the RT website www.rttrialsqa.org.uk.

Treatment technique

Highly conformal treatment planning is a pre-requisite for SABR. SABR may be delivered using a specialist SABR platform, such as CyberKnife, or with a linear accelerator with SABR capabilities. Any SABR delivery platform is acceptable as long as the individual centre has demonstrated they are able to comply with the radiotherapy standards laid out in this protocol.

Patient setup verification protocol

The decision rules for patient setup corrections will be based on the institution's procedures for set-up verification. It is important to verify that the set-up correction will not lead to an OAR dose limit violation.

Patient anatomy verification

CBCT will verify the anatomy of the patient in the thoracic region and the changes in GTV during the treatment (visually and electronically). During the course of irradiation changes may occur that require adaptive re-planning during the course of treatment at the discretion of the local PI. Patients requiring adaptive re-planning remain eligible for the study but please contact RTTQA if a re-plan is necessary.

Dose prescription

Table 1 below summarises the recommended dose and fractionation options that can be used. Where a range of doses is provided, it is advised that the maximum dose that can be achieved whilst meeting the OAR planning constraints is prescribed.

Table 1

Metastasis site	Total Dose (Gy)	No. of Fractions	Dose/fraction (Gy)	Frequency
Lung	54	3	18	Alternate days
	55-60	5	11-12	Alternate days
	60	8	7.5	Alternate days

1.2 Treatment scheduling and gaps

Treatment can start on any day of the week. Treatment is delivered on as per table 1, above, for the maximum number of days the treatment should be delivered over dependent on the dose fractionation schedule being used.

1.3 Standard of care treatment

Standard of care (SOC) is at the discretion of the local oncologist and will follow local practice guidelines. It may include any standard therapy that is clinically appropriate: chemotherapy (including maintenance where appropriate), biological therapy, palliative radiotherapy or observation or any combination of these.

1.4 Systemic therapy

A minimum period of 4 weeks after the final fraction of SBRT is suggested before systemic treatment is recommenced.

1.5 Supportive care guidelines

Toxicity should be managed as per local guidelines and RCR guidance where available (https://www.rcr.ac.uk/clinical-oncology/being-consultant/guidance-and-standards).

1.6 Concomitant therapy

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. A list of concomitant medications (including start/stop dates, dose frequency, route of administration and indication), must be recorded in the patient's notes, as well as the appropriate pages of the CRF.

1.7 Non-permissible medications/therapies

Any potential radio-sensitizers unless stopped for 4 weeks prior to SBRT. The management of potential radio-sensitizers will be in accordance with the dose constraints SABR UK Consortium guidelines (http://actionradiotherapy.org/wp-content/uploads/2014/03/UK-SABR-Consortium-Guidelines.pdf).

1.8 Radiotherapy Quality Assurance (QA)

The NCRI Radiotherapy Trials Quality Assurance (RTTQA) group will oversee the quality assurance of the SABR within the trial to ensure the safety and consistency of radiotherapy delivery at participating sites. Prior to inclusion in the trial, individual centres will need to demonstrate they have robust procedures in place to ensure high quality plan RTTQA guidelines must be met. Thereafter case reviews will be in accordance with the RTTQA group guidelines (www.rttrialsqa.org.uk).

1.9 Radiotherapy related adverse events

Both early and late toxicity will be recorded using CTCAE Version 4. These will include assessments of fatigue, skin reaction, oesophageal, lung or cardiac (including vessel), spinal cord and brachial plexus toxicity. Early toxicity will be side effects occurring within 90 days of RT. Late side effects are those occurring after 90 days or persisting beyond this time period. Please refer to the protocol section 13, under expected adverse events for a list of side effects related to treatment.

Appendix 3

IGTA procedure

Immediately prior to IGTA an unenhanced CT scan of the chest is performed to plan patient positioning, site of puncture and route of needle insertion. Patients will be given deep conscious sedation or general anaesthesia, and heart rate, blood pressure, oxygen saturation and continuous electrocardiogram were monitored during the procedure.

IGTA may be performed using a CE marked percutaneous ablation system using either radio frequency or microwave energy according to the dosimetric data provided by the manufacturer. Several passes may be made to treat an individual tumour deposit, varying ablation power and duration to ensure complete tumour coverage. Satisfactory ablation will be defined by circumferential ground glass surrounding the tumour on CT. Needle track ablation will be performed according to local preference.

All patients will have a chest radiograph at 4 hours after the procedure to assess for immediate complications – i.e. pneumothorax or bleeding. Patients may undergo an unenhanced CT scan the day after ablation to assess the ablation margin and complications according to local protocol. If the tumour was not covered completely by the ablation zone, early retreatment may be discussed.