VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a multi-centre randomised controlled trial with an internal pilot
The VIOLET 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%
ALT	Alanine transaminase
AR	Adverse reaction – any undesirable experience that has happened a subject while taking a drug that is suspected to be caused by the drug or drugs
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
AST	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
BHI	Bristol Heart Institute
BRI	Bristol Royal Infirmary
BRU	Biomedical Research Unit
ctDNA	Circulating tumour DNA
CRF	Case report form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEU	Clinical Trials and Evaluation Unit
DFS	Disease free survival
DMSC	Data monitoring and safety committee
GP	General practitioner
HDU	High dependency unit
HTA	Health Technologies Assessment
IASLC	International Association of the Study of Lung Cancer
ICH-GCP	International conference for harmonisation - good clinical practice
ICU	Intensive care unit
LFV	Low frequency ventilation
MEDDRA	Medical dictionary for regulatory activities
MDT	Multi-disciplinary team
MHRA	Medicines and healthcare products regulatory agency
MRC	Medical Research Council
NGS	Next generation sequencing
NIHR	National Institute for Health Research
PET	Positron emission tomography
PIC	Patient identification centre

PIL	Patient information leaflet
QRI	Qualitative Recruitment Intervention
RCT	Randomised controlled trial
REC	Research ethics committee
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.
SAR	Serious adverse reaction
SIRS	Systemic inflammatory response syndrome
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
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.
TNM	Classification of malignant tumours (TNM)
TMG	Trial management group
TSC	Trial steering committee
UH Bristol	University Hospitals Bristol NHS Foundation Trust
VAS	Visual analogue scale
VATS	Video Assisted Thoracoscopic Surgery
WBC	White blood cell count

1. Trial summary

Lung cancer is the leading cause of cancer death worldwide and survival in the UK remains amongst the lowest in Europe. Surgery remains the main method of managing early stage disease, although it can be associated with complications related to the chest and wound sites. Recently, minimal access video assisted thoracoscopic surgery (VATS) for lung cancer has been introduced and 14% of UK procedures were undertaken with this approach in 2010. VATS is considered to result in less tissue trauma at the access sites than open surgery and there are numerous case series demonstrating the safety of this approach in selected patients; however, it is unknown whether it improves patient outcome in a pragmatic trial.

The aim of the VIOLET study is to generate high quality evidence to compare a range of clinical and patient-reported outcomes between VATS and open surgery in a randomised controlled trial (RCT). A well designed and conducted RCT comparing the effectiveness and cost-effectiveness of minimal access and open surgery is urgently needed to inform current NHS practice, health policy and individual surgeon and patient decision-making.

We hypothesise that VATS will lead to less tissue trauma and therefore better recovery of several aspects of health related quality of life in the early post-operative period than open surgery, but that surrogate clinical outcomes of survival will be similar to those of open surgery. The trial has been designed to include an internal pilot phase and progression to phase 2 will depend on meeting defined success criteria in the pilot phase. The pilot phase is necessary to establish the optimal processes for recruitment and to develop a measure of surgical expertise for participation in phase 2. The full RCT (covering both phases) will evaluate the effectiveness, cost effectiveness and acceptability of VATS vs. open surgery for early stage lung cancer. Phase 2 will also include a sub-study to determine if presence of molecular residual disease detected in blood samples taken at pre-defined time points after surgery is associated with early recurrence and death. If necessary the sub-study will continue beyond the end of recruitment to the trial in order to meet the sub-study recruitment target.

2. Background

2.1 The Clinical Problem

Lung cancer is the leading cause of cancer death worldwide and the survival of patients with lung cancer in the UK remains low, amongst the lowest in Europe [1]. The 2011 National Lung Cancer Audit reported that 13.7% of the 26,947 patients diagnosed with non-small cell lung cancer underwent surgical resection as part of their treatment in England and Wales [2]. This audit also reported that of the >5000 resections performed for primary lung cancer in 2010, the majority (86%) were performed by open surgery [3]. Mortality after lobectomy is 2% and common complications include bleeding, chest and wound infections, prolonged air leak and arrhythmia. The mortality rate for the 14% of resections performed by VATS compares favourably at 1.3% and a recent literature review by Cao and colleagues, also reported lower perioperative morbidity, pneumonia, atrial arrhythmia and a shorter hospital stay in patients who underwent VATS lobectomy compared to open surgery [4].

Over the past decade, there has been a surge in the number of minimal access lung resections performed; increasing from 3% in 2000 to 4% in 2005 and 14% in 2010 [3], which demonstrates the increasing patient and clinician acceptance of this approach. Furthermore, initiatives such as the Enhanced Recovery Partnership Programme which aims to improve the care of patients undergoing major surgery, includes minimal access surgery as an important tenet which may further stimulate interest in minimal access surgery.

However, despite the surge in the numbers of minimal access surgery performed in the UK in the last decade, there remains a need for well-designed and conducted randomised controlled trials (RCTs) to provide the evidence base for the wide spread uptake and delivery of this surgical approach. At present, the use of VATS is largely restricted to a few centres and is being undertaken in the absence of high quality supporting evidence, mainly by surgeons developing innovative approaches in a research setting. Geographical disparity is wide and is likely to widen if the paucity in the evidence base underpinning surgical practice and health policy within the UK remains unfilled. In this instance, surgery for lung cancer will continue to be undertaken using approaches preferred by surgeons rather than informed by evidence leading to patient benefit.

2.2 The rationale for VATS

The uptake of surgery for lung cancer in the UK is low and minimal access surgery may be regarded as a more acceptable intervention (compared to open surgery) by patients, referring respiratory physicians and oncologists. However in the absence of clear benefit in a well-designed randomised setting, uptake of this surgical advance is likely to be unsystematic and patchy at best, as there is currently no impetus for surgeons to change or improve on current surgical techniques.

Indeed, a systematic review of the literature identified only two randomised controlled trials of VATS versus open surgery for lung resection [4, 5]. Both of these RCTs were small single centre studies and neither were adequately powered or reported [6, 7]. However, despite the lack of well-designed RCTs of VATS versus open lobectomy, a small body of evidence has amounted which advocates the potential of this surgical approach. Specifically, fewer in hospital complications [6], excellent survival in patients with stage IA disease [7] and shorter hospital stay [8] were reported in patients undergoing VATS lung resection. Furthermore, a recent systematic review and meta-analysis of 2 randomised and 19 non-randomised studies suggested that both surgical approaches had similar in-hospital pulmonary outcomes and mortality, but that disease free survival (DFS) is better with VATS surgery [5]. It is important to note however, that the reported improvement in DFS could be a reflection of the stage of disease, as most studies were non-randomised.

An update to the meta-analysis, published in 2012, reported less in-hospital morbidity and shorter hospital stay in patients who underwent VATS lobectomy [4]. A propensity matched analysis of ACOSOG Z30 comparing VATS and open lobectomy (66 VATS, 686 open) reported fewer in-hospital pulmonary complications, shorter chest drain duration and shorter hospital stay in favour of VATS [8]. Higher compliance rates with less delay/reduction in the dose of chemotherapy after surgery [9] improved pain control and greater discharge independence [10] have also been reported with VATS lung resection.

2.3 Sustained scientific interest in VATS

The increasing prevalence of minimal access surgery in the last decade has been accompanied by a significant and sustained scientific interest determined to ascertain whether VATS or open surgery provides the best treatment and recovery for patients undergoing surgical resection for lung cancer. In addition to research cited above, there are also several ongoing randomised trials that are identified and discussed below.

The PLEACE trial [11] is a randomised trial of minimal access surgery versus open surgery for lung resection. This study is utilising the EORTC QLQ-C30 questionnaire, which is consistent with the VIOLET protocol. As such, there may be an opportunity to perform joint analysis of the quality of life data for the PLEACE and VIOLET studies. It is important to note, however, that there is an important technical difference between the PLEACE and VIOLET studies, which relates to the access method used during open lobectomy. The method of surgical access for open lobectomy used in the PLEACE trial is via anterolateral thoracotomy (the standard in Denmark). In contrast, the surgical access for the VIOLET study (and the standard in the UK) is via a posterolateral thoracotomy. Both studies are therefore essential to inform clinical practice and health policy within their respective countries.

Professor Long Hao and colleagues, a Chinese research group, are also conducting a RCT to compare VATS with open surgery [12]. Although this group are comparing both the quality of life and survival between VATS and open surgery, quality of life is being recorded with the Lung Cancer Symptom Scale which is not compatible with the EORTC questionnaire (Professor Long Hao, Chief Investigator, personal communication). Joint analysis for this outcome measure is therefore not suitable. However, there may be an opportunity to perform a joint analysis of the survival data.

Finally, the SCOPE study [13] is another trial of minimal access versus open surgery, which is being conducted in the Netherlands. Recruitment to this study is ongoing and we are in communication with Dr Van Brakel (SCOPE Chief Investigator) to discuss how we can standardise data collection across the two studies and plan for a joint analysis of the quality of life and survival data when the trials reach completion.

The above evidence demonstrates the sustained scientific interest of thoracic surgeons, who are committed to establishing the utility of minimal access VATS to perform lobectomy for the treatment of known or suspected lung cancer. As such, a large, multi-centre RCT like the VIOLET study will inform clinical understanding and influence surgical practice in the UK. Where ever possible, we will collaborate with international investigators to share outcome data and inform data synthesis.

2.4 Molecular residual disease detected using next generation sequencing (NGS): sub-study

While surgery involves complete resection of the tumour, disease recurrence is common and is estimated to occur in 30% of participants in the earliest stages (I and II) within the first 5 years. Most guidelines recommend adjuvant chemotherapy for patients with stage 1b or higher as it is associated with a 20% relative improvement in survival. Despite this, the uptake for adjuvant chemotherapy is patchy and inconsistent as it is a difficult decision for patients in light of the potential treatment-related complications in those who have already undergone an extensive operation and are currently “free”

from visible disease. However, work undertaken at the Royal Brompton Hospital in patients after lung cancer surgery identified 18/31 (58%) patients with NGS detectable cancer mutations in their blood despite complete resection, implying molecular residual disease.

We hypothesise that the presence of molecular residual disease implies trace amounts of cancer that leads to early recurrence and death. The aim is to define the frequency of bloodbased cancer mutations in the blood (i.e. the frequency of molecular residual disease) after complete resection of lung cancer and to determine any association with clinical recurrent disease and survival to 5 years.

3. Aims and objectives

The VIOLET study will compare the effectiveness, cost-effectiveness and acceptability of VATS lobectomy versus open surgery for treatment of lung cancer. We will test the hypothesis that VATS surgery is superior to open surgery with respect to self-reported physical function five weeks after randomisation (approx. one month after surgery).

Specific objectives are to estimate:

A. The difference between groups in the average self-reported physical function at five weeks.
B. The difference between groups with respect to a range of secondary outcomes including assessment of efficacy (hospital stay, pain, proportion and time to uptake of chemotherapy), measures of safety (adverse health events), oncological outcomes (proportion of patients upstaged to pN2 disease and disease free survival) and overall survival.
C. The cost effectiveness of VATs and open surgery.

The objective of the “molecular residual disease sub-study” is to estimate the presence of circulating tumour DNA (ctDNA) in the blood and its association with clinical recurrent disease and survival to 5 years. The main objective is to assess this relationship in blood collected 5 weeks after surgery, but the association with ctDNA detected from later blood samples will also be assessed.

4. Plan of Investigation

4.1 Trial schema

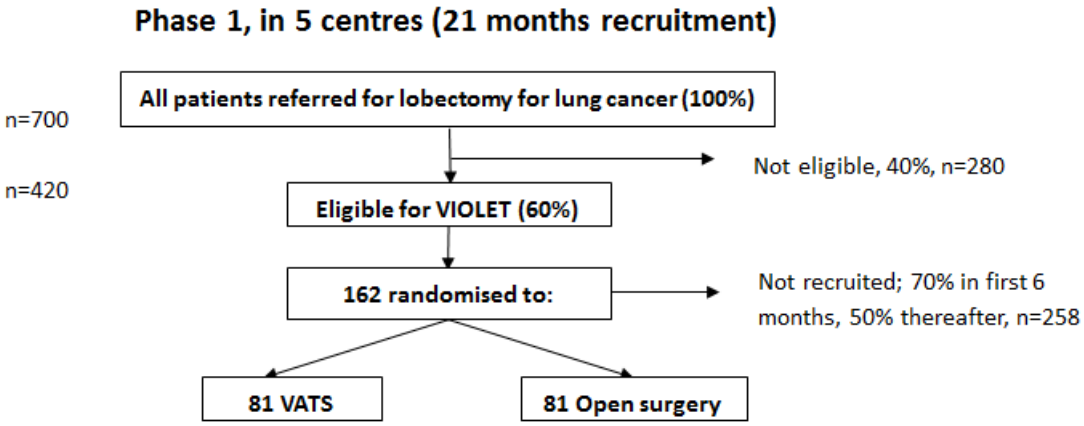


Figure 1: The trial schema for Phase 1 (pilot phase) of the VIOLET study is depicted above

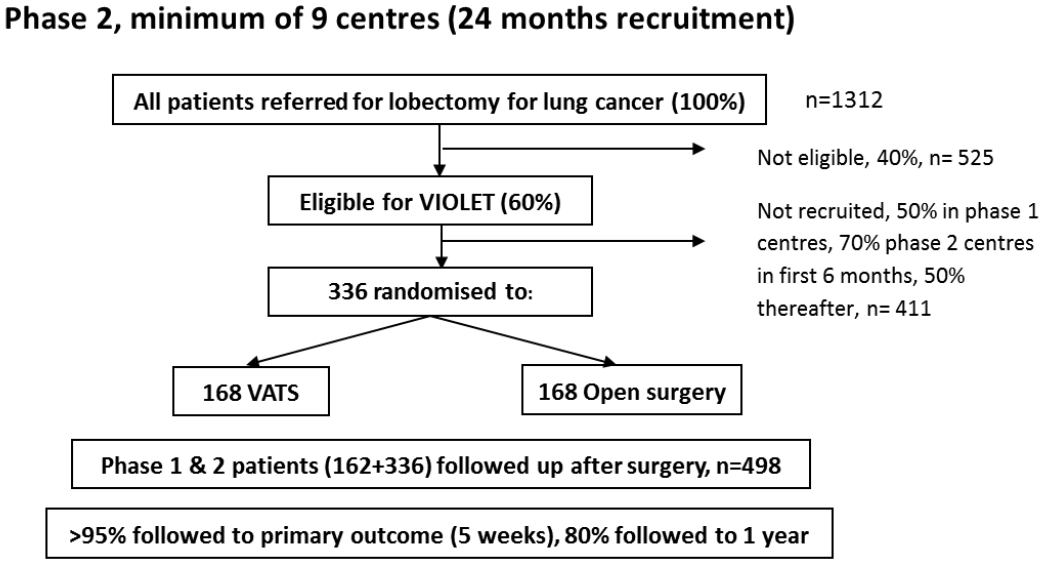


Figure 2: The trial schema for Phase 2 of the VIOLET study is depicted above

4.2 Trial design

VIOLET is a pragmatic multi-centre, parallel group, randomised controlled trial (RCT) with an internal pilot phase (phase 1). The full RCT will evaluate the effectiveness, cost effectiveness and acceptability of VATS vs open surgery for early stage lung cancer. The full trial will recruit 498 participants; 162 in phase 1 and 338 in phase 2. Trial participants will be randomised to lobectomy via VATS or open surgery in a 1:1 ratio.

Phase 1: This feasibility phase with integrated qualitative component is necessary to establish the processes for recruitment and consent. This phase is also essential to develop a study manual and a measure of surgical expertise to proceed to phase 2. Phase 1 will be conducted in five centres; Brompton, Bristol, Liverpool, Middlesbrough & Harefield. These centres are well spread geographically and represent a mix of university and NHS trusts that are representative of NHS practice. Progression to phase 2 will be dependent on meeting defined success criteria (see section 6.4).

Phase 2: This phase will extend the study to at least 9 centres (total). All centres will use the optimum methods of recruitment established in phase 1 and will follow-up all participants to one year. Patients recruited to the sub-study will be followed up beyond the end of the trial to 5 years.

4.3 Trial population

4.3.1 Eligibility criteria - participating centres

Centres are only eligible if they meet ALL of the following eligibility criteria:

1. NHS Trusts with an established and accredited lung cancer multi-disciplinary team (MDT).
2. Annually conduct ≥40 lobectomies
3. Employ at least one surgeon who has carried out ≥ 40 VATS lobectomies.

4.3.2 Eligibility criteria – participating surgeons

Surgeons will be eligible for the trial if they have performed ≥ 40 VATS lobectomies. Lobectomy via open surgery is standard and therefore surgical ability and competence has been assured by Specialist GMC registration. Prospective surgeons will be required to submit their activity logs, which will be validated against local audit data from the MDT meetings, prior to acceptance to the trial.

4.3.3 Eligibility criteria – patients (main RCT)

The target population is the cohort of patients referred by the MDT for lung resection for known or suspected lung cancer. Please see section 5.11 for a full description of the referral pathways for patients with known or suspected lung cancer.

Participants may enter the study if ALL of the following apply:

1. Adults aged ≥16 years of age
2. Able to give written consent, undergoing either:
    i. Lobectomy or bilobectomy for treatment of known or suspected primary lung cancer beyond lobar orifice* in TNM8 stage cT1-3 (by size criteria, equivalent to TNM7 stage cT1a-2b) **or** cT3 (by virtue of 2 nodules in the same lobe), N0-1 and M0 ***or***
    ii. Undergoing frozen section biopsy with the intention to proceed with lobectomy or bilobectomy if primary lung cancer with a peripheral tumour beyond a lobar orifice* in TNM8 stage cT1-3 (by size criteria, equivalent to TNM7 stage cT1a-2b) **or** cT3 (by virtue of 2 nodules in the same lobe), N0-1 and M0 is confirmed

3. Disease suitable for both minimal access (VATS) ***and*** open surgery

*In the case of bilobectomy, the distance for the "lobar" orifice is in reference to the bronchus intermedius

Participants may **not** enter study if ANY of the following apply

1. Adults lacking capacity to consent
2. Previous malignancy that influences life expectancy
3. Patients in whom a pneumonectomy, segmentectomy or non-anatomic resection (e.g. wedge resection) is planned
4. Patients with a serious concomitant disorder that would compromise patient safety during surgery.
5. Planned robotic surgery

4.3.4 Eligibility criteria – patients (sub-study only)

The target population is as for the RCT; namely patients referred by the MDT for lung resection for known or suspected lung cancer.

Participants may enter the sub-study if ALL of the following apply:

1. Adults aged ≥16 years of age
2. Anatomic lung resection or frozen section with option to proceed to anatomic lung resection
3. Known or suspected primary lung cancer

Participants may **not** enter the sub-study if ANY of the following apply

1. Adults lacking capacity to consent
2. Any previous malignancy or current malignancy not primary lung cancer

4.4 Trial interventions

All operations will be undertaken with general anaesthesia and with patients in the lateral decubitus position. Because this is a pragmatic trial, adaptations and variations of both procedures will be left to the discretion of the surgeon although intra-operative details will be collected and monitored.

4.4.1 Lobectomy via Video Assisted Thoracoscopic Surgery (VATS)

VATS lobectomy is undertaken through one to four keyhole incisions **without** rib spreading. The use of 'rib spreading' is prohibited as this is the key intra-operative manoeuvre which disrupts tissues and causes pain (and is used in open surgery). The procedure is performed with videoscopic visualisation without direct vision. The hilar structures are dissected, stapled and divided. Endoscopic ligation of pulmonary arterial branches may be performed. The fissure is completed and the lobe of lung resected. Lymph node management is the same as described for open surgery. The incisions are closed in layers

and may involve muscle, fat and skin layers. This definition of VATS lobectomy is a modification of CALGB 39802.

4.4.2 Lobectomy via Open Surgery

Conventional open surgery is undertaken through a single incision +/- rib resection and with rib spreading. The operation is performed under direct vision with isolation of the hilar structures (vein, artery and bronchus) which are dissected, ligated and divided in sequence and the lobe of lung resected. The procedures may be undertaken using ligatures, over sewing or with staplers. Lymph node management is undertaken in accordance with the International Association of the Study of Lung Cancer (IASLC) recommendations where a minimal of 6 nodes / stations are removed, of which 3 are from the mediastinum that includes the subcarinal station. The thoracotomy is closed in layers starting from pericostal sutures over the ribs, muscle, fat and skin layers.

As this is a pragmatic study post-operative care and the criteria for drain removal will be in accordance with local practice. However, we have identified two elements of patient care, which require standardisation to control for potential bias. The factors that we have identified are pain-control (see section 4.4.3) and the criteria by which a patient's medical fitness-for-discharge is assessed (see section 5.4.5).

4.4.3 Analgesia

Due to the pragmatic nature of this study standardising the use of analgesia across participating centres is impractical and, if implementable, would produce data unrepresentative of real clinical practice. Therefore, for the VIOLET study, each participating centre will prescribe analgesia in accordance with their local protocols. However, all patients recruited to the RCT at that centre will be given the same analgesia regardless of their treatment allocation (i.e. VATS or open surgery). Local protocols for the provision of analgesia will be defined by the Principal Investigator (in collaboration with the local research team) prior to the start of recruitment to the RCT. Details of the analgesia used throughout the patients in-hospital stay will be recorded on the trial CRFs and compliance with the pre-defined and centre-specific analgesia protocols will be monitored.

4.4.4 Translational research

Study participants who agree to take part in the randomised trial of VATS versus open surgery will also be approached for their consent to future research involving a section of their excised tumour. Small samples of the excised tumour are routinely retained for review by a pathologist within the treating hospital. Study participants will be approached for their permission for a small proportion of this tissue to be retained for further research into cancer treatments. The translational component of this study is optional and no additional tests, incisions or biopsies will be required to collect the tumour samples.

4.4.5 Molecular residual disease sub-study

Eligible patients will be approached for their consent to take part in the sub-study. While recruitment to the randomised trial of VATS versus open surgery is ongoing, participation in the sub-study will only be

offered to those who consent to join the main trial (in order not to compromise recruitment to the trial). Once recruitment to the RCT is complete, patients will be invited to join the sub-study only. Those who consent will be asked to provide blood samples on nine occasions up to five years, and complete and return a simple questionnaire at the same time points (see section 5.4.7 for details). Blood samples will either be taken during a planned hospital or study visit, or by the patient's general practitioner (GP) according to participant preference and the samples sent for analysis of ctDNA.

4.5 Primary and secondary outcomes

4.5.1 Primary outcome

The primary endpoint is self-reported physical function (QLQ-C30) at 5 weeks post randomisation. Physical function has been chosen because it is a patient-centred outcome that will reflect the anticipated earlier recovery with video assisted surgery and has been used in other minimal access surgery trials. The primary endpoint has been chosen to be five weeks (one month post-surgery) to capture the early benefits of minimal access surgery on recovery. Secondary outcomes have been selected to assess the efficacy of the two approaches.

4.5.2 Secondary outcomes

1. Time from surgery to hospital discharge
2. Pain scores in the first 2-days post-surgery
3. Adverse health events to 1 year
4. Proportion and time to uptake of adjuvant treatment
5. Proportion of patients upstaged to pN2 disease after the procedure
6. Overall and disease-free survival to 1-year
7. Proportion of patients who undergo complete resection during the procedure
8. Proportion of patients who experience prolonged incision pain (defined as the need of analgesia > 5 weeks post-randomisation)
9. Generic and disease-specific HRQoL: EORTC QLQ-C30, QLQ-LC13 and EQ5D to 1-year (measured at 2 week, 5 weeks, 3 months, 6 months and 1-year post randomisation)
10. Resource use to 1-year (measured for the duration of post-operative hospital stay until discharge, and at 5 weeks, 3 months, 6 months and 1-year post randomisation)

4.5.3 Molecular residual disease sub-study

The primary outcome of the sub-study is the result of the blood test (i.e. positive or negative for ctDNA) at 5 weeks. Blood results at other time points are secondary outcomes.

4.6 Sample size calculation

4.6.1 Main RCT

We hypothesise that self-reported physical function five weeks after randomisation (one month after surgery) for participants undergoing a VATS lobectomy will be superior to the physical function for participants having an open lobectomy, as measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). The sample size has been chosen to test this hypothesis. Data from the literature [14] was used to inform the power calculation.

Although the primary endpoint is at 5 weeks post randomisation, self-reported physical function will also be assessed at other time points (baseline, 2 weeks, 3 months, 6 months and 1-year). In estimating the sample size these additional measurements have been taken into account. The power calculation requires the estimation of four parameters, i.e. the effect size that would be considered clinically important, the number of pre and post-surgery measures, and the correlations between pre and post-surgery scores and between repeated post-surgery scores. The effect size was chosen on the basis of the published literature [14], which suggests that an effect size of 0.2 to 0.6 standard deviations equates to clinically important difference in physical function score of between 5 and 14 points. In the absence of data from which to estimate the correlations between repeated measures, we assumed conservative estimates (0.3 between pre and post measures, 0.6 between repeated post measures). Table 1 shows the sample size needed for a 2-sided test of superiority at the 5% level, for different parameter estimates and power.

Table 1 EORTC QLQ-C30 – physical function scale

Correlation between pre & post-surgery measures	Correlation between post-surgery repeated measures	No. of post-surgery measures	Effect size	Sample size (total)	
				Power	
				90%	80%
0.3	0.6	5	0.2	620	464
0.3	0.6	5	0.25	**398**	298
0.3	0.6	5	0.3	276	206
0.3	n/a	1	0.2	958	716
0.3	n/a	1	0.25	612	458
0.3	n/a	1	0.3	426	318

The study size has been set at 398; allowing for a 20% dropout at one year, therefore the target sample size is 498 participants. This will provide 90% power to test the hypothesis, assuming that an effect size of 0.25 standard deviations in physical function would be clinically important. The calculation based on five post-surgery measures assumes the treatment difference is similar at the five time points. However, it is anticipated that the difference in physical function may change over time. The calculation based on a single measure shows that the study will have >80% power to detect a difference of 0.25 standard deviations and >90% power to detect a difference of 0.3 standard deviations at the primary endpoint where dropout is expected to be less than 5%.

A study in 498 participants will also have 80% power to detect a 1 day difference in length of hospital stay (i.e. median 3 days versus 4 days, hazard ratio 1.3); assuming 2% of patients do not survive to discharge.

4.6.2 Molecular residual disease sub-study

This is an exploratory study (the detection of circulating tumour DNA varies with analytical method and mutation sets), therefore a formal sample size calculation was not undertaken. However, we estimate that 200 participants with a 5-week sample will be sufficient to provide useful data from the sub-study for the exploratory analyses planned. We anticipate that 5-week samples will be available for two-thirds of patients who consent to the sub-study, so the target sample size is 300 consented patients. The sub-study will investigate the association between time to disease recurrence or death and the presence of ctDNA. Pilot data suggest that approximately 60% may have tumour DNA detected. A study of 200 participants will have 90% power to detect a hazard ratio of 1.66 at the 5% level of statistical significance.

5. Trial methods

5.1 Description of randomisation and code breaking

Participants will be randomised in a 1:1 ratio to either VATS lobectomy or open lobectomy. Randomisation will take place through a secure internet based randomisation system; access to which will be restricted. Cohort minimisation (with a random element incorporated) will be used to ensure balance across groups with respect to the surgeon and the allocation will be stratified by centre.

Due to the pragmatic nature of this trial there will inevitably be some variability within surgeons, the surgical teams and the perioperative processes. Such heterogeneity is important as this accurately reflects real clinical practice. Randomisation will incorporate a cohort minimisation by surgeon and each surgeon will perform an approximately equal number of operations of each type.

Randomisation will be performed within one week of the planned operation date, once eligibility has been confirmed and consent given. This will allow sufficient time for theatre schedules to be arranged. If there is a change in surgeon after randomisation, the analysis will take into account the surgeon responsible for the performing the operation and not the surgeon originally allocated to the patient.

Code breaking will not be necessary for this study as only the researcher responsible for data collection and follow-up will remain blinded to the treatment allocation. Patients will not be informed of their surgical allocation until after their procedure and deemed fit-for-discharge.

5.2 Blinding (main RCT only)

5.2.1 Research Team

The operating surgeon and the theatre staff responsible for the care of the patient cannot be blinded to the patients' treatment allocation. However, in order to minimise the risk of bias attempts will be made to blind the research nurse responsible for the collection of follow-up data. Specifically, randomisation will be performed by a member of the research team who is ***not*** responsible for the collection of follow-up data for VIOLET study patients.

Furthermore, efforts will be made to minimise the risk of inadvertent unblinding of the research nurse responsible for data collection during the patient's post-operative stay. To accomplish this, large adhesive dressings will be applied to the thorax of study participants. These adhesive dressings will be positioned similarly for all patients, regardless of their surgical allocation and will cover both real and potential incision/port locations. The initial adhesive dressings will be applied in theatre by the operating team and these will not be changed until 3 days after surgery (or discharge if discharged before day 3), unless soiling or lack of adherence prompts their premature replacement. Three days after surgery, dressings will be changed by a nurse who is ***not*** responsible for conducting the patients' follow-up assessments. Wound cleaning will be performed on all real and potential incision/port locations to promote allocation masking.

5.2.2 Participants

In order to ensure that study patients remain blinded during the post-operative period, patients will be asked to turn their heads away from the wound site(s) whilst wounds are being cleaned and dressed. When patients are considered 'fit-for-discharge' they will be advised of how to best care for their wounds. Patients who express a wish to know which treatment they received will be informed at this point.

5.2.3 The success of blinding

The success of blinding will be monitored during each patients in-hospital stay. Patients will be asked to complete the Bang-blinding Index [15] at 2 days post-operatively and at discharge, but before the treatment allocation is revealed. The research nurse responsible for data collection and follow-up of VIOLET study patients will also be asked to complete the Bang-blinding Index when the patient is ready for discharge and after the patient attends for their 5 week and 1 year follow-up appointments.

5.3 Design features to minimise bias

5.3.1 Selection Bias

Selection bias will be minimised by using a secure internet based randomisation server to generate patient treatment allocations. Access to the randomisation system will be restricted to authorised personnel. Cohort minimisation (with a random element incorporated) will be used to ensure balance across groups by surgeon and the allocation will be stratified by centre.

5.3.2 Performance Bias

Open surgery and VATS will be presented in a balanced manner in the patient information leaflet so trial participants should not have strong expectations of which treatment is better. Furthermore, patients will remain blinded to their treatment allocation until after they are considered fit-for-discharge.

Performance bias will be minimised by enforcing eligibility criteria for the surgeons participating in the trial. Each surgeon must have performed a minimum of 50 VATS procedures to be eligible to participate in VIOLET. By enforcing surgeon eligibility criteria the impact of any training and learning effects [16, 17] and associated bias should be minimised. However, VIOLET is a pragmatic trial and it is anticipated that there will be some variations in intra-operative and post-operative care across the centres. These variations are unavoidable and provide an accurate representation of real clinical settings.

Additional mandatory and prohibited components of VATS will be identified and detailed in a study manual which will be developed during phase 1 of the trial. Such procedural standardisation will establish pragmatic boundaries within which procedures can be performed and should further minimise bias during phase 2.

5.3.3 Detection Bias

Systematic differences between groups in how outcomes are reported will be minimised by reporting outcomes on the basis of objective definitions. Post-operative complications will be classified using the Clavien-Dindo [18] system and adverse health events will be graded in severity according to the Common Terminology Criteria for Adverse Events (CTCAE). In an attempt to further reduce detection bias, the research nurse responsible for data collection during the follow-up period will be blinded to the patients' treatment allocation.

5.3.4 Attrition Bias

Systematic differences between groups in the withdrawals from the study will be minimised by maximising the number of patients for which outcome data is available. Information on vital status will be sought for study patients via the Health and Social Care Information Centre.

5.3.5 Reporting Bias

Study outcomes and analysis plans have been pre-specified in this protocol (see section 4.5 and 6.1 respectively) to minimise the risk of reporting bias. A detailed statistical analysis plan will be written in advance of any formal comparative analysis.

5.4 Quantitative research procedures

5.4.1 Assessment of patient reported outcomes

Health related quality of life: Generic and disease-specific HRQoL measures will assess the profiles of VATS and open lobectomy in the early and mid-postoperative phases. The extensively validated EQ-5D will assess generic aspects of health (http://www.euroqol.org/home.html), and will be used in the analysis of QALYs. The EORTC QLQ-C30 is one of the most widely used instruments for assessing HRQoL in patients with cancer. The questionnaire contains 30-items with five function scales (physical, role, cognition, emotional and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and financial problems), and a global health status/QoL scale.

The QLQ-LC13 is the lung cancer module with 13 items that assesses lung cancer–specific symptoms such as cough, haemoptysis, severity of shortness of breath, chest/ body pain, and chemotherapy/ radiotherapy side effects such as sore mouth, dysphagia, peripheral neuropathy and hair loss. A higher scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, and a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale represents a high level of symptoms and problems.

Participants who agree to take part in the RCT will be asked to complete HRQoL questionnaires at baseline and post-operatively at 2 weeks, 5 weeks, 3 months, 6 months and 12 months post-randomisation. Baseline questionnaires will be administered by the research team at site. Post-operative questionnaires will be sent to participants by the CTEU and returned directly to the CTEU. However, the research nurse at site may obtain questionnaire data during a study visit or telephone call, for those participants who do not return their questionnaire. Participants can choose to receive post-operative questionnaires by post or complete via a secure website.

Patients who decline randomisation but agree to trial follow-up will be asked to complete HRQoL questionnaires at baseline and then 5 weeks post-operatively. Baseline questionnaires will be administered by participating centres. The 5 week post-operative questionnaire will be administered by the CTEU.

Patients who consent to the sub-study only will not be asked to complete HRQoL questionnaires.
Pain scores: The degree of post-operative pain experienced by patients undergoing VATS or open surgery is an important consideration when comparing the two methods of surgical access. To this end, patients will be asked to verbally report their pain on a visual analogue scale (VAS) at baseline (pre-operatively) and on day 1 and day 2 post-operatively.

Disease recurrence and treatment: Patients who consent to the sub-study and choose not to attend the recruiting hospital for follow-up will either be contacted via telephone or asked to complete a questionnaire to retrieve information on their cancer recurrence and treatment at each follow-up. The questionnaire will be sent (with the blood kit) from the CTEU for return directly to the CTEU. Participant-reported cancer recurrence and treatment will be flagged with the study centre so that full details can be obtained. Alternatively, the patients may be contacted via telephone by the study team

to gather the relevant information. For patients who choose to attend the recruiting hospital for follow-up (including providing blood samples) these data will be collected by the study team at the visit.

5.4.2 Assessment of non-patient reported study outcomes

Patients who consent to randomisation will be followed-up at 5 weeks, 3 months, 6 months and 12 months post-randomisation. At these time-points details of adverse events experienced, resource use, uptake of adjuvant chemotherapy and disease recurrence will be collected.

The 5 week follow-up has been scheduled to coincide with the patient's routine post-operative follow-up appointment and may or may not be conducted at the hospital where the patient had their surgery. If a patient is to be followed-up at a peripheral hospital (i.e. not the centre where they underwent their surgery), study follow-up will be via telephone. Conversely, patients who attend the hospital at which they had their procedure, will see a member of the local research team. In both cases, follow-up should be conducted by a member of the research team blinded to the patient's treatment allocation.

Follow-up at 3 and 6 months post-randomisation will be via a telephone call with a study research nurse, who will contact the patient at mutually agreed times. Finally, at 1 year post-randomisation, patients will attend either their operating hospital or their local peripheral hospital for a CT scan of the chest and abdomen. Furthermore, the patient will also be seen (for patients attending their operating hospital) or contacted by telephone (for patients who do not attend their operating hospital) to collect details of adverse events experienced, resource use, uptake of adjuvant chemotherapy and disease recurrence.

For patients who decline randomisation but whom agree to participate in trial follow-up, a minimal dataset will be collected at 5 weeks and 1-year, which will include mortality data.

For patients who consent to the sub-study, blood samples will be taken at the participants' general practice (GP) or at the recruiting hospital according to participant preference (see section 5.4.7 for further details).

5.4.3 Imaging protocol

It is expected that patients entering into the RCT will have undergone a CT scan of the chest and abdomen, as well as whole body PET/CT prior to surgery, to assist with pre-surgical planning and disease staging. These scans will be in accordance with the standard practice at participating sites and therefore, *do not* constitute procedures specific to this study protocol, however the images and reports from these staging scans will however be used in the study.

Furthermore, patients participating in the VIOLET RCT will also undergo a CT scan of the chest and abdomen 12 months post-randomisation – this procedure is considered part of standard care at participating centres. This assessment will then be used to identify disease recurrence/ progression.

It is expected that in a small number of cases, symptomatic patients may have undergone clinically indicated CTs just prior to 12 months. In such cases, local MDTs may decide that a CT scan at 12 months is not required. Any such cases will be recorded on the trial CRFs.

5.4.4 Assessment of disease progression

Assessment of disease will be defined according to objective definitions. Disease progression will be classified according to the following broad categories:

- No unequivocal evidence of progression – normal post lobectomy CT appearances
- No unequivocal evidence of progression – however new CT findings require surveillance (e.g. indeterminate or inflammatory appearing lung nodules)
- Disease status unknown – indeterminate CT findings require immediate work up (e.g. new pleural effusion, new soft tissue at surgical resection site)
- Unequivocal radiological evidence of progression – (e.g. new lymphadenopathy, distant metastases, lymphangitis) – To be sub-categorised as local or distant progression
- Unequivocal evidence of progression – pathologically proven – To be subcategorised as local or distant progression.

The decision to categorise patients into one of the above groups will be determined by the local MDT. Recurrence will be monitored to ensure that MDTs are consistently and appropriately defining disease recurrence. If deemed necessary by the study team a random 10% sample of the 12 month CT scans will be reviewed by a radiologist blinded to the treatment allocation (VATS or open surgery).

Adverse events will be reported in accordance with the CTCAE and postoperative complications will be classified using the Clavien-Dindo [18] system; further details of adverse events can be found in section 8.

5.4.5 Assessment of discharge suitability

In order to objectively compare the time from surgery to hospital discharge (a secondary outcome measure) between VATS and open surgery, the following discharge suitability criteria have been developed. Patients randomised to VATS or open surgery will be evaluated against the following criteria to ensure that they are **medically fit-for-discharge**:

- Patient has achieved satisfactory mobility with,
- Pain under control with analgesia
- Satisfactory serum haemoglobin and electrolytes (i.e. does not require intervention)
- Satisfactory chest-x-ray (which will be performed as part of routine clinical care)
- No complications that require further / additional treatment

Patients who are considered **medically fit-for-discharge** may not necessarily be discharged immediately; in some instances social and other factors may necessitate extended hospitalisation. The time at which patients are considered medically fit-for-discharge and when they are physically discharged from hospital will both be recorded on the trial CRFs.

5.4.6 Trial Interventions

Lobectomy by open surgery or VATS will be conducted as per section 4.4.

5.4.7 Molecular residual disease sub-study

Blood samples will be taken at baseline and 5 weeks, 6 months, 1 year, 18 months, 2, 3, 4 and 5 years after randomisation (RCT participants) or after surgery (non-RCT sub-study participants). The baseline pre-surgery blood sample will be taken in hospital at recruitment. The remaining samples collected after surgery will be taken either at the recruiting hospital during a study visit or by the participant's GP.

A 40mL whole blood sample will be collected in four 10 mL Streck tubes provided in pre-packaged kits provided by Guardant Health. The kits will be sent by the coordinating centre to study participants who choose to have samples taken by their GP who will take the kit to the GP in order for their blood samples to be collected. Recruiting hospitals will have a kits available for those participants who select hospital-based follow-up. The GP practice or hospital will arrange for the kit with samples to be returned the same day in the pre-labelled, prepaid packaging to Guardant Health in the USA via FedEx.

Guardant Health will analyse the samples using LUNAR-I, a proprietary NGS panel, to identify the presence of ctDNA. The 5-week samples will be analysed in batches and the remaining samples will be kept for analysis once all patients have completed the sub-study. Only those participants that have confirmed cancer recurrence during the 5 year follow-up will have their remaining samples analysed, to establish when the ctDNA becomes detectable. Guardant Health will notify the coordinating centre when samples are received and will send the results of the DNA tumour analyses to the coordinating centre.

5.5 Qualitative research procedures (RCT recruitment phase only)

5.5.1 Qualitative research: data collection

Surgical randomised controlled trials (RCTs) face particular recruitment challenges including surgeons' limited experience of RCTs, having more confidence in particular procedures and variations in individual practice [19]. Furthermore, there is a dearth of robust evidence about effective strategies to improve recruitment in RCTs [20]. However, qualitative research can be used to understand recruitment in specific RCTs and has been shown to improve recruitment and informed consent [21-30]. Therefore, it is essential to understand the recruitment process at each centre in real time and investigate the sources of recruitment difficulties. To accomplish this, all face-to-face and telephone consultations between healthcare staff and patients will be audio-recorded. Individual patient equipoise will be through the use of in-depth interviews, which will explore patients views on the two procedures, the trial, the acceptability of randomisation between procedures and the factors that influence their decision to participate in the RCT or not. This information will help to determine whether there is sufficient patient equipoise for such a study to be able to recruit in the specified time frame.

In-depth interviews will also be undertaken with surgeons to explore perceptions and experiences of undertaking both procedures, perceptions of their levels of individual equipoise and the equipoise of their colleagues, commitment to the trial, and views about the likely outcome of the trial. There will also be the opportunity to record discussions in the Trial Management Group (TMG) about issues of

preference and expertise. These interviews and recorded consultations will permit comparisons to be made to detect preferences unwittingly transmitted during recruitment consultations.

Patient pathway through eligibility and recruitment: A comprehensive process of logging potential trial patients through screening and eligibility phases will be undertaken to provide basic data about the levels of eligibility and recruitment, and identify points at which patients opt in or out of the RCT.

Audio recording of recruitment appointments: All face-to-face and telephone consultations of healthcare staff (thoracic surgeons, nurses etc.) with patients will be audio recorded to understand the recruitment process at each centre and to identify and investigate the challenges to recruitment. The QRI researcher will listen to the appointments, document relevant details and provide an account to be fed back to the RCT CI anonymously.

In-depth Interviews: Audio-recorded in-depth, semi-structured interviews will be conducted with:

- Members of the TMG, including the chief investigator (CI) and those closely involved in the design, management, leadership and coordination of the trial.
- Clinical and recruitment staff across the five centres involved in the internal pilot phase.
- Participants eligible for recruitment to the RCT, including those who accept or reject randomisation.

These data will be used by the qualitative team to provide individual and group feedback to recruiters to help them to communicate equipoise, balance treatment options and explain to patients the benefits and purposes of trial participation, whilst also optimising informed consent. Rates of recruitment of eligible patients will be closely monitored against the feedback meetings and it is expected that an improvement will be demonstrated in recruitment over time with experience and training (as we have demonstrated is possible in other similar trials [21, 24]).

Interview topic guides, developed by the lead qualitative researcher, will provide structure to the study interviews. These topic guides will be submitted to the research ethic committee as part of the initial application, but will evolve throughout the trial. This will ensure that the qualitative component of the study provides accurate and real time feedback to recruitment and informed consent process.

Observations of investigator meetings: It is likely that the CI, TMG and clinical investigators will meet or have telephone conferences to discuss the progress of the RCT. The QRI researcher will ask to observe these meetings and to audio-record some, with permission. The aim will be to gather further information about specific issues that may have a bearing on recruitment.

Study documentation: Patient Information Leaflets and consent forms will be scrutinised by the QRI researcher to identify aspects that are unclear or potentially open to misinterpretation. They will be compared with the findings from the interviews and recorded appointments, to identify any disparities or improvements that could be made.

5.5.2 Qualitative Research: Feedback to the CI/TMG & Plan of Action

The QRI researcher will present summaries of anonymised findings to the CI (and TMG, if agreed by CI), identifying the factors that appear to be hindering recruitment with supporting evidence. If the CI/TMG

agrees that particular factors are amenable to change, a plan of action will then be drawn up to try to improve recruitment. Any feedback to centres and individual recruiters will be confidential and positive (i.e. not critical). Some of the issues identified by the QRI researcher are likely to be generic, such as how to explain randomisation and deal with patient preferences. There may also be study specific issues related to the differences between the treatments in the VIOLET study. In previous studies, the action plan has included: re-drafting of study information, training and advice about presenting the study, and changing aspects of organisation in study centres.

5.5.3 Qualitative Research: Evaluation of the Impact of the Plan of Action

Numbers of eligible patients, and the percentages of these that are approached about the RCT, consent to be randomised and immediately accept or reject the allocation will be assessed before the plan of action is implemented, and regularly afterwards to check whether rates are improving. Interviews with recruiters will ask about the acceptability of the QRI and any changes to patient allocations in the trial. It is expected that the qualitative research will permit between 40% and 60% of eligible patients to be enrolled into the trial. The table in section 5.10 shows the numbers of patients undergoing lobectomy in the participating centres each year.

5.6 Duration of treatment period

The duration of the treatment commences when the patient enters the operating room and concludes when the patient leaves the operating room after lobectomy. The duration of the procedure will be between 2 to 4 hours for both VATS lobectomy and open surgery.

5.7 Definition of end of trial

5.7.1 Main RCT

Each participant will have a CT scan at one year post-randomisation and will complete the final HRQoL questionnaires. The patient's involvement in the trial will end at this point. Data collection for the main study will be complete when the final randomised participant has completed the 1 year post randomisation assessments.

5.7.2 Sub-study

Patients participating in the molecular residual disease sub-study will provide their final blood sample and complete their final questionnaire 5 years post randomisation (RCT participants) or 5 years post surgery (non-RCT sub-study participants). If the disease recurs within the 5 years or a new cancer is diagnosed, no further blood samples will be sought, but data collection for cancer treatment and survival will continue.

Data collection for the whole sub-study will be complete when all participants have provided samples and questionnaire data to 5 years, or recurrence/new cancer (whichever is earlier); when all follow-up with study centres for further information on disease recurrence is complete, and Guardant Health have supplied the results of the analyses of the blood samples.

5.7.3 Definition end of trial

The end of the trial will be when the databases for the main study and sub-study are closed, all the data queries have been answered, the data have been analysed and are ready for publication.

5.8 Data collection

5.8.1 Data collection for trial patients

Data collection for the trial participants will include the following elements:

(a) A log of patients screened by the MDT and the date when they were given or sent the Patient Information Leaflets (PILs).

(b) A log of patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.

(c) Consultations between thoracic surgeons and participants will be audio-recorded, transcribed and utilised to assess recruitment challenges. Semi-structured interviews will be conducted with eligible patients, including those who accept or reject randomisation.

(d) Consent and baseline information to include the patient's medical history and disease status. Details of the planned operation and baseline HRQoL questionnaires collected prior to randomisation.

(e) Details of the procedure (open lobectomy or VATS) will be collected intra-operatively. Details of the histopathology of any samples (e.g. biopsies) taken intra-operatively will also be collected.

Post-operatively, details of any adverse events and patient resource utilisation will be recorded on trial CRF's along with details of the patient post-operative care. Post-operative HR QoL's and the results ofany scans taken to assess disease status will be collected (timing detailed in table 2).

Table 2 Data collection for trial participants who agree to randomisation to VATS or open surgery

	Pre-randomisation	Post-randomisation								
	Baseline	Day of Surgery	1 day post-op	2 days post-op	Dis-charge	2 weeks*	5 weeks*	3 months*	6 months*	1 year*
Eligibility	*X*									
Imaging review (CT / PET-CT[¥])	*X*									
Participant characteristics	*X*									
Audio recorded consultation	*X*									
Lobectomy via VATS or Open Surgery		*X*								
Intra-operative details		*X*								
Histopathology staging		*X*								
Tumour sample for research		*X*								
Patient Questionnaires										
QLQ-C30	*X*					*X*	*X*	*X*	*X*	*X*
QLQ-LC13	*X*					*X*	*X*	*X*	*X*	*X*
EQ5D	*X*					*X*	*X*	*X*	*X*	*X*
Bang Blinding Index				*X*	*X*					
Pain score	*X*		*X*	*X*						
Adverse Events		*X*					*X*	*X*	*X*	*X*
Resource use	*X*	*X*					*X*	*X*	*X*	*X*
CT scan of chest & abdomen										*X*

**Follow-up time-points will be calculated from the date of randomisation.*
[¥] Review of images available from staging scans performed in accordance with standard practice at participating centres

5.8.2 Data collection for the Qualitative recruitment intervention

Data collection for the Qualitative Recruitment Intervention (QRI) will include the following elements:

(a) Audio-recorded face-to-face and telephone consultations between healthcare staff and trial participants.

(b) In-depth semi structured interviews will be conducted and audio recorded with:
- The TMG, Chief Investigator (CI) and those closely involved in the design, management and leadership of the trial.
- Clinical and recruitment staff across the five centres participating in the internal pilot phase of the RCT (phase 1)

- Participants eligible for recruitment to the RCT, including those that accept or reject randomisation

(c) Meetings and / or teleconferences with the CI, TMG and clinical investigators regarding the progress of the trial will be observed and audio recorded (with permission) to gather further information about specific issues that may have a bearing on recruitment.

(d) Study documentation, including Patient information leaflets (PILs) and consent forms will be scrutinised by the QRI researcher to identify any aspects that are unclear or potentially open to misinterpretation. These documents will be compared with the findings from interviews and recorded appointments to identify any disparities or improvements that could be made.

5.8.2 Data collection for the research nurse responsible for data collection

The methods of blinding, as described in section 5.2, specify that the research nurse responsible for data collection should remain blinded throughout a patients in-hospital stay and until after the collection of data for the primary outcome measure at 5 weeks post-randomisation. To evaluate the efficacy of this method of blinding, the research nurse responsible for data collection will be asked to complete the Bang-blinding index when the patient is considered fit-for-discharge and again after the patient attends for their 5 week follow-up appointment.

5.8.3 Data collection for the molecular residual disease sub-study

Patients who opt for hospital based follow up will attend the hospital for study visits. Patients who opt for GP based follow up will be contacted via telephone or questionnaires to gather information on hospitalisations for disease recurrence and cancer-treatment. The questionnaire, with pre-paid reply envelope, will be sent with the sample kit for completion and returned to the coordinating centre. Further information on cancer-related hospitalisations reported will be sought from the study centre via the local research nurse (e.g. information on scans and biopsies, and relevant medical reports). Participant's survival status will be checked using NHS tracing before blood sample kits and questionnaires are sent.

Table 3 Data collection for participants who agree to take part in the sub-study

(A) Participants who join the RCT and the sub-study

	Pre-randomisation	**Post-randomisation**							
	Baseline	**5 weeks**	**6 months**	**1 year**	**18 months**	**2 years**	**3 years**	**4 years**	**5 years**
4 x 10 ml blood sample[¥]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Participant questionnaire[*]					*X*	*X*	*X*	*X*	*X*
Details on disease recurrence and treatment received[+]					*X*	*X*	*X*	*X*	*X*

(B) Participants who join the the sub-study only (i.e. are not recruited to the main RCT)

	Pre-surgery	Post-surgery											
	Baseline	**Day of Surgery**	**1 day post-op**	**2 days post-op**	**Dis-charge**	**5 weeks**	**6 months**	**1 year**	**18 months**	**2 years**	**3 years**	**4 years**	**5 years**
Eligibility	*X*												
Participant characteristics	*X*												
Intra-operative details		*X*											
Tumour sample for research		*X*											
Histopathology staging		*X*											
Adverse Events		*X*											
4 x 10 ml blood sample[¥]	*X*					*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Participant questionnaire[*]	*X*					*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Details on disease recurrence and treatment received[+]	*X*					*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*

¥ Samples will be collected in hospital during study visits or by the GP
** Participants who opt for non-hospital-based follow-up*
+ Collected by recruiting hospital, when participant reports hospitalisation(s) and/or disease reoccurrence has occurred

5.9 Source data

Source data for the trial and sub-study participants will include the following:

a. Medical notes for details of the patient's medical history.
b. CT / PET scan reports and images for disease assessment.
c. Histopathology reports for disease staging.
d. Completed participant questionnaires (QLQ-C30, QLQ-LC13 & EQ5D, sub-study follow-up questionnaire) will be considered source data. This will include questionnaires completed electronically through the secure study website and those completed on paper.
e. Trial CRFs will be considered as source data when assessing resource utilisation.

Source data for the Qualitative Recruitment Intervention component of the RCT will include the following:

a. Audio-recordings from the semi-structured interviews with the CI, TMG, study investigators and the recruitment staff at centres.
b. Audio-recordings of Investigators meetings.
c. Audio-recordings of the consultations between the thoracic surgeon and trial participants.
d. Audio-recordings of interviews with trial participants.

Source data for the sub-study will include the following:

a. Laboratory results obtained from blood samples donated at each time point
b. Completed participant questionnaires capturing hospital admissions and disease recurrence
c. Medical notes, CT / PET scan reports and images and histopathology reports for cancer treatment received, disease assessment and staging.

5.10 Planned recruitment rate

Phase 1 recruitment will take 21 months to complete. A review of trial accrual against the pre-defined progression criteria (see section 6.4) will occur 18 months after recruitment commences to phase 1 of the study. Subject to the satisfactory completion of phase 1, phase 2 will recruit over a 24 month period; both recruitment windows account for the staggered start to recruitment across the sites. The anticipated recruitment rate for each of the participating centres is documented in Table 4.

Due to the limited experience of surgeons to randomise patients into trials, the expected recruitment rate is likely to increase throughout the course of the trial. Specifically, it is estimated that the participating surgical teams will initially recruit 30% of eligible patients and with training and feedback this may increase to 50% of eligible patients. This improvement in recruitment rate over time with experience and training has been demonstrated in similar trials [21, 24]. The integrated qualitative research will train surgeons to recruit and therefore recruitment to both phase 1 & phase 2 of the trial should improve over time.

Table 4 Estimated recruitment rates in VIOLET in participating centres, assuming that 60% of patients undergoing lobectomy are eligible for the trial

	No. of lobectomies/yr		**No./yr if 30% of eligible patients recruited**		**No./yr if 50% of eligible patients recruited**		**Total if 30% of eligible patients recruited up to 6 months & 50% thereafter**		
	2015	**2016 onward**	**2015**	**2016 onward**	**2015**	**2016 onward**	**Phase 1 (21 months)**	**Phase 2 (24 months)**	**Total**
Phase 1 sites (PI)									
Brompton (Lim)	120	150	22	27	36	45	67	90	157
Liverpool (Shackcloth)	100	100	18	18	30	30	42	60	102
Bristol (Batchelor)	50	70	9	13	15	21	25	42	67
Middlesbrough (Dunning)	70	90	13	16	21	27	28	54	82
Harefield (Lim – PI duties delegated to Anikin)	40	50	7	9	12	15	20	30	50
Phase 1 centre total	**380**	**460**	**68**	**83**	**114**	**138**	**182**	**276**	**458**

	No. of lobectomies/yr		No./yr if 30% of eligible patients recruited		No./yr if 50% of eligible patients recruited		Total if 30% of eligible patients recruited up to 6 months & 50% thereafter		
	2015	**2016 onward**	**2015**	**2016 onward**	**2015**	**2016 onward**	**Phase 1 (21 months)**	**Phase 2 (24 months)**	**Total**
Phase 2 sites									
UCLH (Panagiotopoulos)	N/A	100	N/A	18	N/A	30	0	54	54
Leeds (Brunelli)	N/A	90	N/A	16	N/A	27	0	44	44
Birmingham (Naidu)	N/A	80	N/A	14	N/A	34	0	35	35
Castle Hill/Hull (Loubani)	N/A	101	N/A	9	N/A	15	0	20	20
Oxford (Belcher)	N/A	67	N/A	6	N/A	11	0	17	17
Edinburgh (Zamvar)									
Phase 2 centre total	**N/A**	**438**	**N/A**	**63**	**N/A**	**117**	**0**	**170**	**170**

5.11 Participant recruitment

5.11.1 Patient referral pathways

Potential patients will be identified from MDT meetings, which consider all new patients referred from local and satellite lung cancer MDTs or from the referral letters of patients referred from tertiary / referring hospitals. Patients known or suspected to have lung cancer will have undergone a CT / PET scan in order to assess their disease. It is common for lung lesions to be of uncertain pathology before surgery and most series show that of all patients listed for lobectomy approximately 25% will be listed without a pre-operative tissue diagnosis [31]. Therefore, two groups of patients are eligible for the VIOLET study:

(a) Patients for whom the MDT confirms the need for lobectomy (patients with proven cancer) or lobectomy without preoperative tissue diagnosis (for patients in which a biopsy is not possible), see figure 3.
(b) Patients for whom the MDT recommends a biopsy with the option to proceed to lobectomy, see figure 4.

Using the above strategy, only a small proportion of patient's randomised (estimated 4% in total) will finally be confirmed to have benign disease. These patients will be included in the final intention to treat analysis and will be followed up to the primary endpoint only.

Figure 3: The patient referral process for those 80% of patients who proceed with lobectomy initially either on recommendation from the MDT or on the basis of known cancer diagnosis.

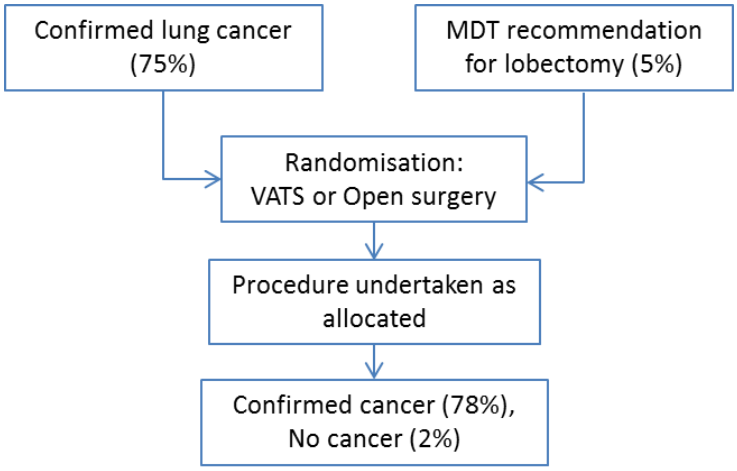
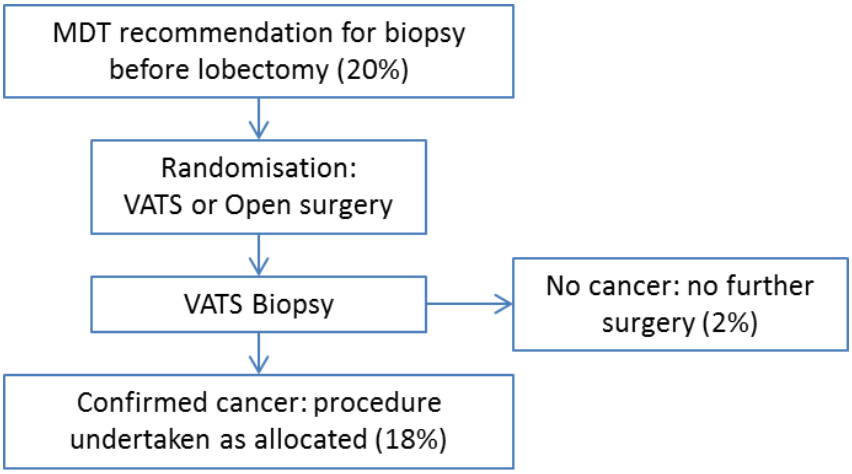


Figure 4: **The referral process for those 20% of patients in which there is no confirmatory pre-operative diagnosis**



If the (real-time) results of the frozen section biopsy diagnose primary lung cancer, surgery will proceed as allocated. Patients with a non-cancerous diagnosis will have no further surgery.

5.11.2 Approaching potential patients

Information provision: Patients recommended for a lobectomy, or a biopsy with the option to proceed to lobectomy, will be given a clinic date to meet with a thoracic surgeon. These patients will be given or sent a study invitation letter and patient information leaflet (PIL), which explains the risks, benefits and burdens of the study.

The majority of potential VIOLET patients will be identified at MDT meetings or through referral letters. Patients who are identified at local MDTs will receive study information well in advance of their clinic appointment and will have plenty of time to discuss participation with friends or family, before being approached for consent.

However, some of the sites participating in this study are large regional centres that receive patients from numerous peripheral hospitals. Indeed, many of the surgeons participating in this study have regular clinics within these peripheral hospitals, where they will see patients due to undergo surgical management for lung cancer. In order to provide study information to patients identified at these clinics, these hospitals will be set-up as Patient Identification Centres (PICs). By doing so, we can ensure the timely provision of study information. Research activities at these PIC's will be limited to screening patients and providing study PILs.

The surgical consultation: During the surgical consultation, each patient will be seen by a surgeon who will introduce the study, answer any questions, confirm the patient's eligibility and take written informed consent (if the patient decides to participate). All individuals taking informed consent will be GCP trained. During the consultation potential participants will be fully apprised of the potential risks, benefits and burdens of the study. The patient will be given the opportunity to deliberate and will be offered a second consultation if they wish to consider and discuss the study again. Patients may also be approached for their consent to participate on admission to hospital, the night before their operation. This provision has been made to ensure that patients who could not be consented at their clinic visit are given the opportunity to participate in the VIOLET study.

In order to identify challenges to recruitment, these appointments will be audio recorded (main trial phases only). This audio recording does not form part of the current standard care pathway but is essential to ensure deliverability of the full RCT.

Patients who decline randomisation to the RCT will be offered the opportunity to participate in the study through the collection of a minimal dataset. Consenting patients will be asked to complete HRQoL questionnaires before surgery and 5 weeks after surgery. Permission will also be sought to collect details of the type of surgery they undergo (be it VATS or open surgery) and mortality data.

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

Patients who consent to join the trial will also be invited to join the molecular residual disease sub-study. Participation in the sub-study will be optional. Once recruitment to the main RCT is complete patients will be invited to join the sub-study only. A sub-study specific PIL will be used during this recruitment phase.

5.12 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time. In addition, the investigator may withdraw the participant from their allocated treatment arm if subsequent to randomisation a clinical reason for not performing the surgical intervention is discovered. If this occurs this will be appropriately documented.

If a participant wishes to withdraw, data collected up until the time of withdrawal will be included in the analyses, unless the participant expresses a wish for their data to be destroyed. Withdrawing patients will be asked at this point if they can be contacted to complete HRQoL questionnaires for an assessment physical function (primary end point).

Participants who join the sub-study who are found to not have cancer, or for whom a 5-week sample is not obtained will not be contacted for further blood samples or follow-up. Similarly, further blood samples during follow-up will not be sought for participants whose cancer recurs or who develop a second malignancy, however data collection for cancer treatment and survival will continue.

5.13 Frequency and duration of follow up

The small proportion of patients who agree to participate in the RCT but in whom benign (non-malignant disease) is confirmed will not be followed-up beyond 5 weeks (the timing of the primary outcome). Furthermore, patients who decline randomisation but consent to the collection of a minimal dataset will be follow-up until the collection of data relating to the primary outcome measure.

Patients who agree to participate in the RCT and in whom a malignant primary cancer is confirmed, will be followed-up post-operatively until discharge, and at 5 weeks, 3 months, 6 months and 12 months post randomisation. At 5 weeks post randomisation the participant will attend hospital and be seen by a research nurse who, wherever possible, will be blinded to the treatment allocation. This visit will coincide with the participant's routine post-surgery follow-up. Thereafter follow-up will be conducted via telephone (at mutually agreed times) to ascertain adverse events, resource use and the uptake of adjuvant treatment. At one year post randomisation the participant will attend hospital to have a CT scan of the chest and abdomen. They will also be seen by a research nurse who, wherever possible, will be blinded to the treatment allocation.

Baseline HRQoL questionnaires will be administered by a research nurse at each participating centre. Participating centres will also be responsible for collecting these from patients. Questionnaires that require completion during the follow-up period will be administered by the CTEU. Participants will have the option to receive and return postal questionnaires or to complete electronic forms via a secure website.

Patients who agree to participate in the sub-study will be followed up at 5 weeks, 6 months, 12 months, 18 months and at 2, 3, 4 and 5 years after surgery. Blood samples will be taken at these time points by the patient's GP or by the research nurse at the study visit and will be shipped either by the GP or research nurse to Guardant Health in the USA for analysis. Participants will be asked to provide blood samples at the GP practice or at their recruiting hospital at each of these follow-up points which will be shipped to the USA. Participants who choose to have samples taken by there GP will have telephone visits or will be asked to complete and return a simple postal questionnaire that will capture information about hospitalisations and disease recurrence once any trial-based follow-up finishes.

5.14 Likely rate of loss to follow-up

Until discharge from hospital, the only losses to follow-up will be due to death or a participant withdrawing; these losses are expected to be very few. In estimating the target sample size for the main trial, a loss to follow-up of 20% has been allowed for. All efforts will be made to stay in contact with trial participants and to seek information on vital status via the Health and Social Care Information Centre.

Loss to follow-up in the sub-study, which extends up to 5-years, is expected to be greater. However, primary outcome is at 5 weeks and we estimate that up to one third will not provide a 5-week blood sample. As indicated above (Section 5.12) patients who do not provide this sample will be considered lost and no further contact will be made.

5.15 Expenses

Travel expenses for this study will only be payable to those participants who are required to attend appointments for study specific commitments. Study specific commitments are only anticipated for those participants who are invited and consent to interview discussions with the qualitative researcher. It is anticipated that the vast majority of these discussions will take place at the participant's usual place of residence (or other mutually agreeable location) or via telephone call. No additional hospital visits are anticipated for those patients participating in the randomised controlled study with the audio-recorded recruitment consultation.

Travel expenses for visits to the GP practice or study centre to provide study blood samples will be available for patients taking part in the sub-study.

6. Statistical analyses

6.1 Plan of analysis

The data will be analysed on intention to treat (ITT) and follow CONSORT reporting guidelines. Randomised participants who are not found to have lung cancer will be included in the primary analysis, but a modified ITT analysis excluding these participants will be performed. Analyses will be adjusted for centre and for design factors included in the cohort minimisation (e.g. the operating surgeon). Should there be a change in surgeon after randomisation, the analysis will take into account the surgeon who performed the intervention and not the surgeon originally allocated to perform the procedure. As the allocation to VATS or open surgery is minimised by surgeon, clustering may occur within the dataset. The structure of the data will be taken into account, i.e. nesting of patients by surgeon and centre, in the primary analysis.

6.1.1 Analysis of quantitative data

Patient reported outcomes scores (HRQoL) and will be compared using a mixed regression model, adjusted for baseline measures where appropriate. Changes in treatment effect with time will be assessed by adding a treatment x time interaction to the model and comparing models using a likelihood ratio test. Deaths will be accounted for by modelling HRQoL and survival jointly. Model fit will be

assessed and alternative models and / or transformations (e.g. to induce normality) will be explored where appropriate.

Reasons for non-completion of any assessment will be recorded and coded. Missing items or errors on questionnaire measures will be dealt with according to the scoring manuals or via imputation methods. Compliance rates will be reported in results, including the numbers of patients who have withdrawn from the study, have been lost to follow up or died. Causes of death for trial participants will be recorded.

The cost and quality of life data for each trial arm and the difference between the arms will be reported. The average cost and outcome on a per patient basis to produce incremental cost-effectiveness ratios for the two arms, producing an incremental cost per QALY [32] will be reported.
Frequencies of adverse events will be described. Treatment differences will be reported with 95% confidence intervals. In this study of 498 patients we are underpowered to detect differences in survival of less than approximately 20% at 2 years. However, survival rates and 95% confidence intervals will be reported.

6.1.2 Analysis of the molecular residual disease sub-study

The proportion of participants with detectable ctDNA at 5 weeks will be described with a 95% confidence interval. Proportional hazards regression will be used to explore the association between a positive blood test result and clinical disease recurrence and/or all-cause mortality (presumed to be, in most cases, cancer-related death). The analyses will be adjusted for pathologic stage and treatment allocation and stratified by centre. The sensitivity, specificity, positive and negative predictive values, of the test will be described, with 95% confidence intervals. Sensitivity/specificity > 90% will be considered excellent, 80-89% good, 70-79% moderate and < 70% poor.

The following will also be described:

(a) Time between positive test result post-surgery and clinical recurrence
(b) Association between ctDNA mutations present at baseline and 5 weeks
(c) Proportion of participants with drug treatable mutations

6.1.3 Analysis of qualitative data

Data analysis in the QRI will involve transcribing the audio-recorded consultations, interviews and meetings with consent. The QRI researcher will a) analyse the transcripts and notes thematically using techniques of constant comparison and case study approaches to explore how information about both procedures is communicated and received, and b) employ targeted conversation analysis to focus on areas in the consultations where communication appears to struggle or break down to identify aspects of recruitment that could be improved. Anonymised findings will be documented and synthesised for presentation to the RCT CI.

6.2 Subgroup analyses

One subgroup analysis is planned, comparing pain scores by type of analgesia (paravertable block vs. intercostal block). This will be tested by adding an analgesia x treatment interaction term to the model.

In addition, as an exploratory analysis we will examine pain scores within the VATS group by number of port sites (single vs multiple port sites), and compare pain scores between the VATS single port site, VATS multiple port site and open surgery groups, accounting for the structure of the data (i.e. nesting of patients by surgeon and centre).

6.3 Frequency of analyses

6.3.1 Main RCT

The trials primary analysis will take place when follow-up is complete for all recruited participants. Interim analysis will be decided in discussion with the DSMC. There is no intention to compare any outcomes between groups after phase 1; the only analyses will be descriptive statistics to summarise recruitment to decide whether the trial satisfies the progression criteria.

6.3.2 *Molecular residual disease sub-study*

The primary sub-study exploratory analyses will take place when follow-up for all participants recruited to the sub-study is complete. Descriptive analyses will be carried out at intervals during follow-up to be agreed with the funder, Guardant Health, defined by number of patients identified with recurrent disease.

6.4 Criteria for the termination of the trial

6.4.1 Progression criteria

The trial will continue into phase 2 if it is possible to demonstrate that, after 18 months of recruitment to phase 1, sufficient numbers of patients referred for a lobectomy are eligible for the trial and can be enrolled to complete the main trial in 45 months.

Specifically:

(a) at least 60% of patients undergoing lobectomy are considered eligible for the trial (if necessary, by revising the eligibility criteria);
(b) at least 50% consent to randomisation after 6 months of recruitment;
(c) less than 5% fail to receive their allocated treatment;
(d) less than 5% are lost to follow up, excluding deaths ;

The trial may also be stopped early on the advice of the DMSC (see section 7.3) or if the results of another study supersede the necessity for completion of this study.

6.5 Economic issues

The economic evaluation will compare the costs and effects of VATS lobectomy versus open surgery for treating of lung cancer and will follow established guidelines as set out by NICE [33].The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs) [34] estimated using the EuroQol EQ-5D 5L, which will be administered at baseline and then at 2 weeks, 5 weeks, 3 months, 6 months and 12 months post randomisation. Participants will be given the option to complete and return paper questionnaires or complete forms online via the study website. Resource use data will be collected on the two alternative surgery methods, length of stay and any post-operative complications such as bleeding, pneumonia and acute coronary events by adding questions to the trial CRFs. Unit costs will be derived from nationally published sources and Trust finances and attached to the resource use data.

7. Trial management

The trial will be managed by the Clinical Trials and Evaluation Unit (CTEU Bristol) of the Bristol Heart Institute. The CTEU Bristol is an UK Clinical Research Collaboration registered Clinical Trials Unit. The CTEU Bristol will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

The CI, CTEU and project sponsor will ensure that the trial runs according to the pre-agreed timetable, recruitment targets are met, the case report forms (CRFs) are completed accurately, compliance with relevant ethical and other regulatory standards, and that all aspects of the study are performed to the highest quality. The CTEU will also assist in the training of investigators at the start-up of the study and in performing monitoring during the study. The sponsor will help to manage and implement the Agreements with the study sites and to ensure R&D approvals are obtained. The Trial manager will be the contact point to provide support and guidance to the participating centres throughout the study.

7.1 Day-to-day management

The trial will be managed by the Trial Management Group, which will meet either in person or by teleconference. The TMG will be chaired by the Chief Investigator and will include all members of the named research team (see Chief Investigators & Research team contact details).

7.2 Monitoring of sites

7.2.1 Initiation visit

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

7.2.2 Site monitoring

The trial coordinating centre (CTEU Bristol) will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures described in section 5.5.

7.3 Trial Steering Committee and Data Monitoring and Safety Committee

7.3.1 Trial Steering Committee

An independent Trial Steering Committee (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 course of the study.

7.3.2 Data Monitoring and Safety Committee

An independent DMSC will be established to review safety data during the course of the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The first DMSC meeting will be held early in the trial and they will meet regularly thereafter (at intervals to be agreed with the Committee). Statistical stopping rules for the trial will be discussed at the first DMSC meeting, and decisions documented in the DMSC Charter.

8. Safety reporting

8.1 Safety Reporting Procedures

Serious and other adverse events will be recorded and reported in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines. Adverse Events (AEs) will be graded in severity in accordance with the Common Terminology Criteria for Adverse Events v5.0 (CTCAE), which is a set of criteria for the standardized classification of adverse events in cancer studies. The safety reporting responsibilities of the CTEU (coordinating centre) and participating sites are identified below.

For patients participating in the sub-study key, no safety reporting will occur as there is only a small risk associated with taking blood samples and it is a routine procedure. The small risk to patients will be that taking blood samples can sometimes cause discomfort and bruising. Adverse events will be collected during the hospital stay for descriptive purposes only and these events will not be reported as safety events. After discharge details of disease recurrence and/or death only will be collected for the 5 year follow-up period.

8.2 Safety Reporting Roles & Responsibilities

8.2.1 CTEU Responsibilities

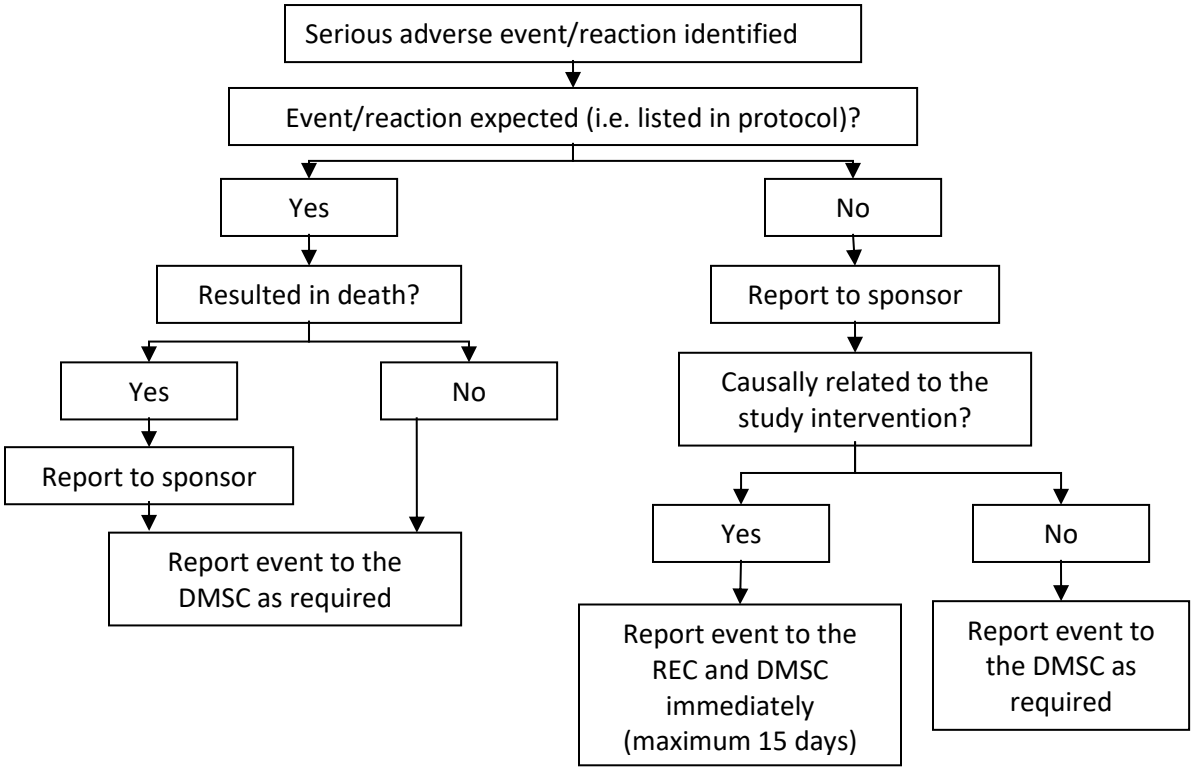
The sponsor (Royal Brompton & Harefield NHS Foundation Trust) have endorsed the Research Related Adverse Event Reporting Policy (see Figure 5) of the coordinating centre (CTEU Bristol). The CTEU will report SUSARs to regulatory authorities and copy all reports to the sponsor. CTEU Bristol will also report all fatal and 'unexpected' non-fatal SAEs experienced by patients participating in the RCT to the trial sponsor. Data on all expected and unexpected SAEs collected during the first twelve months of the main trial will also be reported regularly to the trial DMSC for review (see Figure 5).

Note: Elective surgery/interventions/treatments during the follow-up period that were planned prior to recruitment to the trial will not be reported as unexpected SAEs.

8.2.2 Participating site responsibilities

Participating centres should identify any adverse events which meet the criteria for serious, these events should then be checked against the list of expected AE's identified in section 8.3. Participating centres are only required to report fatal and unexpected non-fatal SAEs experienced by patients participating in the RCT (i.e. up to the 12 month follow-up) to the CTEU. Details of these events should be sent to the CTEU within 24 hours of becoming aware of the event. Events classified as non-serious or serious but expected will be recorded on the trial CRFs.

Figure 5 Serious adverse event reporting flow chart for the coordinating centre (CTEU, Bristol)



8.3 Expected adverse events

Data on adverse events will be collected from the time of consent (to the RCT of VATS vs open surgery) until 1 year post-randomisation. As lung resection via open surgery or VATS is a significant surgical intervention, some adverse events are considered as 'expected'. Adverse events experienced from the time of surgery until discharge from hospital (after surgery), and which are considered as expected, are identified in section 8.3.1. Adverse events experienced from post-operative discharge until the end of study involvement (after the 12 month follow-up visit), and considered as expected, are identified in section 8.3.2.

It is also anticipated that a significant proportion of the VIOLET patient population will go on to have adjuvant (post-operative) chemotherapy or radiotherapy after their resection. Such treatments are commonly associated with serious side effects and toxicities. To this end, a list of adverse events that are considered 'expected' for patients undergoing chemotherapy and radiotherapy, have been identified in section 8.3.3.

8.3.1 Adverse events considered as 'expected' <u>from the time of surgery to post-operative discharge</u>

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:

- Serious arrhythmia (defined by the requirement of intervention)
- Myocardial infarction (defined by elevated Troponin)
- Bleeding (in or around the operation site)
- Blood clots
- Haematoma

Thromboembolic complications:

- Deep vein thrombosis
- Pulmonary embolus
- Venous thromboembolism (VTE)

GI complications, including:

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

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
- Conversion from VATS to open surgery, for any reason
- Open & close thoracotomy in the event of inoperable lung cancer or extensive malignancy
- Laryngeal nerve damage
- Bronchoscopy for any cause

In hospital death due to any cause (fatal event – complete SAE)

8.3.2 Adverse events considered as 'expected' during trial follow-up

Disease specific complications:
- Disease recurrent; includes local, regional and distant recurrence
- New primary and secondary cancers
- Death due to disease progression (fatal event – complete SAE form)

Procedural complications:
Pulmonary:
- Atelectasis/ Pulmonary collapse
- Pneumonia / Chest Infection (defined by the administration of antibiotics)
- Empyema (defined as the requirement for antibiotics or drainage)
- Bronchopleural fistula
- Pleural Effusion
- Prolonged air leak (defined as ≥ 7 days) or other 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)

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

Renal complications:
- New haemofiltration/dialysis

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

Neurological complications:
- Transient ischaemic attack
- Stroke

Cardiovascular:
- Bleeding (in or around the operation site)
- Haematoma

Other:
- Re-operation for any reason (other than recurrence or progression)
- Wound dehiscence requiring treatment
- Bronchoscopy for any cause

8.3.3 Adverse events considered as 'expected' for patients undergoing adjuvant (post-operative) chemo- and radiotherapy

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

Gastrointestinal complications
- Nausea
- Vomiting
- Diarrhoea

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

Immune system complications
- Anaphylaxis / Hypersensitivity reaction

Muscular complications
- Arthralgia

- Constipation

Infectious complications

- Infections (see 8.3.2)
- Myalgia

Abnormal laboratory results

- Leukopenia
- Elevated AST / ALTs
- Elevated alkaline phosphatase

Note: Elective surgery or treatments during the follow-up period that were planned prior to recruitment to the trial will not be reported as an unexpected SAE.

8.4 Period for recording serious adverse events

Data on adverse events will be collected from the time of surgery for the duration of the trial participant's post-operative hospital stay and for the 12 month follow-up period.

9. Ethical considerations

9.1 Review by an NHS Research Ethics Committee

The trial will comply with the Declaration of Helsinki (http://www.wma.net/) on research involving human subjects. The study protocol, PILs and consent forms will be submitted to the UK Research Ethics Committee (REC) for approval and subsequently to the Research and Development (R&D) departments of the sponsor and then each participating centre for site-specific approval. The study will be conducted in accordance with the Data Protection Act and the Research Governance Framework. Ethics review of the protocol for the trial and other trial related essential documents (e.g. PILs and consent forms) will be carried out by a UK Research Ethics Committee (REC).

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

9.2 Patient & Public Involvement

The Royal Brompton Hospital Cancer Consortia PPI group were involved from inception and advised on trial design and identification of the choice and timing of the primary outcome, and secondary outcomes that were considered to be important. They were consulted between August 2012 and September 2013. The aim of PPI involvement in VIOLET is to advise on patient orientated outcomes that matter. The group consists of four patients who have undergone surgery for cancer and one carer. Dr Hall, who is a patient, and a general practitioner by profession, has agreed to sit on the TSC.

The PPI group will also be involved in the screening the PILs and dissemination of the results of the study.

9.3 Risks and anticipated benefits

9.3.1 Surgical Interventions

There should be no additional risk to participants when taking part in this study as neither lobectomy via VATS nor open surgery are new or experimental. However, at present there is a lack of well-designed empirical evidence to suggest that one surgical technique 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.

The main participant benefit is the hypothesised improvement in post-operative physical function in the VATS group. However, this potential benefit may be mitigated by the possibility that open surgery may be required for those allocated to the VATS group in the event of operative complications.

Potential risks and adverse events for the two surgical interventions are identified in section 8.1.

9.3.2 Radiation Exposure

Patients recruited to the RCT will have a CT scan of the chest and abdomen to ascertain disease status at one year post-randomisation. This CT scan will involve the use of radiation in the form of x-rays. The dose of radiation to which the patient will be exposed will equate to approximately 5 years of natural background radiation, which will increase the patient's lifetime risk of cancer by approximately 0.1%. However, it is important to note that this assessment (12 months post-randomisation) is considered part of standard care at participating centres and therefore the radiation exposure does not constitute a burden upon the participant, above that of routine care.

Furthermore, any CT and / or PET-CT scans performed at baseline will be in accordance with the standard practice at participating sites to assist with pre-surgical planning and disease staging. Such scans do not constitute procedures specific to this study protocol.

9.4 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL and will be discussed with potential participants during their consultation.

9.5 Obtaining informed consent from participants

Trained staff at participating centres will be responsible for identifying eligible patients and obtaining written informed consent. Informed consent will be obtained by a research team member and/or a nominated deputy as recorded on Delegation of Responsibilities Log. All individuals taking informed consent will have received GCP training. Potential study subjects will be fully apprised of potential risks and benefits of study participation and will be provided with detailed study information at least twenty four hours prior to written informed consent being sought. Consent will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, and be given a second consultation appointment if they wish to consider and discuss again. Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has

fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group.

The individual taking consent will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. A copy of the signed Informed Consent Form along with a copy of the most recent approved PIL will be given to the study participant. The original signed consent form will be retained at the study site and a third copy will be placed in the patient's medical notes.

9.6 Co-enrolment

Patients who consent to participate in the VIOLET study will be unable to participate in another interventional study unless agreed by the trial manager/ CI prior to enrolment. Patients already enrolled on another interventional study prior to being approached for VIOLET will be ineligible; this will be documented on the trial screening log. Co-enrolment in a concurrent observational study is not precluded and will be considered on a case-by-case basis by the trial manager / CI.

10. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care
- European Union Directive 2001/20/EC on clinical trials (if a drug study)

10.1 Sponsor approval

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

10.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the trial. Furthermore, any amendments to the trial documents approved the REC will be submitted to the Trust for information or approval as required.

10.3 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 participants. Investigators will be required to ensure compliance to the protocol and with the study manual. Investigators must also ensure that trial CRFs are completed accurately and promptly. Furthermore, 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 CTEU Bristol or any regulatory authorities.

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

10.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the CTEU Bristol.

10.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial 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 trial. 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.

10.6 Clinical Trial Authorisation

Neither surgical intervention (VATS or open surgery) are classed as investigational medicinal products; therefore a Clinical Trial Authorisation from the MHRA is not required.

11. Data protection and participant confidentiality

11.1 Data protection

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

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will be entered into a purpose-designed SQL server database. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to VIOLET study staff. Information capable of identifying participants will not be removed from the CTEU or clinical centres or made available in any form to those outside the study. Access to the database will be via a secure password-protected web-interface (NHS clinical portal). Study data transferred electronically between the University of Bristol and the NHS will only be transferred via a secure NHSnet network in an encrypted form.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

11.2.2 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 trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial in accordance to CTEU policy. In compliance with the MRC Policy on Data Sharing, relevant 'meta'-data about the trial 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, but will not be shared with a third party.

11.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, 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 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 pre-specified 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 made available 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. These identifiers will not be shared with a third party.

12. Dissemination of findings

A full report will be written for the HTA and the findings will be written-up as methodology papers for conference presentation, and publication in peer-reviewed journals. Many aspects of the feasibility work will inform surgical RCTs in general and these will be reported at methodology meetings. We will also link with lung cancer clinical studies groups. Social media will be used to disseminate and publicise the trial via a website, facebook and twitter streams. The PPI group that work with the Respiratory Biomedical Research Unit at the Brompton Hospital will help identify how we can best publicise the findings.

Expected outputs include publication of the results of the RCT informing clinicians and patients on the comparative outcome of patients undergoing VATS versus open surgery for lung cancer. Publicity will be generated for surgical research in the UK. Through qualitative assessment and feedback, surgeons participating in the trial will gain education, training and experience in communicating on the subject of

clinical trials participation with patients. This cohort of trained clinical trials "ready" surgeons, should set the foundation for future thoracic surgery trials in the UK. Patients will become more aware of the surgical options which will encourage surgeons to adopt new practices. The health economic analyses will inform NHS tariffs, and if results are favourable, the results of the study could be used to support the request for support for surgeon training and development of national registry to monitor outcomes. The results of the trial will inform national and international guidelines on surgery for lung cancer because they will be sent to the key group and presented at meetings and Lim will represent academic thoracic surgery in these settings.

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14. 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 (NA if non-substantial)
REC: Substantial amendment 1 (AM01)	V1.0	13/11/2014	V2.0	04/06/2015	○ Removal of the resource use questionnaires ○ Additional 'expected' adverse events for patients who undergo neoadjuvant chemo- & radiotherapy ○ CT chest/abdo/pelvis amended to CT chest / abdo	07/07/2015
REC: Minor Amendment (AM02)	N/A	N/A	N/A	N/A	○ No change to protocol. AM02 is a minor amendment to patient questionnaires	N/A
REC: Substantial amendment 2 (AMO3)	V2.0	08/06/2015	V3.0	08/10/2015	○ Removal of reference to RECIST criteria for disease assessment ○ Addition of PIC sites ○ Addition of pain scores to the table of assessments	19/10/2015
HRA: Substantial amendment 3 (AM04)	V3.0	08/10/2015	V4.0	03/04/2017	○ Inclusion criteria amended to reflect the inclusion of patients undergoing bi-lobectomy and the transition to TNM 8 ○ Clarification that events planned before surgery are not unexpected ○ Recruitment table 3 updated with details of phase 2 sites	06/06/2017
HRA:	V4.0	03/04/2017	V5.0	13/02/2018	○ Added molecular residual disease sub-study	07/06/2018

Substantial amendment 5 (AM05)					○ Removed scanning of documents as part of the archiving process as this is no longer CTEU practiceClarified 'bleeding' area in expected AE during trial follow up ○ Clarification of patient questionnaire completion ○ Change of PI at UCLH	
HRA Substantial amendment 6 (AM06)	V5.0	13/02/2018	V6.0	04/01/2019	○ CTCAE grade changed to v5.0 ○ New substudy documents: Letter to practice manager, letter to healthcare professional included in blood pack.	21/01/2019
HRA Substantial amendment 7 (AM07)	V6.0	04/01/2019	V7.0	26/03/2019	○ Added option for patients to be recruited to the sub-study after recruitment to the main trial ends. ○ Added inclusion/exclusion criteria for the sub-study. ○ Follow up samples will not be sought for sub-study patients who do not provide a 5 week blood sample or for participants who develop a second malignancy (non-lung cancer). ○ Participants will be able to have either hospital or GP based follow-up for the sub-study. ○ Sample size for sub-study increased based on predicted loss to follow up. ○ Data collection for sub-study clarified. ○ Pain score added as secondary outcome as previously missed. ○ Clarified exploratory analysis of pain scores	17/04/2019

					○ Patient documents amended in line with continuation of sub-study.	
HRA Non-Substantial amendment (AM08)	V7.0	26/03/2019	V8.0	03/10/2019	○ Clarified sub-study recruitment pre – and post-main study end. ○ Removed HRQoL and 12 month CT scan from sub-study only data collection. ○ Clarified follow up for patients with recurrence, new cancer and benign patients in sub-study. ○ Corrected reference 14.	04/12/2019
HRA Substantial amendment (AM12)	V8.0	03/10/2019	V9.0	13/01/2021	○ Clarified end of study definition	03/02/2021