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# BMJ Open

## Study Protocol for Video assisted thoracoscopic lobectomy versus conventional Open LobEctomy for lung cancer, a UK multi-centre randomised controlled trial with an internal pilot (The VIOLET study)

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3 **Study Protocol for Video assisted thoracoscopic lobectomy versus**  
4 **conventional Open LobEcTomy for lung cancer, a UK multi-centre randomised**  
5 **controlled trial with an internal pilot (The VIOLET study)**  
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19 open surgery; video assisted; lung cancer; lobectomy.

## ABSTRACT

**Introduction:** Lung cancer is a leading cause of cancer deaths worldwide and surgery remains the main treatment for early stage disease. Prior to the introduction of video-assisted thoracoscopic surgery (VATS), lung resection for cancer was undertaken through an open thoracotomy. To date the evidence base supporting the different surgical approaches is based on non-randomised studies, small randomised trials and is focused mainly on short term in- hospital outcomes.

**Methods and analysis:** The VIOLET study is a UK multicentre parallel group randomised controlled trial (RCT) with blinding of outcome assessors and participants (to hospital discharge) comparing the effectiveness, cost-effectiveness and acceptability of VATS lobectomy versus open lobectomy for treatment of lung cancer. We will test the hypothesis that VATS lobectomy is superior to open lobectomy with respect to self-reported physical function five weeks after randomisation (approximately one month after surgery). Secondary outcomes include 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), overall survival, and health related quality of life to 1-year. The QuinteT Recruitment Intervention is integrated into the trial to optimise recruitment.

**Ethics and dissemination:** This trial has been approved by the UK (Dulwich) National Research Ethics Service Committee London. 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. The patient and public involvement (PPI) group that works with the Respiratory Biomedical Research Unit at the Brompton Hospital will help identify how we can best publicise the findings.

**Trial registration:** VIOLET is registered at ISRCTN13472721 (doi 10.1186/ISRCTN13472721)

## Article Summary

### Strengths and limitations of this study

- First multicentre randomised trial on this topic
- All surgeons carry out both interventions; the randomisation scheme ensures surgeon balance across the groups to minimise performance bias
- Masking of the incision and evaluation of the success of blinding
- Procedures reflective of UK practice (majority are postero-lateral thoracotomy)
- Surgeon crossovers (i.e. surgeon changes after randomisation) can occur in centres with pooled service provision

## INTRODUCTION

### Background and objectives

Lung cancer is a leading cause of cancer death worldwide and survival in the United Kingdom (UK) remains amongst the lowest in Europe. Surgery, conventionally undertaken through an open thoracotomy for lung resection, remains the treatment for early stage disease. Since the introduction of minimal access video-assisted thoracoscopic surgery (VATS) techniques, lung cancer resection undertaken through a VATS approach increased from 14% in 2010 to 40% in 2014 in the UK.(1)

Much of the evidence generated to date is based on non-randomised studies(2, 3) or small randomised trials focusing on short term (in-hospital) outcomes(4), that are underpowered to detect differences in longer term outcomes such as survival(5) or have focused solely on operative technique.(6) Currently, the most well-designed randomised controlled trial (RCT) has reported shorter hospital stay and less pain in patients randomised to VATS lobectomy.(7) In this study, all patients received epidural anaesthesia and anterior thoracotomy for open surgery, which is not the current practice for most thoracic surgery centres in the UK.

A well designed and conducted RCT comparing the effectiveness and cost-effectiveness of minimal access and open surgery is needed to inform current UK (NHS) practice, health policy and individual surgeon and patient decision-making.

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3 The VIOLET study is a UK multicentre pragmatic RCT comparing the effectiveness,  
4 cost-effectiveness and acceptability of VATS lobectomy versus open lobectomy for  
5 treatment of lung cancer.  
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## 10 **Aims and objectives**

11  
12 The VIOLET study will test the hypothesis that VATS lobectomy is superior to open  
13 lobectomy with respect to self-reported physical function five weeks after  
14 randomisation (approximately one month after surgery).  
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19 Specific objectives are to estimate:

- 20  
21 A. The difference between groups in the average self-reported physical function at  
22 five weeks.  
23  
24 B. The difference between groups with respect to a range of secondary outcomes  
25 including assessment of efficacy (hospital stay, pain, proportion and time to uptake  
26 of chemotherapy), measures of safety (adverse health events), oncological  
27 outcomes (proportion of patients upstaged to pN2 disease and disease-free survival)  
28 and overall survival.  
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30 C. The cost effectiveness of VATS lobectomy compared to open lobectomy.  
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## 38 **METHODS**

### 39 **Trial design**

40  
41 A UK-based multicentre parallel group RCT with blinding of outcome assessors and  
42 participants until hospital discharge after surgery. Figures 1 and 2 show the expected  
43 patient pathway for both phases of recruitment to the VIOLET study.  
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49 *Phase 1:* The first phase with an integrated qualitative component is necessary to  
50 establish the processes for recruitment and consent. This phase is also essential to  
51 develop a study manual and a measure of surgical expertise to proceed to phase 2.  
52 Phase 1 will be conducted in five centres; Royal Brompton Hospital in London, The  
53 University Hospitals Bristol in Bristol, Liverpool Heart and Chest Hospital in  
54 Liverpool, The James Cook University Hospital in Middlesbrough and Harefield  
55 Hospital in Harefield. These centres are well spread geographically and represent a  
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3 mix of university and NHS trusts that are representative of NHS practice.  
4 Progression from pilot to the full trial will be dependent on pre-agreed progression  
5 criteria (assessed after 18 months of recruitment):  
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10 Specifically:

- 11 (a) at least 60% of patients undergoing lobectomy are considered eligible for the  
12 trial (if necessary, by revising the eligibility criteria);  
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14 (b) at least 50% consent to randomisation after 6 months of recruitment;  
15  
16 (c) less than 5% fail to receive their allocated treatment;  
17  
18 (d) less than 5% lost to follow up, excluding deaths;  
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22 *Phase 2:* This phase will extend the study to up to a further five centres. All centres  
23 will use the optimum methods of recruitment established in phase 1 and will follow-  
24 up all participants to one year.  
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### 30 **Study population**

31 Participating *centres* will only be eligible if they meet all the following eligibility  
32 criteria: 1. NHS Trust with an established and accredited lung cancer multi-  
33 disciplinary team (MDT); 2. Centre carries out  $\geq 40$  VATS lobectomies each year and  
34 employs at least one surgeon who has carried out  $\geq 50$  VATS lobectomies.  
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40 Participating *surgeons* will be eligible for the trial if they have performed  $\geq 50$  VATS  
41 lobectomies. Prospective surgeons will be required to submit their activity logs,  
42 which will be validated against local audit data from the MDT meetings, prior to  
43 acceptance to the trial. Lobectomy via open surgery is currently standard procedure  
44 and therefore surgical ability and competence will be assured by Specialist GMC  
45 registration.  
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52 *Patients* may enter the study if all the following apply:

- 53 1. Adult aged  $\geq 16$  years of age  
54  
55 2. Able to give written informed consent, undergoing either  
56  
57 i. Lobectomy or bilobectomy for treatment of known or suspected primary lung  
58 cancer beyond lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent  
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3 to TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-  
4 1 and M0 or

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6 ii. Undergoing frozen section biopsy with the intention to proceed with  
7 lobectomy or bilobectomy if primary lung cancer with a peripheral tumour  
8 beyond a lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent to  
9 TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-1  
10 and M0 is confirmed  
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15 3. Disease suitable for both minimal access (VATS lobectomy) and lobectomy via  
16 open surgery

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18 \*In the case of bilobectomy, the distance for the “lobar” orifice is in reference to the  
19 bronchus intermedius  
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24 *Patients* may not enter the study if any of the following apply:

- 25 1. Previous malignancy that influences life expectancy
- 26 2. Pneumonectomy, segmentectomy or non-anatomic resection (e.g. wedge  
27 resection) is planned
- 28 3. Patient has a serious concomitant disorder that would compromise patient safety  
29 during surgery
- 30 4. Planned robotic surgery.  
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### 38 **Randomisation**

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40 Participants will be randomised in a 1:1 ratio to either VATS lobectomy or open  
41 lobectomy. Randomisation will take place through a secure internet-based  
42 randomisation system, access to which will be restricted to authorised study  
43 personnel. Cohort minimisation (with a random element incorporated) will be used to  
44 ensure balance across groups with respect to the surgeon and the allocation will be  
45 stratified by centre.  
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52 Due to the pragmatic nature of this trial there will inevitably be some variability  
53 between surgeons, the surgical teams and the perioperative processes. Such  
54 heterogeneity is important as this accurately reflects real clinical practice.  
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3 Randomisation will be performed one week prior to the planned operation date, once  
4 eligibility has been confirmed and written consent taken by a research nurse. This  
5 will allow sufficient time for operating theatre schedules to be arranged. If there is a  
6 change in surgeon after randomisation, the analysis will account for the surgeon  
7 responsible for performing the operation and not the surgeon originally allocated to  
8 the patient.  
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### 15 16 **Trial interventions**

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18 All operations will be undertaken with general anaesthesia and with the patient in the  
19 lateral decubitus position.  
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23 VATS lobectomy is undertaken through one to four keyhole incisions without rib  
24 spreading. The use of 'rib spreading' is prohibited as this is the key intra-operative  
25 manoeuvre which disrupts tissues and causes pain (and is used in open surgery).  
26 The procedure is performed with videoscopic visualisation without direct vision. The  
27 hilar structures are dissected, stapled and divided. Endoscopic ligation of pulmonary  
28 arterial branches may be performed. The fissure is completed and the lobe of lung  
29 resected. The incisions are closed in layers and may involve muscle, fat and skin  
30 layers. This definition of VATS lobectomy is a modification of Cancer and Leukaemia  
31 Group B (CALGB) 39802.(8)  
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40 Conventional open lobectomy is undertaken through a single incision with or without  
41 rib resection and with rib spreading. The operation is performed under direct vision  
42 with isolation of the hilar structures (vein, artery and bronchus) which are dissected,  
43 ligated and divided in sequence and the lobe of lung resected. The procedures may  
44 be undertaken using ligatures, over sewing or with staplers. The thoracotomy is  
45 closed in layers starting from pericostal sutures over the ribs, muscle, fat and skin  
46 layers.  
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54 In both groups, lymph node management is undertaken in accordance with the  
55 International Association of the Study of Lung Cancer (IASLC) recommendations  
56 where a minimum of six nodes / stations are removed, of which three are from the  
57 mediastinum that includes the subcarinal station.(9)  
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5 Because this is a pragmatic trial, adaptations and variation in both procedures (with  
6 the exception of the mandated elements outlined above) will be permitted although  
7 intra-operative details will be collected, and compliance monitored.  
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## 10 11 12 **Primary and secondary outcomes**

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14 The primary outcome is self-reported physical function measured using the  
15 European Organization for Research and Treatment of Cancer Quality of Life  
16 Questionnaire-C30 (EORTC QLQ-C30) at 5 weeks post-randomisation. Physical  
17 function has been chosen because it is a patient-centred outcome that will reflect the  
18 anticipated earlier recovery with VATS lobectomy and has been used in other  
19 minimal access surgery trials. The primary endpoint has been chosen to be five  
20 weeks (one-month post-surgery) to capture the early benefits of minimal access  
21 surgery on recovery. Secondary outcomes have been selected to assess the efficacy  
22 of the two approaches.  
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32 Secondary outcomes are 1. Time from surgery to hospital discharge; 2. Adverse  
33 health events; 3. Proportion and time to uptake of adjuvant treatment; 4. Proportion  
34 of patients upstaged to pN2 disease after the procedure; 5. Overall and disease-free  
35 survival to one-year; 6. Proportion of patients who undergo complete resection  
36 during the procedure; 7. Proportion of patients who experience prolonged incision  
37 pain defined as the need for analgesia > 6 weeks after surgery; 8. Generic and  
38 disease-specific Health-related quality of life (HRQoL) assessed using the EORTC  
39 QLQ-C30, QLQ-LC13 and EQ-5D-5L questionnaires completed at 2 weeks, 5  
40 weeks, 3 months, 6 months and 1-year post-randomisation); 9. Resource use  
41 measured for the duration of post-operative hospital stay until discharge, and at 5  
42 weeks, 3 months, 6 months and one-year post-randomisation.  
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## 51 52 53 **Data Collection**

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55 The schedule of data collection for the study is shown in Table 1. Data will be  
56 collected on paper and then entered onto a bespoke database. Access to the  
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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 NHS.net network in an encrypted form.

**Table 1. Data collection for trial participants who agree to randomisation to VATS lobectomy or open lobectomy**

	Pre-randomisation	Post-randomisation								
	Baseline	Day of Surgery	Post-op	2 days post-op	Dis-charge	2 weeks*	5 weeks*	3 months*	6 months*	1 year*
1 Eligibility	X									
2 Imaging review (CT / PET-CT*)	X									
3 Participant characteristics	X									
4 Audio recorded consultation	X									
5 Lobectomy via VATS Lobectomy or Open Lobectomy		X								
6 Intra-operative details		X								
7 Histopathology staging		X								
8 Tumour sample for research		X								
9 Patient Questionnaires										
10 QLQ-C30	X					X	X	X	X	X
11 QLQ-LC13	X					X	X	X	X	X
12 EQ5D	X					X	X	X	X	X
13 Bang Blinding Index				X	X					
14 Pain score	X		X	X						
15 Adverse Events				X			X	X	X	X
16 Resource use	X			X			X	X	X	X
17 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

### Blinding of staff and study participants

The operating surgeon and staff responsible for the care of the participant during the operation cannot be blinded to the participants' 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

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3 performed by a member of the research team who is not responsible for the  
4 collection of follow up data for VIOLET study participants.  
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8 Furthermore, efforts will be made to minimise the risk of inadvertent unblinding of the  
9 research nurse responsible for data collection during the patient's post-operative  
10 stay. To accomplish this, large adhesive dressings will be applied to thorax. These  
11 adhesive dressings will be positioned similarly for all participants, regardless of their  
12 surgical allocation and will cover both real and potential incision/port locations. The  
13 initial adhesive dressings will be applied in the operating theatre by the operating  
14 team and these will not be changed until 3 days after surgery (or discharge if  
15 discharged before day 3), unless soiling or lack of adherence prompts their  
16 premature replacement. Three days after surgery, dressings will be changed by a  
17 nurse who is not responsible for conducting the participants' follow-up assessments.  
18 Wound cleaning will be performed on all real and potential incision/port locations to  
19 promote allocation masking.  
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30 Patients who agree to participate in the RCT will not be informed of their treatment  
31 allocation until they are discharged from hospital after their operation. In order to  
32 ensure that study patients are not unblinded during wound cleaning and dressing  
33 change, participants will be asked to turn their head away from the wound site that is  
34 being tended to. When participants are considered 'fit-for-discharge', they will be  
35 informed of their treatment allocation and advised as to how best to care for their  
36 surgical wounds.  
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45 The success of blinding will be monitored during each participant's in-hospital stay.  
46 Participants will be asked to complete the Bang-blinding Index(10) at 2 days post-  
47 operatively and at discharge, but before the treatment allocation is revealed. The  
48 research nurse responsible for data collection and follow-up of VIOLET study  
49 participants will also be asked to complete the Bang-blinding Index when the  
50 participant is ready for discharge and after the participant attends for their 5 week  
51 and 1-year follow-up appointments.  
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## Standardisation of post-operative management

As this is a pragmatic RCT, 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 minimise the potential for bias, namely pain-control and the criteria by which a participant's medical fitness-for-discharge is assessed.

Standardising the use of analgesia across participating centres is impractical and does not reflect the intended pragmatic nature of the trial, it, would also produce data unrepresentative of real clinical practice. Therefore, each participating centre will prescribe analgesia in accordance with their local protocols. All patients recruited to the RCT at that centre will be given the same analgesia regardless of their treatment allocation (i.e. VATS lobectomy or open lobectomy). Local protocols for the provision of analgesia will be defined by the local Principal Investigator (in collaboration with the local research team) prior to the start of recruitment to the RCT. Analgesia administered throughout the participant's in-hospital stay will be recorded on the trial case report forms (CRFs) and compliance with the pre-defined and centre-specific analgesia protocols will be monitored.

In order to objectively compare the time from surgery to hospital discharge between VATS lobectomy and open lobectomy, the following discharge suitability criteria have been developed. Study participants will be evaluated against these criteria to ensure that they are medically fit-for-discharge:

- Participant has achieved satisfactory mobility
- 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

Participants 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 participants are considered medically fit-

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3 for-discharge and when they are physically discharged from hospital will both be  
4 recorded on the trial CRFs.  
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### 9 **Sample size calculation**

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11 We hypothesise that self-reported physical function (scale 0 – 100, with higher  
12 scores indicating better function) five weeks after randomisation for participants  
13 undergoing a VATS lobectomy will be superior to the physical function for  
14 participants having an open lobectomy, as measured using the EORTC QLQ-C30.  
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16 The sample size has been chosen to test this hypothesis.  
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21 Although the primary endpoint is at 5 weeks post-randomisation self-reported  
22 physical function will also be assessed at other time points (baseline, 2 weeks, 3  
23 months, 6 months and 1-year). In estimating the sample size these additional  
24 measurements have been taken into account. The power calculation requires the  
25 estimation of four parameters, i.e. the effect size that would be considered clinically  
26 important, the number of pre and post-surgery measures, and the correlations  
27 between pre and post-surgery scores and between repeated post-surgery scores.  
28  
29 The effect size was chosen based on the published literature(11), which suggests  
30 that an effect size of 0.2 to 0.6 standard deviations equates to a clinically important  
31 difference in physical function score of between 5 and 14 points. In the absence of  
32 data from which to estimate the correlations between repeated measures we  
33 assumed conservative estimates (0.3 between pre and post measures, 0.6 between  
34 repeated post measures).  
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45 The study size has been set at 398; allowing for a 20% dropout at 1-year, the target  
46 sample size is 498 participants. This will provide 90% power to test the hypothesis,  
47 assuming an effect size of 0.25 standard deviations in physical function would be  
48 clinically important. The calculation based on five post-surgery measures assumes  
49 the treatment difference is similar at the five time points.  
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55 However, it is anticipated that the difference in physical function may change over  
56 time. The calculation based on a single measure shows that the study will have  
57 >80% power to detect a difference of 0.25 standard deviations and >90% power to  
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3 detect a difference of 0.3 standard deviations at the primary endpoint where dropout  
4 is expected to be less than 5%.  
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8 A study in 498 participants will also have 80% power to detect a 1-day difference in  
9 length of hospital stay (i.e. median 3 days versus 4 days, hazard ratio 1.3); assuming  
10 2% of patients do not survive to discharge.  
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## 14 15 16 **Research procedures**

17  
18 Generic and disease-specific HRQoL measures will assess the profiles of VATS and  
19 open lobectomy in the early and mid-postoperative phases. The extensively  
20 validated EQ-5D-5L will assess generic aspects of HRQoL and will be used in the  
21 economic evaluation(12, 13). The EORTC QLQ-C30 is one of the most widely used  
22 instruments for assessing HRQoL in patients with cancer and the QLQ-LC13 is the  
23 lung cancer module with 13 items that assesses lung cancer-specific symptoms.  
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30 Study participants will be asked to complete HRQoL questionnaires at baseline and  
31 post-operatively at 2 weeks, 5 weeks, 3 months, 6 months and 1-year post-  
32 randomisation. Baseline questionnaires will be administered by the research team at  
33 site, whereas the questionnaires completed post-operatively will be administered by  
34 the coordinating centre. Participants can choose to receive post-operative  
35 questionnaires by post or complete via a secure website.  
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## 43 **Patient and Public Involvement (PPI)**

44  
45 The Royal Brompton Hospital Cancer Consortia PPI group were involved from  
46 inception and advised on trial design, identification of the choice and timing of the  
47 primary outcome, and secondary outcomes that were considered to be important.  
48 They were consulted between August 2012 and September 2013. The aim of PPI  
49 involvement in VIOLET was to advise on patient-orientated outcomes that matter.  
50 The group consists of four patients who have undergone surgery for cancer and one  
51 carer. Dr Hall, who is a patient, and a general practitioner by profession, has agreed  
52 to sit on the Trial Steering Committee (TSC).  
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3 The PPI group will also be involved in reviewing the content and format of PILs and  
4 dissemination of the results of the study.  
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### 9 **Integrated QuinteT Recruitment Intervention (QRI)**

10  
11 The VIOLET study will employ an integrated QRI to optimise and sustain recruitment  
12 throughout the recruitment period. Surgical RCTs face recruitment challenges  
13 including surgeons' limited experience of RCTs, having more confidence in particular  
14 procedures and variations in individual practice(14). Furthermore, there is a dearth of  
15 robust evidence about effective strategies to improve recruitment in RCTs(15).  
16 However, qualitative research can be used to understand recruitment in specific  
17 RCTs(16-18) as well as across RCTs(19-21), and has been shown to optimise  
18 recruitment and informed consent, thereby contributing to successful recruitment and  
19 trial completion(22-34). In order to understand the recruitment process at each  
20 centre in real time and investigate the sources of recruitment difficulties, some of the  
21 key methods employed(35) will be as follows:  
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32 *Patient pathway through eligibility and recruitment:* A comprehensive process of  
33 logging potential trial patients through screening and eligibility phases will be  
34 undertaken to provide basic data about the levels of eligibility and recruitment, and  
35 identify points at which patients opt in or out of the RCT.  
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40 *Individual patient equipoise:* Individual patient equipoise will be explored using semi-  
41 structured in-depth interviews, which will explore patients views on the two  
42 procedures, the trial, the acceptability of randomisation between procedures and the  
43 factors that influence their decision to participate in the RCT or not. Interviewees will  
44 include eligible patients who accept randomisation and eligible patients who decline  
45 randomisation. This information will help to determine whether there is sufficient  
46 patient equipoise for such a study to be able to recruit in the specified time frame.  
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54 *Surgeon equipoise:* In-depth interviews will also be undertaken with surgeons to  
55 explore perceptions and experiences of undertaking both procedures, perceptions of  
56 their levels of individual equipoise and the equipoise of their colleagues, commitment  
57 to the trial, and views about the likely outcome of the trial.  
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5 *Study team:* Key members of the Trial Management Group (TMG), including the  
6 Chief Investigator (CI) and those closely involved in the design, management,  
7 leadership and coordination of the trial will be interviewed and there will be the  
8 opportunity to record discussions in the TMG about issues of preference and  
9 expertise. These interviews and recorded consultations will permit comparisons to be  
10 made to detect preferences unwittingly transmitted during recruitment consultations.  
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17 *In-depth interviews:* In-depth, semi-structured interviews will be conducted and  
18 audio-recorded with a purposive sample of staff members involved with aspects of  
19 trial design/management and recruitment across centres in phase 1 (and phase 2  
20 where necessary). Patients eligible for recruitment to the RCT may also be  
21 interviewed. Across the different groups, interviews will explore participants'  
22 perspectives of the trial, the two procedures and acceptability of randomisation  
23 between procedures. In addition, recruitment staff (primarily surgeons) interviews will  
24 explore their experiences of undertaking both procedures (where appropriate),  
25 perceptions of equipoise for themselves and their colleagues, and views on likely  
26 outcome of the trial. Interview topic guides will be used to ensure similar topic areas  
27 are covered across interviews, while still providing the scope for participants to raise  
28 issues of pertinence to them.  
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39 *Audio recording of recruitment appointments:* Face-to-face and telephone  
40 consultations of healthcare staff (thoracic surgeons, nurses etc) with potentially  
41 eligible patients will be routinely audio recorded across centres to understand the  
42 recruitment process at each centre and to identify and investigate the challenges to  
43 recruitment. The QRI researcher will listen to and qualitatively analyse the  
44 appointments, documenting instances such as unclear, insufficient or imbalanced  
45 information provision and unintentional transferring of clinician treatment preferences  
46 to patients,  
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55 An account of the anonymised findings from all the data will be fed back to the RCT  
56 CI, with a plan of action to optimise recruitment developed collaboratively with key  
57 stakeholders. The data will be used by the QRI team to provide supportive and  
58 confidential individual and group feedback to recruiters to help them to communicate  
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3 equipoise, balance treatment options and explain to patients the benefits and  
4 purposes of trial participation, whilst optimising informed consent. Feedback  
5 sessions will include comparisons between what clinicians think they say to patients  
6 (interview data) and what they actually say to patients (consultation data). Rates of  
7 recruitment of eligible patients will be closely monitored against the feedback  
8 meetings and it is expected that an improvement will be demonstrated in recruitment  
9 over time with experience and training for recruiters (as we have demonstrated is  
10 possible in other similar trials(18, 19)).  
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### 20 **Economic evaluation**

21 The economic evaluation will compare the costs and effects of VATS lobectomy  
22 versus open lobectomy, and will follow established guidelines as set out by the  
23 National Institute for Health and Care Excellence(36). The within-trial cost-  
24 effectiveness analysis will be undertaken from an NHS and personal social services  
25 perspective, with a one-year time horizon from the day of surgery. The primary  
26 outcome measure for the economic evaluation will be quality-adjusted life-years  
27 (QALYs), estimated using the EuroQol EQ-5D-5L, administered at baseline (pre-  
28 randomisation), and five time points post-randomisation (see Table 1). Resource use  
29 data collection will be integrated into the trial CRFs for the index admission for items  
30 such as duration of surgery, number of staples used, and length of stay; and  
31 captured from participants regularly during the one-year follow up (see Table 1) for  
32 events such as hospital readmissions, outpatient attendances, and GP or nurse  
33 visits in the community.  
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### 46 **Statistical analysis plan**

47 The data will be analysed on intention to treat (ITT) and follow CONSORT reporting  
48 guidelines (<http://www.consort-statement.org/>). Randomised participants who are  
49 not found to have lung cancer will be included in the primary analysis, but a modified  
50 ITT analysis excluding these participants will also be performed. Analyses will be  
51 adjusted for centre and for design factors included in the cohort minimisation (e.g.  
52 the operating surgeon). As the allocation to VATS or open lobectomy is minimised by  
53 surgeon, clustering may occur within the dataset. The structure of the data, i.e.  
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3 nesting of patients by surgeon and centre, will be accounted for in the primary  
4 analysis.  
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8 Patient reported outcome scores (HRQoL) and will be compared using a mixed  
9 regression model, adjusted for baseline measures where appropriate. Changes in  
10 treatment effect with time will be assessed by adding a treatment x time interaction  
11 to the model and comparing models using a likelihood ratio test. Deaths will be  
12 accounted for by modelling HRQoL and survival jointly. Model fit will be assessed  
13 and alternative models and / or transformations (e.g. to induce normality) will be  
14 explored where appropriate.  
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22 Missing items or errors on questionnaire measures will be dealt with according to the  
23 scoring manuals or via imputation methods. For other outcomes a complete case  
24 analysis will be undertaken if fewer than 5% of cases have missing data, otherwise  
25 multiple imputation methods will be considered. Compliance rates will be reported,  
26 including the numbers of patients who have withdrawn from the study, have been  
27 lost to follow up or died. Causes of death for trial participants will be recorded.  
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34 Frequencies of adverse events will be described. Treatment differences will be  
35 reported with 95% confidence intervals. In this study of 498 patients we are  
36 underpowered to detect differences in survival of less than approximately 20% at 2  
37 years. However, survival rates and 95% confidence intervals will be reported.  
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43 One subgroup analysis is planned, comparing pain scores by type of analgesia  
44 (paravertebral block vs. intercostal block). This will be tested by adding an analgesia  
45 by treatment interaction term to the model. In addition, as an exploratory analysis we  
46 will report pain scores within the VATS lobectomy group by number of port sites  
47 (single vs multiple port sites), but a formal comparison between the sub-sets of the  
48 VATS group is not planned.  
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55 The primary analysis will take place when follow-up is complete for all recruited  
56 participants. Interim analysis will be decided in discussion with the Data Monitoring  
57 and Safety Committee (DMSC). There is no intention to compare any outcomes  
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3 between groups after phase 1; the only analyses will be descriptive statistics to  
4 summarise recruitment to decide whether the trial satisfies the progression criteria.  
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8 *Economic Evaluation:* For the economic evaluation, unit costs will be derived from  
9 nationally published sources and attached to resource use data, and the total costs  
10 per participant calculated. Responses to the EQ-5D-5L will be assigned valuations  
11 derived from published UK population tariffs(37-39), and combined with survival to  
12 calculate QALYs gained per participant. Missing resource use and EQ-5D-5L data  
13 will be handled using multiple imputation methods(40). From the average costs and  
14 QALYs gained in each trial group, the incremental cost-effectiveness ratio will be  
15 derived, producing an incremental cost per QALY gained of VATS lobectomy  
16 compared to open lobectomy. Univariate and multivariate sensitivity analyses will  
17 assess the impact of varying key parameters in the analysis on baseline cost-  
18 effectiveness results. Results will be expressed in terms of a cost-effectiveness  
19 acceptability curve, which indicates the likelihood that VATS lobectomy is cost-  
20 effective for different levels of willingness to pay for health gain.  
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32 *Qualitative analysis:* Analysis of qualitative data will involve transcribing the audio-  
33 recorded consultations, interviews and meetings with consent. The QRI researcher  
34 will a) analyse the transcripts and notes thematically using techniques of constant  
35 comparison(41) and case study approaches to explore the 'clear obstacles' and  
36 'hidden challenges(19) to recruitment in Violet, and b) employ targeted conversation  
37 analysis(16) to focus on areas in the consultations where communication appears to  
38 struggle or break down to identify aspects of recruitment that could be improved.  
39 Subsets of interview and consultation transcripts will be independently coded by two  
40 qualitative researchers, with the coding discussed and any discrepancies resolved,  
41 to establish a coding frame that can be applied to other transcripts. Descriptive  
42 accounts will summarise key challenges to recruitment. Anonymised findings will be  
43 documented and synthesised for presentation to the RCT CI.  
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54 *Access to study data:* Access to the study data will be limited to authorised  
55 personnel. Data will be collected and retained in accordance with the UK Data  
56 Protection Act 1998. An anonymised dataset will be held for future research as per  
57 the National Institute for Health Research (NIHR) contractual arrangements.  
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## ETHICS

Research ethics approval was granted by the UK (Dulwich) National Research Ethics Service Committee London (reference 14/LO/2129) on 7 January 2015. The trial is managed by the Clinical Trials and Evaluation Unit Bristol (CTEU Bristol) and sponsored by Royal Brompton & Harefield NHS Foundation Trust. Participants have the right to withdraw at any time and if they do 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 of physical function (primary end point). Participants who choose to withdraw from the study will be treated according to their hospitals' standard procedures.

### Changes to the protocol since it was first approved

The number of VATS lobectomies performed for surgeons to be eligible to participate in the VIOLET study was reduced from >50 to >40 to allow more surgeons to participate as there was no evidence to suggest a material difference in outcome. Version 5.0 (dated 13/02/2018) of the protocol is currently in use.

Trial entry criteria by stage were amended following the introduction of the 8<sup>th</sup> edition of the TNM grading to:

- 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.

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

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3 The protocol was amended so that the research nurse at the site could obtain  
4 questionnaire data during a study visit or telephone call, for those participants who  
5 do not return their questionnaire. The relevant regulatory approvals were obtained  
6 for amendments to the protocol. Relevant parties (e.g. investigators, trial  
7 participants) were informed.  
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### 14 **Study status**

15  
16 The actual numbers recruited at 18 months were 160 randomised participants and  
17 having received Trial Steering Committee and Funder approval, phase 2 is ongoing  
18 and the study is actively recruiting in eight centres. The centres opened in Phase 2  
19 are Heartlands Hospital in Birmingham, John Radcliffe Hospital in Oxford and Castle  
20 Hill Hospital in Hull.  
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24 The full protocol is available from:

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26 <https://www.journalslibrary.nihr.ac.uk/programmes/hta/130403/>  
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### 31 **AUTHOR CONTRIBUTIONS**

32  
33 EL: Study design, preparation and drafting of protocol and manuscript, Chief  
34 Investigator for the trial

35  
36 CAR: Study design, sample size and statistical analysis plan, drafting of protocol and  
37 manuscript  
38

39  
40 JB: Study design, preparation of study protocol and review of manuscript

41  
42 SP, ARR & DE: Design of integrated qualitative study, preparation of study protocol,  
43 review of manuscript  
44

45  
46 ES & SW: Study design, preparation of study protocol, design of health economic  
47 component, review of manuscript  
48

49  
50 TB: Study design, preparation of protocol and review of manuscript

51  
52 MS: Study design, preparation of protocol and review of manuscript

53  
54 JD: Preparation of protocol and review of manuscript

55  
56 NMcG: Preparation of protocol and review of manuscript

57  
58 TBr,DP, LD, HM & CB: Preparation of study protocol.

59  
60 RH: Statistical analysis plan, review of manuscript.

All authors read and approved the final manuscript.



## DECLARATION OF INTERESTS

EL reports personal fees from Ethicon (Johnson and Johnson), Covidien (Medtronic). There are no other competing interests from the authors.

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CR was supported by the British Heart Foundation (BHF) until April 2016.

This study was designed and delivered in collaboration with the Clinical Trials and Evaluation Unit (CTEU), a UKCRC registered clinical trials unit which, as part of the Bristol Trials Centre, is in receipt of NIHR Clinical Trials Unit (CTU) support funding.

The NIHR, MRC and BHF will not be involved in the study management.

## ADDITIONAL FIGURES

**Figure 1.** The trial schema showing the recruitment pathway for Phase 1 (pilot phase) of the VIOLET study

**Figure 2.** The trial schema showing the recruitment pathway for Phase 2 of the VIOLET study



## LIST OF ABBREVIATIONS

BHF	British Heart Foundation
CALGB	Cancer and Leukemia Group B
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
ConDuCT-II	Collaboration and Innovation for Difficult Trials in Invasive Procedures
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data monitoring and safety committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EQ-5D	EuroQoL-5D
GMC	General Medical Council
HRQoL	Health related quality of life
HTA	Health Technology Assessment
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
NIHR	National Institute for Health Research
PIL	Patient information leaflet
PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
QRI	QuinteT Recruitment Intervention
RCT	Randomised controlled trial
REC	Research ethics committee
TSC	Trial Steering Committee
TMG	Trial Management Group
TNM	TNM Classification of Malignant Tumours
UKCRC	The UK Clinical Research Collaboration
VATS	Video-assisted thoracoscopic surgery

## ACKNOWLEDGEMENTS

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VIOLET is supported by the UK Thoracic Surgery Research Collaborative

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12 Professor Joy Adamson

13  
14 Mr Ian Hunt

15  
16 Professor Peter Licht

17  
18 Dr Arjun Nair

19  
20 Mr Chris Hall

21  
22 Mr Mike Cowen (from study start to Jan 2017)

23  
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28 Mr Alan Kirk

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30 Professor Keith Kerr

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32 Mr Rajesh Shah

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34 Dr Nagmi Qureshi

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36 Professor Tom Treasure (Chair from study start to March 2017)

37  
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14 [guidance/eq5d5l\\_nice\\_position\\_statement.pdf](https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf).

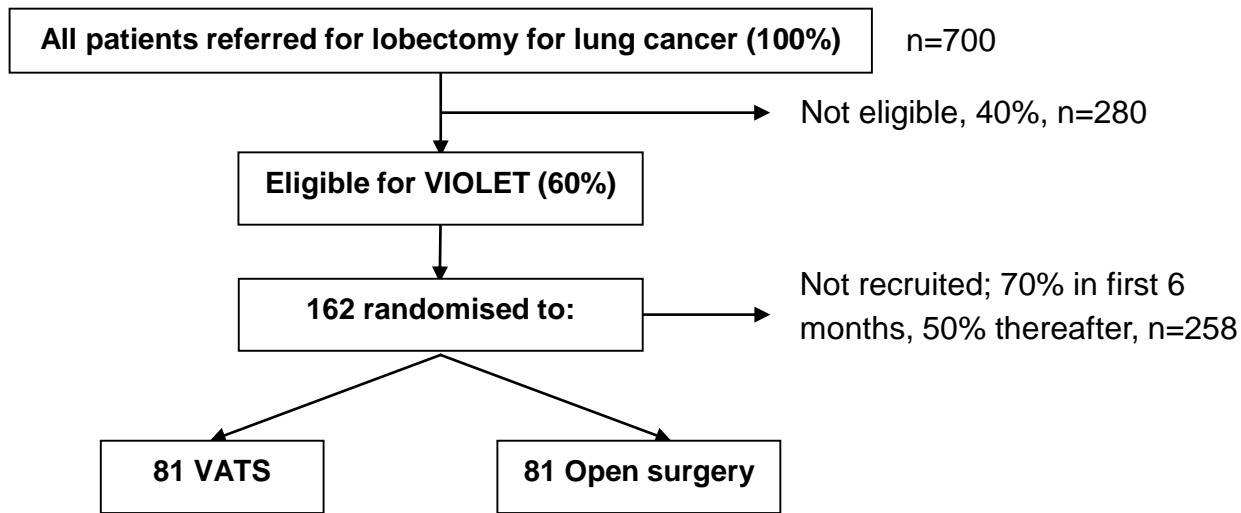
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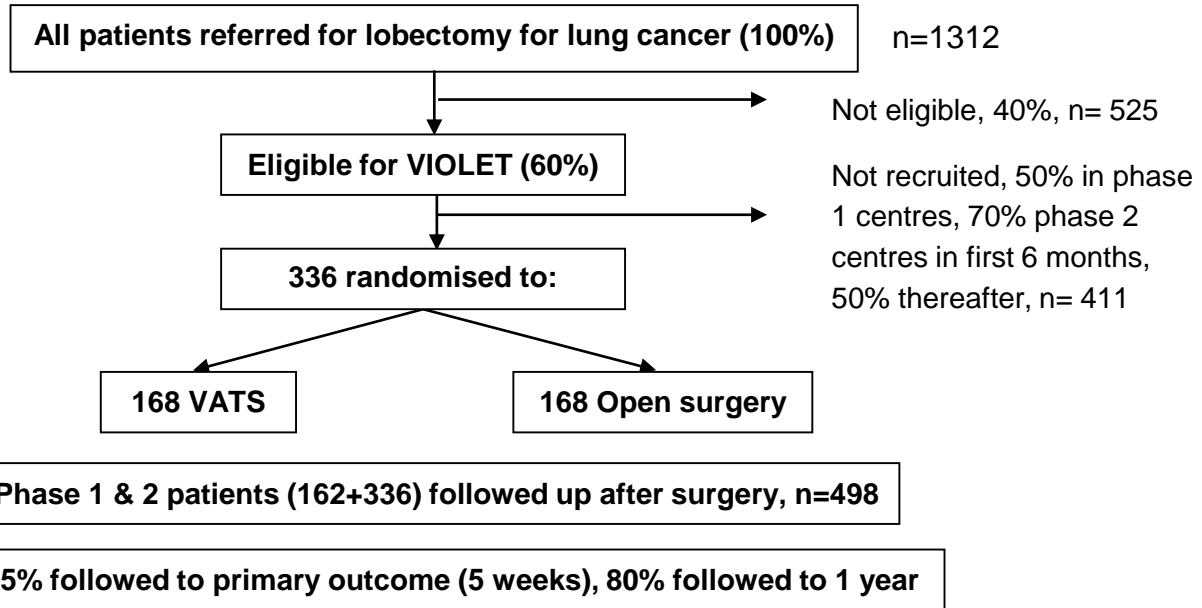
## Phase 1, in 5 centres (21 months recruitment)



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

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## Phase 2, in 9 centres (24 months recruitment)



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



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention 4, 5

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6 6b Explanation for choice of comparators 5

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8 Objectives 7 Specific objectives or hypotheses 5

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 5, 6

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained 5, 6

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) 6, 7

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 8, 9

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25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) 8-11

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 11, 12

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 8-11

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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended 9, 10

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40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) 9, 10

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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13, 14
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3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-17
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

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10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7, 8
11				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7, 8
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7, 8
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 11
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31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10, 13, 14
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-16, 20
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17, 18
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
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14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20, 21
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	3, 15
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 10
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20, 22
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 15
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
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33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
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# BMJ Open

## Study Protocol for Video assisted thoracoscopic lobectomy versus conventional Open LobEctomy for lung cancer, a UK multi-centre randomised controlled trial with an internal pilot (The VIOLET study)

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Oncology, Respiratory medicine
Keywords:	Randomised controlled trial, minimally invasive, Cardiothoracic surgery < SURGERY, open surgery, video assisted, lung cancer

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Manuscripts



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3 **Study Protocol for Video assisted thoracoscopic lobectomy versus**  
4 **conventional Open LobEcTomy for lung cancer, a UK multi-centre randomised**  
5 **controlled trial with an internal pilot (The VIOLET study)**  
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**Keywords:** Randomised controlled trial; minimally invasive; Cardiothoracic surgery; open surgery; video assisted; lung cancer; lobectomy.

## ABSTRACT

**Introduction:** Lung cancer is a leading cause of cancer deaths worldwide and surgery remains the main treatment for early stage disease. Prior to the introduction of video-assisted thoracoscopic surgery (VATS), lung resection for cancer was undertaken through an open thoracotomy. To date the evidence base supporting the different surgical approaches is based on non-randomised studies, small randomised trials and is focused mainly on short term in- hospital outcomes.

**Methods and analysis:** The VIOLET study is a UK multicentre parallel group randomised controlled trial (RCT) with blinding of outcome assessors and participants (to hospital discharge) comparing the effectiveness, cost-effectiveness and acceptability of VATS lobectomy versus open lobectomy for treatment of lung cancer. We will test the hypothesis that VATS lobectomy is superior to open lobectomy with respect to self-reported physical function five weeks after randomisation (approximately one month after surgery). Secondary outcomes include 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), overall survival, and health related quality of life to 1-year. The QuinteT Recruitment Intervention is integrated into the trial to optimise recruitment.

**Ethics and dissemination:** This trial has been approved by the UK (Dulwich) National Research Ethics Service Committee London. 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. The patient and public involvement (PPI) group that works with the Respiratory Biomedical Research Unit at the Brompton Hospital will help identify how we can best publicise the findings.

**Trial registration:** VIOLET is registered at ISRCTN13472721 (doi 10.1186/ISRCTN13472721)

## Article Summary

### Strengths and limitations of this study

- First multicentre randomised trial on this topic
- All surgeons carry out both interventions; the randomisation scheme ensures surgeon balance across the groups to minimise performance bias
- Masking of the incision and evaluation of the success of blinding
- Procedures reflective of UK practice (majority are postero-lateral thoracotomy)
- Surgeon crossovers (i.e. surgeon changes after randomisation) can occur in centres with pooled service provision

## INTRODUCTION

### Background and objectives

Lung cancer is a leading cause of cancer death worldwide and survival in the United Kingdom (UK) remains amongst the lowest in Europe. Surgery, conventionally undertaken through an open thoracotomy for lung resection, remains the treatment for early stage disease. Since the introduction of minimal access video-assisted thoracoscopic surgery (VATS) techniques, lung cancer resection undertaken through a VATS approach increased from 14% in 2010 to 40% in 2014 in the UK.(1)

Much of the evidence generated to date is based on non-randomised studies(2, 3) or small randomised trials focusing on short term (in-hospital) outcomes(4), that are underpowered to detect differences in longer term outcomes such as survival(5) or have focused solely on operative technique.(6) Currently, the most well-designed randomised controlled trial (RCT) by Bendixen et al, reported shorter hospital stay and less pain in patients randomised to VATS lobectomy.(7) In this study, all patients received epidural anaesthesia and anterior thoracotomy for open surgery, which is not the current practice for most thoracic surgery centres in the UK. In contrast, a recent trial by Hao et al from China, published in 2018, reported a similar hospital stay in the VATS and axillary thoracotomy groups.(8) In addition, little high quality randomised data has been published to ascertain the cost effectiveness (i.e. quality of life and costs) for VATS, highlighted in a follow up report by Bendixen et al and an

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3 on-going trial in France (Lungsc01) that will specifically compare VATS lobectomy  
4 versus open thoracotomy from an economic cost to society perspective.(9, 10)  
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8 A well designed and conducted RCT comparing the effectiveness and cost-  
9 effectiveness of minimal access and open surgery is needed to inform current UK  
10 (NHS) practice, health policy and individual surgeon and patient decision-making.  
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15 The VIOLET study is a UK multicentre pragmatic RCT comparing the effectiveness,  
16 cost-effectiveness and acceptability of VATS lobectomy versus open lobectomy for  
17 treatment of lung cancer.  
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## 21 22 23 **Aims and objectives**

24  
25 The VIOLET study will test the hypothesis that VATS lobectomy is superior to open  
26 lobectomy with respect to self-reported physical function five weeks after  
27 randomisation (approximately one month after surgery).  
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32 Specific objectives are to estimate:

- 33 A. The difference between groups in the average self-reported physical function at  
34 five weeks.  
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36 B. The difference between groups with respect to a range of secondary outcomes  
37 including assessment of efficacy (hospital stay, pain, proportion and time to uptake  
38 of chemotherapy), measures of safety (adverse health events), oncological  
39 outcomes (proportion of patients upstaged to pN2 disease and disease-free survival)  
40 and overall survival.  
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42 C. The cost effectiveness of VATS lobectomy compared to open lobectomy.  
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## 50 51 **METHODS**

### 52 53 **Trial design**

54 A UK-based multicentre parallel group RCT with blinding of outcome assessors and  
55 participants until hospital discharge after surgery. Figures 1 and 2 show the expected  
56 patient pathway for both phases of recruitment to the VIOLET study.  
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3 *Phase 1:* The first phase with an integrated qualitative component is necessary to  
4 establish the processes for recruitment and consent. This phase is also essential to  
5 develop a study manual and a measure of surgical expertise to proceed to phase 2.  
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7 Phase 1 will be conducted in five centres; Royal Brompton Hospital in London, The  
8 University Hospitals Bristol in Bristol, Liverpool Heart and Chest Hospital in  
9 Liverpool, The James Cook University Hospital in Middlesbrough and Harefield  
10 Hospital in Harefield. These centres are well spread geographically and represent a  
11 mix of university and NHS trusts that are representative of NHS practice.  
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13 Progression from pilot to the full trial will be dependent on pre-agreed progression  
14 criteria (assessed after 18 months of recruitment):  
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22 Specifically:

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24 (a) at least 60% of patients undergoing lobectomy are considered eligible for the  
25 trial (if necessary, by revising the eligibility criteria);  
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27 (b) at least 50% consent to randomisation after 6 months of recruitment;  
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29 (c) less than 5% fail to receive their allocated treatment;  
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31 (d) less than 5% lost to follow up, excluding deaths;  
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34 *Phase 2:* This phase will extend the study to up to a further five centres. All centres  
35 will use the optimum methods of recruitment established in phase 1 and will follow-  
36 up all participants to one year.  
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## 42 **Study population**

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44 Participating *centres* will only be eligible if they meet all the following eligibility  
45 criteria: 1. NHS Trust with an established and accredited lung cancer multi-  
46 disciplinary team (MDT); 2. Centre carries out  $\geq 40$  VATS lobectomies each year and  
47 employs at least one surgeon who has carried out  $\geq 50$  VATS lobectomies.  
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52 Participating *surgeons* will be eligible for the trial if they have performed  $\geq 50$  VATS  
53 lobectomies. Prospective surgeons will be required to submit their activity logs,  
54 which will be validated against local audit data from the MDT meetings, prior to  
55 acceptance to the trial. Lobectomy via open surgery is currently standard procedure  
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3 and therefore surgical ability and competence will be assured by Specialist GMC  
4 registration.  
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8 *Patients* may enter the study if all the following apply:  
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- 10 1. Adult aged  $\geq 16$  years of age
- 11 12 2. Able to give written informed consent, undergoing either  
13 i. Lobectomy or bilobectomy for treatment of known or suspected primary lung  
14 cancer beyond lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent  
15 to TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-  
16 1 and M0 or  
17 ii. Undergoing frozen section biopsy with the intention to proceed with  
18 lobectomy or bilobectomy if primary lung cancer with a peripheral tumour  
19 beyond a lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent to  
20 TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-1  
21 and M0 is confirmed  
22 3. Disease suitable for both minimal access (VATS lobectomy) and lobectomy via  
23 open surgery  
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32 \*In the case of bilobectomy, the distance for the “lobar” orifice is in reference to the  
33 bronchus intermedius  
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38 *Patients* may not enter the study if any of the following apply:  
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- 40 1. Previous malignancy that influences life expectancy
- 41 42 2. Pneumonectomy, segmentectomy or non-anatomic resection (e.g. wedge  
43 resection) is planned
- 44 45 3. Patient has a serious concomitant disorder that would compromise patient safety  
46 during surgery
- 47 48 4. Planned robotic surgery.  
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## 52 **Randomisation**

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54 Participants will be randomised in a 1:1 ratio to either VATS lobectomy or open  
55 lobectomy. Randomisation will take place through a secure internet-based  
56 randomisation system, access to which will be restricted to authorised study  
57 personnel. Cohort minimisation (with a random element incorporated) will be used to  
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3 ensure balance across groups with respect to the surgeon and the allocation will be  
4 stratified by centre.  
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8 Due to the pragmatic nature of this trial there will inevitably be some variability  
9 between surgeons, the surgical teams and the perioperative processes. Such  
10 heterogeneity is important as this accurately reflects real clinical practice.  
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15 Randomisation will be performed one week prior to the planned operation date, once  
16 eligibility has been confirmed and written consent taken by a research nurse. This  
17 will allow sufficient time for operating theatre schedules to be arranged. If there is a  
18 change in surgeon after randomisation, the analysis will account for the surgeon  
19 responsible for performing the operation and not the surgeon originally allocated to  
20 the patient.  
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### 28 **Trial interventions**

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30 All operations will be undertaken with general anaesthesia and with the patient in the  
31 lateral decubitus position.  
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35 VATS lobectomy is undertaken through one to four keyhole incisions without rib  
36 spreading. The use of 'rib spreading' is prohibited as this is the key intra-operative  
37 manoeuvre which disrupts tissues and causes pain (and is used in open surgery).  
38 The procedure is performed with videoscopic visualisation without direct vision. The  
39 hilar structures are dissected, stapled and divided. Endoscopic ligation of pulmonary  
40 arterial branches may be performed. The fissure is completed and the lobe of lung  
41 resected. The incisions are closed in layers and may involve muscle, fat and skin  
42 layers. This definition of VATS lobectomy is a modification of Cancer and Leukaemia  
43 Group B (CALGB) 39802.(11)  
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52 Conventional open lobectomy is undertaken through a single incision with or without  
53 rib resection and with rib spreading. The operation is performed under direct vision  
54 with isolation of the hilar structures (vein, artery and bronchus) which are dissected,  
55 ligated and divided in sequence and the lobe of lung resected. The procedures may  
56 be undertaken using ligatures, over sewing or with staplers. The thoracotomy is  
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3 closed in layers starting from pericostal sutures over the ribs, muscle, fat and skin  
4 layers.  
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8 In both groups, lymph node management is undertaken in accordance with the  
9 International Association of the Study of Lung Cancer (IASLC) recommendations  
10 where a minimum of six nodes / stations are removed, of which three are from the  
11 mediastinum that includes the subcarinal station.(12)  
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16 Because this is a pragmatic trial, adaptations and variation in both procedures (with  
17 the exception of the mandated elements outlined above) will be permitted although  
18 intra-operative details will be collected, and compliance monitored.  
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### 23 24 **Primary and secondary outcomes**

25 The primary outcome is self-reported physical function measured using the  
26 European Organization for Research and Treatment of Cancer Quality of Life  
27 Questionnaire-C30 (EORTC QLQ-C30) at 5 weeks post-randomisation. Physical  
28 function has been chosen because it is a patient-centred outcome that will reflect the  
29 anticipated earlier recovery with VATS lobectomy and has been used in other  
30 minimal access surgery trials. The primary endpoint has been chosen to be five  
31 weeks (one-month post-surgery) to capture the early benefits of minimal access  
32 surgery on recovery. Secondary outcomes have been selected to assess the efficacy  
33 of the two approaches.  
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44 Secondary outcomes are 1. Time from surgery to hospital discharge; 2. Adverse  
45 health events; 3. Proportion and time to uptake of adjuvant treatment; 4. Proportion  
46 of patients upstaged to pN2 disease after the procedure; 5. Overall and disease-free  
47 survival to one-year; 6. Proportion of patients who undergo complete resection  
48 during the procedure; 7. Proportion of patients who experience prolonged incision  
49 pain defined as the need for analgesia > 6 weeks after surgery; 8. Generic and  
50 disease-specific Health-related quality of life (HRQoL) assessed using the EORTC  
51 QLQ-C30, QLQ-LC13 and EQ-5D-5L questionnaires completed at 2 weeks, 5  
52 weeks, 3 months, 6 months and 1-year post-randomisation); 9. Resource use  
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measured for the duration of post-operative hospital stay until discharge, and at 5 weeks, 3 months, 6 months and one-year post-randomisation.

## Data Collection

The schedule of data collection for the study is shown in Table 1. Data will be collected on paper and then entered onto a bespoke database. 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 NHS.net network in an encrypted form.

**Table 1. Data collection for trial participants who agree to randomisation to VATS lobectomy or open lobectomy**

	Pre-randomisation	Post-randomisation								
	Baseline	Day of Surgery	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 lobectomy or Open lobectomy		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

### **Blinding of staff and study participants**

The operating surgeon and staff responsible for the care of the participant during the operation cannot be blinded to the participants' 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 participants.

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 thorax. These adhesive dressings will be positioned similarly for all participants, regardless of their surgical allocation and will cover both real and potential incision/port locations. The initial adhesive dressings will be applied in the operating 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 participants' follow-up assessments. Wound cleaning will be performed on all real and potential incision/port locations to promote allocation masking.

Patients who agree to participate in the RCT will not be informed of their treatment allocation until they are discharged from hospital after their operation. In order to ensure that study patients are not unblinded during wound cleaning and dressing change, participants will be asked to turn their head away from the wound site that is being tended to. When participants are considered 'fit-for-discharge', they will be informed of their treatment allocation and advised as to how best to care for their surgical wounds.

The success of blinding will be monitored during each participant's in-hospital stay. Participants will be asked to complete the Bang-blinding Index(13) 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

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3 participants will also be asked to complete the Bang-blinding Index when the  
4 participant is ready for discharge and after the participant attends for their 5 week  
5 and 1-year follow-up appointments.  
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### 10 **Standardisation of post-operative management**

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13 As this is a pragmatic RCT, post-operative care and the criteria for drain removal will  
14 be in accordance with local practice. However, we have identified two elements of  
15 patient care, which require standardisation to minimise the potential for bias, namely  
16 pain-control and the criteria by which a participant's medical fitness-for-discharge is  
17 assessed.  
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24 Standardising the use of analgesia across participating centres is impractical and  
25 does not reflect the intended pragmatic nature of the trial, it, would also produce data  
26 unrepresentative of real clinical practice. Therefore, each participating centre will  
27 prescribe analgesia in accordance with their local protocols. All patients recruited to  
28 the RCT at that centre will be given the same analgesia regardless of their treatment  
29 allocation (i.e. VATS lobectomy or open lobectomy). Local protocols for the  
30 provision of analgesia will be defined by the local Principal Investigator (in  
31 collaboration with the local research team) prior to the start of recruitment to the  
32 RCT. Analgesia administered throughout the participant's in-hospital stay will be  
33 recorded on the trial case report forms (CRFs) and compliance with the pre-defined  
34 and centre-specific analgesia protocols will be monitored.  
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44 In order to objectively compare the time from surgery to hospital discharge between  
45 VATS lobectomy and open lobectomy, the following discharge suitability criteria have  
46 been developed. Study participants will be evaluated against these criteria to ensure  
47 that they are medically fit-for-discharge:  
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- 52 • Participant has achieved satisfactory mobility
  - 53 • Pain under control with analgesia
  - 54 • Satisfactory serum haemoglobin and electrolytes (i.e. does not require intervention)
  - 55 • Satisfactory chest-x-ray (which will be performed as part of routine clinical care)
  - 56 • No complications that require further / additional treatment
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5 Participants who are considered medically fit-for-discharge may not necessarily be  
6 discharged immediately; in some instances, social and other factors may necessitate  
7 extended hospitalisation. The time at which participants are considered medically fit-  
8 for-discharge and when they are physically discharged from hospital will both be  
9 recorded on the trial CRFs.  
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### 16 **Sample size calculation**

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18 We hypothesise that self-reported physical function (scale 0 – 100, with higher  
19 scores indicating better function) five weeks after randomisation for participants  
20 undergoing a VATS lobectomy will be superior to the physical function for  
21 participants having an open lobectomy, as measured using the EORTC QLQ-C30.  
22 The sample size has been chosen to test this hypothesis.  
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29 Although the primary endpoint is at 5 weeks post-randomisation self-reported  
30 physical function will also be assessed at other time points (baseline, 2 weeks, 3  
31 months, 6 months and 1-year). In estimating the sample size these additional  
32 measurements have been taken into account. The power calculation requires the  
33 estimation of four parameters, i.e. the effect size that would be considered clinically  
34 important, the number of pre and post-surgery measures, and the correlations  
35 between pre and post-surgery scores and between repeated post-surgery scores.  
36 The effect size was chosen based on the published literature,(14) which suggests  
37 that an effect size of 0.2 to 0.6 standard deviations equates to a clinically important  
38 difference in physical function score of between 5 and 14 points or approximately a  
39 one category change in performance status. In the absence of data from which to  
40 estimate the correlations between repeated measures we assumed conservative  
41 estimates (0.3 between pre and post measures, 0.6 between repeated post  
42 measures).  
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54 The study size has been set at 398; allowing for a 20% dropout at 1-year, the target  
55 sample size is 498 participants. This will provide 90% power to test the hypothesis,  
56 assuming an effect size of 0.25 standard deviations in physical function would be  
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3 clinically important. The calculation based on five post-surgery measures assumes  
4 the treatment difference is similar at the five time points.  
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8 However, it is anticipated that the difference in physical function may change over  
9 time. The calculation based on a single measure shows that the study will have  
10 >80% power to detect a difference of 0.25 standard deviations and >90% power to  
11 detect a difference of 0.3 standard deviations at the primary endpoint where dropout  
12 is expected to be less than 5%.  
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18 A study in 498 participants will also have 80% power to detect a 1-day difference in  
19 length of hospital stay (i.e. median 3 days versus 4 days, hazard ratio 1.3); assuming  
20 2% of patients do not survive to discharge.  
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## 26 **Research procedures**

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28 Generic and disease-specific HRQoL measures will assess the profiles of VATS and  
29 open lobectomy in the early and mid-postoperative phases. The extensively  
30 validated EQ-5D-5L will assess generic aspects of HRQoL and will be used in the  
31 economic evaluation.(15, 16) The EORTC QLQ-C30 is one of the most widely used  
32 instruments for assessing HRQoL in patients with cancer and the QLQ-LC13 is the  
33 lung cancer module with 13 items that assesses lung cancer-specific symptoms.  
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40 Study participants will be asked to complete HRQoL questionnaires at baseline and  
41 post-operatively at 2 weeks, 5 weeks, 3 months, 6 months and 1-year post-  
42 randomisation. Baseline questionnaires will be administered by the research team at  
43 site, whereas the questionnaires completed post-operatively will be administered by  
44 the coordinating centre. Participants can choose to receive post-operative  
45 questionnaires by post or complete via a secure website.  
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## 52 **Patient and Public Involvement (PPI)**

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54 The Royal Brompton Hospital Cancer Consortia PPI group were involved from  
55 inception and advised on trial design, identification of the choice and timing of the  
56 primary outcome, and secondary outcomes that were considered to be important.  
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3 They were consulted between August 2012 and September 2013. The aim of PPI  
4 involvement in VIOLET was to advise on patient-orientated outcomes that matter.  
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6 The group consists of four patients who have undergone surgery for cancer and one  
7 carer. Dr Hall, who is a patient, and a general practitioner by profession, has agreed  
8 to sit on the Trial Steering Committee (TSC).  
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13 The PPI group will also be involved in reviewing the content and format of PILs and  
14 dissemination of the results of the study.  
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### 19 **Integrated QuinteT Recruitment Intervention (QRI)**

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21 The VIOLET study will employ an integrated QRI to optimise and sustain recruitment  
22 throughout the recruitment period because recruitment is anticipated to be difficult.  
23 Although recruitment to RCTs is recognised as a research priority,(17) there is a  
24 dearth of robust evidence about effective strategies to improve recruitment in  
25 RCTs.(18). Surgical RCTs face specific recruitment challenges due to the complex  
26 nature of surgical procedures, the dependence on many healthcare professionals  
27 across disciplines and surgeon-related factors such as variations in individual  
28 practice/expertise.(19) In addition, surgical RCTs, such as VIOLET, that compare  
29 minimally invasive and open operations have historically been difficult to conduct and  
30 recruit to.(20, 21)  
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40 The QRI, employing primarily qualitative research methods can be used to  
41 understand recruitment in specific RCTs(22-24) as well as across RCTs.(25-27) It  
42 has been shown to optimise recruitment and informed consent, thereby contributing  
43 to successful recruitment and trial completion.(28-30) In VIOLET, in order to  
44 understand the recruitment process at each centre in real time, investigate the  
45 sources of recruitment difficulties and address the challenges, some of the key  
46 methods employed(31) will be as follows:  
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54 *Patient pathway through eligibility and recruitment:* A comprehensive process of  
55 logging potential trial patients through screening and eligibility phases will be  
56 undertaken to provide basic data about the levels of eligibility and recruitment, and  
57 identify points at which patients opt in or out of the RCT.  
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5 *In-depth interviews:* In-depth, semi-structured interviews will be conducted and  
6 audio-recorded with a purposive sample of staff members involved with aspects of  
7 trial design/management and recruitment across centres in phase 1 (and phase 2  
8 where necessary). Patients eligible for recruitment to the RCT may also be  
9 interviewed. Across the different groups, interviews will explore participants'  
10 perspectives of the trial, the two procedures and acceptability of randomisation  
11 between procedures. In addition, recruitment staff (primarily surgeons) interviews will  
12 explore their experiences of undertaking both procedures (where appropriate),  
13 perceptions of equipoise for themselves and their colleagues, and views on likely  
14 outcome of the trial. Interview topic guides will be used to ensure similar topic areas  
15 are covered across interviews, while still providing the scope for participants to raise  
16 issues of pertinence to them.  
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27 *Audio recording of recruitment appointments:* Face-to-face and telephone  
28 consultations of healthcare staff (thoracic surgeons, nurses etc) with potentially  
29 eligible patients will be routinely audio recorded across centres to understand the  
30 recruitment process at each centre and to identify and investigate the challenges to  
31 recruitment. The QRI researcher will listen to and qualitatively analyse the  
32 appointments, documenting instances such as unclear, insufficient or imbalanced  
33 information provision and unintentional transferring of clinician treatment preferences  
34 to patients,  
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43 An account of the anonymised findings from all the data will be fed back to the RCT  
44 CI, with a plan of action to optimise recruitment developed collaboratively with key  
45 stakeholders. The data will be used by the QRI team to provide supportive and  
46 confidential individual and group feedback to recruiters to help them to communicate  
47 equipoise, balance treatment options and explain to patients the benefits and  
48 purposes of trial participation, whilst optimising informed consent. Feedback  
49 sessions will include comparisons between what clinicians think they say to patients  
50 (interview data) and what they actually say to patients (consultation data). Rates of  
51 recruitment of eligible patients will be closely monitored against the feedback  
52 meetings and it is expected that an improvement will be demonstrated in recruitment  
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3 over time with experience and training for recruiters (as we have demonstrated is  
4 possible in other similar trials.(22-24, 28-30))  
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### 8 9 **Economic evaluation**

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11 The economic evaluation will compare the costs and effects of VATS lobectomy  
12 versus open lobectomy, and will follow established guidelines as set out by the  
13 National Institute for Health and Care Excellence(32). The within-trial cost-  
14 effectiveness analysis will be undertaken from an NHS and personal social services  
15 perspective, with a one-year time horizon from the day of surgery. The primary  
16 outcome measure for the economic evaluation will be quality-adjusted life-years  
17 (QALYs), estimated using the EuroQoL EQ-5D-5L, administered at baseline (pre-  
18 randomisation), and five time points post-randomisation (see Table 1). Resource use  
19 data collection will be integrated into the trial CRFs for the index admission for items  
20 such as duration of surgery, number of staples used, and length of stay; and  
21 captured from participants regularly during the one-year follow up (see Table 1) for  
22 events such as hospital readmissions, outpatient attendances, and GP or nurse  
23 visits in the community.  
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### 34 35 36 **Statistical analysis plan**

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38 The data will be analysed on intention to treat (ITT) and follow CONSORT reporting  
39 guidelines (<http://www.consort-statement.org/>). Randomised participants who are  
40 not found to have lung cancer will be included in the primary analysis, but a modified  
41 ITT analysis excluding these participants will also be performed. Analyses will be  
42 adjusted for centre and for design factors included in the cohort minimisation (e.g.  
43 the operating surgeon). As the allocation to VATS or open lobectomy is minimised by  
44 surgeon, clustering may occur within the dataset. The structure of the data, i.e.  
45 nesting of patients by surgeon and centre, will be accounted for in the primary  
46 analysis.  
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55 Patient reported outcome scores (HRQoL) and will be compared using a mixed  
56 regression model, adjusted for baseline measures where appropriate. Changes in  
57 treatment effect with time will be assessed by adding a treatment x time interaction  
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3 to the model and comparing models using a likelihood ratio test. Deaths will be  
4 accounted for by modelling HRQoL and survival jointly. Model fit will be assessed  
5 and alternative models and / or transformations (e.g. to induce normality) will be  
6 explored where appropriate.  
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10  
11 Missing items or errors on questionnaire measures will be dealt with according to the  
12 scoring manuals or via imputation methods. For other outcomes a complete case  
13 analysis will be undertaken if fewer than 5% of cases have missing data, otherwise  
14 multiple imputation methods will be considered. Compliance rates will be reported,  
15 including the numbers of patients who have withdrawn from the study, have been  
16 lost to follow up or died. Causes of death for trial participants will be recorded.  
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24 Frequencies of adverse events will be described. Treatment differences will be  
25 reported with 95% confidence intervals. In this study of 498 patients we are  
26 underpowered to detect differences in survival of less than approximately 20% at 2  
27 years. However, survival rates and 95% confidence intervals will be reported.  
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32  
33 One subgroup analysis is planned, comparing pain scores by type of analgesia  
34 (paravertebral block vs. intercostal block). This will be tested by adding an analgesia  
35 by treatment interaction term to the model. In addition, as an exploratory analysis we  
36 will report pain scores within the VATS lobectomy group by number of port sites  
37 (single vs multiple port sites), but a formal comparison between the sub-sets of the  
38 VATS group is not planned.  
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45 The primary analysis will take place when follow-up is complete for all recruited  
46 participants. Interim analysis will be decided in discussion with the Data Monitoring  
47 and Safety Committee (DMSC). There is no intention to compare any outcomes  
48 between groups after phase 1; the only analyses will be descriptive statistics to  
49 summarise recruitment to decide whether the trial satisfies the progression criteria.  
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55 *Economic Evaluation:* For the economic evaluation, unit costs will be derived from  
56 nationally published sources and attached to resource use data, and the total costs  
57 per participant calculated. Responses to the EQ-5D-5L will be assigned valuations  
58 derived from published UK population tariffs(33-35), and combined with survival to  
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3 calculate QALYs gained per participant. Missing resource use and EQ-5D-5L data  
4 will be handled using multiple imputation methods(36). From the average costs and  
5 QALYs gained in each trial group, the incremental cost-effectiveness ratio will be  
6 derived, producing an incremental cost per QALY gained of VATS lobectomy  
7 compared to open lobectomy. Univariate and multivariate sensitivity analyses will  
8 assess the impact of varying key parameters in the analysis on baseline cost-  
9 effectiveness results. Results will be expressed in terms of a cost-effectiveness  
10 acceptability curve, which indicates the likelihood that VATS lobectomy is cost-  
11 effective for different levels of willingness to pay for health gain.  
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21 *Qualitative analysis:* Analysis of qualitative data will involve transcribing the audio-  
22 recorded consultations, interviews and meetings with consent. The QRI researcher  
23 will a) analyse the transcripts and notes thematically using techniques of constant  
24 comparison(37) and case study approaches to explore the 'clear obstacles' and  
25 'hidden challenges(25) to recruitment in Violet, and b) employ targeted conversation  
26 analysis(22) to focus on areas in the consultations where communication appears to  
27 struggle or break down to identify aspects of recruitment that could be improved.  
28 Subsets of interview and consultation transcripts will be independently coded by two  
29 qualitative researchers, with the coding discussed and any discrepancies resolved,  
30 to establish a coding frame that can be applied to other transcripts. Descriptive  
31 accounts will summarise key challenges to recruitment. Anonymised findings will be  
32 documented and synthesised for presentation to the RCT CI.  
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43 *Access to study data:* Access to the study data will be limited to authorised  
44 personnel. Data will be collected and retained in accordance with the UK Data  
45 Protection Act 1998. An anonymised dataset will be held for future research as per  
46 the National Institute for Health Research (NIHR) contractual arrangements.  
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## 50 **ETHICS**

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53 Research ethics approval was granted by the UK (Dulwich) National Research  
54 Ethics Service Committee London (reference 14/LO/2129) on 7 January 2015. The  
55 trial is managed by the Clinical Trials and Evaluation Unit Bristol (CTEU Bristol) and  
56 sponsored by Royal Brompton & Harefield NHS Foundation Trust. Participants have  
57 the right to withdraw at any time and if they do withdraw, data collected up until the  
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3 time of withdrawal will be included in the analyses, unless the participant expresses  
4 a wish for their data to be destroyed. Withdrawing patients will be asked at this point  
5 if they can be contacted to complete HRQoL questionnaires for an assessment of  
6 physical function (primary end point). Participants who choose to withdraw from the  
7 study will be treated according to their hospitals' standard procedures.  
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### 14 **Changes to the protocol since it was first approved**

15  
16 The number of VATS lobectomies performed for surgeons to be eligible to participate  
17 in the VIOLET study was reduced from >50 to >40 to allow more surgeons to  
18 participate as there was no evidence to suggest a material difference in outcome.  
19  
20 Version 5.0 (dated 13/02/2018) of the protocol is currently in use.  
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25 Trial entry criteria by stage were amended following the introduction of the 8<sup>th</sup> edition  
26 of the TNM grading to:

- 27  
28 i. Lobectomy or bilobectomy for treatment of known or suspected primary lung  
29 cancer beyond lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent to  
30 TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-1 and M0  
31  
32 or  
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35 ii. Undergoing frozen section biopsy with the intention to proceed with lobectomy or  
36 bilobectomy if primary lung cancer with a peripheral tumour beyond a lobar orifice\* in  
37 TNM8 stage cT1-3 (by size criteria, equivalent to TNM7 stage cT1a-2b) or cT3 (by  
38 virtue of 2 nodules in the same lobe), N0-1 and M0 is confirmed.  
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42 \*In the case of bilobectomy, the distance for the "lobar" orifice is in reference to the  
43 bronchus intermedius  
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48 The protocol was amended so that the research nurse at the site could obtain  
49 questionnaire data during a study visit or telephone call, for those participants who  
50 do not return their questionnaire. The relevant regulatory approvals were obtained  
51 for amendments to the protocol. Relevant parties (e.g. investigators, trial  
52 participants) were informed.  
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## Study status

The actual numbers recruited at 18 months were 160 randomised participants and having received Trial Steering Committee and Funder approval, phase 2 is ongoing and the study is actively recruiting in eight centres. The centres opened in Phase 2 are Heartlands Hospital in Birmingham, John Radcliffe Hospital in Oxford and Castle Hill Hospital in Hull.

The full protocol is available from:

<https://www.journalslibrary.nihr.ac.uk/programmes/hta/130403/>

## AUTHOR CONTRIBUTIONS

EL: Study design, preparation and drafting of protocol and manuscript, Chief Investigator for the trial

CAR: Study design, sample size and statistical analysis plan, drafting of protocol and manuscript

JB: Study design, preparation of study protocol and review of manuscript

SP & DE: Design of integrated qualitative study, preparation of study protocol, review of manuscript

ES & SW: Study design, preparation of study protocol, design of health economic component, review of manuscript

TB: Study design, preparation of protocol and review of manuscript

MS: Study design, preparation of protocol and review of manuscript

JD: Preparation of protocol and review of manuscript

NMcG: Preparation of protocol and review of manuscript

TBr, LD, HM: Preparation of study protocol.

RH: Statistical analysis plan, review of manuscript.

All authors read and approved the final manuscript.

## DECLARATION OF INTERESTS

EL and TB report personal fees from Ethicon (Johnson and Johnson), Covidien (Medtronic). There are no other competing interests from the authors.

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JMB is an NIHR Senior Investigator. JMB, DE and SP are supported by the Medical Research Council (MRC) Hub for Trials Methodology Research ConDuCT-II (Collaboration and Innovation for Difficult Trials in Invasive Procedures) (MR/K025643/1). JMB and DE are also supported by the NIHR Bristol Biomedical Research Centre. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

CR was supported by the British Heart Foundation (BHF) until April 2016.

This study was designed and delivered in collaboration with the Clinical Trials and Evaluation Unit (CTEU), a UKCRC registered clinical trials unit which, as part of the Bristol Trials Centre, is in receipt of NIHR Clinical Trials Unit (CTU) support funding.

The NIHR, MRC and BHF will not be involved in the study management.

## ADDITIONAL FIGURES

**Figure 1.** The trial schema showing the recruitment pathway for Phase 1 (pilot phase) of the VIOLET study

**Figure 2.** The trial schema showing the recruitment pathway for Phase 2 of the VIOLET study

## LIST OF ABBREVIATIONS

BHF	British Heart Foundation
CALGB	Cancer and Leukemia Group B
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
ConDuCT-II	Collaboration and Innovation for Difficult Trials in Invasive Procedures
CTEU	Clinical Trials and Evaluation Unit

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3	DMSC	Data monitoring and safety committee
4	EORTC QLQ-C30	European Organization for Research and Treatment of
5		Cancer Quality of Life Questionnaire-C30
6		
7	EORTC QLQ-LC13	European Organisation for Research and Treatment of
8		Cancer Quality of Life Questionnaire Lung Cancer 13
9	EQ-5D	EuroQoL-5D
10	GMC	General Medical Council
11	HRQoL	Health related quality of life
12	HTA	Health Technology Assessment
13	MDT	Multi-Disciplinary Team
14	MRC	Medical Research Council
15	NIHR	National Institute for Health Research
16	NIHR	National Institute for Health Research
17	PIL	Patient information leaflet
18	PPI	Patient and Public Involvement
19	QALY	Quality-adjusted life year
20	QRI	QuinteT Recruitment Intervention
21	RCT	Randomised controlled trial
22	REC	Research ethics committee
23	TSC	Trial Steering Committee
24	TMG	Trial Management Group
25	TNM	TNM Classification of Malignant Tumours
26	UKCRC	The UK Clinical Research Collaboration
27	VATS	Video-assisted thoracoscopic surgery
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## ACKNOWLEDGEMENTS

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VIOLET is supported by the UK Thoracic Surgery Research Collaborative

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7 Intervention

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47  
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54  
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56  
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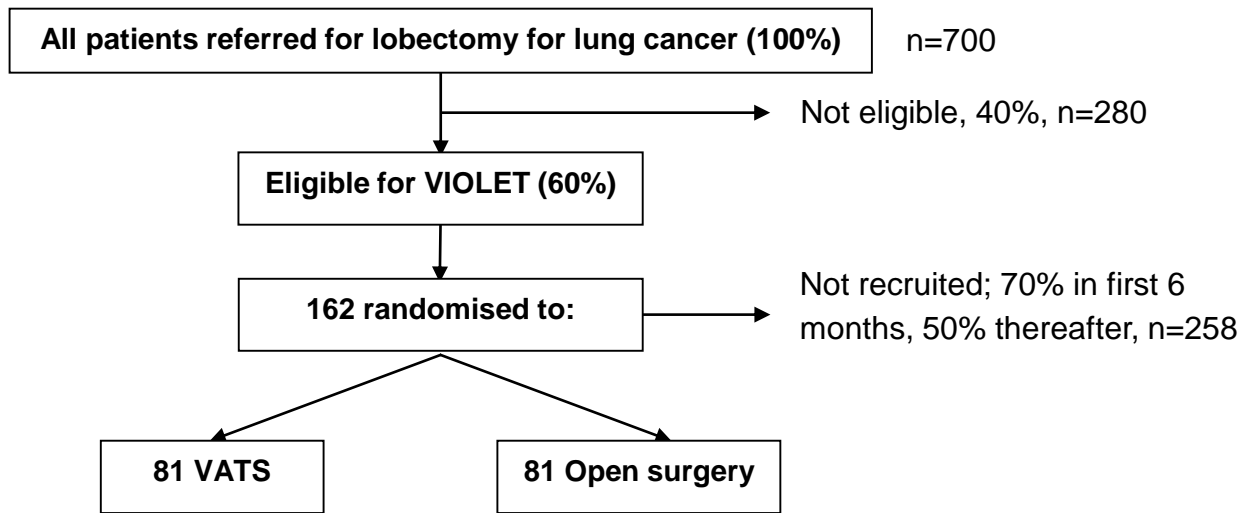
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8 [do/NICE-guidance/NICE-technology-appraisal-](https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf)  
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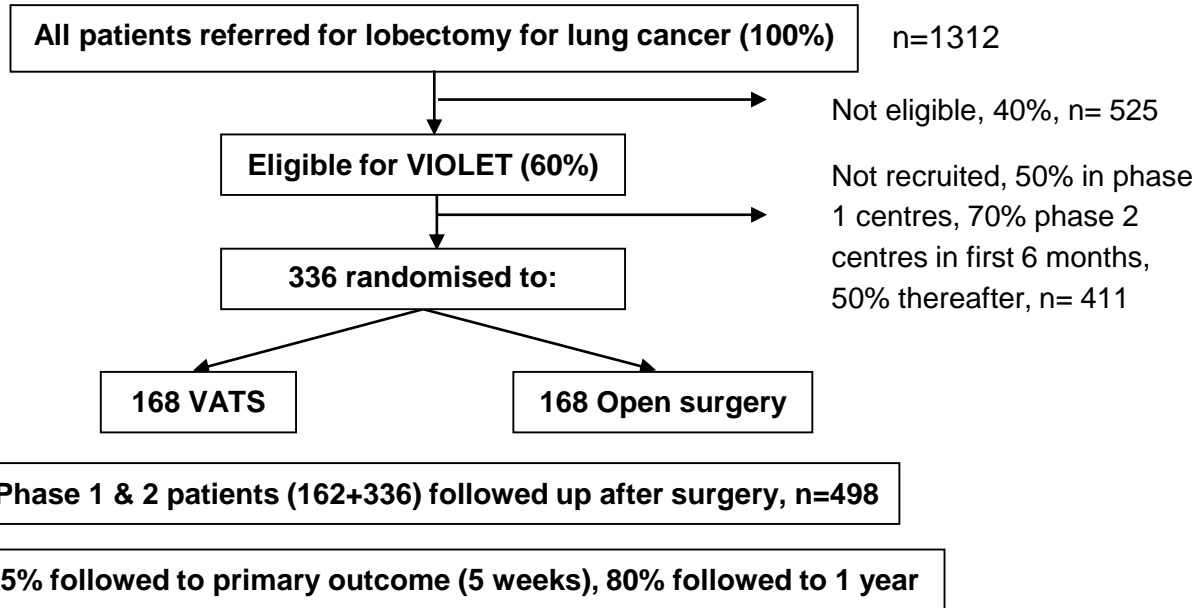
## Phase 1, in 5 centres (21 months recruitment)



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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

## Phase 2, in 9 centres (24 months recruitment)



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





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention 4, 5

4

5

6 6b Explanation for choice of comparators 5

7

8 Objectives 7 Specific objectives or hypotheses 5

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 5, 6

11

12

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14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained 5, 6

17

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) 6, 7

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 8, 9

23

24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) 8-11

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 11, 12

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 8-11

32

33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended 9, 10

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40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) 9, 10

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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13, 14
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-17
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7, 8
11				
12				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7, 8
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7, 8
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 11
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10, 13, 14
34				
35				
36				
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38				
39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-16, 20
40				
41				
42				

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17, 18
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20, 21
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	3, 15
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 10
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20, 22
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 15
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
35				
36				

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## Study Protocol for Video assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a UK multi-centre randomised controlled trial with an internal pilot (The VIOLET study)

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Keywords:	Randomised controlled trial, minimally invasive, Cardiothoracic surgery < SURGERY, open surgery, video assisted, lung cancer

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3 **Study Protocol for Video assisted thoracoscopic lobectomy versus**  
4 **conventional Open LobEcTomy for lung cancer, a UK multi-centre randomised**  
5 **controlled trial with an internal pilot (The VIOLET study)**  
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25 of The VIOLET Trialists\*\*6  
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## ABSTRACT

**Introduction:** Lung cancer is a leading cause of cancer deaths worldwide and surgery remains the main treatment for early stage disease. Prior to the introduction of video-assisted thoracoscopic surgery (VATS), lung resection for cancer was undertaken through an open thoracotomy. To date the evidence base supporting the different surgical approaches is based on non-randomised studies, small randomised trials and is focused mainly on short term in- hospital outcomes.

**Methods and analysis:** The VIOLET study is a UK multicentre parallel group randomised controlled trial (RCT) with blinding of outcome assessors and participants (to hospital discharge) comparing the effectiveness, cost-effectiveness and acceptability of VATS lobectomy versus open lobectomy for treatment of lung cancer. We will test the hypothesis that VATS lobectomy is superior to open lobectomy with respect to self-reported physical function five weeks after randomisation (approximately one month after surgery). Secondary outcomes include 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), overall survival, and health related quality of life to 1-year. The QuinteT Recruitment Intervention is integrated into the trial to optimise recruitment.

**Ethics and dissemination:** This trial has been approved by the UK (Dulwich) National Research Ethics Service Committee London. 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. The patient and public involvement (PPI) group that works with the Respiratory Biomedical Research Unit at the Brompton Hospital will help identify how we can best publicise the findings.

**Trial registration:** VIOLET is registered at ISRCTN13472721 (doi 10.1186/ISRCTN13472721)

## Article Summary

### Strengths and limitations of this study

- First multicentre randomised trial on this topic
- All surgeons carry out both interventions; the randomisation scheme ensures surgeon balance across the groups to minimise performance bias
- Masking of the incision and evaluation of the success of blinding
- Procedures reflective of UK practice (majority are postero-lateral thoracotomy)
- Surgeon crossovers (i.e. surgeon changes after randomisation) can occur in centres with pooled service provision

## INTRODUCTION

### Background and objectives

Lung cancer is a leading cause of cancer death worldwide and survival in the United Kingdom (UK) remains amongst the lowest in Europe. Surgery, conventionally undertaken through an open thoracotomy for lung resection, remains the treatment for early stage disease. The randomised trial comparing lobectomy with limited resection (segment or wedge), published in 1995 concluded that lobectomy should be the surgical procedure for patients with lung cancer.(1) The only grade 1 evidence published since is a post-hoc analysis of the CALGB/Alliance 140503 trial in patients with peripheral non-small-cell lung cancer, which concluded that lobar and sublobar resection had similar perioperative mortality and morbidity outcomes.(2) Since the introduction of minimal access video-assisted thoracoscopic surgery (VATS) techniques, lung cancer resection undertaken through a VATS approach increased from 14% in 2010 to 40% in 2014 in the UK.(3)

Much of the evidence generated to date is based on non-randomised studies(4, 5) or small randomised trials focusing on short term (in-hospital) outcomes(6), that are underpowered to detect differences in longer term outcomes such as survival(7) or have focused solely on operative technique.(8) Currently, the most well-designed randomised controlled trial (RCT) by Bendixen et al, reported shorter hospital stay and less pain in patients randomised to VATS lobectomy.(9) In this study, all patients received epidural anaesthesia and anterior thoracotomy for open surgery, which is

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3 not the current practice for most thoracic surgery centres in the UK. In contrast, a  
4 recent trial by Hao et al from China, published in 2018, reported a similar hospital  
5 stay in the VATS and axillary thoracotomy groups.(10) In addition, little high quality  
6 randomised data has been published to ascertain the cost effectiveness (i.e. quality  
7 of life and costs) for VATS, highlighted in a follow up report by Bendixen et al and an  
8 on-going trial in France (Lungsc01) that will specifically compare VATS lobectomy  
9 versus open thoracotomy from an economic cost to society perspective.(11, 12)  
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17 A well designed and conducted RCT comparing the effectiveness and cost-  
18 effectiveness of minimal access and open surgery is needed to inform current UK  
19 (NHS) practice, health policy and individual surgeon and patient decision-making.  
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24 The VIOLET study is a UK multicentre pragmatic RCT comparing the effectiveness,  
25 cost-effectiveness and acceptability of VATS lobectomy versus open lobectomy for  
26 treatment of lung cancer.  
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### 31 **Aims and objectives**

32  
33 The VIOLET study will test the hypothesis that VATS lobectomy is superior to open  
34 lobectomy with respect to self-reported physical function five weeks after  
35 randomisation (approximately one month after surgery).  
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40 Specific objectives are to estimate:

- 41 A. The difference between groups in the average self-reported physical function at  
42 five weeks.
- 43 B. The difference between groups with respect to a range of secondary outcomes  
44 including assessment of efficacy (hospital stay, pain, proportion and time to uptake  
45 of chemotherapy), measures of safety (adverse health events), oncological  
46 outcomes (proportion of patients upstaged to pN2 disease and disease-free survival)  
47 and overall survival.
- 48 C. The cost effectiveness of VATS lobectomy compared to open lobectomy.  
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## METHODS

### Trial design

A UK-based multicentre parallel group RCT with blinding of outcome assessors and participants until hospital discharge after surgery. Figures 1 and 2 show the expected patient pathway for both phases of recruitment to the VIOLET study.

*Phase 1:* The first phase with an 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; Royal Brompton Hospital in London, The University Hospitals Bristol in Bristol, Liverpool Heart and Chest Hospital in Liverpool, The James Cook University Hospital in Middlesbrough and Harefield Hospital in Harefield. These centres are well spread geographically and represent a mix of university and NHS trusts that are representative of NHS practice. Progression from pilot to the full trial will be dependent on pre-agreed progression criteria (assessed after 18 months of recruitment):

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% lost to follow up, excluding deaths;

*Phase 2:* This phase will extend the study to up to a further five centres. All centres will use the optimum methods of recruitment established in phase 1 and will follow-up all participants to one year.

### Study population

Participating *centres* will only be eligible if they meet all the following eligibility criteria: 1. NHS Trust with an established and accredited lung cancer multi-disciplinary team (MDT); 2. Centre carries out  $\geq 40$  VATS lobectomies each year and employs at least one surgeon who has carried out  $\geq 50$  VATS lobectomies.

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5 Participating *surgeons* will be eligible for the trial if they have performed  $\geq 50$  VATS  
6 lobectomies. Prospective surgeons will be required to submit their activity logs,  
7 which will be validated against local audit data from the MDT meetings, prior to  
8 acceptance to the trial. Lobectomy via open surgery is currently standard procedure  
9 and therefore surgical ability and competence will be assured by Specialist GMC  
10 registration.  
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17 *Patients* may enter the study if all the following apply:

- 18 1. Adult aged  $\geq 16$  years of age
- 19 2. Able to give written informed consent, undergoing either
- 20 i. Lobectomy or bilobectomy for treatment of known or suspected primary lung
- 21 cancer beyond lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent
- 22 to TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-
- 23 1 and M0 or
- 24 ii. Undergoing frozen section biopsy with the intention to proceed with
- 25 lobectomy or bilobectomy if primary lung cancer with a peripheral tumour
- 26 beyond a lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent to
- 27 TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-1
- 28 and M0 is confirmed
- 29 3. Disease suitable for both minimal access (VATS lobectomy) and lobectomy via
- 30 open surgery
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41 \*In the case of bilobectomy, the distance for the “lobar” orifice is in reference to the  
42 bronchus intermedius  
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46 *Patients* may not enter the study if any of the following apply:

- 47 1. Previous malignancy that influences life expectancy
- 48 2. Pneumonectomy, segmentectomy or non-anatomic resection (e.g. wedge
- 49 resection) is planned
- 50 3. Patient has a serious concomitant disorder that would compromise patient safety
- 51 during surgery
- 52 4. Planned robotic surgery.
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## Randomisation

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 to authorised study personnel. 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 between surgeons, the surgical teams and the perioperative processes. Such heterogeneity is important as this accurately reflects real clinical practice.

Randomisation will be performed one week prior to the planned operation date, once eligibility has been confirmed and written consent taken by a research nurse. This will allow sufficient time for operating theatre schedules to be arranged. If there is a change in surgeon after randomisation, the analysis will account for the surgeon responsible for performing the operation and not the surgeon originally allocated to the patient.

## Trial interventions

All operations will be undertaken with general anaesthesia and with the patient in the lateral decubitus position.

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. The incisions are closed in layers and may involve muscle, fat and skin layers. This definition of VATS lobectomy is a modification of Cancer and Leukaemia Group B (CALGB) 39802.(13)

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2  
3 Conventional open lobectomy is undertaken through a single incision with or without  
4 rib resection and with rib spreading. The operation is performed under direct vision  
5 with isolation of the hilar structures (vein, artery and bronchus) which are dissected,  
6  
7 ligated and divided in sequence and the lobe of lung resected. The procedures may  
8  
9 be undertaken using ligatures, over sewing or with staplers. The thoracotomy is  
10  
11 closed in layers starting from pericostal sutures over the ribs, muscle, fat and skin  
12  
13 layers.  
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17 In both groups, lymph node management is undertaken in accordance with the  
18 International Association of the Study of Lung Cancer (IASLC) recommendations  
19 where a minimum of six nodes / stations are removed, of which three are from the  
20  
21 mediastinum that includes the subcarinal station.(14)  
22  
23

24  
25 Because this is a pragmatic trial, adaptations and variation in both procedures (with  
26 the exception of the mandated elements outlined above) will be permitted although  
27  
28 intra-operative details will be collected, and compliance monitored.  
29  
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### 31 32 33 **Primary and secondary outcomes**

34  
35 The primary outcome is self-reported physical function measured using the  
36 European Organization for Research and Treatment of Cancer Quality of Life  
37 Questionnaire-C30 (EORTC QLQ-C30) at 5 weeks post-randomisation. Physical  
38  
39 function has been chosen because it is a patient-centred outcome that will reflect the  
40  
41 anticipated earlier recovery with VATS lobectomy and has been used in other  
42  
43 minimal access surgery trials. The primary endpoint has been chosen to be five  
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45 weeks (one-month post-surgery) to capture the early benefits of minimal access  
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47 surgery on recovery. The EORTC QLQ-C30 has been validated for use in European  
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49 cohorts. As well as assessing physical function the questionnaire also assesses  
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51 psychological and social well-being. Secondary outcomes have been selected to  
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53 assess the efficacy of the two approaches.  
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56 Secondary outcomes are 1. Time from surgery to hospital discharge; 2. Adverse  
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58 health events; 3. Proportion and time to uptake of adjuvant treatment; 4. Proportion  
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60 of patients upstaged to pN2 disease after the procedure; 5. Overall and disease-free



survival to one-year; 6. Proportion of patients who undergo complete resection during the procedure; 7. Proportion of patients who experience prolonged incision pain defined as the need for analgesia > 6 weeks after surgery; 8. Generic and disease-specific Health-related quality of life (HRQoL) assessed using the EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L questionnaires completed at 2 weeks, 5 weeks, 3 months, 6 months and 1-year post-randomisation); 9. Resource use measured for the duration of post-operative hospital stay until discharge, and at 5 weeks, 3 months, 6 months and one-year post-randomisation.

### Data Collection

The schedule of data collection for the study is shown in Table 1. Data will be collected on paper and then entered onto a bespoke database. 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 NHS.net network in an encrypted form.

**Table 1. Data collection for trial participants who agree to randomisation to VATS lobectomy or open lobectomy**

	Pre-randomisation	Post-randomisation								
	Baseline	Day of Surgery	Post-op	2 days post-op	Dis-charge	2 weeks*	5 weeks*	3 month s*	6 month s*	1 year*
Eligibility	X									
Imaging review (CT / PET-CT*)	X									
Participant characteristics	X									
Audio recorded consultation	X									
Lobectomy via VATS or Open Lobectomy		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



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	Pre-randomisation	Post-randomisation								
	Baseline	Day of Surgery	Post-op	2 days post-op	Dis-charge	2 weeks*	5 weeks*	3 months*	6 months*	1 year*
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

14

15

\*Follow-up time-points will be calculated from the date of randomisation.

16

‡Review of images available from staging scans performed in accordance with standard practice at participating centres

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### Blinding of staff and study participants

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The operating surgeon and staff responsible for the care of the participant during the operation cannot be blinded to the participants' 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 participants.

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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 thorax. These adhesive dressings will be positioned similarly for all participants, regardless of their surgical allocation and will cover both real and potential incision/port locations. The initial adhesive dressings will be applied in the operating 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 participants' follow-up assessments. Wound cleaning will be performed on all real and potential incision/port locations to promote allocation masking.

Patients who agree to participate in the RCT will not be informed of their treatment allocation until they are discharged from hospital after their operation. In order to ensure that study patients are not unblinded during wound cleaning and dressing

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3 change, participants will be asked to turn their head away from the wound site that is  
4 being tended to. When participants are considered 'fit-for-discharge', they will be  
5 informed of their treatment allocation and advised as to how best to care for their  
6 surgical wounds. Blinding in surgical trials are considered challenging yet an  
7 important aspect to reduce bias, patient drop-out and increase the validity of  
8 results.(15-17) Participants are made aware at consent that they will not be  
9 informed of their treatment allocation until after their surgery. Blinding was approved  
10 by the Research Ethics Committee.

11  
12 The success of blinding will be monitored during each participant's in-hospital stay.  
13 Participants will be asked to complete the Bang-blinding Index(18) at 2 days post-  
14 operatively and at discharge, but before the treatment allocation is revealed. The  
15 research nurse responsible for data collection and follow-up of VIOLET study  
16 participants will also be asked to complete the Bang-blinding Index when the  
17 participant is ready for discharge and after the participant attends for their 5 week  
18 and 1-year follow-up appointments.

### 31 **Standardisation of post-operative management**

32  
33 As this is a pragmatic RCT, post-operative care and the criteria for drain removal will  
34 be in accordance with local practice. However, we have identified two elements of  
35 patient care, which require standardisation to minimise the potential for bias, namely  
36 pain-control and the criteria by which a participant's medical fitness-for-discharge is  
37 assessed.

38  
39 Standardising the use of analgesia across participating centres is impractical and  
40 does not reflect the intended pragmatic nature of the trial, it, would also produce data  
41 unrepresentative of real clinical practice. Therefore, each participating centre will  
42 prescribe analgesia in accordance with their local protocols. All patients recruited to  
43 the RCT at that centre will be given the same analgesia regardless of their treatment  
44 allocation (i.e. VATS lobectomy or open lobectomy). Local protocols for the  
45 provision of analgesia will be defined by the local Principal Investigator (in  
46 collaboration with the local research team) prior to the start of recruitment to the  
47 RCT. Analgesia administered throughout the participant's in-hospital stay will be  
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3 recorded on the trial case report forms (CRFs) and compliance with the pre-defined  
4 and centre-specific analgesia protocols will be monitored.  
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8 In order to objectively compare the time from surgery to hospital discharge between  
9 VATS lobectomy and open lobectomy, the following discharge suitability criteria have  
10 been developed. Study participants will be evaluated against these criteria to ensure  
11 that they are medically fit-for-discharge:  
12  
13  
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- 15
- 16
- 17 • Participant has achieved satisfactory mobility
- 18 • Pain under control with analgesia
- 19 • Satisfactory serum haemoglobin and electrolytes (i.e. does not require intervention)
- 20 • Satisfactory chest-x-ray (which will be performed as part of routine clinical care)
- 21 • No complications that require further / additional treatment
- 22  
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27 Participants who are considered medically fit-for-discharge may not necessarily be  
28 discharged immediately; in some instances, social and other factors may necessitate  
29 extended hospitalisation. The time at which participants are considered medically fit-  
30 for-discharge and when they are physically discharged from hospital will both be  
31 recorded on the trial CRFs.  
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### 38 **Sample size calculation**

39 We hypothesise that self-reported physical function (scale 0 – 100, with higher  
40 scores indicating better function) five weeks after randomisation for participants  
41 undergoing a VATS lobectomy will be superior to the physical function for  
42 participants having an open lobectomy, as measured using the EORTC QLQ-C30.  
43 The sample size has been chosen to test this hypothesis.  
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51 Although the primary endpoint is at 5 weeks post-randomisation self-reported  
52 physical function will also be assessed at other time points (baseline, 2 weeks, 3  
53 months, 6 months and 1-year). In estimating the sample size these additional  
54 measurements have been taken into account. The power calculation requires the  
55 estimation of four parameters, i.e. the effect size that would be considered clinically  
56 important, the number of pre and post-surgery measures, and the correlations  
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3 between pre and post-surgery scores and between repeated post-surgery scores.  
4 The effect size was chosen based on the published literature,(19) which suggests  
5 that an effect size of 0.2 to 0.6 standard deviations equates to a clinically important  
6 difference in physical function score of between 5 and 14 points or approximately a  
7 one category change in performance status. In the absence of data from which to  
8 estimate the correlations between repeated measures we assumed conservative  
9 estimates (0.3 between pre and post measures, 0.6 between repeated post  
10 measures).

11  
12 The study size has been set at 398; allowing for a 20% dropout at 1-year, the target  
13 sample size is 498 participants. This will provide 90% power to test the hypothesis,  
14 assuming an effect size of 0.25 standard deviations in physical function would be  
15 clinically important. The calculation based on five post-surgery measures assumes  
16 the treatment difference is similar at the five time points.

17  
18 However, it is anticipated that the difference in physical function may change over  
19 time. The calculation based on a single measure shows that the study will have  
20 >80% power to detect a difference of 0.25 standard deviations and >90% power to  
21 detect a difference of 0.3 standard deviations at the primary endpoint where dropout  
22 is expected to be less than 5%.

23  
24 A study in 498 participants will also have 80% power to detect a 1-day difference in  
25 length of hospital stay (i.e. median 3 days versus 4 days, hazard ratio 1.3); assuming  
26 2% of patients do not survive to discharge.

## 27 28 29 **Research procedures**

30  
31 Generic and disease-specific HRQoL measures will assess the profiles of VATS and  
32 open lobectomy in the early and mid-postoperative phases. The extensively  
33 validated EQ-5D-5L will assess generic aspects of HRQoL and will be used in the  
34 economic evaluation.(20, 21) The EORTC QLQ-C30 is one of the most widely used  
35 instruments for assessing HRQoL in patients with cancer and the QLQ-LC13 is the  
36 lung cancer module with 13 items that assesses lung cancer-specific symptoms.

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3 Study participants will be asked to complete HRQoL questionnaires at baseline and  
4 post-operatively at 2 weeks, 5 weeks, 3 months, 6 months and 1-year post-  
5 randomisation. Baseline questionnaires will be administered by the research team at  
6 site, whereas the questionnaires completed post-operatively will be administered by  
7 the coordinating centre. Participants can choose to receive post-operative  
8 questionnaires by post or complete via a secure website.  
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### 16 **Patient and Public Involvement (PPI)**

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18 The Royal Brompton Hospital Cancer Consortia PPI group were involved from  
19 inception and advised on trial design, identification of the choice and timing of the  
20 primary outcome, and secondary outcomes that were considered to be important.  
21 They were consulted between August 2012 and September 2013. The aim of PPI  
22 involvement in VIOLET was to advise on patient-orientated outcomes that matter.  
23 The group consists of four patients who have undergone surgery for cancer and one  
24 carer. Dr Hall, who is a patient, and a general practitioner by profession, has agreed  
25 to sit on the Trial Steering Committee (TSC).  
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34 The PPI group will also be involved in reviewing the content and format of PILs and  
35 dissemination of the results of the study.  
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### 40 **Integrated QuinteT Recruitment Intervention (QRI)**

41 The VIOLET study will employ an integrated QRI to optimise and sustain recruitment  
42 throughout the recruitment period because recruitment is anticipated to be difficult.  
43 Although recruitment to RCTs is recognised as a research priority,(22) there is a  
44 dearth of robust evidence about effective strategies to improve recruitment in  
45 RCTs.(23). Surgical RCTs face specific recruitment challenges due to the complex  
46 nature of surgical procedures, the dependence on many healthcare professionals  
47 across disciplines and surgeon-related factors such as variations in individual  
48 practice/expertise.(24) In addition, surgical RCTs, such as VIOLET, that compare  
49 minimally invasive and open operations have historically been difficult to conduct and  
50 recruit to.(25, 26)  
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3 The QRI, employing primarily qualitative research methods can be used to  
4 understand recruitment in specific RCTs(27-29) as well as across RCTs.(30-32) It  
5 has been shown to optimise recruitment and informed consent, thereby contributing  
6 to successful recruitment and trial completion.(33-35) In VIOLET, in order to  
7 understand the recruitment process at each centre in real time, investigate the  
8 sources of recruitment difficulties and address the challenges, some of the key  
9 methods employed(36) will be as follows:

16  
17 *Patient pathway through eligibility and recruitment:* A comprehensive process of  
18 logging potential trial patients through screening and eligibility phases will be  
19 undertaken to provide basic data about the levels of eligibility and recruitment, and  
20 identify points at which patients opt in or out of the RCT.  
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26 *In-depth interviews:* In-depth, semi-structured interviews will be conducted and  
27 audio-recorded with a purposive sample of staff members involved with aspects of  
28 trial design/management and recruitment across centres in phase 1 (and phase 2  
29 where necessary). Patients eligible for recruitment to the RCT may also be  
30 interviewed. Across the different groups, interviews will explore participants'  
31 perspectives of the trial, the two procedures and acceptability of randomisation  
32 between procedures. In addition, recruitment staff (primarily surgeons) interviews will  
33 explore their experiences of undertaking both procedures (where appropriate),  
34 perceptions of equipoise for themselves and their colleagues, and views on likely  
35 outcome of the trial. Interview topic guides will be used to ensure similar topic areas  
36 are covered across interviews, while still providing the scope for participants to raise  
37 issues of pertinence to them.  
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48 *Audio recording of recruitment appointments:* Face-to-face and telephone  
49 consultations of healthcare staff (thoracic surgeons, nurses etc) with potentially  
50 eligible patients will be routinely audio recorded across centres to understand the  
51 recruitment process at each centre and to identify and investigate the challenges to  
52 recruitment. The QRI researcher will listen to and qualitatively analyse the  
53 appointments, documenting instances such as unclear, insufficient or imbalanced  
54 information provision and unintentional transferring of clinician treatment preferences  
55 to patients,  
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5 An account of the anonymised findings from all the data will be fed back to the RCT  
6 CI, with a plan of action to optimise recruitment developed collaboratively with key  
7 stakeholders. The data will be used by the QRI team to provide supportive and  
8 confidential individual and group feedback to recruiters to help them to communicate  
9 equipoise, balance treatment options and explain to patients the benefits and  
10 purposes of trial participation, whilst optimising informed consent. Feedback  
11 sessions will include comparisons between what clinicians think they say to patients  
12 (interview data) and what they actually say to patients (consultation data). Rates of  
13 recruitment of eligible patients will be closely monitored against the feedback  
14 meetings and it is expected that an improvement will be demonstrated in recruitment  
15 over time with experience and training for recruiters (as we have demonstrated is  
16 possible in other similar trials.(27-29, 33-35))  
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### 28 **Economic evaluation**

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30 The economic evaluation will compare the costs and effects of VATS lobectomy  
31 versus open lobectomy, and will follow established guidelines as set out by the  
32 National Institute for Health and Care Excellence(37). The within-trial cost-  
33 effectiveness analysis will be undertaken from an NHS and personal social services  
34 perspective, with a one-year time horizon from the day of surgery. The primary  
35 outcome measure for the economic evaluation will be quality-adjusted life-years  
36 (QALYs), estimated using the EuroQol EQ-5D-5L, administered at baseline (pre-  
37 randomisation), and five time points post-randomisation (see Table 1). Resource use  
38 data collection will be integrated into the trial CRFs for the index admission for items  
39 such as duration of surgery, number of staples used, and length of stay; and  
40 captured from participants regularly during the one-year follow up (see Table 1) for  
41 events such as hospital readmissions, outpatient attendances, and GP or nurse  
42 visits in the community.  
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### 54 **Statistical analysis plan**

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56 The data will be analysed on intention to treat (ITT) and follow CONSORT reporting  
57 guidelines (<http://www.consort-statement.org/>). Randomised participants who are  
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3 not found to have lung cancer will be included in the primary analysis, but a modified  
4 ITT analysis excluding these participants will also be performed. Analyses will be  
5 adjusted for centre and for design factors included in the cohort minimisation (e.g.  
6 the operating surgeon). As the allocation to VATS or open lobectomy is minimised by  
7 surgeon, clustering may occur within the dataset. The structure of the data, i.e.  
8 nesting of patients by surgeon and centre, will be accounted for in the primary  
9 analysis.  
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17 Patient reported outcome scores (HRQoL) and will be compared using a mixed  
18 regression model, adjusted for baseline measures where appropriate. Changes in  
19 treatment effect with time will be assessed by adding a treatment x time interaction  
20 to the model and comparing models using a likelihood ratio test. Deaths will be  
21 accounted for by modelling HRQoL and survival jointly. Model fit will be assessed  
22 and alternative models and / or transformations (e.g. to induce normality) will be  
23 explored where appropriate.  
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31 Missing items or errors on questionnaire measures will be dealt with according to the  
32 scoring manuals or via imputation methods. For other outcomes a complete case  
33 analysis will be undertaken if fewer than 5% of cases have missing data, otherwise  
34 multiple imputation methods will be considered. Compliance rates will be reported,  
35 including the numbers of patients who have withdrawn from the study, have been  
36 lost to follow up or died. Causes of death for trial participants will be recorded.  
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43 Frequencies of adverse events will be described. Treatment differences will be  
44 reported with 95% confidence intervals. In this study of 498 patients we are  
45 underpowered to detect differences in survival of less than approximately 20% at 2  
46 years. However, survival rates and 95% confidence intervals will be reported.  
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51 One subgroup analysis is planned, comparing pain scores by type of analgesia  
52 (paravertebral block vs. intercostal block). This will be tested by adding an analgesia  
53 by treatment interaction term to the model. In addition, as an exploratory analysis we  
54 will report pain scores within the VATS lobectomy group by number of port sites  
55 (single vs multiple port sites), but a formal comparison between the sub-sets of the  
56 VATS group is not planned.  
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5 The primary analysis will take place when follow-up is complete for all recruited  
6 participants. Interim analysis will be decided in discussion with the Data Monitoring  
7 and Safety Committee (DMSC). There is no intention to compare any outcomes  
8 between groups after phase 1; the only analyses will be descriptive statistics to  
9 summarise recruitment to decide whether the trial satisfies the progression criteria.  
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15 *Economic Evaluation:* For the economic evaluation, unit costs will be derived from  
16 nationally published sources and attached to resource use data, and the total costs  
17 per participant calculated. Responses to the EQ-5D-5L will be assigned valuations  
18 derived from published UK population tariffs(38-40), and combined with survival to  
19 calculate QALYs gained per participant. Missing resource use and EQ-5D-5L data  
20 will be handled using multiple imputation methods(41). From the average costs and  
21 QALYs gained in each trial group, the incremental cost-effectiveness ratio will be  
22 derived, producing an incremental cost per QALY gained of VATS lobectomy  
23 compared to open lobectomy. Univariate and multivariate sensitivity analyses will  
24 assess the impact of varying key parameters in the analysis on baseline cost-  
25 effectiveness results. Results will be expressed in terms of a cost-effectiveness  
26 acceptability curve, which indicates the likelihood that VATS lobectomy is cost-  
27 effective for different levels of willingness to pay for health gain.  
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39 *Qualitative analysis:* Analysis of qualitative data will involve transcribing the audio-  
40 recorded consultations, interviews and meetings with consent. The QRI researcher  
41 will a) analyse the transcripts and notes thematically using techniques of constant  
42 comparison(42) and case study approaches to explore the 'clear obstacles' and  
43 'hidden challenges(30) to recruitment in Violet, and b) employ targeted conversation  
44 analysis(27) to focus on areas in the consultations where communication appears to  
45 struggle or break down to identify aspects of recruitment that could be improved.  
46 Subsets of interview and consultation transcripts will be independently coded by two  
47 qualitative researchers, with the coding discussed and any discrepancies resolved,  
48 to establish a coding frame that can be applied to other transcripts. Descriptive  
49 accounts will summarise key challenges to recruitment. Anonymised findings will be  
50 documented and synthesised for presentation to the RCT CI.  
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3 *Access to study data:* Access to the study data will be limited to authorised  
4 personnel. Data will be collected and retained in accordance with the UK Data  
5 Protection Act 1998. An anonymised dataset will be held for future research as per  
6 the National Institute for Health Research (NIHR) contractual arrangements.  
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## 10 **ETHICS**

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13 Research ethics approval was granted by the UK (Dulwich) National Research  
14 Ethics Service Committee London (reference 14/LO/2129) on 7 January 2015. The  
15 trial is managed by the Clinical Trials and Evaluation Unit Bristol (CTEU Bristol) and  
16 sponsored by Royal Brompton & Harefield NHS Foundation Trust. Participants have  
17 the right to withdraw at any time and if they do withdraw, data collected up until the  
18 time of withdrawal will be included in the analyses, unless the participant expresses  
19 a wish for their data to be destroyed. Withdrawing patients will be asked at this point  
20 if they can be contacted to complete HRQoL questionnaires for an assessment of  
21 physical function (primary end point). Participants who choose to withdraw from the  
22 study will be treated according to their hospitals' standard procedures.  
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### 33 **Changes to the protocol since it was first approved**

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35 The number of VATS lobectomies performed for surgeons to be eligible to participate  
36 in the VIOLET study was reduced from >50 to >40 to allow more surgeons to  
37 participate as there was no evidence to suggest a material difference in outcome.  
38  
39 Version 5.0 (dated 13/02/2018) of the protocol is currently in use.  
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44 Trial entry criteria by stage were amended following the introduction of the 8<sup>th</sup> edition  
45 of the TNM grading to:

- 46  
47 i. Lobectomy or bilobectomy for treatment of known or suspected primary lung  
48 cancer beyond lobar orifice\* in TNM8 stage cT1-3 (by size criteria, equivalent to  
49 TNM7 stage cT1a-2b) or cT3 (by virtue of 2 nodules in the same lobe), N0-1 and M0  
50  
51 or  
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53  
54 ii. Undergoing frozen section biopsy with the intention to proceed with lobectomy or  
55 bilobectomy if primary lung cancer with a peripheral tumour beyond a lobar orifice\* in  
56 TNM8 stage cT1-3 (by size criteria, equivalent to TNM7 stage cT1a-2b) or cT3 (by  
57 virtue of 2 nodules in the same lobe), N0-1 and M0 is confirmed.  
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3 \*In the case of bilobectomy, the distance for the “lobar” orifice is in reference to the  
4 bronchus intermedius  
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8 The protocol was amended so that the research nurse at the site could obtain  
9 questionnaire data during a study visit or telephone call, for those participants who  
10 do not return their questionnaire. The relevant regulatory approvals were obtained  
11 for amendments to the protocol. Relevant parties (e.g. investigators, trial  
12 participants) were informed.  
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### 18 19 **Study status**

20  
21 The actual numbers recruited at 18 months were 160 randomised participants and  
22 having received Trial Steering Committee and Funder approval, phase 2 is ongoing  
23 and the study is actively recruiting in eight centres. The centres opened in Phase 2  
24 are Heartlands Hospital in Birmingham, John Radcliffe Hospital in Oxford and Castle  
25 Hill Hospital in Hull.  
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29 The full protocol is available from:

30 <https://www.journalslibrary.nihr.ac.uk/programmes/hta/130403/>  
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### 36 **AUTHOR CONTRIBUTIONS**

37  
38 EL: Study design, preparation and drafting of protocol and manuscript, Chief  
39 Investigator for the trial

40  
41 CAR: Study design, sample size and statistical analysis plan, drafting of protocol and  
42 manuscript  
43

44  
45 JB: Study design, preparation of study protocol and review of manuscript

46  
47 SP & DE: Design of integrated qualitative study, preparation of study protocol, review  
48 of manuscript  
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51 ES & SW: Study design, preparation of study protocol, design of health economic  
52 component, review of manuscript  
53

54  
55 TB: Study design, preparation of protocol and review of manuscript

56  
57 MS: Study design, preparation of protocol and review of manuscript

58  
59 JD: Preparation of protocol and review of manuscript

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61 NMcG: Preparation of protocol and review of manuscript

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3 TBr, LD, HM: Preparation of study protocol.

4  
5 RH: Statistical analysis plan, review of manuscript.

6  
7 All authors read and approved the final manuscript.

## 8 9 10 **DECLARATION OF INTERESTS**

11  
12  
13 EL and TB report personal fees from Ethicon (Johnson and Johnson), Covidien  
14 (Medtronic). There are no other competing interests from the authors.

## 15 16 17 18 19 **FUNDING STATEMENT**

20  
21 This project is funded by the NIHR Health Technology Assessment (HTA)  
22 Programme (ref 13/04/03). The views expressed are those of the author(s) and not  
23 necessarily those of the NHS, the NIHR or the Department of Health and Social  
24 Care.  
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28  
29 JMB is an NIHR Senior Investigator. JMB, DE and SP are supported by the Medical  
30 Research Council (MRC) Hub for Trials Methodology Research ConDuCT-II  
31 (Collaboration and Innovation for Difficult Trials in Invasive Procedures)  
32 (MR/K025643/1). JMB and DE are also supported by the NIHR Bristol Biomedical  
33 Research Centre. The funders had no role in the study design, data collection and  
34 analysis, decision to publish or preparation of the manuscript.  
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40  
41 CR was supported by the British Heart Foundation (BHF) until April 2016.

42  
43 This study was designed and delivered in collaboration with the Clinical Trials and  
44 Evaluation Unit (CTEU), a UKCRC registered clinical trials unit which, as part of the  
45 Bristol Trials Centre, is in receipt of NIHR Clinical Trials Unit (CTU) support funding.  
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50 The NIHR, MRC and BHF will not be involved in the study management.

## 51 52 53 **ADDITIONAL FIGURES**

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56 **Figure 1.** The trial schema showing the recruitment pathway for Phase 1 (pilot  
57 phase) of the VIOLET study  
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**Figure 2.** The trial schema showing the recruitment pathway for Phase 2 of the VIOLET study

## LIST OF ABBREVIATIONS

BHF	British Heart Foundation
CALGB	Cancer and Leukemia Group B
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
ConDuCT-II	Collaboration and Innovation for Difficult Trials in Invasive Procedures
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data monitoring and safety committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EQ-5D	EuroQoL-5D
GMC	General Medical Council
HRQoL	Health related quality of life
HTA	Health Technology Assessment
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
NIHR	National Institute for Health Research
PIL	Patient information leaflet
PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
QRI	QuinteT Recruitment Intervention
RCT	Randomised controlled trial
REC	Research ethics committee
TSC	Trial Steering Committee
TMG	Trial Management Group
TNM	TNM Classification of Malignant Tumours
UKCRC	The UK Clinical Research Collaboration
VATS	Video-assisted thoracoscopic surgery

## ACKNOWLEDGEMENTS

The VIOLET trial is sponsored by The Royal Brompton and Harefield NHS Foundation Trust. The sponsor will be responsible for the oversight of the VIOLET study and to ensure the trial is managed appropriately.

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**\*\*VIOLET Trialists****Project management team members**

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Professor Chris Rogers, Methodological lead and Statistician

Tim Brush, Clinical Trial Coordinator

Lucy Dabner, Clinical Trial Coordinator

Dawn Phillips, Clinical Trial Coordinator

Holly Mckeen, Clinical Trial Coordinator

Chloe Beard, Assistant Trial Coordinator

Rosie Harris, Medical Statistician

Dr Daisy Elliott, Senior Research Associate, QuinteT Research Intervention

Dr Sangeetha Paramasivan, Senior Research Associate, QuinteT Research Intervention

Dr Alba Realpe Rojas, Senior Research Associate, QuinteT Research Intervention

Dr Sarah Wordsworth, Lead Health Economist

Dr Elizabeth Stokes, Health Economist

Professor Jane Blazeby, Methodologist and Surgeon

Professor Andrew G Nicholson, Pathologist

**Participating sites members phase 1****Royal Brompton Hospital:**

Professor Eric Lim, Principal Investigator, Consultant Thoracic Surgeon

Miss Sofina Begum, Consultant Thoracic Surgeon

Mr Simon Jordan, Consultant Thoracic Surgeon

Paulo De Sousa, Senior Research Nurse

Monica Tavares Barbosa, Research Nurse

**Bristol Royal Infirmary:**

Mr Tim Batchelor, Principal Investigator, Consultant Thoracic Surgeon

Ms Eveline Internullo, Consultant Thoracic Surgeon

Mr Rakesh Krishnadas, Consultant Thoracic Surgeon

Mr Gianluca Casali, Consultant Thoracic Surgeon

1  
2  
3 Mr Doug West, Consultant Thoracic Surgeon

4  
5 Karen Bobruk, Research Nurse

6  
7 Catherine O'Donovan, Research Nurse

8  
9 Louise Flintoff, Research Nurse

10  
11 Amelia Lowe, Trial Coordinator

12  
13 Joanna Nicklin, Research Nurse

14  
15 Emma Heron, Research Nurse

16  
17 Jo Chambers, Research Nurse

18  
19 Becky Houlihan, Research Nurse

20  
21 Laura Beacham, Research Nurse

22  
23 Heather Hudson, Research Nurse

24  
25 Katy Tucker, Trial Coordinator

26  
27 Toni Farmery, Trial Coordinator

28  
29 Danielle Davis, Trial Coordinator

30  
31 **Liverpool Heart and Chest Hospital:**

32  
33 Mr Mike Shackcloth, Principal Investigator, Consultant Thoracic Surgeon

34  
35 Mr Julius Asante-Siaw, Consultant Thoracic Surgeon

36  
37 Ms Susannah Love, Consultant Thoracic Surgeon

38  
39 Sarah Feeney, Research Nurse

40  
41 Lindsey Murphy, Research Nurse

42  
43 Almudena Duran Rosas, Research Nurse

44  
45 Andrea Young, Research Nurse

46  
47 **James Cook Hospital:**

48  
49 Mr Joel Dunning, Principal Investigator, Consultant Thoracic Surgeon

50  
51 Mr Ian Paul, Consultant Thoracic Surgeon

52  
53 Hyder Latif, Clinical Trial Coordinator

54  
55 Charlotte Jacobs, Clinical Trial Coordinator

56  
57 Alison Chilvers, Clinical Trial Coordinator

58  
59 Edward Stephenson, Research Data Assistant

60  
61 Martyn Cain, Research Data Assistant

62  
63 Nazalie Iqbal, Research Data Assistant

**Harefield Hospital:**

Mr Vladimir Anikin, Principal Investigator, Consultant Thoracic Surgeon

Mr Niall McGonigle, previous Principal Investigator, Consultant Thoracic Surgeon

Claire Prendergast, Research Nurse

Lisa Jones, Research Nurse

Paula Rogers, Research Nurse Manager

**Participating sites members phase 2****Birmingham Heartlands Hospital:**

Mr Babu Naidu, Principal Investigator, Consultant Thoracic Surgeon

Mr Hazem Fallouh, Consultant Thoracic Surgeon

Mr Luis Hernandez, Consultant Thoracic Surgeon

Mr Maninder Kalkat, Consultant Thoracic Surgeon

Mr Richard Steyn, Consultant Thoracic Surgeon

Nicola Oswald, Thoracic Research Fellow

Amy Kerr, Senior Research Nurse

Charlotte Ferris, Research Nurse

Jo Webb, Research Nurse

Joanne Taylor, Research Nurse

Hollie Bancroft, R&D Biomedical scientist

Salma Kadiri, Research Practitioner

Zara Jalal Senior, Thoracic Research Data Manager

**Oxford University Hospitals NHS Foundation Trust:**

Miss Elizabeth Belcher, Principal Investigator, Consultant Thoracic Surgeon

Mr Dionisios Stavroulias, Consultant Thoracic Surgeon

Mr Francesco Di Chiara, Consultant Thoracic Surgeon

Kathryn Saunders, Research Nurse

May Havinden-Williams, Research Nurse

Mark Ainsworth, Research Nurse

**Castle Hill Hospital:**

Professor Mahmoud Loubani, Principal Investigator, Consultant Cardiothoracic Surgeon



1  
2  
3 Mr Syed Qadri, Consultant Thoracic Surgeon

4  
5 Karen Dobbs, Research Nurse

6  
7 Paul Atkin, Research Nurse

8  
9 Dominic Fellowes, Research Nurse

10  
11 Leanne Cox, Clinical Trials Assistant

12  
13  
14 **Edinburgh Royal Infirmary:**

15 Mr Vipin Zamvar, Principal Investigator, Consultant Cardiothoracic Surgeon

16  
17 Lucy Marshall, Research Nurse

18  
19 Fiona Strachan, Research Nurse Manager

20  
21 Stacey Stewart, Research Nurse

22  
23  
24 **Independent Trial Steering Committee members**

25 Professor Ruth Langley (Chair), Professor of Oncology and Clinical Trials

26  
27 Professor Joy Adamson, Professor of Applied Health Research & Ageing

28  
29 Mr Ian Hunt, Consultant Thoracic Surgeon

30  
31 Professor Peter Licht, Professor of Cardiothoracic Surgery

32  
33 Dr Arjun Nair, Consultant Radiologist

34  
35 Mr Chris Hall, Patient representative

36  
37 Mr Mike Cowen, Consultant Cardiothoracic Surgeon (from study start to Jan 2017)

38  
39  
40 **Independent Data Monitoring and Safety Committee members**

41 Ms Susan J Dutton (Chair since May 2017, previously member of the Committee),

42  
43 University Research Lecturer and Oxford Clinical Trials Research Unit (OCTRU)

44  
45 Lead Statistician

46  
47 Mr Alan Kirk, Consultant Thoracic Surgeon

48  
49 Professor Keith Kerr, Professor of Pulmonary Pathology

50  
51 Mr Rajesh Shah, Consultant Thoracic Surgeon

52  
53 Dr Nagmi Qureshi, Consultant Radiologist

54  
55 Professor Tom Treasure, Professor of Cardiothoracic Surgery (Chair from study start  
56 to March 2017)

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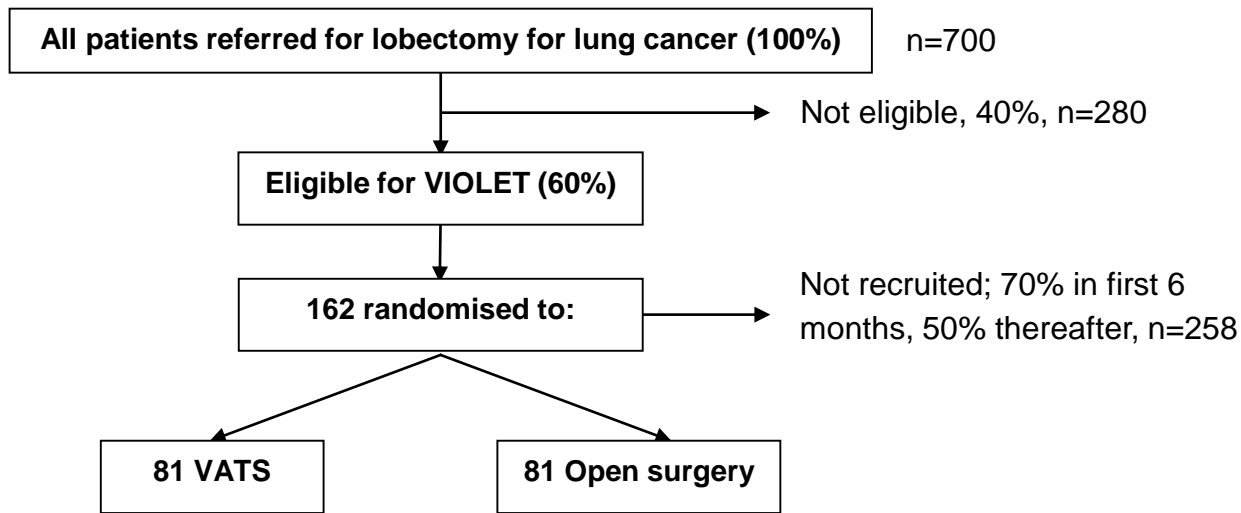
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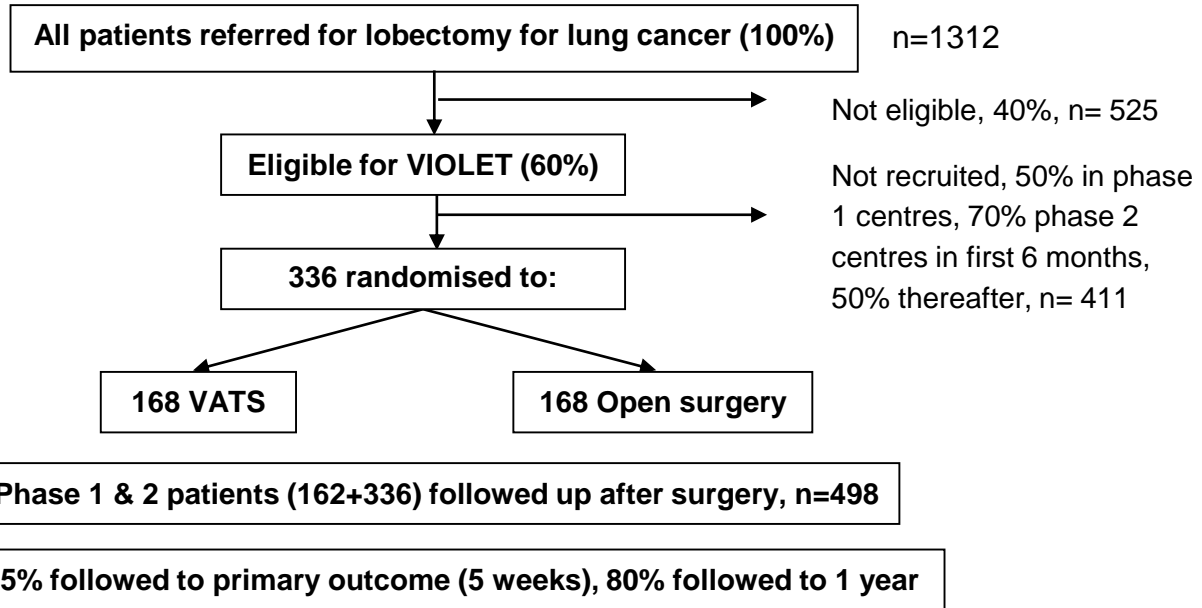
## Phase 1, in 5 centres (21 months recruitment)



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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

## Phase 2, in 9 centres (24 months recruitment)



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



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 4, 5  
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention  
 5

6 6b Explanation for choice of comparators 5  
 7

8 Objectives 7 Specific objectives or hypotheses 5  
 9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), 5, 6  
 11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  
 12  
 13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 5, 6  
 17 be collected. Reference to where list of study sites can be obtained  
 18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 6, 7  
 20 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
 21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 8, 9  
 23 administered  
 24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 8-11  
 26 change in response to harms, participant request, or improving/worsening disease)  
 27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 11, 12  
 29 (eg, drug tablet return, laboratory tests)  
 30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 8-11  
 32

33 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 9, 10  
 34 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,  
 35 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen  
 36 efficacy and harm outcomes is strongly recommended  
 37

38 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 9, 10  
 39 participants. A schematic diagram is highly recommended (see Figure)  
 40  
 41  
 42



1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13, 14
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-17
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7, 8
11				
12				
13				
14				
15				
16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7, 8
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7, 8
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10, 11
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10, 13, 14
34				
35				
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37				
38				
39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14-16, 20
40				
41				
42				

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17, 18
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27
17				
18				
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20				
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20, 21
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	3, 15
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 10
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20, 22
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
14				
15				
16				
17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 15
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
35				
36				

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
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 41  
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