The VIOLET study

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Effective Date:	11/11/2019

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List of abbreviations

Acronym	Details
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTEU	Clinical Trials and Evaluation Unit
CVA	Cerebrovascular accident
DLCO	Diffusing capacity of the lungs for carbon monoxide
DMSC	Data monitoring and safety committee
DVT	Deep vein thrombosis
ECOG	Eastern cooperative oncology group
EORTC	European organisation for research and treatment of cancer
EQ5D	European Quality of Life-5 Dimensions
FVC	Forced vital capacity
GI	Gastrointestinal
GMR	Geometric mean ratio
HR	Hazard ratio
IQR	Inter quartile range
ITT	Intention to treat
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MD	Mean difference
MDT	Multi-disciplinary team
OR	Odds ratio
PIC	Patient identification centre
QLQ-C30	Quality-of-life Questionnaire Core 30
QLQ-LC13	Quality-of-life Questionnaire Lung Cancer 13
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TIA	Transient ischemic attack
TNM	Classification of malignant tumours (TNM)
VAS	Visual analogue scale
VATS	Video assisted thorascopic surgery

1. INTRODUCTION TO SAP

1.1 Scope

This statistical analysis plan (SAP) details information regarding the statistical analysis of the VIOLET randomised controlled trial (RCT) and covers all analyses of study data outlined in the study protocol, with the exception of the health economic evaluation.

1.2 Editorial changes

Any changes made to this SAP after approval must be clearly justified and documented as an amendment at the end of this document. The SAP should then be re-approved.

1.3 SAP document approval

The co-director of the Clinical Trials and Evaluation Unit (CTEU) should authorise this document.

1.4 Skeleton tables and figures

Throughout this document references are made to any skeleton tables and figures to be used in the reporting of the study (e.g. **Figure F1** or **Table T1**). Such tables and figures can be found in **Appendix A** of this document and are intended as a guide for study reporting. Final versions of the tables/figures may differ: tables may be combined, and/or their layout or numbering may differ. However, the content should be consistent with **Appendix A.**

2. STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

The VIOLET study is a multi-centre double-blind parallel RCT. It aims to test the superiority of video assisted thorascopic surgery (VATS) lobectomy versus open lobectomy in adult patients with early stage lung cancer.

2.2 Study objectives

The VIOLET study aims to compare the effectiveness, cost-effectiveness and acceptability of VATS lobectomy versus open surgery for treatment of lung cancer.

Specific objectives are to estimate:

(a) The difference between groups in self-reported physical function at five weeks

(b) The difference between groups with respect to a range of secondary outcomes including assessment of efficacy (hospital stay, pain, proportion and time to uptake of chemotherapy), measures of safety (adverse health events), oncological outcomes (proportion of patients upstaged to pN2 disease and disease-free survival) and overall survival.

(c) The cost effectiveness of VATS and open surgery.

2.3 Primary outcome

The primary outcome is self-reported physical function, assessed using the QLQ-C30 questionnaire, at 5 weeks post-randomisation.

2.4 Secondary outcomes

Secondary outcomes are listed in the study protocol as:

(1) Time from surgery to hospital discharge

(2) Pain scores in the first two days post-surgery

(3) Adverse health events to one year

(4) Proportion and time to uptake of adjuvant treatment

(5) Proportion of patients upstaged to pN2 disease

(6) Overall and disease-free survival to one year

(7) Proportion of patients who undergo complete resection (i.e. R(0) resection) during the procedure

(8) Proportion of patients who experience prolonged incision pain (defined as the need of analgesia > 5 weeks post randomisation that was not being taken pre-operatively)

(9) Generic and disease-specific HRQoL: EORTC QLQ-C30, QLQ-LC13 and EQ5D to one-year (measured at 2 weeks, 5 weeks, 3 months, 6 months and 12 months post-randomisation)

(10) Resource use to one year (measured for the duration of post-operative hospital stay until discharge, and at 5 weeks, 3 months, 6 months and 12 months post-randomisation)

Additional secondary outcomes:

(11) Proportion of patients upstaged to pN1 disease

As stated in section 1.1, outcome (10) is not covered in this SAP. Outcome (11) is not specified in the protocol but was added at the request of the chief investigator before any knowledge of the accruing data.

2.5 Changes to the study objectives during the course of the study

There have been several changes to the protocol since Research Ethics Committee (REC) approval was granted and the first centre opened to recruitment. These changes are summarised below.

October 2015	Removal of reference to RECIST criteria for disease assessment Addition of PIC sites
June 2017	Amended inclusion criteria to reflect inclusion of patients undergoing bi-lobectomy and the transition to TNM8 Clarification that events planned before surgery are not unexpected Details of phase 2 sites added
February 2018	Clarified location of 'bleeding' that is classified as an expected adverse event
January 2019	CTCAE grade changed to v5.0

The impact of these changes for the analysis of the study data are as follows:

- Transition to TNM8 – all patients staged under TNM7 will be restaged under TNM8
- Changes to eligibility criteria – eligibility will be assessed according to the protocol in place at the time of recruitment
- Changes to CTCAE grading – adverse events will be graded according to the CTCAE version in place at the time of the event

3. STUDY POPULATION

The study population is all patients aged ≥16 years of age who have been referred by the multi-disciplinary team (MDT) for lung resection for known or suspected lung cancer. Eligibility criteria are as inclusive as possible to promote the applicability of the evidence obtained during the trial. For specific inclusion/exclusion criteria see **Figure F1**.

Recruitment over time against targets will be presented overall (**Figure F2**).

The planned sample size for the VIOLET study is 498 patients. This sample size would be sufficient to detect a different of 0.25 standard deviations in physical function between the VATS and open groups with 90% power and 5% significance (2-tailed). The total sample size will allow for a 20% dropout at one year.

3.1 Flow of participants

Participant flow will be described via a flowchart (see **Figure F1**). Follow-up will last 12 months with follow-up visits planned at 5 weeks, 3 months, 6 months and 12 months post-randomisation.

3.2 Randomisation

Patients are randomised (1:1 ratio) to either VATS lobectomy or open lobectomy. Randomisation will be stratified by study centre and minimised by surgeon. Randomisation will take place within one week of the planned operation date, once eligibility has been confirmed and consent given. The randomisation will take place using a secure password protected internet-based system.

3.3 Protocol deviations

The following types of protocol deviation will be considered:

- Patient did not meet the study eligibility criteria but was treated in the study.
- Patient did not undergo lobectomy
- Patient received the alternative intervention to that they were allocated (only includes patients who underwent a lobectomy

Note it may be possible for patients to be classified as a protocol deviation for more than one reason.

The frequency of each type of deviation will be tabulated by treatment allocation (see **Table T1**).

3.4 Withdrawals

A patient (or a clinician on their behalf) can withdraw from the study at any time. In some cases, patients may be happy for data collection to continue, and therefore such patients will be included in the study analyses on an intention to treat basis (ITT), see **section 3.5**.

Data on all withdrawals is captured on a specific case report form (CRF) and will be tabulated by treatment allocation; see **Table T2.**

3.5 Analysis population

The analysis population consists of all randomised patients excluding:

- Patients who died after randomisation but prior to any data collection.

- Patients withdrawn who were unwilling for data collected to be used.

The main study analyses will be performed on an ITT basis, including randomised participants who are not found to have lung cancer. A modified ITT analysis excluding these participants will also be performed for the primary outcome.

3.6 Safety population

The safety population for the main trial analyses will consist of **all** randomised patients, excluding patients withdrawn who were unhappy for data collected to be used.

Participants will be grouped according to the treatment allocated and events in participants who received the alternative treatment (e.g. VATS received by participant randomised to open or vice versa), did not undergo a lobectomy, or received no treatment will be detailed in footnotes.

4. DATA COLLECTION

A summary of data collection is shown below.

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

5. DERIVATIONS

5.1 Primary outcome

The primary outcome is self-reported physical function (QLQ-C30) at 5 weeks post randomisation. Physical function will be measured at baseline, 2 weeks, 5 weeks, 3, 6 and 12 months.

New variable	Rules
Physical functioning (PF2) raw score	**At each time point:** = mean of questions 1 to 5, if at least three of the questions are non-missing **MISSING:** otherwise
PF2 overall score	**At each time point:** = [1- (PF2 raw score-1)/3] * 100

5.2 Secondary outcomes

1. Time from surgery to hospital discharge

Both time from surgery until first fit for discharge, and time from surgery until hospital discharge will be described. Time from surgery until hospital discharge will be compared between groups.

New variable	Rules
Time from surgery to hospital discharge	= (Discharge date – operation date)
Fit for discharge	**YES:** if satisfactory mobility = YES AND pain under control with oral analgesia = YES AND satisfactory Hb & electrolytes = YES AND satisfactory chest X-ray = YES (or satisfactory on a previous day and not necessary to repeat) AND free from complications requiring treatment = YES **NO:** if satisfactory mobility = NO OR pain under control with oral analgesia = NO OR satisfactory Hb & electrolytes = NO OR satisfactory chest X-ray = NO (or not done and not previously satisfactory) OR free from complications requiring treatment = NO **MISSING:** otherwise
Time from surgery to fit for discharge	= (First day fit for discharge – operation date)

2. Pain scores in the first two days post-surgery

Pain scores are collected at baseline (prior to surgery), day one post-surgery and day two post-surgery. Pain scores are collected directly on CRFs using the visual analogue scale (VAS) and so no derivation is required.

3. Adverse health events to 1 year

All adverse events occurring at any time during the 12 month follow-up period will be reported.

New variable	Rules
Maximum intensity of SAE (CTCAE)	Maximum of CTCAE variable on initial SAE form and all follow-up SAE forms

4. Proportion and time to uptake of adjuvant treatment

The proportion of patients receiving adjuvant treatment at any time during the 12 month follow-up period will be described. The time to uptake of adjuvant treatment will be calculated as follows:

New variable	Rules
Uptake of adjuvant treatment	**YES:** if at any study visit, chemotherapy or radiotherapy started = YES **NO:** if at all attended study visits, chemotherapy and radiotherapy started = NO **MISSING:** otherwise
Time to uptake of adjuvant therapy	= (Earliest chemotherapy/radiotherapy start date - randomisation date)

5. Proportion of patients upstaged to pN2 disease after the procedure

The proportion of patients upstaged to pathological N2 disease following surgery will be derived as follows:

New variable	Rules
Upstaged to pN2	**YES:** if pathological disease stage of primary tumour = N2 **NO:** if pathological disease stage of primary tumour = N0 OR N1 **NOT CANCER:** no cancer, sample benign **MISSING:** otherwise

6. Overall and disease-free survival to 1 year

Both overall and disease-free survival to 12 months will be compared between groups.

New variable	Rules
Time to death (days)	(Death date – randomisation date)
Death censor variable	**YES:** if patient did not die before the end of follow-up **NO:** if patient died before the end of follow-up **MISSING:** otherwise
Time to disease progression (days)	(Date of earliest disease recurrence – randomisation date)
Disease progression censor variable	**YES:** if patient did not have disease progression before the end of follow-up **NO:** if patient had disease progression before the end of follow-up **MISSING:** otherwise

7. Proportion of patients who undergo complete resection during the procedure

Completeness of the resection will be defined as follows:

New variable	Rules
Complete resection	**YES:** if resection completeness = R0 (no residual tumour) **NO:** if resection completeness = R1 (microscopic residual tumour) OR R1 (other than microscopic residual tumour) OR R2 (macroscopic residual tumour) **MISSING:** otherwise

8. Proportion of patients who experience prolonged incision pain

Prolonged incision pain is defined as the need for analgesia after 5 weeks post-randomisation.

New variable	Rules
Prolonged incision pain	**YES:** if patient continuously prescribed analgesia until after 5 weeks post-randomisation that was not being taken preoperatively **NO:** if patient not continuously prescribed analgesia until after 5 weeks post-randomisation OR patient continuously prescribed analgesia that was administered pre-operatively until after 5 weeks **MISSING:** otherwise

9. General and disease-specific HRQoL: EORTC QLQ-C30, QLQ-LC13 and EQ5D to 1 year

The QLQ-C30, QLQ-LC13 and EQ5D questionnaires are completed at baseline, 2 weeks, 5 weeks, 3, 6 and 12 months. Details for how to derive the overall and sub-scale scores for these three questionnaires can be found below in the respective tables. The EORTC core questionnaire and associated modules scoring manual will be used to derive the QLQ-C30 and QLQ-LC13 scores [(1)].

New variable – QLQ-C30	Rules
Global health status (QL2) raw score	**At each time point:** = mean of question 29 and 30, if both non-missing **MISSING:** otherwise
QL2 overall score	**At each time point:** = [(QL2 raw score-1)/6] * 100
Role functioning (RF2) raw score	**At each time point:** = mean of question 6 and 7, if both non-missing **MISSING:** otherwise
RF2 overall score	**At each time point:** = [1- (RF2 raw score-1)/3] * 100
Emotional functioning (EF) raw score	**At each time point:** = mean of questions 21 to 24, if at least two questions are non-missing **MISSING:** otherwise
EF overall score	**At each time point:** = [1- (EF raw score-1)/3] * 100

Cognitive functioning (CF) raw score	**At each time point:** = mean of question 20 and 25, if both non-missing **MISSING:** otherwise
CF overall score	**At each time point:** = [1- (CF raw score-1)/3] * 100
Social functioning (SF) raw score	**At each time point:** = mean of question 26 and 27, if both non-missing **MISSING:** otherwise
SF overall score	**At each time point:** = [1- (SF raw score-1)/3] * 100
Fatigue (FA) raw score	**At each time point:** = mean of questions 10, 12 and 18, if at least two are non-missing **MISSING:** otherwise
FA overall score	**At each time point:** = [(FA raw score-1)/3] * 100
Nausea and vomiting (NV) raw score	**At each time point:** = mean of questions 14 and 15, if both non-missing **MISSING:** otherwise
NV overall score	**At each time point:** = [(NV raw score-1)/3] * 100
Pain (PA) raw score	**At each time point:** = mean of questions 9 and 19, if both non-missing **MISSING:** otherwise
PA overall score	**At each time point:** = [(PA raw score-1)/3] * 100
Dyspnoea (DY) raw score	**At each time point:** = question 8 **MISSING:** otherwise
DY overall score	**At each time point:** = [(DY raw score-1)/3] * 100
Insomnia (SL) raw score	**At each time point:** = question 11 **MISSING:** otherwise
SL overall score	**At each time point:** = [(SL raw score-1)/3] * 100
Appetite loss (AP) raw score	**At each time point:** = question 13 **MISSING:** otherwise
AP overall score	**At each time point:** = [(AP raw score-1)/3] * 100
Constipation (CO) raw score	**At each time point:** = question 16 **MISSING:** otherwise
CO overall score	**At each time point:** = [(CO raw score-1)/3] * 100
Diarrhoea (DI) raw score	**At each time point:** = question 17 **MISSING:** otherwise
DI overall score	**At each time point:** = [(DI raw score-1)/3] * 100
Financial difficulties (FI) raw score	**At each time point:** = question 28 **MISSING:** otherwise
FI overall score	**At each time point:** = [(FI raw score-1)/3] * 100

New variable – QLQ-LC13	Rules
Dyspnoea (LCDY) raw score	**At each time point:** = mean of questions 3 to 5, if all three questions are non-missing **MISSING:** otherwise
LCDY overall score	**At each time point:** = [(LCDY raw score-1)/3] * 100
Coughing (LCCO) raw score	**At each time point:** = question 1 **MISSING:** otherwise
LCCO overall score	**At each time point:** = [(LCCO raw score-1)/3] * 100
Haemoptysis (LCHA) raw score	**At each time point:** = question 2 **MISSING:** otherwise
LCHA overall score	**At each time point:** = [(LCHA raw score-1)/3] * 100
Sore mouth (LCSM) raw score	**At each time point:** = question 6 **MISSING:** otherwise
LCSM overall score	**At each time point:** = [(LCSM raw score-1)/3] * 100
Dysphagia (LCDS) raw score	**At each time point:** = question 7 **MISSING:** otherwise
LCDS overall score	**At each time point:** = [(LCDS raw score-1)/3] * 100
Peripheral neuropathy (LCPN) raw score	**At each time point:** = question 8 **MISSING:** otherwise
LCPN overall score	**At each time point:** = [(LCPN raw score-1)/3] * 100
Alopecia (LCHR) raw score	**At each time point:** = question 9 **MISSING:** otherwise
LCHR overall score	**At each time point:** = [(LCHR raw score-1)/3] * 100
Pain in chest (LCPC) raw score	**At each time point:** = question 10 **MISSING:** otherwise
LCPC overall score	**At each time point:** = [(LCPC raw score-1)/3] * 100
Pain in arm or shoulder (LCPA) raw score	**At each time point:** = question 11 **MISSING:** otherwise
LCPA overall score	**At each time point:** = [(LCPA raw score-1)/3] * 100
Pain in other parts (LCPO) raw score	**At each time point:** = question 12 **MISSING:** otherwise
LCPO overall score	**At each time point:** = [(LCPO raw score-1)/3] * 100

Pain medication (LCPM) raw score	**At each time point:** = question 13 **MISSING:** otherwise
LCPM overall score	**At each time point:** = [(LCPM raw score-1)/3] * 100

New variable – EQ5D	**Rules**
EQ5D single summary index score	Five digit 'state' score is derived as: 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score. Each state score is then assigned a single summary index score according to reference scales. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health.

10. Proportion of patients upstaged to pN1 disease after the procedure

The proportion of patients upstaged to pathological N1 disease following surgery will be derived as follows:

New variable	**Rules**
Upstaged to pN1	**YES:** if clinical disease stage of primary tumour = N0 AND pathological disease stage of primary tumour = N1 **NO:** if either: • pathological disease stage of primary tumour = N0 OR N2 • clinical disease stage of primary tumour = N1 **NOT CANCER:** no cancer, sample benign **MISSING:** otherwise

5.3 Other variables

Details for any other variables which will be derived for use in any other figures or tables are given below:

New variable	**Rules**
Exclusion category	**INELIGIBLE:** any of the inclusion criteria are NO, or any of the exclusion criteria are YES **NOT APPROACHED:** patient is eligible, patient approached = NO **DID NOT CONSENT:** patient is eligible, patient approached = YES, patient consented = NO **OTHER:** patient is eligible, patient approached = YES, patient consented = YES, randomised = NO
Age at randomisation (years)	= (date of randomisation – date of birth)/365.25
Body mass index (BMI)	= weight (kg) / height $(cm)^2$ * 10,000
Protocol deviation 1 – patient did not meet the study eligibility criteria but was randomised	**YES:** if patient was not eligible at screening but was randomised **NO:** if patient was eligible **MISSING:** otherwise

Protocol deviation 2 – patient did not undergo a lobectomy	**YES:** if lobectomy = NO **NO:** if lobectomy = YES **MISSING:** otherwise
Protocol deviation 3 – patient received alternative allocation (only includes those who underwent a lobectomy)	**YES:** if either: • Allocation = VATS AND lobectomy received = open • Allocation = open AND lobectomy received = VATS **NO:** if either: • Allocation = VATS AND lobectomy received = VATS • Allocation = open AND lobectomy received = open **MISSING:** otherwise
Protocol deviation 4 – more than four ports/incisions used	**YES:** if more than four ports/incisions used during procedure **NO:** if less than four ports/incisions used during procedure **MISSING:** otherwise
Conversion from VATS to open	**YES:** if allocated to VATS AND open lobectomy received **NO:** if allocated to VATS AND VATS lobectomy received **MISSING:** otherwise
Benign disease on frozen section	**YES:** if frozen section = YES AND frozen section diagnostic = YES AND malignancy confirmed = NO **NO:** if either: • Frozen section = NO • Frozen section = YES AND frozen section diagnostic = NO • Frozen section = YES AND frozen section diagnostic = YES AND malignancy confirmed = YES **MISSING:** otherwise
Benign disease on post-operative pathology	**YES:** if post-operative pathology = benign **NO:** if post-operative pathology = cancer **MISSING:** if benign disease on frozen section = YES
Blinding indices	Blinding indices will be calculated for both patients (2 days post-surgery and discharge) and nurses (discharge, 5 weeks and 12 months) using the method proposed by Bang el al [(2)].
Duration of drain	= drain of drain removal – operation date
FEV_1, FVC expected values	Expected values are calculated using the method proposed by Quanjer et al [(3)].
TLco expected values	Expected values are calculated using the method proposed by Stanojevic et al [(4)].
FEV_1, FVC, TLco % predicted	= (observed value/expected value)*100

6. STATISTICAL ANALYSES

6.1 Baseline data and operative data

Baseline data (i.e. patient demography and past history) will be described by treatment group for patients in the analysis population. **Table T4** will be used as a template for this.

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number (n/N) and percentage.

Any imbalances in the characteristics of the patients at the start of the study will be described but statistical tests for baseline imbalance will not be carried out.

Operative details will be described by treatment group for patients in the analysis population. **Table T5** will be used as a template for this.

6.2 Primary and secondary outcome data

Primary and secondary outcome data will be described by treatment group for patients in the analysis population. The choice of summary statistics will be as for the baseline data. Treatment effects will be reported graphically with 95% confidence intervals (CIs), and with numerical details alongside (cf. Forest plot). **Figures F4 to F7** will be used as templates for this.

6.2.1 Adjustment in models

The intention is to adjust all models for centre and the factors included in the cohort minimisation: operating surgeon, both as random effects. If there is a change in surgeon after randomisation, models will adjust for the surgeon who performed the intervention and not the surgeon originally allocated to perform the procedure.

If the frequency of the outcome is insufficient to allow estimation of regression coefficients for all these variables (e.g. rare binary outcomes), the variables with coefficients that cannot be estimated will be omitted.

For continuous outcomes that are measured preoperatively as well as postoperatively, preoperative and postoperative values will be modelled jointly in preference to the preoperative value being modelled as a covariate. Joint modelling will avoid the necessity to either exclude cases with missing baseline measures or to impute missing baseline values.

6.2.2 Analysis models

All outcomes listed in the study protocol will be presented as per the template tables **Table T11** to **T18**. General methods of presentation and assessing treatment effects are outlined below. For all treatment comparisons, the open lobectomy group will be the reference group. Details specific to each outcome are described as appropriate.

Each outcome will be considered under a certain data type, as outlined in the table below:

Date type	Outcomes
Binary	Proportion of patients receiving adjuvant treatment
	Proportion of patients who undergo complete resection during the procedure
	Proportion of patients who experience prolonged incision pain
	Any in-hospital adverse event
	Any in-hospital serious adverse event
Categorical	Proportion upstaged to pN1 disease after the procedure
	Proportion upstaged to pN2 disease after the procedure
Time to event	Time from surgery to hospital discharge
	Time to uptake of adjuvant treatment
	Overall survival
	Disease-free survival
Longitudinal	Physical function (primary)
	Pain scores in the first two days post-surgery
	HRQoL (QLQ-C30, QLQ-LC13, EQ5D)

Each type of data will be summarised and compared between the groups according to the following:

- **Binary outcomes** will be presented as numbers and percentages of patients in each treatment group. Outcomes will be compared between treatment groups using generalised linear models, with treatment comparison estimates presented as adjusted risk ratios (RR) and risk differences (RD) with 95% confidence intervals (95% CI). Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome (with at least one event in each treatment group).
- **Categorical outcomes** will be presented as numbers and percentages of patients in each treatment group in each category. Outcomes will be compared between treatment groups using multinomial logistic regression, with treatment comparison estimates presented as adjusted RR and 95% CI.
- **Time to event outcomes** will be summarised by the median and IQR or mean and SD in each treatment group, estimated from survival modelling. Outcomes will be compared using Cox's proportional hazards, parametric models, or interval censoring methods for analysing discrete time data, as appropriate. The choice of model used will depend on the outcome event and the distribution of the data. Treatment comparisons will be presented as hazard ratios (HRs) and 95% CI if a proportional hazards model is used, time ratios (TRs) and 95% CI if an accelerated failure time model is used, or OR and 95% CI if a discrete time proportional odds model is used. Times will be censored using censoring variables defined below:

Outcome	Censor variable
Time from surgery to hospital discharge	Date of death, if patient died before hospital discharge
Time to uptake of adjuvant treatment	Last visit date, if patient did not receive any adjuvant treatment
Overall survival	Last visit date, if patient was alive at the end of the study follow-up
Disease free survival	Last visit date, if patient was disease free at the end of the study follow-up

- **Continuous longitudinal outcomes** will be summarised as means and SDs (or medians and IQRs if distributions are skewed) at each time point. Outcomes will be compared using linear mixed effects methodology with the treatment group and study design variables fitted as per section 5.2.1, and patient terms fitted as random effects. Separate parameter estimates will be incorporated into models for 1) the mean baseline response across both treatment groups and 2) at each post-intervention time point for each treatment (i.e. saturated model with time fitted as a categorical variable). If the time x treatment interaction (post-intervention) is not statistically significant at the 10% level an overall treatment effect will be reported. If the interaction is statistically significant the changes in treatment effect with time will be described. Deaths will be accounted for by modelling HRQoL and survival jointly. When modelling EQ5D, patients who have died will be assigned a score of 0 for all future time points. Different variance/covariance structures will be explored, and the structure that provides the best fit in terms of information criteria such as AIC, BIC and likelihood ratio tests will be used. Treatment comparisons will be presented as adjusted differences in means with 95% CI.

6.2.3 Statistical significance

For hypothesis tests two-tailed p-values<0.05 are considered statistically significant. Likelihood ratio tests will be used in preference to Wald tests for hypothesis testing.

6.2.4 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods, e.g. residual plots, tests for proportional hazards, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses and comments made in footnotes. Sensitivity analyses may be performed to examine the effect on the study's conclusions of excluding outlying observations.

6.2.5 Subgroup analyses

A pre-specified subgroup analysis, comparing pain scores by type of analgesia (paravertable block versus intercostal block versus both versus neither) will be performed. This will consist of adding analgesia*treatment interaction terms to the pain score model (**see Figure F8)**.

6.2.6 Sensitivity analyses

A pre-specified sensitivity analysis excluding participants with benign disease will be performed for the primary outcome **(see Table T21)**.

Sensitivity analyses of overall survival and disease-free survival will be performed, adjusting for patient's disease stage based on pathological findings **(see Figure F11)**.

Note: these analyses of survival were not pre-specified in the protocol but added upon recommendation from the Data Monitoring and Safety Committee (DMSC).

6.2.7 Exploratory analyses

Two exploratory analyses of pain scores will be undertaken, the first is stated in the protocol, the second was requested by the DMSC.

1. Comparing pain scores in the first two days by incisions (VATS single port versus VATS with multiple port sites versus open surgery) **(see Tables T22 and T23)**.
2. Comparing pain scores in the first two-days post-surgery and at follow-up by type of thoracotomy performed (anterior thoracotomy versus posterolateral thoracotomy versus VATS; muscle sparing versus no muscle sparing; and rib-resection versus no rib-resection) (**see Figure F12 and Figure F13**).

An exploratory analysis comparing length of stay by incisions (VATS single port versus VATS multiple port versus open surgery) will be performed **(see Table T24)**. This analysis of length of stay was not pre-specified in the protocol but requested by the chief investigator before any comparative analyses were performed.

6.2.8 Missing data

In all tables missing data for continuous variables will be indicated by footnotes. For category variables missing data will be highlighted by use of observation counts. If the amount of missing data differs substantially between treatment groups potential reasons will be explored.

Missing predictors:

There will be no missing data for any of the randomisation factors (by design). All other potential predictors are baseline measurements of continuous longitudinal outcomes, and due to the joint modelling approach described previously the handling of missing values for such data is considered in the context of missing longitudinal data (see below).

Missing outcomes measured at one time point:

- If the proportion of missing data is less than 5% then complete case analysis will be performed (i.e. excluding cases with missing data).
- If the proportion of missing data is above 5% multiple imputation methods will be considered. A general imputation model that uses an iterative procedure to generate imputed values will be used to generate multiple complete data sets (e.g. using Stata's mi impute). The model of interest will be the fitted to each of the complete data sets and effect estimates combined using Rubin's rules. If appropriate, methods such as predictive mean matching will be used in order to ensure that imputed values lie within specific ranges.

Missing longitudinal data:

- For continuous data measured at multiple time points preoperative values will be modelled jointly with those measured postoperatively, as described previously, thereby allowing all cases with at least one observation to be included. If the proportion of cases that do not have at least one observation is above 5% then multiple imputation methods will be considered (see above). If appropriate (the level of missingness is >20%) then any variables that are predictive of missingness will be identified, and if there is reason to suggest that an assumption of missing at random (MAR) given these variables is reasonable (especially likely if the variable was measured pre-operatively) then such variables will be adjusted for in the models of interest. These models can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.

6.2.9 Multiple testing

For quality of life outcomes derived from the QLQ-C30 and QLQ-LC13 questionnaires, multiple testing will be accounted for by applying the false discovery rate method proposed by Benjamini Y and Hochberg Y[5]. This method will be applied within each instrument (e.g. for QLQ-C30 functional scale scores, QLQ-C30 symptom scale scores and QLQ-LC13 scores). No formal adjustment will be made for multiple testing for other outcomes. However as previously described formal statistical comparisons will not be made for outcomes with low event rates and only pre-specified subgroup analyses will be performed. Consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

6.3 Safety data

Adverse events (AEs) and serious adverse events (SAEs) occurring in the study period for all patients in the safety population will be tabulated as per **Table T19 and T20**.

Table T19 summarises AEs and SAEs experienced during the period from randomisation to hospital discharge. Such events are captured via the study CRFs.

Table T20 summarises SAEs experienced during the follow-up period from hospital discharge to 12 months post-randomisation.

All events will be coded using MedDRA and reported according to this classification system. The difference in the proportion of patients with any adverse event and with any serious adverse event (according to the standard GCP definition of serious) will be reported with a 95% CI. The outcome of serious events (alive or died following the event) will be described. The difference in proportion of patients experiencing an event (serious or non-serious) in each MedDRA system organ class group (SOC) will also be reported with 95% CIs for each SOC with events in both groups and at least five events in total across the two groups. These estimates will be displayed in a Forest plot (see Figure F9). P-values will not be included.

7. BIBLIOGRAPHY

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8. AMENDMENTS TO THE SAP

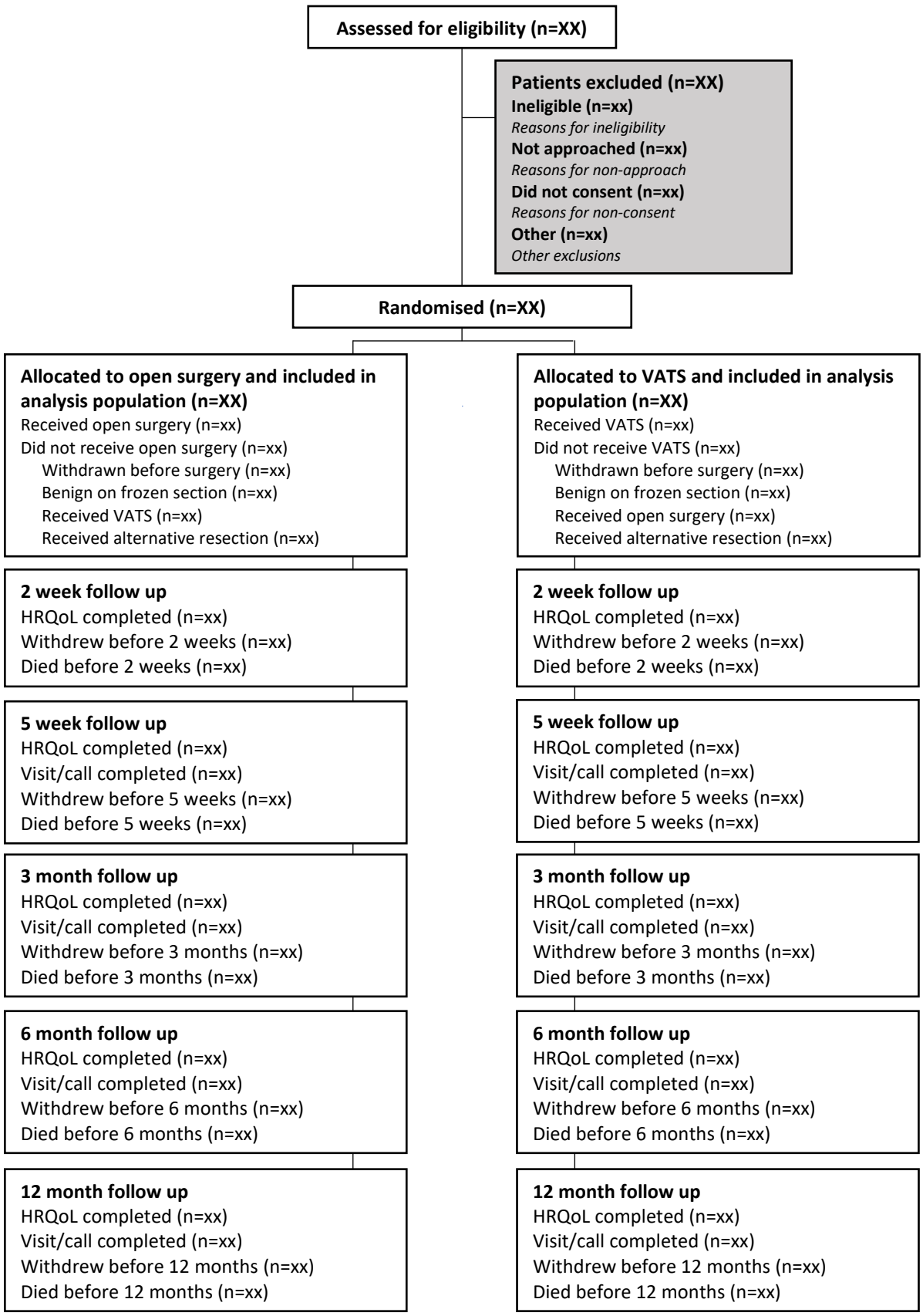
Previous version	Previous date	New version	New date	Brief summary of changes
1.0	04/07/2019	2.0	11/11/2019	Addition of the outcome upstaging to pN1 at the request of the chief investigator. Updating analysis models section to state risk ratios and risk differences will be presented instead of odds ratios for binary outcomes. Addition to safety data section to state all events will be MedDRA coded and the difference in proportion of patients experiencing an event in each MedDRA system organ class group will be reported. Update to adjustment in models section to remove adjustment for analgesia in pain score models as it was decided analgesia lay on the causal pathway and may therefore lead to biased estimates. Analgesia will be summarised by group instead.

APPENDIX A: SKELETON TABLES AND FIGURES

The following summarises the planned outputs:

Section	Outputs	
Section 1 Population	**Tables, figures and listings detailing the study population**	
	Figure F1	Flow of participants
	Figure F2	Predicted and actual recruitment
	Table T1	Protocol deviations
	Table T2	Details of conversions from VATS to open surgery
	Table T3	Withdrawals
Section 2 Baseline and intra-operative data	**Summary tables of demographic and operative information**	
	Table T4	Baseline demographic and clinical characteristics
	Table T5	Operative details
Section 3 Additional descriptive information	**Summary tables of additional descriptive information**	
	Figure F3	Pathology flow chart
	Table T6	Patient blinding at 2 days post-surgery
	Table T7	Patient blinding at discharge
	Table T8	Nurse blinding at discharge
	Table T9	Nurse blinding at 5 weeks
	Table T10	Nurse blinding at 12 months
Section 4 Primary and secondary outcome data	**Summary data and treatment estimates for primary and secondary outcomes**	
	Table T11	Primary outcome
	Figure F4	Primary outcome
	Table T12	In-hospital secondary outcomes
	Table T13	Additional secondary outcomes
	Table T14	Pain scores in the first two days post-surgery
	Figure F5	In-hospital secondary outcomes
	Figure F6	Mean ratios of in-hospital analgesia
	Figure F7	Additional secondary outcomes
	Table T15	QLQ-C30 global health status/functional scale scores
	Figure F8	Global health status over time
	Table T16	QLQ-C30 symptoms scale scores
	Table T17	QLQ-LC13
	Table T18	EQ5D
	Table T19	Adverse events and serious adverse events in-hospital
	Table T20	Serious adverse events during follow-up
	Table T21	Sensitivity analysis of primary outcome excluding patients with benign disease
	Figure F9	Adverse events in-hospital
	Figure F10	Subgroup analysis of pain score
	Figure F11	Sensitivity analysis of survival outcomes adjusting for pathological disease stage
	Figure F12	Exploratory analysis of in-hospital pain score by of thoracotomy performed
	Figure F13	Exploratory analysis of QLQ-C30 pain score by type of thoracotomy performed
	Table T22	Pain scores by number of port sites
	Table T23	Exploratory analysis comparing pain scores by number of port sites
	Table T24	Exploratory analysis comparing length of stay by number of port sites

Figure F1 Flow of participants



Notes:
[1] Patients may be ineligible for more than one reason
Benign patients are only followed-up to 5 weeks post-randomisation; allocated to open (n=xx), allocated to VATS (n=xx)

Figure F2 Predicted and actual recruitment

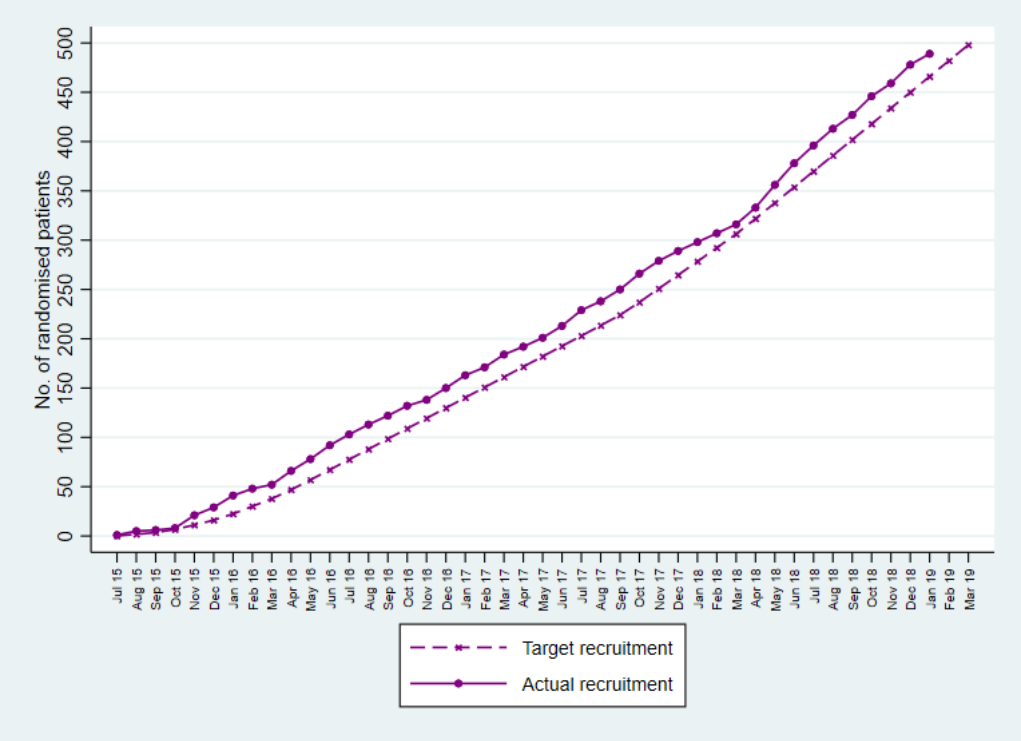


Table T1 Protocol deviations

	Randomised to open (n=XX)		Randomised to VATS (n=XX)		Overall (n=XX)	
	n	%	n	%	n	%
Any protocol deviation						
Patient ineligible but treated in the study						
Patient did not undergo lobectomy						
Patient received the opposite intervention to that they were allocated*						

Notes: **only includes patients who underwent a lobectomy*

Table T2 Details of conversions from VATS to open surgery

	Randomised to VATS (n=XX)	
	n	**%**
Converted from VATS to open		
Reason for conversion		
Technical problems		
Equipment malfunction		
Failure to progress		
Poor visualisation		
Anatomical problems		
Absent or thick fissure		
Calcified peri-arterial nodes		
Chest wall invasion		
Diffuse pleural adhesion		
Requirement for sleeve resection		
Oncological problems		
Discovery of N2 tumours		
Invasion of the artery		
Invasion of the parietal pleura		
Margin extension		

Table T3 Withdrawals

	Randomised to open (n=XX)		Randomised to VATS (n=XX)		Overall (n=XX)	
	n	**%**	**n**	**%**	**n**	**%**
Any withdrawal						
Timing of withdrawal						
Post-consent pre-randomisation						
Post-randomisation but before surgery						
After surgery						
Reason for withdrawal						
Clinician's advice						
Surgery no longer appropriate						
Patient no longer eligible						
Other						
Patient's decision						
Referral to another centre						

Patient changed their mind about the study	
Patient no longer wants surgery	
Refused to give reason	
Other	
Admin/logistical reasons	
Surgeon changed	
Other	
Further details	
Withdrawn from follow-up	

Notes:
Other reasons will be provided in footnotes

Table T4 Baseline demographic and clinical characteristics

		Randomised to open (n=XX)	Randomised to VATS (n=XX)	Overall (n=XX)
Baseline characteristics				
Age (years)				
Sex	Male			
	Female			
Smoking status (ever smoked)				
Ethnicity	White or Caucasian			
	Black / Black British			
	Mixed / multiple ethnic groups			
	Asian / Asian British			
	Other ethnic group			
Clinical TNM8 stage				
T1a				
T1b				
T1c				
T2a				
T2b				
T3				
N0				
N1				
M0				
Location of primary tumour				
Left upper lobe				

Left lower lobe	
Right upper lobe	
Right middle lobe	
Right lower lobe	
Other	
Baseline clinical measures	
BMI (kg/m^2)	
ECOG status	0
	1
	2
	3
Haemoglobin (g/dl)	
Platelets (x10^9/l)	
White cell count (x10^9/l)	
Neutrophils (x10^9/l)	
Lymphocytes (x10^9/l)	
CRP (Mg/L)	
Creatinine (µmol/l)	
Urea (µmol/l)	
-Lung function	
FEV_1 (% predicted)	
FVC (% predicted)	
DLCO (% predicted)	
Medical history	
Family history of lung cancer	
Respiratory comorbidity	
Neurological dysfunction	
Diabetes mellitus	
Alcoholism	
Previous lung surgery	
CVA/TIAs	
Cardiovascular comorbidity	
Chronic pain syndrome	
Deep vein thrombosis	
Previously treated malignancy	
Neoadjuvant treatment	
Pre-operative treatment	

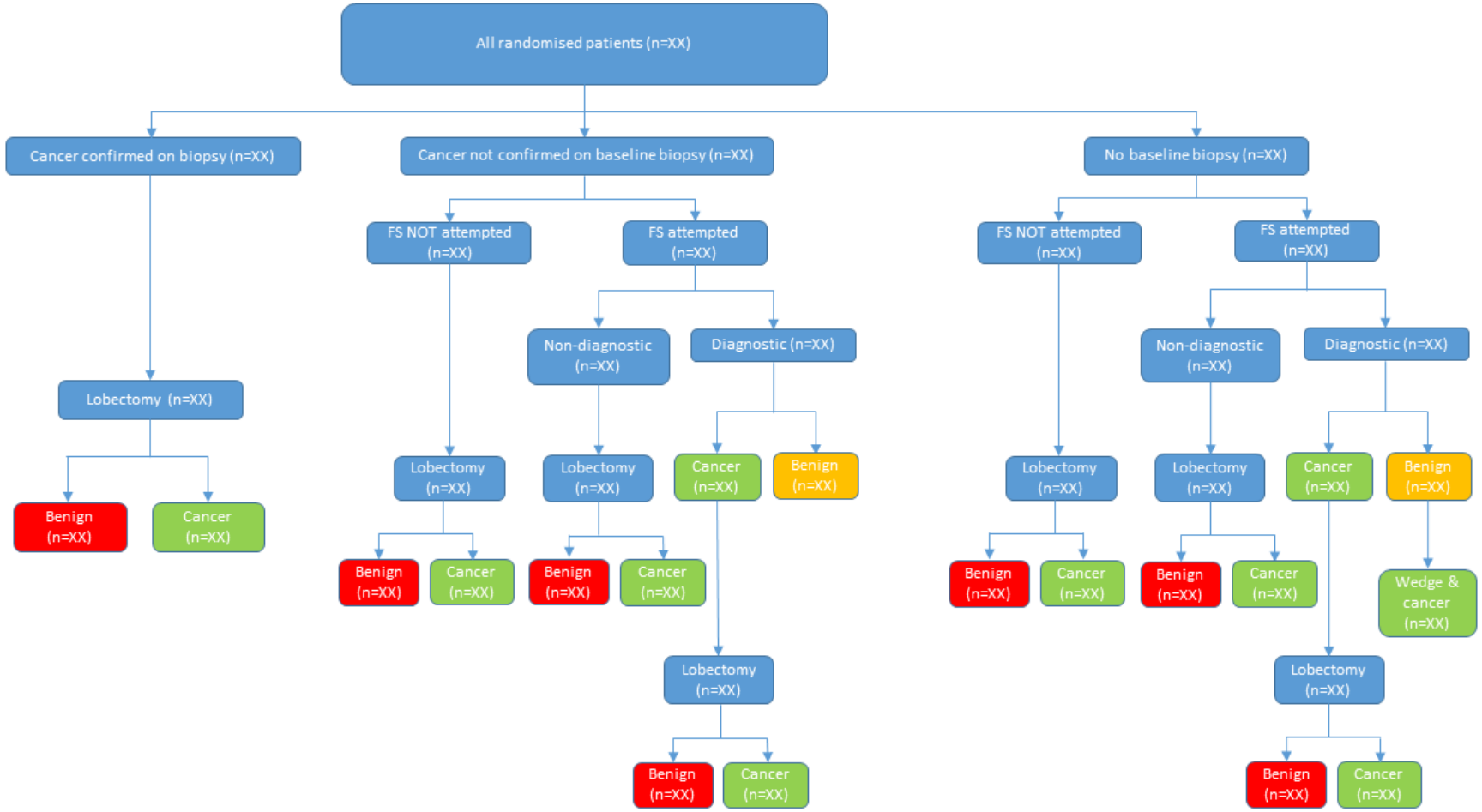
Data are presented as median (interquartile range), mean (standard deviation), or n (%).

Table T5 Operative details

		Randomised to open (n=XX)		Randomised to VATS (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
Operative strategy							
Frozen section biopsy planned							
Biopsy attempted							
Biopsy diagnostic							
Malignancy confirmed							
Resection details							
Benign disease on frozen section							
Open and close (inoperable/extensive malignancy)							
Resection of airway without removal of lung parenchyma							
Pneumonectomy							
Lobectomy/bilobectomy							
Segmentectomy							
Wedge resection							
Lobectomy and segmentectomy							
Lobectomy and wedge resection							
Lobectomy and resection of airway without removal of lung parenchyma							
Benign disease on frozen section and lobectomy							
Benign disease on frozen section and wedge resection							
Operation details							
First operator classification	Consultant surgeon						
	Trainee surgeon						
Prophylactic mini-tracheostomy tube used							
Number of N1 lymph node stations sampled	0						
	1-2						
	3-4						
	5						
Number of N2 lymph node stations sampled	0						
	1-2						
	3-4						
	5-6						
Anterior thoracotomy performed							

Postero-lateral thoracotomy performed	
Muscle sparing approach used	
Serratus muscle 'spared'	
Latissimus muscle 'spared'	
Number of ports/incisions used	1
	2
	3
	4
Duration of drain	
Intra-operative analgesia	
Single-shot paravertebral block	
Epidural	
Paravertebral catheter	
Intercostal block	
Other analgesia	

Figure F3 Pathology flow chart



Notes: *details of the resection in patients undergoing an alternative resection will be provided in footnotes*

Table T6 Patient blinding at two days post-surgery

Intervention	Patient's answer, n (%)				Question not asked, n
	VATS	Open	Do not know	Total	
VATS					
Open					
Total					

Blinding index (VATS: open) = X.XX (95% confidence interval [CI], X.XX to X.XX): X.XX (95% CI, X.XX to X.XX) (P=X.XX).

Table T7 Patient blinding at discharge

Intervention	Patient's answer, n (%)				Question not asked, n
	VATS	Open	Do not know	Total	
VATS					
Open					
Total					

Blinding index (VATS: open) = X.XX (95% confidence interval [CI], X.XX to X.XX): X.XX (95% CI, X.XX to X.XX) (P=X.XX).

Table T8 Nurse blinding at discharge

Intervention	Nurse's answer, n (%)				Question not asked, n
	VATS	Open	Do not know	Total	
VATS					
Open					
Total					

Blinding index (VATS: open) = X.XX (95% confidence interval [CI], X.XX to X.XX): X.XX (95% CI, X.XX to X.XX) (P=X.XX).

Table T9 Nurse blinding at 5 weeks

Intervention	Nurse's answer, n (%)				Question not asked, n
	VATS	Open	Do not know	Total	
VATS					
Open					
Total					

Blinding index (VATS: open) = X.XX (95% confidence interval [CI], X.XX to X.XX): X.XX (95% CI, X.XX to X.XX) (P=X.XX).

Table T10 Nurse blinding at 12 months

Intervention	Nurse's answer, n (%)				Question not asked, n
	VATS	Open	Do not know	Total	
VATS					
Open					
Total					

Blinding index (VATS: open) = X.XX (95% confidence interval [CI], X.XX to X.XX): X.XX (95% CI, X.XX to X.XX) (P=X.XX).

Table T11 Primary outcome

Outcome		Randomised to open (n=XX)		Randomised to VATS (n=XX)		Effect (95% CI)	p-value
		Mean/ Median	SD/IQR	Mean/ Median	SD/IQR		
Physical functioning	Baseline						
	2 weeks						
	5 weeks					MD/GMR	
	3 months						
	6 months						
	12 months						
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	

Notes: *higher scores indicate higher levels of functioning*
Analyses are adjusted for operating surgeon and centre

Figure F4 Primary outcome

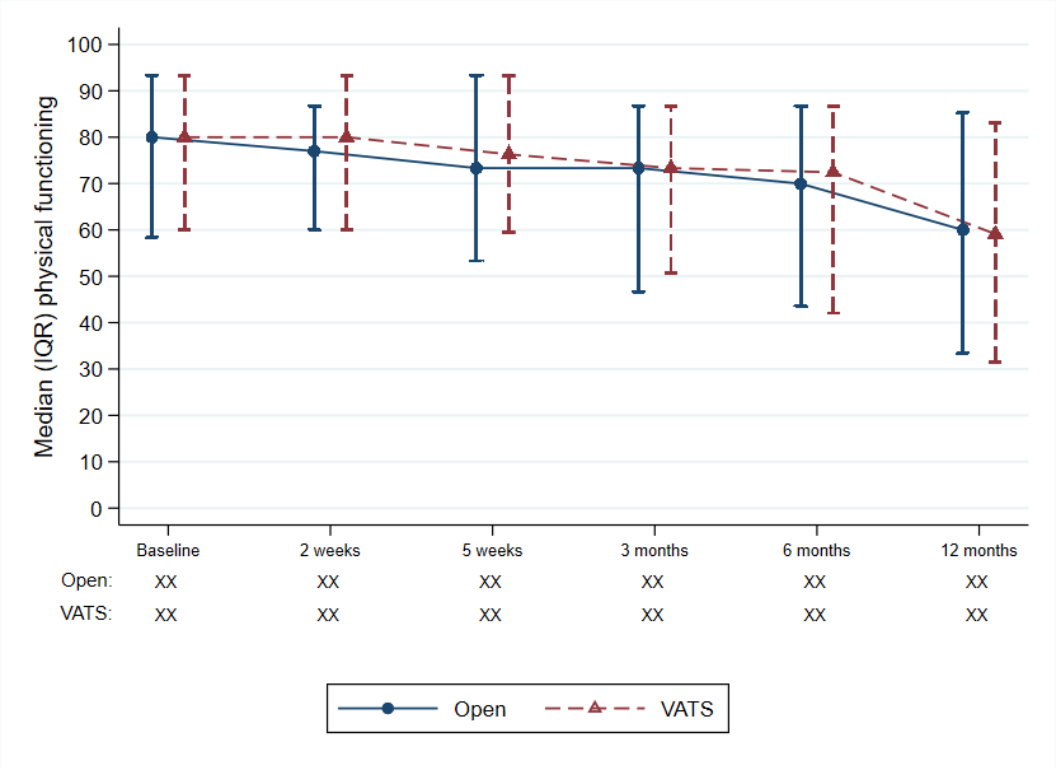


Table T12 In-hospital secondary outcomes

Outcome	Randomised to open (n=XX)	Randomised to VATS (n=XX)	Effect (95% CI)	p-value
Duration of hospital stay (days)			HR	
Upstaged from cN0 to pN1 disease after procedure			HR	
Upstaged from cN0 to pN2 disease after procedure			RR/RD	
Complete R(0) resection during procedure			RR/RD	
Any in-hospital adverse event			RR/RD	
Any in-hospital serious adverse event			RR/RD	

Values are presented as median (interquartile range), mean (standard deviation), or n (%).
Analyses are adjusted for operating surgeon and centre

Table T13 Post-discharge secondary outcomes

Outcome	Randomised to open (n=XX)	Randomised to VATS (n=XX)	Effect (95% CI)	p-value
Received adjuvant treatment			RR/RD	
Time to uptake of adjuvant treatment (months)			HR	
Overall survival (months)			HR	
Disease-free survival (months)			HR	
Prolonged incision pain			RR/RD	

Values are presented as median (interquartile range) or n (%).
Analyses are adjusted for operating surgeon and centre

Table T14 Pain scores in the first two days post-surgery

Outcome		Randomised to open (n=XX)		Randomised to VATS (n=XX)		Effect (95% CI)	p-value
		Mean/ Median	SD/IQR	Mean/ Median	SD/IQR		
Pain score	Baseline						
	Day 1 post-surgery					MD/GMR	
	Day 2 post-surgery					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	

Analyses are adjusted for operating surgeon and centre

Figure F5 In-hospital secondary outcomes

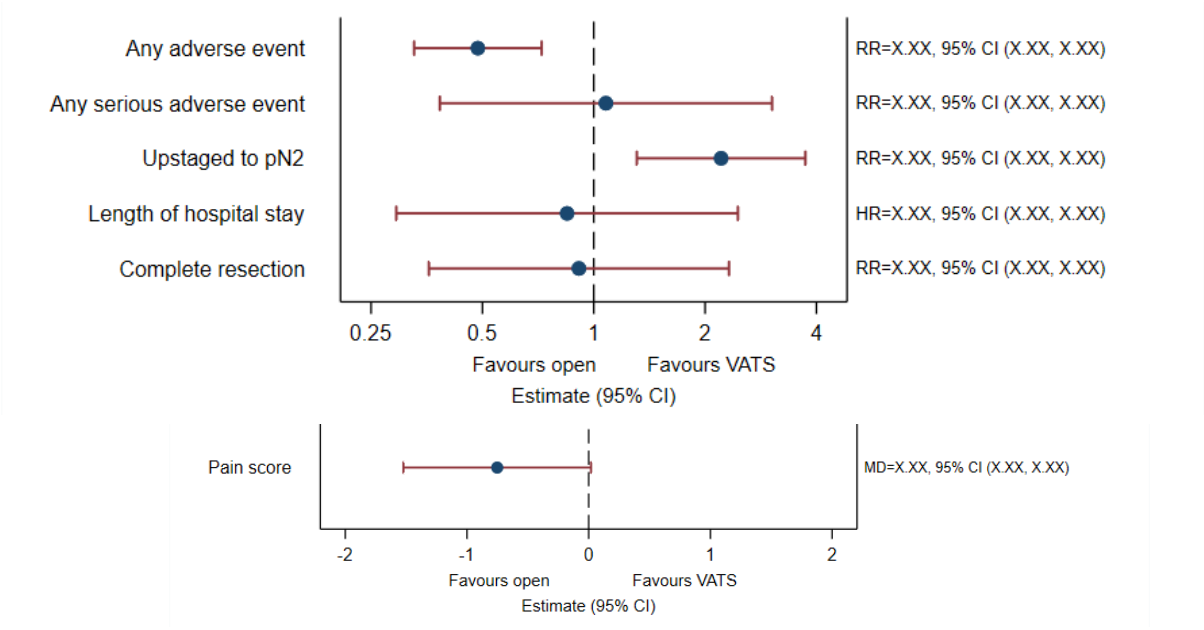
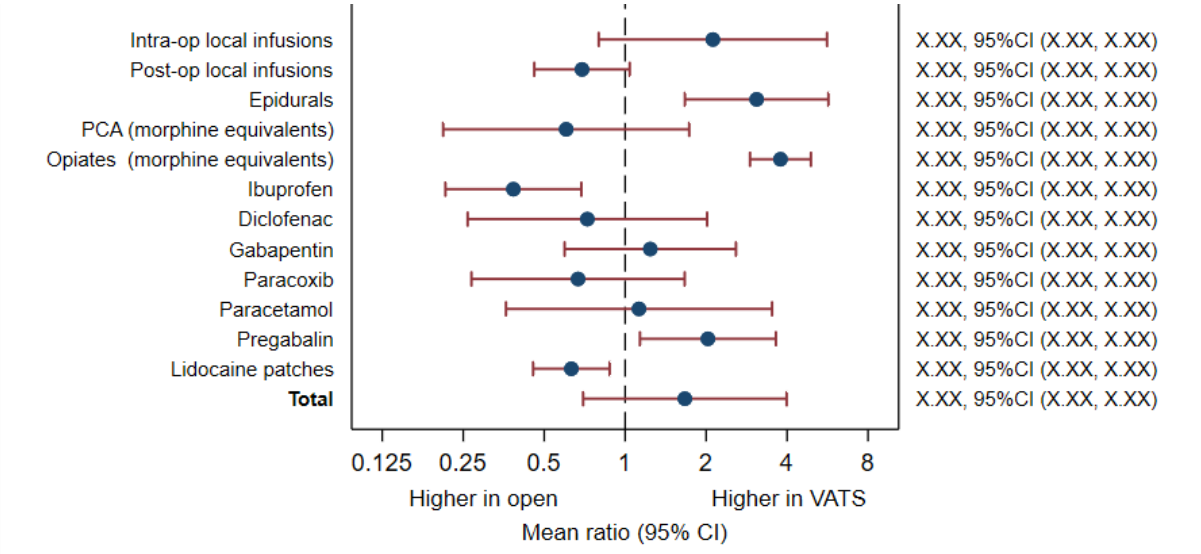


Figure F6 Mean ratios of in-hospital analgesia



Notes: *point estimate is ratio of mean daily dose of each analgesia in each group. 95% CI calculated by using bootstrap estimation with 10,000 replications to estimate the standard error of the mean ratio*

Figure F7 Primary outcome and post-discharge secondary outcomes

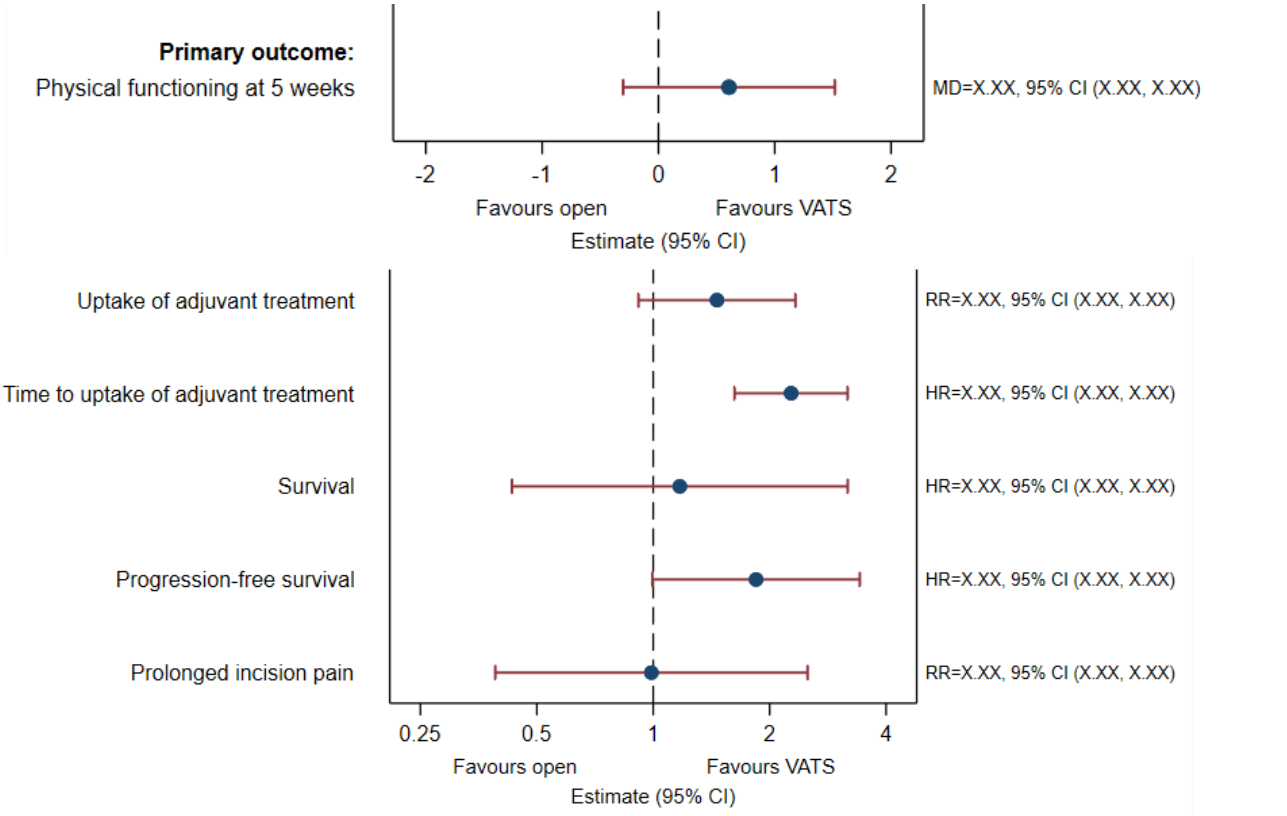


Table T15 QLQ-C30 global health status/functional scale scores

Outcome		Randomised to open (n=XX)		Randomised to VATS (n=XX)		Effect (95% CI)	p-value
		Mean/ Median	SD/IQR	Mean/ Median	SD/IQR		
Global health status/QoL	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Role functioning	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Emotional functioning	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Cognitive functioning	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
	Baseline						

Social functioning	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR

Notes: *higher scores indicate higher levels of functioning*
Analyses are adjusted for operating surgeon and centre

Figure F8 Global health status over time

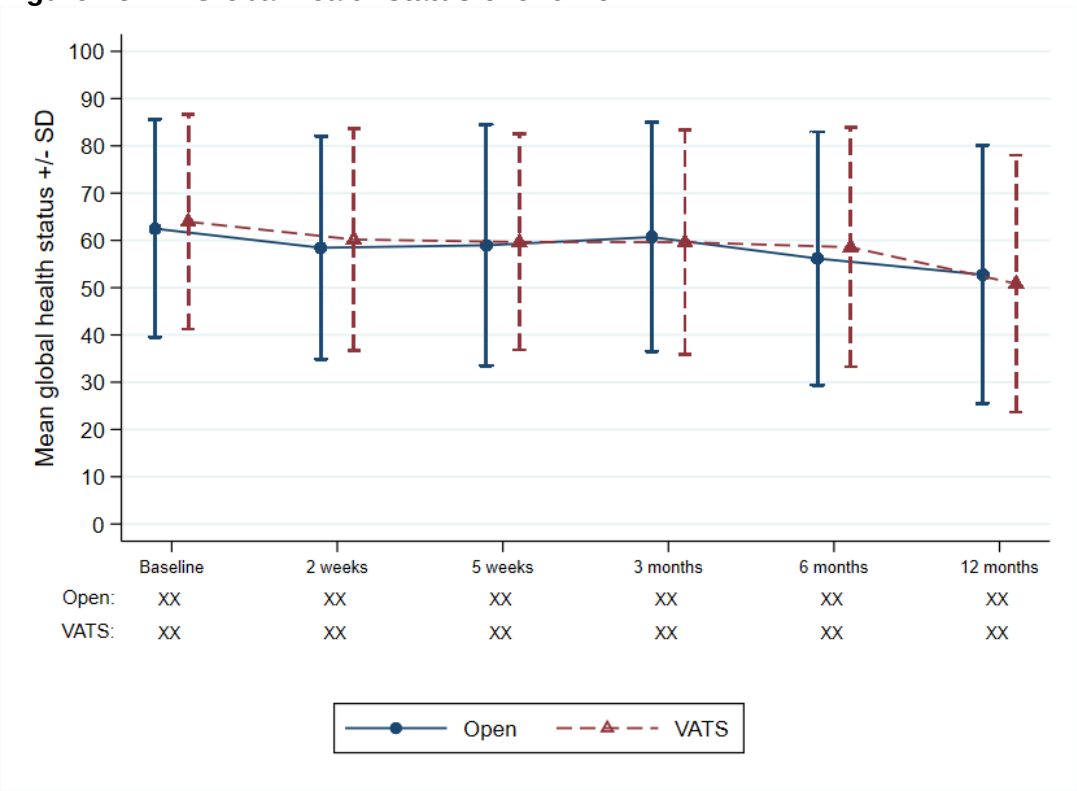


Table T16 QLQ-C30 symptom scale scores

Outcome		Randomised to open (n=XX)		Randomised to VATS (n=XX)		Effect (95% CI)	p-value
		Mean/ Median	SD/IQR	Mean/ Median	SD/IQR		
Fatigue	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Nausea and vomiting	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Pain	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Dyspnoea	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Insomnia	Baseline						

	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Appetite loss	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Constipation	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Diarrhoea	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Financial difficulties	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			

Overall treatment effect estimate						MD/GMR	

Notes: *higher scores indicate higher levels of symptoms*
Analyses are adjusted for operating surgeon and centre.

Table T17 QLQ-LC13

Outcome		**Randomised to open (n=XX)**		**Randomised to VATS (n=XX)**		**Effect (95% CI)**	**p-value**
		Mean/ Median	**SD/IQR**	**Mean/ Median**	**SD/IQR**		
Dyspnoea	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Cough	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Haemoptysis	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	
Sore mouth	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	

	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Dysphagia	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Peripheral neuropathy	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Alopecia	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Pain in chest	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR
	3 months		MD/GMR
	6 months		MD/GMR
	12 months		MD/GMR
Test for treatment*time interaction			
Overall treatment effect estimate			MD/GMR
Pain in arm or shoulder	Baseline		
	2 weeks		MD/GMR
	5 weeks		MD/GMR

	3 months				MD/GMR	
	6 months				MD/GMR	
	12 months				MD/GMR	
Test for treatment*time interaction						
Overall treatment effect estimate					MD/GMR	
Pain in other parts	Baseline					
	2 weeks				MD/GMR	
	5 weeks				MD/GMR	
	3 months				MD/GMR	
	6 months				MD/GMR	
	12 months				MD/GMR	
Test for treatment*time interaction						
Overall treatment effect estimate					MD/GMR	
Pain medication	Baseline					
	2 weeks				MD/GMR	
	5 weeks				MD/GMR	
	3 months				MD/GMR	
	6 months				MD/GMR	
	12 months				MD/GMR	
Test for treatment*time interaction						
Overall treatment effect estimate					MD/GMR	

Notes: *higher scores indicate higher levels of symptoms*
Analyses are adjusted for operating surgeon and centre

Table T18 EQ5D

Outcome		**Randomised to open (n=XX)**		**Randomised to VATS (n=XX)**		**Effect (95% CI)**	**p-value**
		Mean/ Median	**SD/IQR**	**Mean/ Median**	**SD/IQR**		
EQ5D	Baseline						
	2 weeks					MD/GMR	
	5 weeks					MD/GMR	
	3 months					MD/GMR	
	6 months					MD/GMR	
	12 months					MD/GMR	
Test for treatment*time interaction							
Overall treatment effect estimate						MD/GMR	

Analyses are adjusted for operating surgeon and centre

Table T19 Adverse events and serious adverse events in-hospital

Event	Randomised to open (n=XX)				Randomised to VATS (n=XX)			
	All events		SAEs		All events		SAEs	
	n	%	n	%	n	%	n	%
SOC 1								
Event 1								
Event 2								
…								
Event N								
SOC 2								
Event 1								
Event 2								
…								
Event N								
…								
SOC N								
Event 1								
Event 2								
…								
Event N								
Any event								

Figure F9 Adverse events in-hospital

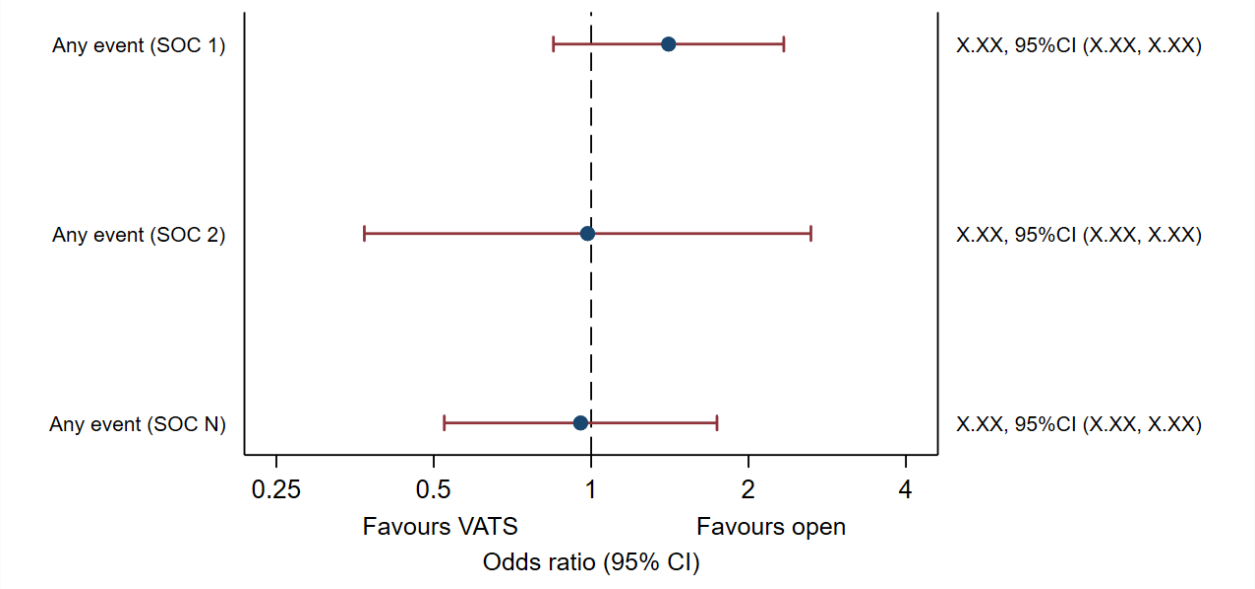


Table T20 Serious adverse events during follow-up

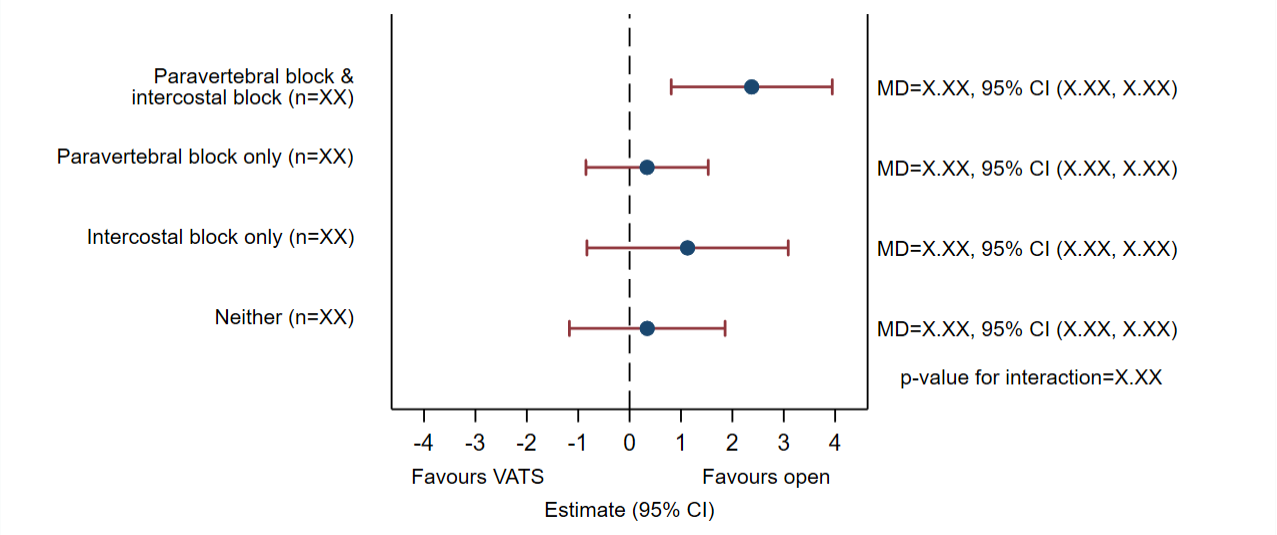
Event	Randomised to open (n=XX) SAEs		Randomised to VATS (n=XX) SAEs	
	Events/ patients	%	Events/ patients	%
SOC 1				
Event 1				
Event 2				
…				
Event N				
SOC 2				
Event 1				
Event 2				
…				
Event N				
…				
SOC N				
Event 1				
Event 2				
…				
Event N				
Any event				

Table T21 Sensitivity analysis of primary outcome excluding patients with benign disease

Outcome		Randomised to open (n=XX)		Randomised to VATS (n=XX)		Effect (95% CI)	p-value
		Mean/ Median	SD/IQR	Mean/ Median	SD/IQR		
Physical functioning	Baseline						
	2 weeks						
	5 weeks					MD/GMR	
	3 months						
	6 months						
	12 months						
Test for treatment*time interaction							

Notes: *higher scores indicate higher levels of functioning*
Analyses are adjusted for operating surgeon and centre

Figure F10 Subgroup analysis of pain score



Notes: *p-value is from the test for interaction, p-values for treatment estimates within each subgroup will not be presented.*

Figure F11 Sensitivity analyses of survival outcomes adjusting for pathological disease stage

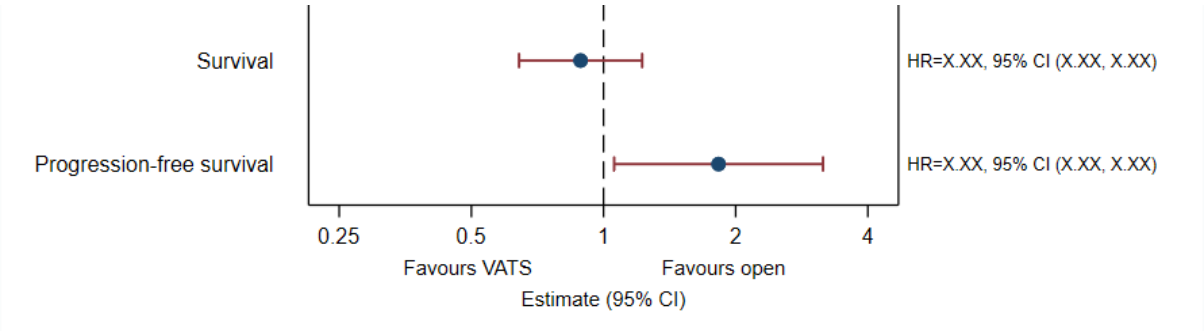


Figure F12 Exploratory analyses of in-hospital pain score by type of thoracotomy performed

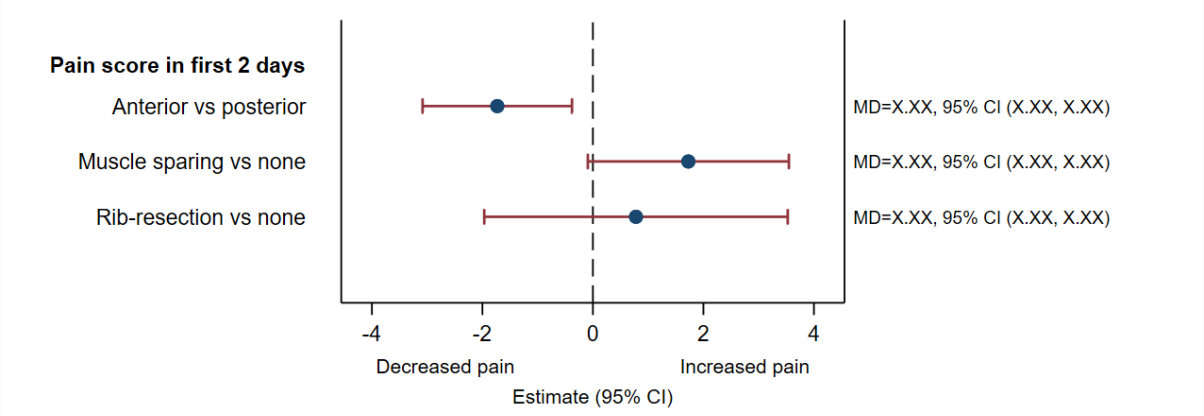


Figure F13 Exploratory analyses of QLQ-C30 pain score by type of thoracotomy performed

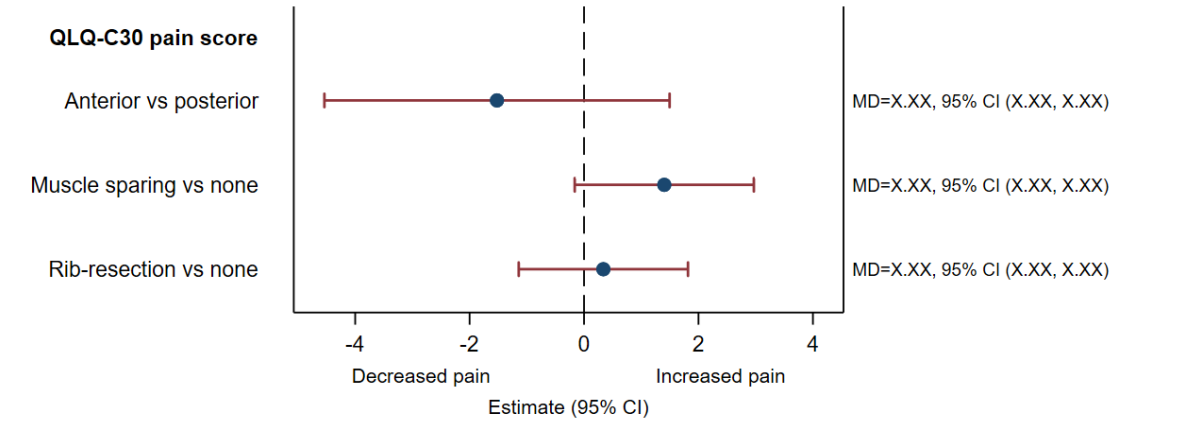


Table T22 Pain scores by number of port sites

Time point	Randomised to VATS (n=XX)				Randomised to open (n=XX)	
	Single port (n=XX)		Multi-port (n=XX)			
	Median	IQR	Median	IQR	Median	IQR
Baseline						
Day 1						
Day 2						

Analyses are adjusted for operating surgeon and centre

Table T23 Exploratory analysis comparing pain scores by number of port sites

Outcome	Effect size	95% confidence interval	p-value
Pain score in first two days post-surgery			
Single port VATS vs multi port VATS	MD=X.XX	(X.XX, X.XX)	
Single port VATS vs open	MD=X.XX	(X.XX, X.XX)	X.XX
Multi port VATS vs open	MD=X.XX	(X.XX, X.XX)	

Analyses are adjusted for operating surgeon and centre

Table T24 Exploratory analysis comparing length of stay by number of port sites

Outcome	Median	IQR	Effect size	95% confidence interval	p-value
Length of stay					
Single port VATS vs multi port VATS			MD=X.XX	(X.XX, X.XX)	
Single port VATS vs open			MD=X.XX	(X.XX, X.XX)	X.XX
Multi port VATS vs open			MD=X.XX	(X.XX, X.XX)	

Analyses are adjusted for operating surgeon and centre

APPENDIX B: IN-HOSPITAL ANALGESIC RATIOS

Mean ratios of analgesia received throughout the hospital stay will be summarised (Figure F6). Each analgesic will be summed for the duration of the hospital stay and the final score will be total dose (mg) if received intra-operatively or average daily dose (mg/day) if received post-operatively. Average daily dose will be calculated by dividing the total dose (mg) for the entire hospital stay by the total number of days each analgesia was received. Analgesic agents will be combined into groups where possible. If less than 5% of the entire cohort received an analgesic agent, then this analgesic will be excluded from the summary figure and will be tabulated by group instead.

Analgesics will be grouped as follows:

1. Intra-operative local anaesthetic infusions
    - Intercostal blocks
    - Paravertebral blocks
    - Paravertebral catheter
2. Post-operative local anaesthetic infusions
    - Intercostal blocks
    - Paravertebral blocks
    - Paravertebral catheter
3. Epidurals
    - Intra-operative epidural
    - Post-operative epidural
4. PCA (morphine equivalents)
5. Opiates (morphine equivalents)
6. Ibuprofen
7. Diclofenac
8. Gabapentin
9. Paracoxib
10. Paracetamol
11. Pregabalin
12. Lidocaine patches (patches/day)

Morphine equivalents

All analgesic doses will be converted to mg before converting to their morphine equivalent dose**.** Morphine equivalent daily dose will be calculated as:

= current dose x conversion factor

The conversion factors used will be as specified by the Royal College of Anaesthetists: Dose Equivalent and Changing Opioids. [(1)] Morphine equivalents will only be calculated for those analgesic medications for which a morphine equivalent is present and specified in the guidelines.

Appendix bibliography

(1) Rcoa.ac.uk. (2019). *Dose Equivalent and Changing Opioids | The Royal College of Anaesthetists*. [online] Available at: https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/dose-equivalents-and-changing-opioids [Accessed 3 Oct. 2019].