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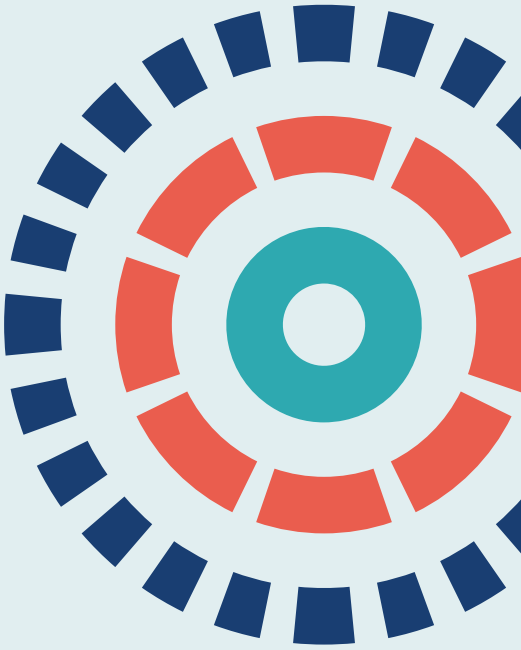

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Impact of video-assisted thoracoscopic lobectomy versus open lobectomy for lung cancer on recovery assessed using self-reported physical function: VIOLET RCT

Eric Lim[1*] Rosie A Harris[2] Holly E McKeon[2] Timothy JP Batchelor[3] Joel Dunning[4] Michael Shackcloth[5] Vladimir Anikin[1] Babu Naidu[6] Elizabeth Belcher[7] Mahmoud Loubani[8] Vipin Zamvar[9] Lucy Dabner[2] Timothy Brush[2] Elizabeth A Stokes[10,11] Sarah Wordsworth[10,11] Sangeetha Paramasivan[12] Alba Realpe[12] Daisy Elliott[13] Jane Blazeby[13] and Chris A Rogers[2] on behalf of the VIOLET investigators

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Abstract

Impact of video-assisted thoracoscopic lobectomy versus open lobectomy for lung cancer on recovery assessed using self-reported physical function: VIOLET RCT

Eric Lim[1*] Rosie A Harris[2] Holly E McKeon[2] Timothy JP Batchelor[3] Joel Dunning[4] Michael Shackcloth[5] Vladimir Anikin[1] Babu Naidu[6] Elizabeth Belcher[7] Mahmoud Loubani[8] Vipin Zamvar[9] Lucy Dabner[2] Timothy Brush[2] Elizabeth A Stokes[10,11] Sarah Wordsworth[10,11] Sangeetha Paramasivan[12] Alba Realpe[12] Daisy Elliott[13] Jane Blazeby[13] and Chris A Rogers[2] on behalf of the VIOLET investigators

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Background: Lung cancer is the leading cause of cancer death. Surgery remains the main method of managing early-stage disease. Minimal-access video-assisted thoracoscopic surgery results in less tissue trauma than open surgery; however, it is not known if it improves patient outcomes.

Objective: To compare the clinical effectiveness and cost-effectiveness of video-assisted thoracoscopic surgery lobectomy with open surgery for the treatment of lung cancer.

Design, setting and participants: A multicentre, superiority, parallel-group, randomised controlled trial with blinding of participants (until hospital discharge) and outcome assessors conducted in nine NHS hospitals. Adults referred for lung resection for known or suspected lung cancer, with disease suitable for both surgeries, were eligible. Participants were followed up for 1 year.

Interventions: Participants were randomised 1 : 1 to video-assisted thoracoscopic surgery lobectomy or open surgery. Video-assisted thoracoscopic surgery used one to four keyhole incisions without rib spreading. Open surgery used a single incision with rib spreading, with or without rib resection.

Main outcome measures: The primary outcome was self-reported physical function (using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30) at 5 weeks. Secondary outcomes included upstaging to pathologic node stage 2 disease, time from surgery to hospital discharge, pain in the first 2 days, prolonged pain requiring analgesia at > 5 weeks, adverse health events, uptake of adjuvant treatment, overall and disease-free survival, quality of life (Quality of Life Questionnaire Core 30, Quality of Life Questionnaire Lung Cancer 13 and EQ-5D) at 2 and 5 weeks and 3, 6 and 12 months, and cost-effectiveness.

Results: A total of 503 patients were randomised between July 2015 and February 2019 (video-assisted thoracoscopic surgery, $n = 247$; open surgery, $n = 256$). One participant withdrew before surgery. The mean age of patients was 69 years; 249 (49.5%) patients were men and 242 (48.1%) did not have a confirmed diagnosis. Lobectomy was performed in 453 of 502 (90.2%) participants and complete resection was achieved in 429 of 439 (97.7%) participants. Quality of Life Questionnaire Core 30 physical function was better in the video-assisted thoracoscopic surgery group than in the open-surgery group at 5 weeks (video-assisted thoracoscopic surgery, $n = 247$; open surgery, $n = 255$; mean difference 4.65, 95% confidence interval 1.69 to 7.61; $p = 0.0089$). Upstaging from clinical node stage 0 to pathologic node stage 1 and from clinical node stage 0 or 1 to pathologic node stage 2 was similar ($p \geq 0.50$). Pain scores were similar on day 1, but lower in the video-assisted thoracoscopic surgery group on day 2 (mean difference −0.54, 95% confidence interval −0.99 to −0.09; $p = 0.018$). Analgesic consumption was 10% lower (95% CI −20% to 1%) and the median hospital stay was less (4 vs. 5 days, hazard ratio 1.34, 95% confidence interval 1.09, 1.65; $p = 0.006$) in the video-assisted thoracoscopic surgery group than in the open-surgery group. Prolonged pain was also less (relative risk 0.82, 95% confidence interval 0.72 to 0.94; $p = 0.003$). Time to uptake of adjuvant treatment, overall survival and progression-free survival were similar ($p \geq 0.28$). Fewer participants in the video-assisted thoracoscopic surgery group than in the open-surgery group experienced complications before and after discharge from hospital (relative risk 0.74, 95% confidence interval 0.66 to 0.84; $p < 0.001$ and relative risk 0.81, 95% confidence interval 0.66 to 1.00; $p = 0.053$, respectively). Quality of life to 1 year was better across several domains in the video-assisted thoracoscopic surgery group than in the open-surgery group. The probability that video-assisted thoracoscopic surgery is cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year is 1.

Limitations: Ethnic minorities were under-represented compared with the UK population (< 5%), but the cohort reflected the lung cancer population.

Conclusions: Video-assisted thoracoscopic surgery lobectomy was associated with less pain, fewer complications and better quality of life without any compromise to oncologic outcome. Use of video-assisted thoracoscopic surgery is highly likely to be cost-effective for the NHS.

Future work: Evaluation of the efficacy of video-assisted thoracoscopic surgery with robotic assistance, which is being offered in many hospitals.

Trial registration: This trial is registered as ISRCTN13472721.

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Contents

List of tables xiii

List of figures xvii

Glossary xxi

List of abbreviations xxiii

Plain English summary xxv

Scientific summary xxvii

Chapter 1 Introduction 1
Background and rationale 1
Aims and objectives 1

Chapter 2 Methods 3
Trial design 3
Criteria for progression from Phase I to Phase II 3
Changes to trial design after commencement of the trial 3
Participants 5
Patient population 5
Patient eligibility criteria 5
Changes to trial eligibility criteria after commencement of the trial 5
Settings 6
Trial interventions 6
VATS lobectomy (experimental) 6
Open lobectomy (control) 6
Aspects common to both groups 6
Outcomes 7
Primary outcome 7
Secondary outcomes 7
Changes to trial outcomes after commencement of the trial 7
Sample size 8
Interim analyses 8
Randomisation 8
Blinding 8
Research team 8
Participants 9
Assessment of blinding 9
Data collection 9
Overview 9
Collection of health-related quality-of-life data 11
Collection of adverse event data 11
Identification of potential participants: referral and multidisciplinary team review 11
QuinteT Recruitment Intervention 12
Overview and aims 12
Preventing recruitment difficulties: training and guidance prior to recruitment 12

Understanding recruitment issues 12
Plan of action: strategies to optimise recruitment and informed consent 14
Evaluating the impact of the QRI 15
Statistical methods 15
Summary statistics and analysis population 15
Models used to compare primary and secondary outcomes 15
Adjustment in models 17
Subgroup analysis 17
Sensitivity analyses 17
Exploratory analyses 17
Missing data 17
Significance levels and adjustment for multiplicity 18
Economic evaluation 18
Economic evaluation aim 18
Economic evaluation overview 18
Form of analysis, primary outcome and cost-effectiveness decision rules 18
Time horizon 18
Collection of resource use and costs 19
Attaching unit costs to resource use 20
Measurement of health-related quality of life and quality-adjusted life-years 20
Missing data 21
Adjustment for baseline utility 21
Within-trial statistical analysis of cost-effectiveness results 21
Discounting 22
Sensitivity analysis 22
Subgroup analysis 22

Chapter 3 Results: trial cohort **23**
Study sites 23
Phase I: study sites and dates opened to recruitment 23
Phase II: study sites and dates opened to recruitment 23
Patients screened and recruited 23
Recruitment 23
Recruitment rate 23
Progression from Phase I to Phase II 25
Comparison of recruited and non-recruited patients 25
Patient withdrawals 25
Protocol deviations 26
Eligibility and surgery 26
Success of blinding 27
Patient follow-up 28
Numbers analysed 28
Baseline data and operative characteristics 28

Chapter 4 Results: QuinteT Recruitment Intervention **31**
Overview 31
Data set 31
Understanding recruitment processes and issues 31
Patient pathways through eligibility and recruitment 31
Recruiter equipoise 35
Patient preferences 38
Explaining the VIOLET trial and related concepts 39
Summary of recruitment processes and issues 40

Plan of action: strategies to optimise recruitment and informed consent 41
Preventing recruitment difficulties: training and guidance prior to recruitment 42
Individual feedback 42
Group feedback 42
Recruitment and informed consent guidance (tips) documents 42
Trial Management Group, investigator and study update meetings 42
Rapid communication strategy 43
QRI evaluation 43

Chapter 5 Results: primary and secondary outcomes **45**
Primary outcome: EORTC QLQ-C30 physical function at 5 weeks 45
Secondary outcomes 45
EORTC QLQ-C30 physical function over time 45
Complete resection 45
Lymph node upstaging 45
Pain in the first 2 days post surgery 46
Prolonged incision pain beyond 5 weeks 49
Time from surgery to hospital discharge: postoperative length of hospital stay 49
Overall survival and progression-free survival to 1 year 50
Uptake of adjuvant treatment 53
EORTC QLQ-C30 quality-of-life questionnaire 53
EORTC QLQ-LC13 quality-of-life questionnaire 56
EQ-5D-5L utility score 56
Adverse events 58

Chapter 6 Results: economic evaluation **61**
Analysis data set 61
Missing data 61
Quality-adjusted life-years 62
Resource use and costs 62
Base-case cost-effectiveness results 64
Sensitivity analyses 66
Summary 66

Chapter 7 Discussion **67**
Main findings 67
Trial conduct 67
QRI 67
Trial results 68
Health economic evaluation 70
Patient and public involvement 70
Strengths and limitations 71
Strengths 71
Limitations 71
Future research 72

Chapter 8 Conclusion **73**

Acknowledgements **75**

References **81**

Appendix 1 Evolution of the QRI **87**

Appendix 2 Additional tables and figures for the economic evaluation **89**

Appendix 3 Unit costs used in the economic evaluation **93**

Appendix 4 Sensitivity analyses for the economic evaluation **107**

Appendix 5 Additional tables and figures **111**

Appendix 6 Additional QRI quotations and table demonstrating imbalanced information provision/loaded terminology **151**

Appendix 7 Summary of issues related to trial design identified through QRI **153**

Appendix 8 Good practice in addressing preferences as the trial progressed (quotations from the main phase) **159**

Appendix 9 Trial committee membership **161**

List of tables

TABLE 1 Schedule of data collection 10

TABLE 2 Methods of analysis for HRQoL longitudinal outcomes 16

TABLE 3 Summary of economic evaluation methods 19

TABLE 4 Post-randomisation withdrawals 26

TABLE 5 Protocol deviations 26

TABLE 6 Reasons for conversion from VATS to open surgery 27

TABLE 7 Assessment of the success of blinding 27

TABLE 8 Numbers analysed 28

TABLE 9 Participant characteristics and surgical details 29

TABLE 10 Recruitment challenges in relation to key themes mapped against QRI actions and strategies 41

TABLE 11 Primary outcome results: difference in EORTC QLQ-C30 physical function at 5 weeks 45

TABLE 12 Resection details 46

TABLE 13 Lymph node upstaging 47

TABLE 14 Pain scores by number of port sites 49

TABLE 15 Prolonged incision pain 49

TABLE 16 Length of stay by number of port sites 50

TABLE 17 Fitness for hospital discharge 51

TABLE 18 Causes of death in-hospital and following discharge from hospital to 1 year 51

TABLE 19 Survival and progression-free survival to 1 year 52

TABLE 20 Location of recurrence/new cancer/metastases 52

TABLE 21 Relative risk of AEs and SAEs following surgery 58

TABLE 22 EQ-5D-5L scores and QALYs to 12 months for all participants (imputed) 62

TABLE 23 Observed resource use for participants 63

TABLE 24 Base-case cost-effectiveness results 64

TABLE 25 Resource use categories and sources of unit cost information **89**

TABLE 26 Number of participants with complete data by trial group **89**

TABLE 27 Costs for all participants to 12 months **91**

TABLE 28 Unit costs associated with surgery and inpatient stays in the index admission **93**

TABLE 29 Resource use assumed for complications and total costs **94**

TABLE 30 Unit costs of treatments/actions associated with complications (see *Table 29*) **96**

TABLE 31 Costs for resource use associated with SAEs during the index admission (not previously presented) **99**

TABLE 32 Unit costs for reattending hospital **99**

TABLE 33 Resource use assumed for prespecified readmission complications (CRF E5) and total costs (if not previously reported) **100**

TABLE 34 Unit costs associated with prespecified readmission complications and other free-text events (not previously presented) **100**

TABLE 35 Costs for resource use associated with SAEs post hospital discharge (not previously presented) **102**

TABLE 36 Unit costs for outpatient appointments **103**

TABLE 37 Unit costs for chemotherapy and radiotherapy **104**

TABLE 38 Unit costs for other hospital attendances **105**

TABLE 39 Unit costs for post-discharge community health and social care contacts **105**

TABLE 40 Sensitivity analyses performed around unit costs **107**

TABLE 41 Results of sensitivity analyses around unit costs **107**

TABLE 42 Sensitivity analyses around high-cost patients **108**

TABLE 43 Results of sensitivity analyses around outcomes **109**

TABLE 44 Reasons why screened patients were excluded **112**

TABLE 45 Anticipated recruitment at each study site **114**

TABLE 46 Randomisations by centre **114**

TABLE 47 Assessment of the trial performance against the progression criteria **114**

TABLE 48 Age of non-randomised patients and trial participants **115**

TABLE 49 Participant characteristics and surgical details: additional information **115**

TABLE 50 QLQ-C30 physical functioning over time **116**

TABLE 51 Pain scores **117**

TABLE 52 Pain scores: complete-case sensitivity analysis **118**

TABLE 53 Additional analgesics prescribed **118**

TABLE 54 Exploratory analysis comparing pain scores in first 2 days post surgery by number of port sites **118**

TABLE 55 Time from surgery to hospital discharge **119**

TABLE 56 Exploratory analysis comparing length of stay by number of port sites **119**

TABLE 57 Uptake of adjuvant treatment **120**

TABLE 58 QLQ-C30 global health status, role and social functioning scale scores **121**

TABLE 59 QLQ-C30 cognitive and emotional functioning scale scores **123**

TABLE 60 QLQ-C30 fatigue, nausea, pain, dyspnoea, insomnia and constipation symptom scale scores **128**

TABLE 61 QLQ-C30 appetite, diarrhoea and financial difficulties scale scores **130**

TABLE 62 QLQ-LC13 scores for dyspnoea, cough, haemoptysis, pain in chest and pain in other parts (not chest, arm or shoulder) **136**

TABLE 63 QLQ-LC13 scores for sore mouth, dysphagia, peripheral neuropathy, alopecia and pain in the arm/shoulder **138**

TABLE 64 EQ-5D-5L scores over time **142**

TABLE 65 In-hospital AEs and SAEs **142**

TABLE 66 Post-discharge SAEs **145**

TABLE 67 Reasons for readmission to hospital **149**

TABLE 68 Imbalanced information provision and loaded terminology used in consultations to describe the two operations **152**

TABLE 69 Examples of good practice in addressing patient preference and concerns **159**

List of figures

FIGURE 1 The trial schema for the VIOLET study 3

FIGURE 2 The VIOLET trial CONSORT flow diagram 24

FIGURE 3 Predicted and actual recruitment 25

FIGURE 4 Recruitment to the VIOLET trial and QRI actions by month 32

FIGURE 5 Patient pathway from referral for treatment to decision about trial participation 33

FIGURE 6 QLQ-C30 physical function over time 46

FIGURE 7 Pain scores over time 47

FIGURE 8 Analgesia prescribed intraoperatively and postoperatively 48

FIGURE 9 Subgroup analysis of pain scores by analgesia received 48

FIGURE 10 Exploratory analysis of the impact of type of thoracotomy on pain scores 49

FIGURE 11 Time from surgery to hospital discharge 50

FIGURE 12 Uptake of adjuvant treatment in the primary analysis population 53

FIGURE 13 Uptake of adjuvant treatment in the NICE-eligible subset of participants 53

FIGURE 14 QLQ-C30 global health status and role and social functioning: treatment effects 54

FIGURE 15 QLQ-C30 cognitive functioning over time 54

FIGURE 16 QLQ-C30 emotional functioning over time 55

FIGURE 17 QLQ-C30 symptoms and problems subscales: treatment effects 55

FIGURE 18 Impact of type of thoracotomy on QLQ-C30 pain scores 57

FIGURE 19 QLQ-LC13 symptoms and problems subscales: treatment effects 57

FIGURE 20 EQ-5D-5L utility scores over time 58

FIGURE 21 In-hospital AEs summarised by MedDRA system organ class 59

FIGURE 22 Post-discharge SAEs summarised by MedDRA system organ class 59

FIGURE 23 Total costs to 12 months for all participants 64

FIGURE 24 Cost-effectiveness plane 65

FIGURE 25 Cost-effectiveness acceptability curve 65

FIGURE 26 Observed mean (95% CI) EQ-5D-5L scores at each time point **90**

FIGURE 27 Relative risk for complete R(0) resection **117**

FIGURE 28 Relative risks for upstaging to N1 and upstaging to N2 **117**

FIGURE 29 Relative risk for prolonged incision pain **119**

FIGURE 30 Overall survival **119**

FIGURE 31 Progression-free survival **120**

FIGURE 32 QLQ-C30 global health status over time **120**

FIGURE 33 QLQ-C30 role functioning over time **121**

FIGURE 34 QLQ-C30 social functioning over time **121**

FIGURE 35 QLQ-C30 pain scores over time **125**

FIGURE 36 QLQ-C30 fatigue scores over time **125**

FIGURE 37 QLQ-C30 nausea symptoms over time **125**

FIGURE 38 QLQ-C30 dyspnoea symptoms over time **126**

FIGURE 39 QLQ-C30 insomnia symptoms over time **126**

FIGURE 40 QLQ-C30 constipation symptoms over time **126**

FIGURE 41 QLQ-C30 loss of appetite symptoms over time **127**

FIGURE 42 QLQ-C30 diarrhoea symptoms over time **127**

FIGURE 43 QLQ-C30 financial difficulties over time **127**

FIGURE 44 QLQ-LC13 dyspnoea symptoms over time **132**

FIGURE 45 QLQ-LC13 scores for cough over time **133**

FIGURE 46 QLQ-LC13 scores for haemoptysis over time **133**

FIGURE 47 QLQ-LC13 scores for pain in the chest over time **133**

FIGURE 48 QLQ-LC13 scores for pain in other parts (not chest, arm or shoulder) over time **134**

FIGURE 49 QLQ-LC13 scores for sore mouth over time **134**

FIGURE 50 QLQ-LC13 scores for dysphagia over time **134**

FIGURE 51 QLQ-LC13 scores for peripheral neuropathy over time **135**

FIGURE 52 QLQ-LC13 scores for alopecia over time **135**

FIGURE 53 QLQ-LC13 scores for pain in the arm over time **135**

Glossary

Adverse event Any undesirable event in a subject receiving treatment in accordance with the protocol, including occurrences that are not necessarily caused by, or related to, administration of the research procedures.

Serious adverse event Events that result in death, are life-threatening, require hospitalisation or prolongation of hospitalisation, or result in persistent or significant disability or incapacity.

List of abbreviations

AE	adverse event
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
cN0	clinical node stage 0
cN0/1	clinical node stage 0 or 1
ConDuCT	Collaboration and Innovation in Difficult and complex randomised controlled Trials
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CT	computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMSC	Data Monitoring and Safety Committee
ED	emergency department
eMIT	electronic marketing information tool
EORTC	European Organisation for Research and Treatment of Cancer
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
M0	metastasis stage 0
MD	mean difference
MDT	multidisciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
N0–1	node stage 0–1
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OR	odds ratio
PET	positron emission tomography
PI	principal investigator
PIL	patient information leaflet
pN1	pathologic node stage 1
pN2	pathologic node stage 2
PPI	patient and public involvement
QALY	quality-adjusted life-year
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
QRI	QuinteT Recruitment Intervention
RCT	randomised controlled trial
RN	research nurse
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEAR	screened, eligible, approached, randomised
SIV	site initiation visit
TMG	Trial Management Group
TNM7	*TNM Classification of Malignant Tumours, Seventh Edition*
TNM8	*TNM Classification of Malignant Tumours, Eighth Edition*
TSC	Trial Steering Committee
VAS	visual analogue scale
VATS	video-assisted thoracoscopic surgery
VIOLET	VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer

Plain English summary

Background

Lung cancer is a common cause of cancer death worldwide. If the disease is caught early, the part of the lung containing the tumour can be removed in an operation called a lobectomy. The operation can be carried out through a large cut so that the surgeon has a full view of the lung, which is called open surgery, or using several small cuts and a camera, which is called video-assisted thoracoscopic (keyhole) surgery. It is thought that, as keyhole surgery is less invasive, patients recover quicker. However, to the best of our knowledge, there are no high-quality research studies that are applicable to UK practice to support this. This study was conducted so that it could be determined, based on high-quality evidence, which operation provides the best treatment and recovery for patients.

Who participated?

Five hundred and three adults referred for lobectomy for known or suspected lung cancer from nine hospitals in the UK.

What was involved?

Participants were randomly allocated to either receive keyhole or open surgery. Participants were followed up for 12 months. We collected information on further treatment, hospital visits, safety information and disease progression over this period. Participants were also asked to complete questionnaires about their health and recovery.

What did the trial find?

For patients with early-stage lung cancer who underwent a lobectomy, keyhole surgery led to less pain, less time in hospital and better quality of life than open surgery, without having a detrimental effect on cancer progression or survival. Keyhole surgery was found to be cost-effective and to provide excellent value for money for the NHS.

Scientific summary

Introduction

Lung cancer is a leading cause of cancer death. In early-stage lung cancer, surgery is commonly undertaken through an open thoracotomy. Since minimal access video-assisted thoracoscopic surgery (VATS) was introduced, the technique has evolved and has been applied in lung cancer resections on the premise that smaller incisions without rib spreading may allow for quicker recovery. Most evidence for VATS is from non-randomised studies or randomised trials that are not directly applicable to UK practice.

Objectives

To compare the clinical effectiveness and cost-effectiveness of VATS lobectomy with open surgery for the treatment of lung cancer.

Methods

Study design

A multicentre, superiority, parallel-group randomised controlled trial with an integrated QuinteT Recruitment Intervention and blinding.

Settings and participants

Nine NHS hospitals with an accredited lung cancer multidisciplinary team and surgeon(s) were eligible to take part. Surgeons were eligible if they had performed at least 40 VATS lobectomies. Lobectomy via open surgery is standard, and competence is assured by specialist registration.

Patients aged ≥ 16 years with suspected or confirmed primary lung cancer [i.e. clinical tumour stage 1–3 (cT1–3), node stage 0–1 (N0–1) or metastasis stage 0 (M0)] whose disease was considered suitable for both surgeries were eligible.

Royal Brompton Hospital (London, UK) and Harefield Hospital (Uxbridge, UK) sponsored the trial, which was approved by the Research Ethics Committee London–Dulwich (reference 14/LO/2129).

Interventions

Video-assisted thoracoscopic surgery lobectomy was undertaken through one to four keyhole incisions without rib spreading. Open surgery used a single incision, rib spreading and optional rib resection. Operations were carried out under general anaesthesia and with patients in the lateral decubitus position.

Randomisation and blinding

Participants were randomised 1 : 1 to VATS or open surgery using a secure internet-based randomisation system, with cohort minimisation to ensure balance across groups by surgeon and site. Randomisation was performed within 1 week of surgery once eligibility had been confirmed and consent given.

Outcome assessors were blinded throughout and participants were blinded until hospital discharge. Blinding was achieved by applying adhesive dressings so that they were positioned to cover both real and potential incision/port locations. Dressings were applied in the operating room and changed after 3 days by a nurse not involved in data collection. Participants were asked to turn their head away while actual and potential wounds were being cleaned and dressed.

Follow-up

Participants were followed up at discharge and at 2 weeks, 5 weeks, 3 months, 6 months and 12 months post randomisation. Participants attended hospital at 5 weeks and 12 months. Other follow-ups were via telephone.

Outcomes

The primary outcome was patient-reported physical function, which was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) at 5 weeks. Secondary outcomes were complete resection, upstaging to pathologic node stage 2 (pN2) disease, time from surgery to hospital discharge, pain in the first 2 days, adverse health events, uptake of adjuvant treatment, overall and disease-free survival, incision pain requiring analgesia for > 5 weeks post randomisation, quality of life at each follow-up [assessed using the EORTC QLQ-C30, Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) and EQ-5D-5L questionnaires] and resource use to 1 year.

Sample size

Physical function at 5 weeks was hypothesised to be superior with VATS lobectomy. The target effect size was 0.25 standard deviations (SDs). Conservative estimates of the correlations between repeated measures were used (0.3 between pre and post measures and 0.6 between repeated post measures). The sample size was 498 participants, which provided 90% power at the 5% significance level, allowing for 20% dropout.

QuinteT Recruitment Intervention

The QuinteT Recruitment Intervention involved identifying and addressing challenges and training recruiters to deal with potential difficulties. Recruitment issues were identified through staff interviews, audio-recordings of recruitment discussions, review of screening/eligibility information, charting patient pathways and observing study meetings. Collaboratively developed strategies to address issues were disseminated through group and individual feedback to recruiters, tips documents, meetings and newsletters.

Statistical analyses

Data were analysed by intention to treat. The analysis population was all randomised participants, excluding patients who had withdrawn and were unwilling for their data to be used.

The model used to compare longitudinal outcomes was dependent on model fit, with a joint longitudinal–survival model being the preferred choice. Time-by-treatment interactions were included and overall treatment effects are presented unless the interaction reached 10% statistical significance, when effects for each time point are reported. The primary outcome was estimated from a model with a time-by-treatment interaction. Time-to-event outcomes were compared using Cox proportional hazards regression. Binary and multinomial outcomes were analysed using generalised linear and structural equation models, respectively. Model assumptions and fit were assessed graphically.

Open surgery was the reference group. Analyses were adjusted for centre, surgeon and baseline preoperative score, where measured. Subgroup effects were estimated by adding a treatment-by-subgroup interaction term into the model. Sensitivity analysis of the primary outcome, excluding participants with benign disease, and exploratory analysis of pain scores by number of incisions were prespecified.

For QLQ-C30 and QLQ-LC13 outcomes, missing data were imputed, results were combined using Rubin's rules and significance levels were adjusted for multiplicity. Analyses were performed using Stata® version 16.1 (StataCorp LP, College Station, TX, USA).

Economic evaluation

The within-trial economic evaluation used the perspective of the NHS and Personal Social Services. The primary outcome was quality-adjusted life-years (QALYs), estimated using the EQ-5D-5L. Resource use was costed using published reference costs. The area under the curve was used to calculate the QALYs accrued by each participant.

Missing data were imputed and QALYs between groups were adjusted for baseline EQ-5D-5L utility. Bootstrapping was used to quantify uncertainty in costs and outcomes. Sensitivity analyses were used to investigate the impact of varying unit costs for key cost drivers, high-cost participants and not adjusting for baseline utility. Analyses were conducted in Stata version 15 and Microsoft Excel® 2016 (Microsoft Corporation, Redmond, WA, USA).

Results

Patient screening and recruitment

Between July 2015 and February 2019, 2109 patients were assessed for eligibility, of whom 503 (50% of eligible patients and 59% of patients approached) were recruited and randomised (VATS, $n = 247$; open surgery, $n = 256$). Recruitment exceeded target throughout.

Withdrawals

Nineteen participants withdrew (three participants before surgery and 16 participants after surgery). The most cited reason was 'participant changed their mind'.

Protocol deviations

There were 66 deviations. Forty-nine patients did not undergo a lobectomy. In addition, 17 patients crossed over: 15 patients randomised to VATS received open surgery (participant choice, $n = 1$; intraoperative conversions, $n = 14$) and two patients randomised to open surgery had VATS (participant choice, $n = 2$). The primary reason for not undergoing lobectomy was benign disease on frozen section. The most common reasons for conversion from VATS to open surgery were diffuse pleural adhesion ($n = 4$) and bleeding from vascular injury ($n = 4$).

Patient follow-up

Follow-up data at 1 year were available for 81% of participants.

Numbers analysed

The analysis population comprised 502 randomised participants.

Baseline data and operative characteristics

Baseline characteristics were similar in the two groups. The mean age of participants was 69 (SD 8.8) years, and 249 (49.5%) participants were men. Most participants were white (96.4%) and past or current smokers (87.3%). Most participants were cT stage 1 (67.2%) and cN stage 0 (95.6%). A total of 242 participants did not have a tissue-confirmed diagnosis and underwent a biopsy first, 32 (13.2%) of whom had confirmed benign disease. All surgeons adhered to the surgical protocol.

QuinteT Recruitment Intervention

Examples of good practice (e.g. expressing uncertainty) and recruitment challenges (e.g. recruiters using imbalanced/loaded terminology to explain the operations) were identified. Feedback was aimed at addressing challenges by providing tips on optimising recruitment consultations. There were noticeable improvements after feedback, although the precise impact of the feedback is difficult to discern because of the many contributing factors.

Primary outcome: QLQ-C30 physical function at 5 weeks

Participants allocated to VATS had a median score of 73 [interquartile range (IQR) 60.0–86.7], compared with a median score of 67 (53.3–86.7) for participants allocated to open surgery [mean difference (MD) (VATS – open surgery) 4.65, 95% confidence interval (CI) 1.69 to 7.61; $p = 0.0089$], indicating better physical function in the VATS group. Excluding participants with benign disease gave consistent results.

Secondary outcomes

Complete resection

The median number of lymph node stations and mediastinal nodes harvested was 5 (IQR 4–6) and 3 (IQR 3–4), respectively, in both groups. Complete R(0) resection was achieved in 429 of 439 (97.7%) participants (relative risk 0.999, 95% CI 0.97 to 1.26; $p = 0.94$). Those participants with residual disease had R1 disease.

Lymph node upstaging

Upstaging from clinical node stage 0 (cN0) to pathologic node stage 1 (pN1) and from clinical node stage 0 or 1 (cN0/1) to pN2 was similar in both groups (relative risk 1.18, 95% CI 0.54 to 2.58; $p = 0.68$ and relative risk 1.31 95% CI 0.60 to 2.86; $p = 0.50$, respectively).

Pain in the first 2 days post surgery

Pain scores were similar in the two groups on day 1 (median 4, MD –0.02, 95% CI –0.46 to 0.41; $p = 0.913$), but the VATS group had lower pain scores on day 2 (median 3 vs. 4, MD –0.54, 95% CI –0.99 to –0.09; $p = 0.018$). There was no evidence to suggest that the difference between groups differed by type of analgesia (test for interaction $p = 0.19$). Pain scores did not vary significantly with type of thoracotomy, use of muscle sparing or not, rib resection or not, or number of VATS port sites. Analgesic consumption was 10% lower in the VATS group (mean ratio 0.9, 95% CI 0.80 to 1.01).

Incision pain beyond 5 weeks

Prolonged incision pain was less common in the VATS group (relative risk 0.82, 95% CI 0.72 to 0.94; $p = 0.003$).

Time from surgery to hospital discharge

Median stay was lower in the VATS group [4 vs. 5 days, hazard ratio (HR) 1.34, 95% CI 1.09 to 1.65; $p = 0.006$]. The median time to first meeting predefined 'fit-for-discharge' criteria was 1 day earlier than the median stay in both groups. The proportion of patients discharged 'early' was similar (8.4% overall). Discharge was 'delayed' in one-quarter of participants.

Overall survival and progression-free survival to 1 year

There were 31 deaths (VATS, $n = 13$; open surgery, $n = 18$; HR 0.67, 95% CI 0.32 to 1.40; $p = 0.28$). Thirty-three participants (VATS, $n = 16$; open surgery, $n = 17$) experienced disease recurrence (HR 0.73, 95% CI 0.42 to 1.27; $p = 0.26$). There were 24 cases of locoregional recurrence (VATS, $n = 11$; open surgery, $n = 13$), 17 cases of distant recurrence (VATS, $n = 7$; open surgery, $n = 10$) and 10 cases of new cancer (VATS, $n = 4$; open surgery, $n = 6$).

Uptake of adjuvant treatment

A total of 73 participants had adjuvant treatment, 56 of whom met the eligibility criteria defined by the National Institute for Health and Care Excellence. Time to uptake of adjuvant treatment was similar in both groups (HR 1.12, 95% CI 0.62 to 2.02; $p = 0.716$ for eligible subset).

EORTC QLQ-C30 quality-of-life questionnaire

Global health status, role and social functioning were all significantly higher in the VATS group than in the open-surgery group, and where cognitive function was impaired, the impairment was less. The effect of surgery on emotional function varied over time. At 2 weeks, fewer participants in the VATS

group than in the open-surgery group reported impaired emotional function, but thereafter the results were similar. The improvement in physical functioning was more marked in the early discharge period and less pronounced after 6 months. On average, the score was 4.22 points higher in the VATS group than in the open-surgery group (95% CI 1.48 to 6.97 points; $p = 0.009$).

Participants randomised to VATS experienced less pain and fatigue and had less difficulty sleeping in the first 2 weeks than participants randomised to open surgery. These participants were also less likely to experience appetite loss and nausea, and constipation in the early period post surgery. Other measures were similar in the two groups. Pain scores to 1 year were significantly higher in participants who had rib resection than in patients who did not (MD 9.8, 95% CI 2.07 to 17.52).

EORTC QLQ-LC13 quality-of-life questionnaire

Participants randomised to VATS experienced significantly less pain in the chest and arm at 5 weeks than participants randomised to open surgery, but other outcomes (i.e. cough, dyspnoea, alopecia, peripheral neuropathy, dysphagia, sore mouth and haemoptysis) were similar in the two groups.

EQ-5D-5L utility score

EQ-5D-5L median scores were higher in the VATS group than in the open-surgery group at all time points. Participants in the VATS group were less likely to have less than perfect health (i.e. a score < 1) (odds ratio 0.57, 95% CI 0.38 to 0.86; $p = 0.007$) than participants in the open-surgery group, and of those with less than perfect health, participants in the VATS group had, on average, higher scores (better health) than participants in the open-surgery group (geometric mean ratio 0.90, 95% CI 0.84 to 0.96; $p = 0.003$).

Adverse events

Eighty-one (32.8%) participants in the VATS group and 113 (44.3%) participants in the open-surgery group experienced at least one adverse event before hospital discharge (relative risk 0.74, 95% CI 0.66 to 0.84; $p < 0.001$), but the proportions of patients experiencing serious adverse events (SAEs) were similar (8.1% vs. 8.2%). Participants in the VATS group had fewer infective (relative risk 0.89, 95% CI 0.84 to 0.94), psychiatric (relative risk 0.98, 95% CI 0.97 to 1.00) and renal (relative risk 0.96, 95% CI 0.91 to 1.00) complications than participants in the open-surgery group. There were seven deaths before hospital discharge (VATS, $n = 2$; open surgery, $n = 5$).

Seventy-five (30.7%) participants allocated to VATS and 94 (37.8%) participants allocated to open surgery experienced at least one SAE after hospital discharge (relative risk 0.81, 95% CI 0.66 to 1.00; $p = 0.053$), of which 158 (93.5%) resulted in a hospital admission. There were 24 deaths after hospital discharge (VATS, $n = 11$; open surgery, $n = 13$), half of which were due to disease progression.

Economic evaluation

The mean QALY gain up to 1 year was 0.841 in the VATS group and 0.780 in the open-surgery group (MD 0.060, 95% CI 0.029 to 0.092). The total cost of care was £10,879 in the VATS group and £13,581 in the open group (MD −£2702, 95% CI −£5632 to £228). The probability that VATS is cost-effective at a willingness-to-pay threshold of £20,000 per QALY is > 0.99.

Discussion

Main findings

Video-assisted thoracoscopic surgery lobectomy was associated with less pain, fewer complications and a shorter hospital stay than open surgery, without any compromise to oncologic outcome. The benefits extended beyond the in-hospital period. Physical function at 5 weeks was significantly improved in the VATS group and was consistent for all secondary measures of quality of life up to 1 year. There were

fewer readmissions in the VATS group than in the open-surgery group, and no difference in survival. VATS was also cost-effective at all thresholds.

One concern about keyhole surgery has been the ability to perform a cancer operation adequately. The quality of the lymph node harvesting and similar rates of lymph node upstaging and complete pathological resection confirm the completeness of the operation. Comparable survival provides further assurance on the longer-term oncologic safety of a VATS approach.

Strengths and limitations

Strengths include the ability to successfully blind the procedure and the ability to train surgeons in the communication skills required to successfully recruit patients. Ethnic minorities were under-represented compared with the UK population, but surgical technique is not influenced by ethnicity and the cohort reflected the ethnicity of people with lung cancer.

Conclusion

For patients with early-stage lung cancer in whom a lobectomy is proposed, our results strongly support the use of VATS as the procedure of choice. The clinical benefits were achieved without any compromise to important oncologic outcomes and the procedure provides excellent value for money for the NHS. It is important that thoracic surgeons have appropriate opportunities for training in minimally invasive surgical techniques.

Areas for further research include a meta-analysis of long-term survival (≈ 1800 participants when all trials are completed) and an evaluation of the clinical efficacy of robotic VATS surgery.

Trial registration

This trial is registered as ISRCTN13472721.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 48. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Background and rationale

Lung cancer is a leading cause of cancer death worldwide and survival in the UK remains among the lowest in Europe.[2] In early-stage lung cancer, surgery is commonly undertaken through an open thoracotomy. However, minimal-access video-assisted thoracoscopic surgery (VATS) was introduced in the 1990s, and the evolution of the technique from minor procedures eventually led to its successful application in anatomic lung cancer resections, undertaken using a telescope and television screen, with small incisions in the chest. Since then, minimal access surgery has increased in popularity on the premise that smaller incisions without rib spreading may improve recovery after lung surgery. Data from the UK demonstrates exponential growth in popularity of this technique. In 2010, 14% of lobectomy procedures were performed using VATS access, and this increased to 40% in 2014.[3]

To date, much of the evidence generated for VATS is based on non-randomised studies[4,5] or small randomised controlled trials (RCTs) that focus on in-hospital outcomes.[6] These studies are underpowered to detect clinically meaningful differences in longer-term outcomes[7] or have focused solely on operative technique.[8] Currently, the largest RCT, comparing VATS with open surgery in 206 participants followed for 1 year, reported shorter hospital stay and less pain in patients randomised to VATS lobectomy.[9] In this study,[9] carried out in Denmark, 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[10] in 425 patients recruited in China reported a similar hospital stay and rate of morbidity and mortality at 28 days in both the VATS and axillary thoracotomy groups.[10] To the best of our knowledge, there are no high-quality comparative data on physical function (as a global measure of recovery from surgery), hospital readmissions, the uptake and timing of chemotherapy nor cancer recurrence, and few high-quality RCT data on the cost-effectiveness of VATS compared with open surgery. The Danish investigators[11] have compared VATS with open surgery from an economic societal cost perspective and there is an ongoing multicentre trial in (Lungsco01) France with a target sample size of 600 participants that plans a similar comparison.[12]

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

Aims and objectives

The VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer (VIOLET) study aimed to compare the clinical effectiveness, cost-effectiveness and acceptability of VATS lobectomy with open surgery for treatment of lung cancer.

Specific objectives were to estimate the differences in the primary outcome (i.e. self-reported physical function at 5 weeks) and a range of secondary outcomes, including efficacy, safety, oncological outcomes and survival, between participants allocated to VATS and participants allocated to open surgery, and to compare the cost-effectiveness of the two surgical strategies.

Chapter 2 Methods

Trial design

A multicentre, parallel-group, superiority RCT, with blinding of outcome assessors and participants (until hospital discharge after surgery) and active follow-up to 1 year. The trial included an internal pilot phase and a QuinteT Recruitment Intervention (QRI) to optimise recruitment (*Figure 1*).

Criteria for progression from Phase I to Phase II

During the first phase, processes for trial conduct, including recruitment and consent, were established. Progression from the internal pilot (Phase I) to the full trial (Phase II) was dependent on the following criteria being met when assessed 18 months after the start of recruitment:

- At least 60% of patients undergoing lobectomy are considered eligible for the trial (if necessary, by revising the eligibility criteria).
- At least 50% of patients consent to randomisation after 6 months of recruitment.
- Less than 5% of patients fail to receive their allocated treatment.
- Less than 5% of patients are lost to follow-up (excluding deaths).

In Phase II, the number of study sites was increased and all sites used the optimum methods of recruitment established in Phase I.

Changes to trial design after commencement of the trial

There were several substantial amendments made to the study protocol throughout the course of the trial. The changes are summarised below. The protocol version in use when the trial started was version 2.0. The current full trial protocol can be found in the National Institute for Health and Care Research (NIHR) Journals Library [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/130403/#/ (accessed 27 October 2021)].

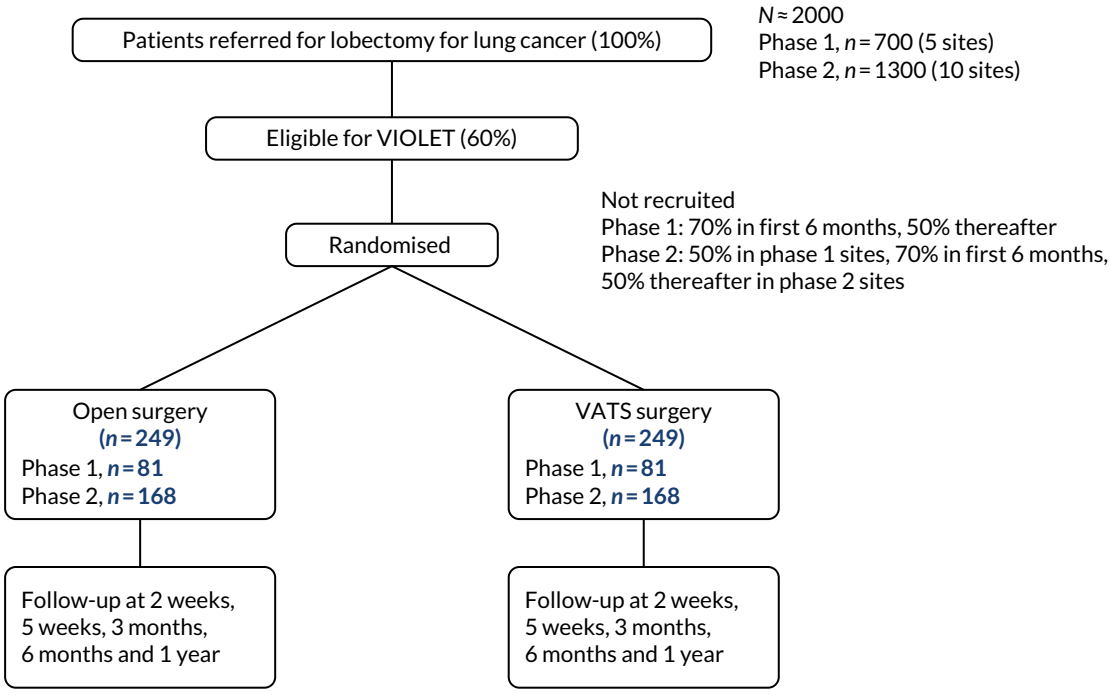

FIGURE 1 The trial schema for the VIOLET study.

First amendment (before recruitment started)

- Definition of prolonged incision pain was changed from 'need of analgesia for > 6 weeks after surgery' to 'need of analgesia for > 5 weeks after randomisation'.
- Clarification that adverse health events would be collected to 1 year and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) criteria, with postoperative complications classified in accordance with the Clavien–Dindo system. Surgical emphysema requiring intervention, reoperation for reasons other than recurrence or progression, and adverse events (AEs) associated with adjuvant chemotherapy and radiotherapy were added to the list of expected AEs.
- Patient resource use questionnaires, collection of resource use at 2 weeks and computerised tomography (CT) of the pelvis were removed.
- Clarification of measures to promote blinding of the trial participants.

Second amendment (approved 19 October 2015)

- CT-based Response Evaluation Criteria in Solid Tumours criteria to assess recurrence/progression was replaced by specific objective criteria, as postoperative CT imaging is not routinely undertaken for patients following lobectomy. Therefore, there were no comparative images against which to reference the 12-month CT scan.
- Addition of patient-reported pain scores at baseline and at 1 day and 2 days postoperatively.
- Option for research team at sites to follow-up patients by telephone at 5 weeks and 1 year to facilitate data collection as some patients are referred back to tertiary or peripheral hospitals for follow-up.
- Clarification of patient referral pathways, where potential participants may be identified and provided information, including the setup of patient identification centres.

Third amendment (approved 6 June 2017)

- Inclusion criteria modified to include patients undergoing bi-lobectomy, and reflect the transition to *TNM Classification of Malignant Tumours, Eighth Edition* (TNM8)[13] of the TNM staging system.
- Clarification that elective surgery, interventions and treatments during follow-up that were planned prior to recruitment to the trial will not be reported as unexpected serious adverse events (SAEs).
- Addition of pleural effusion, venous thromboembolism and other infection to the list of expected AEs.

Fourth amendment (approved 7 June 2018)

- Addition of molecular residual disease substudy (not reported here, funded by industry).
- Revision to archiving plan to remove scanning of documents.
- Clarification of form of bleeding (e.g. in or around the operation site) considered an expected AE.
- Addition of the option for research nurses (RNs) to obtain the questionnaire data directly from participants.

Fifth amendment (approved 21 January 2019)

- CTCAE grade scheme changed from v4.0 to v5.0.

Sixth amendment (approved 17 April 2019)

- Addition of the secondary outcome 'pain scores in the first 2 days post surgery', which had previously been missed from the protocol.
- Clarification of exploratory analysis of pain scores.
- Clarification of molecular residual disease substudy.

Seventh amendment (approved 4 December 2019)

- Clarification of molecular residual disease substudy.
- Reference corrected.

Eighth amendment (approved 3 February 2021)

- Clarification of end-of-study definition.

Participants

Patient population

Adults referred for lung resection for known or suspected lung cancer to one of the participating centres.

Patient eligibility criteria

Patients were eligible to enter the study if all the following applied:

- Aged ≥ 16 years.
- Undergoing lobectomy or bi-lobectomy for treatment of known or suspected primary lung cancer beyond a lobar orifice, or undergoing frozen section biopsy with the intention to proceed with lobectomy or bi-lobectomy if primary lung cancer beyond a lobar orifice is confirmed. (Note that for bi-lobectomy, the distance for the lobar orifice is in reference to the bronchus intermedius.)
- Cancer staging using TMN8:
    - clinical tumour stage 1–3 (cT1–3) [by size criteria, equivalent to *TNM Classification of Malignant Tumours*, *Seventh Edition*[14] (TNM7) stage cT1a-2b] or cT3 (by virtue of two nodules in the same lobe)
    - node stage 0–1 (N0–1)
    - metastasis stage 0 (M0).
- Multidisciplinary team (MDT) consider the disease is suitable for both VATS lobectomy and lobectomy via open surgery.
- Ability to give written informed consent.

Patients were not eligible to enter the study if any of the following applied:

- Previous malignancy that influences life expectancy.
- Planned pneumonectomy, segmentectomy or non-anatomic resection (e.g. wedge resection).
- Serious concomitant disorder that would compromise patient safety during surgery.
- Planned robotic surgery.

Changes to trial eligibility criteria after commencement of the trial

In July 2015, planned segmentectomy was added as an exclusion.

In June 2017, the inclusion criteria were revised to allow for the inclusion of patients undergoing bi-lobectomy and to update the cancer staging from TNM7 to TMN8. The Trial Management Group (TMG) recommended widening the inclusion criteria to include patients scheduled for a bi-lobectomy (i.e. resection of two lobes rather than one), as this can be performed via VATS or open surgery and, therefore, the research question is equally applicable to patients having this procedure. The revisions to the TNM staging system necessitated a change to the eligibility criteria, which were widened to include patients with cT1–3 tumours (by size criteria, equivalent to TNM7 stage cT1a-2b) or cT3 by virtue of two nodules in the same lobe. The entry criteria for nodal and metastatic involvement remained unchanged at N0–1 and M0, respectively.

Settings

NHS trusts with an established and accredited lung cancer MDT, which included trusts from across the UK, were eligible to participate in the VIOLET trial if the site undertook at least 40 VATS lobectomies each year and employed at least one surgeon that had carried out ≥ 50 VATS lobectomies. Phase I was restricted to five sites and further sites were opened in Phase II.

Surgeons were eligible to participate if they had performed at least 40 VATS lobectomies. Lobectomy via open surgery is a standard procedure and, therefore, surgical ability and competence was assured by specialist General Medical Council registration.

Trial interventions

VATS lobectomy (experimental)

Surgeons were permitted to undertake the VATS lobectomy using between one and four keyhole incisions. The use of rib spreading was prohibited, as this intraoperative manoeuvre disrupts the intercostal nerves and is thought to be an important cause of pain (and is a key feature of open surgery). The procedure was to be performed with videoscopic visualisation without direct vision. The hilar structures (i.e. vein, artery and bronchus) were dissected, stapled and divided. Endoscopic ligation of pulmonary arterial branches was optional. The fissure was completed and the lobe of lung resected. The incisions were closed in layers and may have involved muscle, fat and skin layers. This definition of VATS lobectomy is a modification of CALGB 39802.[15]

Open lobectomy (control)

Conventional open surgery was undertaken through a single incision. Rib spreading was mandated, but rib resection was optional. The operation was performed under direct vision, with isolation of the hilar structures (i.e. vein, artery and bronchus), which were dissected, ligated and divided in sequence, and the lobe of lung resected. Ligatures, over sewing or staplers could be used. The thoracotomy was closed in layers, starting from pericostal sutures over the ribs, muscle, fat and skin layers.

Aspects common to both groups

Participants without a confirmed tissue diagnosis at surgery

The surgeon could either take a confirmatory biopsy or proceed directly to surgery, as per MDT recommendation (see *Identification of potential participants: referral and multidisciplinary team review*).

Lymph node management

In both groups, lymph node management was undertaken in accordance with the International Association for the Study of Lung Cancer recommendations. The Association recommends that a minimum of six nodes/stations are removed, of which three are from the mediastinum that includes the subcarinal station.

Anaesthesia and postoperative pain management

All operations were undertaken with general anaesthesia and with the patient in the lateral decubitus position. This was a pragmatic trial and so adaptations and variations of both procedures were permitted at the discretion of the surgeon (intraoperative details were captured and monitored).

Standardising the use of analgesia across all participating sites was considered impractical and, if implementable, would be unrepresentative of clinical practice in the NHS. Each participating site prescribed analgesia in accordance with their local protocols. To minimise potential bias in pain outcomes, all sites were required to administer analgesia in accordance with a standard protocol applied, regardless of treatment allocation. Local protocols for the provision of analgesia were defined by the local principal investigator (PI) prior to the start of recruitment at the site. Details of the analgesia used throughout a participant's hospital stay were recorded and compliance with the prespecified site-specific analgesia protocol was monitored.

Other aspects of postoperative care

As this was a pragmatic study, postoperative care and the criteria for drain removal were in accordance with local practice. The decision to discharge a patient home after surgery was at the surgeon's discretion; however, to minimise the potential for bias, the criteria by which a patient was assessed as medically fit for discharge was prespecified and adherence to these criteria was monitored.

Outcomes

Primary outcome

The primary end point was self-reported physical function assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) at 5 weeks post randomisation. Physical function was chosen because it is a patient-centred outcome that would reflect the anticipated earlier recovery with VATS. It had also been used in other minimal access surgery trials. The 5-week primary end point (approximately 1-month post surgery) was chosen to capture the early benefits of minimal access surgery on recovery.

The EORTC QLQ-C30 is used to assess quality of life in cancer patients. The EORTC QLQ-C30 comprises 30 questions, which are used to derive an overall measure of global health, and a number of subscales, of which physical function is one. For all scales, higher scores indicate a higher level of functioning, symptoms or problems. The EORTC QLQ-C30 has been validated for use in European cohorts. Version 3 of the questionnaire was used.

Secondary outcomes

The following secondary outcomes were selected to assess the efficacy of the two approaches:

- Time from surgery to hospital discharge.
- Pain scores in the first 2 days post surgery.
- Adverse health events in the period from randomisation to 1 year.
- Uptake of adjuvant treatment (i.e. frequency and time from surgery).
- Frequency of upstaging to pathologic node stage 2 (pN2) disease after the procedure.
- Overall and disease-free survival to 1 year.
- Frequency of complete resection during the procedure.
- Frequency of prolonged incision pain (defined as the need of analgesia for > 5 weeks post randomisation).
- Generic and disease-specific patient-reported health-related quality of life (HRQoL) measured using the EORTC QLQ-C30, Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) and EQ-5D-5L questionnaires completed at 2 weeks, 5 weeks, 3 months, 6 months and 1-year post randomisation.
- Resource use during the hospital stay and post discharge to 1 year after randomisation.

Changes to trial outcomes after commencement of the trial

In 2015, minor amendments were made to clarify some secondary outcomes prior to the study opening to recruitment (see *Changes to trial design after commencement of the trial* for details). In a further amendment in the same year, the collection of patient-reported pain scores at baseline and at 1 day and 2 days postoperatively was added to the table of assessments, but the list of secondary outcomes was inadvertently not updated in line with this addition. This error was corrected in 2019 when pain scores were added to the list of secondary outcomes in the protocol. Pain scores were added to allow further comparison between the two surgical techniques during the early postoperative period. Pain assessments are routinely undertaken by the clinical team to determine whether or not the analgesia provision is sufficient and so a patient verbal assessment of pain represented minimal additional burden to the patient.

Sample size

We hypothesised that self-reported physical function 5 weeks after randomisation for participants undergoing a VATS lobectomy would be superior to the physical function for participants having an open lobectomy, as derived from responses to the EORTC QLQ-C30 questionnaire. Data from the literature on minimal clinically important differences in HRQoL scores from the EORTC QLQ-C30 were used to inform the target effect size.[16]

Although the primary end point was at 5 weeks, the questionnaire was also completed at other time points, namely at baseline, 2 weeks, 3 months, 6 months and 1 year. In estimating the sample size, the following assumptions were made:

- One pre-surgery measure and five post-surgery measures.
- A correlation between pre- and post-surgery measures of 0.3.
- A correlation between repeated post-surgery measures of 0.6.
- An effect size of 0.25 standard deviations (SDs) would be considered clinically important.

Under these assumptions, and allowing for up to 20% loss to follow-up at 1 year, the sample size was set at 498 patients (i.e. 249 patients per group), which provided 90% power to test the superiority hypothesis at the 5% significance level.

Interim analyses

There were no interim analyses planned nor undertaken for the VIOLET trial.

Randomisation

Participants were randomly allocated to either VATS lobectomy or open lobectomy in a 1 : 1 ratio. Randomisation took place through a secure internet-based randomisation system (Sealed Envelope Ltd, London, UK) approximately 1 week before the planned surgery, after eligibility had been confirmed and written informed consent given. This time frame was chosen to allow sufficient time for operating schedules to be arranged.

The randomisation was stratified by centre, and cohort minimisation (with a random element incorporated) was used to ensure balance across groups with respect to surgeon. Allocations were concealed until information to uniquely identify the participant and confirm eligibility was entered into the randomisation system, after which the randomised allocation was revealed. If there was a change in surgeon after randomisation, the analysis accounted for the surgeon responsible for the performing the operation and not the surgeon originally assigned to the patient.

Blinding

Research team

The surgical team, anaesthetist and other staff caring for the participant during the operation were not blinded to the patients' treatment allocation. However, to minimise the risk of bias in the assessment of outcomes, the randomisation was performed by a member of the research team who was not responsible for the collection of outcome data.

Wound dressings

Efforts were made to minimise the risk of inadvertently unblinding the RN responsible for data collection during the patient's postoperative stay by applying large adhesive dressings to the thorax of participants. These adhesive dressings were positioned similarly for all patients, regardless of their surgical allocation, to cover both real and potential incision/port locations. The initial adhesive dressings were applied in the operating room by the operating team. The dressings remained in place for 3 days unless the patient was discharged before day 3, when they were removed, or if the patient required replacing early because of soiling. After 3 days, dressings were changed by a nurse not involved in conducting follow-up assessments or data collection for the trial. Wound cleaning was performed on both actual and potential wounds to promote masking.

Fitness for discharge after surgery

To minimise bias in the decision-making around when a participant was discharged home, the following discharge suitability criteria were developed. Participants were evaluated against the following criteria to ensure that they are medically fit for discharge:

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

Patients who were considered medically fit for discharge were not necessarily discharged immediately. In some instances, social and other factors may have necessitated extended hospitalisation. The time at which patients are considered medically fit for discharge and when they are physically discharged from hospital were both captured in the trial. For the two groups, the data were monitored for evidence of both early discharge before all the discharge criteria were met and delayed discharge.

Participants

To ensure that study participants remained blinded during the postoperative period to discharge home, participants were asked to turn their head away from the wound site(s) while wounds were being cleaned and dressed. Participants were advised of how best to care for their wounds when they were considered 'fit for discharge'. Those participants who asked to know which treatment they had received were informed at this point.

Assessment of blinding

The success of blinding was assessed using Bang *et al.*'s Blinding Index.[17] Participants were asked to complete the assessment 2 days postoperatively and at discharge, but before the treatment allocation was revealed. The RNs responsible for data collection and follow-up of participants completed the Blinding Index when the patient was ready for discharge, and after the 5-week and 1-year follow-up appointments.

Data collection

Overview

Data collection for the trial participants included the following elements:

- A log of patients screened by the MDT for suitability for the trial and the date when patients were given or sent the patient information leaflet (PIL).
- A log of patients assessed against the eligibility criteria and reason(s) if ineligible.

- Audio-recording and transcription of consultations between surgeons and potential participants (see *QuinteT Recruitment Intervention* for further details).
- Semistructured interviews with a sample of eligible patients, including patients who accept or decline to join the trial.
- Approach and consent details, including reason(s) for non-approach or decline.
- Baseline data, including the participant's medical history, disease status and HRQoL prior to randomisation.
- Operative details.
- Histopathology of any samples (e.g. biopsies) taken intraoperatively.
- Postoperative care, including analgesia and pain scores.
- AEs and resource use in the period from randomisation to 1 year.
- HRQoL during follow-up.
- Results of scans taken to assess disease status.

An overview of the schedule of data collection is given in *Table 1*.

TABLE 1 Schedule of data collection

	Study period										
	Enrolment	Allocation	Post allocation[a]								Close-out
Item	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9
Enrolment											
Eligibility	✓										
Informed consent	✓										
Allocation		✓									
Assessment											
Imaging review (CT or PET-CT)	✓										
Participant characteristics	✓										
Audio-recorded consultation	✓										
Lobectomy via VATS or open surgery			✓								
Intraoperative details			✓								
Histopathology staging			✓								
Tumour sample for research			✓								
QLQ-C30	✓						✓	✓	✓	✓	✓
QLQ-LC13	✓						✓	✓	✓	✓	✓
EQ-5D-5L	✓						✓	✓	✓	✓	✓
Bang *et al.*'s Blinding Index[17]					✓	✓					
Pain score	✓			✓	✓						
AEs				✓	✓	✓		✓	✓	✓	✓
Resource use				✓	✓	✓		✓	✓	✓	✓
CT of chest and abdomen											✓

PET, positron emission tomography; $-t_1$, baseline; t_1, day of surgery; t_2, 1-day post surgery; t_3, 2 days post surgery; t_4, discharge; t_5, 2 weeks; t_6, 5 weeks; t_7, 3 months; t_8, 6 months; t_9, 12 months.
a If a patient was confirmed to have benign disease following surgery, follow-up ceased at 5 weeks.

Collection of health-related quality-of-life data

Health-related quality-of-life data were collected on paper or online, according to participant preference. If data were not returned, the participant may have been telephoned by the local RN and the data collected over the telephone.

Collection of adverse event data

Serious adverse events and other AEs were recorded and reported in accordance with Good Clinical Practice guidelines. Data were collected from the time of consent until 1-year post randomisation. Events were graded in severity using the CTCAE, which is a standardised classification system used in cancer studies.

As lung resection surgery is a major surgical intervention, events related to the surgery were considered 'expected'. Many participants would go on to receive adjuvant chemotherapy or radiotherapy after their lung resection surgery. Such treatments have a range of common serious side effects and toxicities, which were also considered 'expected' for participants undergoing adjuvant chemotherapy and/or radiotherapy. These expected events were listed in the study protocol. Events that occurred that were not listed in the protocol were considered unexpected.

Safety data were reviewed regularly by the study team and at least annually by the Data Monitoring and Safety Committee (DMSC). Reporting to the sponsor was required only if an AE was considered serious (i.e. resulted in a hospital admission, prolonged a hospital admission, was life-threatening, resulted in significant disability or death) and unexpected or expected and fatal. Reporting to the Research Ethics Committee and DMSC was required if an unexpected SAE was found to be causally related to the intervention.

Identification of potential participants: referral and multidisciplinary team review

Potential participants were identified from MDT meetings at each study site, where patient referrals from local and satellite lung cancer MDTs or from peripheral hospitals are considered. Several peripheral referring hospitals were set up as patient identification centres to allow potential participants to receive study information in a timely way and to allow participants time to consider the trial and discuss it with friends and family before their clinical appointment with a study surgeon.

Patients had undergone CT/CT plus positron emission tomography (PET) to assess the extent of their disease, but it is common for lung lesions to be of uncertain pathology before surgery: up to 25% of patients are listed without a preoperative tissue diagnosis.[18] Both patients with proven cancer and those without preoperative tissue diagnosis were eligible to participate in the VIOLET trial. Patients without a preoperative tissue diagnosis were considered eligible if the MDT either recommended lobectomy surgery or a biopsy with the option to proceed to lobectomy if cancer is confirmed, or if there was sufficient clinical certainty for direct lobectomy without biopsy. It was estimated that 75% of patients referred had a confirmed diagnosis. Of the remaining 25% of patients, the recommendation was a biopsy with the option to proceed in 20% of cases, and in 5% of patients the MDT recommended lobectomy without biopsy confirmation. This strategy could lead to a small proportion of participants (estimated 4% in total) finally being confirmed to have benign disease. These patients are included in the primary analyses. If the (real-time) results of the frozen section biopsy diagnosed primary lung cancer, surgery proceeded as allocated. Participants with a non-cancerous diagnosis received no further surgery.

QuinteT Recruitment Intervention

Overview and aims

A QRI[19,20] was integrated throughout the recruitment period of the VIOLET trial because of anticipated recruitment challenges[1] arising from the nature of the trial interventions [i.e. different approaches to undertaking lung resection (lobectomy) via VATS or open surgery]. The QRI methods, first developed in the ProtecT (Prostate testing for cancer and Treatment) study,[21,22] have been refined and applied in nearly 70 RCTs, including other surgical RCTs.[23–25]

The aim of the QRI in the VIOLET trial was to optimise and sustain recruitment and informed consent by preventing recruitment difficulties from arising, identifying new challenges as they arose and addressing those that did arise rapidly. The VIOLET trial QRI began with QRI-informed recruitment training workshops aimed at helping recruiters prepare for impending recruitment activities and preventing the development of recruitment barriers. Next, when recruitment commenced, we employed established QRI methods, which comprised two iterative components[19,20] aimed at (1) understanding the recruitment issues in real time and identifying the clear obstacles and hidden challenges to recruitment,[26,27] and (2) developing and implementing a plan of action comprising strategies[28–31] to overcome the challenges, in collaboration with the chief investigator, TMG, Bristol Trials Centre and the recruiting sites. Evaluation of the QRI was carried out throughout the recruitment period by regularly monitoring recruitment figures [using the screened, eligible, approached, randomised (SEAR) framework][32] and recruitment practice. Each of these methods is described in detail below (for further context regarding the evolution of the QRI, see *Appendix 1*).

Preventing recruitment difficulties: training and guidance prior to recruitment

We aimed to prevent recruitment difficulties in the VIOLET trial by disseminating strategies to optimise recruitment and informed consent to recruiting surgeons, drawing from the QRI evidence base and using multiple avenues. These activities occurred prior to recruitment and involved study-wide, as well as site-specific, activities.

At the trial set-up phase, PIs and other recruiting surgeons from the five sites in the internal pilot phase were invited to attend a 1-day QRI-informed recruitment training workshop.[29] Surgeons from the new centres were invited to subsequent workshops. The evidence-based training was aimed at raising awareness of, and providing practical tips to manage, the clear obstacles[27] (e.g. logistical issues) and hidden challenges to recruitment (e.g. conveying equipoise, addressing patient preferences).[26–28,30,33] The evidence that informed the above workshops was also presented to each site during site initiation visits (SIVs), summarised in a brief tips document circulated to all internal pilot sites and used to identify aspects of patient- and recruiter-facing study documentation (e.g. information leaflets, consent forms and trial protocol) that were potentially unclear, imbalanced or open to misinterpretation.

Understanding recruitment issues

We employed a range of methods, primarily qualitative, but also drawing on descriptive quantitative data obtained from the SEAR logs, to understand the recruitment processes in the VIOLET trial and to identify the challenges to optimal recruitment.

Sampling and recruitment

Our sampling frame consisted of the VIOLET trial sites (i.e. five sites in the internal pilot Phase I and four sites added in Phase II), all staff involved in recruitment at these sites and TMG members.

Sites

All sites in the VIOLET trial were approached for participation in the integrated QRI at the time of the SIV or subsequently. QRI researchers liaised with the PIs or RNs at the sites to explain the QRI purpose and methods.

In-depth interviews

We employed a combination of sampling strategies to ensure that a wide range of views were gathered. We purposefully selected and approached staff members who were involved in trial oversight, including TMG members, as well as clinical/research staff in different roles (e.g. surgeons, RNs) who were involved with recruitment, to ensure maximum variation in the views captured. We also selected participants who were likely to provide insights into recruitment challenges identified in previous interviewees or other sources of data (e.g. theoretical sampling). Participants were initially contacted via e-mail, with a follow-up reminder when necessary.

Audio-recordings of recruitment discussions

All sites were requested to routinely audio-record the discussions that recruitment staff had with patients regarding treatment options and the trial until a decision was made regarding trial participation. The sites were provided with digital audio-recording equipment and 'recruiter packs', which outlined the process of obtaining consent for the QRI and provided instructions on how to operate the audio-recorders and to name and upload the audio files in a safe and confidential manner. Prior to each feedback session, audio-recordings were sampled using strategies similar to those employed to select interviewees described above (i.e. purposive, maximum variation and theoretical sampling). We purposively selected recordings of randomised and declined patients, ensuring that they featured different recruiters and spanned across centres, with further selections being made based on the themes identified in previous feedback sessions.

Data collection

In-depth interviews

Staff members who agreed to participate were sent information sheets and their written consent was obtained prior to the interview. In-depth semistructured interviews were conducted at a mutually convenient time and place (face to face or via telephone) and were digitally audio-recorded. Topic guides drew from those used in previous QRIs and helped ensure consistency across interviews, but these were used flexibly to allow the exploration of issues of importance to participants. Topics covered in interviews included the development, purpose and design of the trial; potential participants' pathway through eligibility and recruitment; views on equipoise in relation to the VIOLET trial; and how the trial and the interventions would be discussed with patients.

Audio-recordings of recruitment discussions

Staff and patient consent were obtained prior to audio-recording of recruitment discussions. Staff members were provided with an information sheet and one-off written consent was obtained (usually by RNs), which allowed the audio-recording of their subsequent VIOLET trial recruitment discussions. The PIL for the QRI was posted to patients before their first clinical consultation with the surgeons to ensure that they had sufficient time to consider QRI participation. When patients arrived for the consultation, research teams confirmed that the patients had read and understood the information and then obtained written consent if the patient was willing to participate in the QRI. Recruitment discussions of these patients were then audio-recorded.

Patient pathway through eligibility and recruitment

All study sites were asked to maintain detailed screening logs, capturing SEAR[32] information (see section *Overview*). Sites entered screening and recruitment data to a study database designed by the trials centre. Information on the recruitment pathways (i.e. the pathway for patients from the time they were referred for treatment to the point at which a decision was made regarding trial participation) was gathered through the in-depth interviews described above.

Observations of study meetings

QuinteT Recruitment Intervention researchers also attended regular study meetings to gain an overview of trial conduct and overarching challenges. Meetings attended included TMG meetings that took place every few months (consisting of the chief investigator and all VIOLET trial co-applicants),

investigators' meetings (similar to TMG meetings, but also attended by the key recruiting teams from participating sites) and monthly study update meetings (for key members of the TMG and research team). These meetings provided insights into the recruitment concerns of key stakeholders that warranted further exploration.

Data analysis

In-depth interviews

Audio-recorded interviews were transcribed in full and verbatim. Transcripts were imported into NVivo version 10 (QSR International, Warrington, UK) and analysed using techniques of constant comparison, drawing from grounded theory.[34] This involved repeatedly moving within and across transcripts in the light of newly identified themes. We sought to develop a holistic understanding of recruitment challenges, as well as elements of good practice, and were attentive to shared, as well as disparate, views among staff members. Data collection and analysis were iterative and continued until we achieved data saturation (i.e. when we were no longer able to identify new themes).

Audio-recordings of recruitment discussions

Audio-recordings of recruitment discussions were transcribed verbatim and in a targeted manner, focusing on discussions of the trial and the operations. We employed similar methods of constant comparison as described for the interviews above. In addition, we used targeted conversation analytical techniques[35] to delineate elements of good practice among recruiters for wider dissemination, as well as aspects of the discussion that could have contributed to misunderstandings among patients, precipitated patient preferences or adversely affected recruitment in other ways.

Patient pathways through eligibility and recruitment

Drawing from the interview data, we compiled recruitment pathways for each clinical centre. This comprised noting points at which patients received study information, underwent tests, had their eligibility determined and met clinical staff in different professional roles, and the timelines across these key points in the pathway. Recruitment pathways were compared across centres to identify good practice and bottlenecks that hindered recruitment.

Screened, eligible, approached, randomised data were collated and descriptively analysed by the trial statistician, with monthly summaries provided to the QRI team for each site (to aid group feedback) and individual surgeon (to inform individual feedback). QRI researchers carried out further analysis by designing a colour-coded spreadsheet for each recruiting site to facilitate easy identification of inconsistencies or missing data, as well as site-specific patterns in recruitment flow. These inconsistencies and patterns were discussed with the chief investigator/TMG during study update meetings. Data queries were often resolved by contacting site research teams or by alerting the trial manager. Patterns, such as lack of screening activity, patients not being approached or large numbers of patients declining to take part in the RCT, usually triggered further data collection and agreement on a plan of action to help sites address unhelpful patterns of recruitment.

The findings from the above data sets were brought together and detailed in a descriptive account that drew from all data sources to identify key challenges to recruitment, with brief update reports written throughout the recruitment period of the trial.

Plan of action: strategies to optimise recruitment and informed consent

Initial anonymised QRI findings that identified factors appearing to hinder recruitment were presented to the chief investigator/TMG (in February 2016, 8 months after recruitment to the VIOLET trial had commenced) so that they could agree on a plan of action to address factors impeding recruitment. This plan was implemented through the first set of group and individual feedback sessions covering all the internal pilot phase sites (May–June 2016), with the aim of optimising recruitment and informed consent. As recruitment progressed and the trial moved into the main phase, there was further QRI

data collection, analysis and presentation of findings at TMG and investigator meetings and at VIOLET trial sites, which aimed to sustain the recruitment momentum gained early in the trial. The key findings were also summarised in succinct 'tips' documents circulated to all centres, especially during periods of low recruitment activity. Towards the end of the recruitment period, the QRI team, in collaboration with the chief investigator/TMG, developed a rapid communication strategy, which aimed to reiterate the most important QRI findings and strategies and disseminate them through monthly newsletters developed by the trials centre and e-mail communications with infographics on recruitment figures.

Evaluating the impact of the QRI

We evaluated the impact of the QRI in two ways through (1) monthly monitoring of recruitment figures (i.e. SEAR data) and (2) recruitment practice. First, SEAR data were monitored from the onset of recruitment until the achievement of the final recruitment target to check if recruitment commenced well following the training/guidance provided prior to recruitment, if any recruitment momentum gained was sustained thereafter and if there were periods of low recruitment activity that improved after rapid intervention. Second, we monitored recruitment practice by listening to the audio-recordings (and interviews where relevant) to document changes in practice following the provision of trial- and site-specific feedback and instances where recruitment challenges appeared to have been averted following the training/guidance prior to recruitment. A conventional pre- and post-intervention evaluation was not feasible in the VIOLET trial QRI, as it did not have a precise pre-QRI period of recruitment because of the preventative activities undertaken in advance of recruitment.

Statistical methods

All analyses were directed by a prespecified statistical analysis plan (SAP), which was finalised before the database was locked for analysis. The data are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[36]

Summary statistics and analysis population

Data were described using summary statistics, using mean and SD for continuous variables [or median and interquartile range (IQR) if distributions were skewed] and number and percentage for categorical variables. HRQoL questionnaires were scored in accordance with the developer's scoring instructions and summary scales derived from the questionnaires are reported in summary tables.

Participants were grouped according to the randomised allocation (intention to treat). The analysis population consisted of all randomised participants, excluding those who withdrew and were unwilling for data already collected to be used. Data from any participant who withdrew and was unwilling for their data to be used were included in the study flow chart, but not in any subsequent data tables or figures.

Models used to compare primary and secondary outcomes

The models used to compare longitudinal HRQoL outcomes, including the primary outcome, are presented in *Table 2*. The adequacy of a model fit was assessed graphically.

The strategy for modelling longitudinal HRQoL outcomes, listed in order of preference, is as follows:

- Joint longitudinal survival model.
- Linear mixed-effects model (chosen if the joint longitudinal survival model did not provide an adequate fit to the data).
- Mixed-effects ordinal logistic regression (chosen if the HRQoL score could take only four possible values, the proportional odds assumptions held and the previous models were not appropriate) or partial proportional odds model (chosen if proportional odds assumption did not hold for all variables to be included in the model).
- Mixed-effects logistic regression (chosen if the ordinal logistic regression model did not converge or the proportional odds assumption did not hold for time or treatment variables).

TABLE 2 Methods of analysis for HRQoL longitudinal outcomes

Outcome	Model	Time adjustment	Survival adjustment	Effect(s) reported
QLQ-C30: physical functioning, global health status/quality of life, role functioning, social functioning and dyspnoea scores QLQ-LC13: dyspnoea, cough, pain in chest and pain in other parts scores	Joint longitudinal survival model	Fixed or random, depending on model fit assessed using likelihood ratio tests	Survival time modelled jointly with HRQoL score	MD
QLQ-C30: fatigue, pain and insomnia scores	Linear mixed-effects model	Fixed: different variance/covariance structures assessed using likelihood ratio tests	None	MD
QLQ-C30: emotional functioning and cognitive functioning scores EQ-5D-5L	Two-part model, with logit first part and log-linear second part	Fixed	No adjustment in emotional functioning model EQ-5D-5L score of 0 imputed after death	OR and GMR
QLQ-C30: appetite loss, diarrhoea and financial difficulties scores QLQ-LC13: sore mouth, dysphagia, peripheral neuropathy, alopecia and pain in shoulder or arm scores	Ordinal logistic regression	Fixed	None	OR
QLQ-C30: nausea and vomiting, and constipation scores QLQ-LC13: haemoptysis score	Logistic regression	Fixed	None	OR

GMR, geometric mean ratio; MD, mean difference; OR, odds ratio.

If the distribution of the HRQoL score was non-monotonic, with a high proportion of participants scoring perfect functioning/health, a two-part model was used. Scores were dichotomised into perfect functioning/health (i.e. a QLQ-C30 score of 100 and an EQ-5D-5L utility score of 1) and less than perfect functioning/health. The first part of the model was an occurrence model, that is a mixed-effects logistic regression model comparing perfect functioning/health with less than perfect functioning/health. The second part was an intensity model, that is a log-linear mixed-effects model for the score, conditional on a less than perfect functioning/health score.

Time-by-treatment interactions were added to all longitudinal models. Overall treatment effects are presented unless the interaction reached 10% statistical significance, in which case treatment effects for each time point are reported. For the primary outcome, the treatment effect at 5 weeks is reported, estimated from the longitudinal model with a time-by-treatment interaction included.

Time-to-event outcomes were compared using Cox proportional hazards models and treatment estimates are presented as hazard ratios (HRs). Time to uptake of adjuvant treatment was analysed using competing-risks regression, with death modelled as a competing risk. Overall survival, progression-free survival (with progression defined as progression of lung cancer or new primary lung cancer or death from any cause, whichever occurred first) and uptake of adjuvant treatment were censored at last follow-up for those who had not experienced the event (or competing risk). For duration of hospital stay, in-hospital deaths were censored at the maximum observed time to discharge for survivors. The exact partial-likelihood method was used to account for tied times. Model assumptions were assessed graphically.

In-hospital pain scores were analysed using a linear mixed-effects model. Binary outcomes [i.e. complete R(0) resection and prolonged incision pain] were analysed using generalised linear models and multinomial outcomes (i.e. upstaging to pathologic node stage 1 (pN1) disease and upstaging to pN2 disease) using generalised structural equation models. Effect estimates are presented as relative risk (RR).

The mean daily dose of each analgesic, averaged over the hospital stay, was derived for each participant. Analgesic agents were combined into groups, where appropriate. The mean ratios were derived for each analgesic group and 95% confidence intervals (CIs) were estimated using bootstrapping.

Open surgery was the reference group in all analyses. Treatment estimates are reported with 95% CIs.

Adjustment in models

The plan was to adjust all models for centre and operating surgeon fitted as random effects (or as stratification variables in time-to-event outcomes). For binary outcomes, a clustered sandwich estimator was used to account for the clustering within surgeon, as random effects were not estimable. All longitudinal analyses were adjusted for baseline preoperative score as a fixed effect.

Subgroup analysis

A prespecified subgroup analysis, comparing in-hospital pain scores by type of analgesia (e.g. paravertebral block, intercostal block, both, neither) was performed. This was implemented by adding a treatment-by-analgesia interaction term into the model, comparing pain scores between groups.

Sensitivity analyses

A sensitivity analysis of the primary outcome, excluding participants with benign disease, was prespecified in the protocol. Sensitivity analyses of overall survival and progression-free survival were also performed, adjusting the model for participant's disease stage based on pathological findings. These analyses were not in the protocol, but were added to the SAP on recommendation from the DMSC.

Exploratory analyses

Two exploratory analyses of pain scores were undertaken. The first was stated in the protocol and the second was requested by the DMSC:

1. An exploratory analysis comparing in-hospital pain scores by number of incisions (i.e. VATS with a single port site, VATS with multiple port sites and open surgery).
2. An exploratory analysis comparing in-hospital pain scores and QLQ-C30 pain scores by type of thoracotomy (i.e. anterior thoracotomy vs. posterolateral thoracotomy, muscle sparing vs. no muscle sparing, and rib resection vs. no rib resection).

An exploratory analysis comparing length of stay by incisions (i.e. single-port VATS vs. multiport VATS vs. open surgery) was not prespecified in the protocol, but was requested by the chief investigator before any comparative analyses had been undertaken.

Missing data

Missing data are described in footnotes to all tables. Rules for imputing missing data outlined in the SAP were dependent on the level of missing data. All HRQoL analyses and the in-hospital visual analogue scale (VAS) pain score analysis met the threshold for multiple imputation. For other outcomes, participants with missing data were excluded. For HRQoL analyses, each subscale was imputed separately. Imputation by chained equations was used to generate multiple complete data sets [using the Stata® version 16.1 (StataCorp LP, College Station, TX, USA) -ice- command] and results were combined using Rubin's rules. Factors included in the imputation models used were baseline HRQoL score, treatment allocation, centre and operating surgeon.

Significance levels and adjustment for multiplicity

For hypothesis tests, two-tailed *p*-values of < 0.05 were considered statistically significant. Likelihood ratio tests were used in preference to Wald tests. For HRQoL outcomes derived from the QLQ-C30 and QLQ-LC13 questionnaires, significance levels were adjusted for multiplicity using the false discovery rate method proposed by Benjamini and Hochberg.[37] The adjustment was applied within each instrument (e.g. for QLQ-C30 functional scale scores, QLQ-C30 symptom scale scores and QLQ-LC13 scores). No formal adjustment for multiplicity was made for other outcomes. Formal statistical comparisons were not made for outcomes with low-event rates and only prespecified subgroup analyses were performed. The number of statistical tests performed should be considered when interpreting results.

All statistical analyses were performed with the use of Stata software.

Economic evaluation

Economic evaluation aim

The economic evaluation aimed to estimate the incremental cost-effectiveness of VATS lobectomy compared with open lobectomy for the treatment of lung cancer, in line with the VIOLET trial.

Economic evaluation overview

The perspective of the evaluation was that of the UK NHS and Personal Social Services, as recommended by the National Institute for Health and Care Excellence (NICE).[38] The perspective for outcomes comprised the patients undergoing treatment. The primary outcome measure for the cost-effectiveness analysis was quality-adjusted life-years (QALYs), estimated using the EQ-5D-5L.[39,40] Established guidelines on the conduct of economic evaluations set out by NICE were followed.[38] *Table 3* summarises the key aspects of the economic evaluation, and further details are provided below.

Form of analysis, primary outcome and cost-effectiveness decision rules

As advocated by NICE, a cost-effectiveness analysis (specifically a cost–utility analysis) was conducted, using QALYs as the primary outcome measure.[38] QALYs combine both quantity and quality of life into a single measure. Incremental costs (i.e. the difference in mean costs between the VATS and open lobectomy groups) were divided by incremental QALYs (i.e. the difference in mean QALYs between the groups) and presented as the incremental cost-effectiveness ratio (ICER), which quantifies the incremental cost per QALY gained by switching from using open surgery to VATS lobectomy. The economic evaluation analyses were performed on an intention-to-treat basis.

Video-assisted thoracoscopic surgery lobectomy was considered cost-effective if the ICER fell below £20,000, which is generally considered as the threshold that NICE adopts for considering an intervention to be cost-effective.[41]

Time horizon

A within-trial analysis, taking a 1-year time horizon, was conducted. It was anticipated that all major resource use (i.e. surgery, complications relating to surgery and adjuvant therapy) would occur within this time frame and would, therefore, be captured.

The starting point for our analysis was from the point of surgery, rather than the point of randomisation, as was the case with the trial effectiveness analysis. Randomisation was performed within 1 week of the planned operation date. The time point for baseline costs and outcomes was not quite the same. The EQ-5D-5L data were collected preoperatively, whereas detailed resource use data collection began on the day of surgery. However, as no difference in resource use was expected between the groups until the time of surgery, we did not anticipate this being an issue. Our time horizon continued until 1-year postoperatively.

TABLE 3 Summary of economic evaluation methods

Aspect of methodology	Strategy used in base-case analysis
Form of economic evaluation	Cost-effectiveness analysis for comparison between VATS lobectomy and open surgery
Perspective	NHS and Personal Social Services
Time horizon	A within-trial analysis, taking a 1-year time horizon
Data set	All randomised participants were included (see *Patient eligibility criteria* for eligibility criteria)
Costs included in analysis	Index admission: • Surgery • Length of stay by ward type (including ICU and HDU) • Investigations and treatments relating to complications, and SAEs Post discharge: • Adjuvant therapy • Imaging • Recurrence/progression of cancer • Readmissions to hospital • Outpatient and ED attendances • Community health and social care contacts
Utility measurement	EQ-5D-5L administered at baseline (pre randomisation), 2 weeks, 5 weeks, 3 months, 6 months and 1 year post randomisation
QALY calculations	Assume that participants' utility changes linearly between utility measurements[a]
Adjustment for baseline utility	Regression used to adjust QALY calculations for differences in baseline utility
Missing data	Multiple imputation

ED, emergency department; HDU, high-dependency unit; ICU, intensive care unit.
a Participants' utility changes at a constant rate (in a straight line) between measurements.

Collection of resource use and costs

Resource use data were collected on all significant health service resource inputs for the trial participants to the end of the 1-year follow-up period. Collection of detailed resource use data was integrated into the trial case report forms (CRFs) for the index admission, and captured from telephone calls with participants at 5 weeks, 3 months, 6 months and 1-year post randomisation. The main resource use categories that were captured and costed were initial thoracic surgery, hospital stay post surgery (by ward type), complications, adjuvant therapy, imaging, recurrence/progression of cancer, hospital readmissions, outpatient and emergency department (ED) attendances, and community health and social care contacts. *Appendix 2*, *Table 25*, details the sources of unit cost information for each of these categories. Costing decisions (e.g. resource use assumed for complications) were made without knowledge of the allocation of participants to trial groups.

Thoracic surgery

The key differences in resources required for VATS lobectomy and open surgery are the time in theatre and the number of staples required. These were captured on the trial CRFs and were used to cost the index surgery. Pathology costs associated with a biopsy and frozen section analysis are also included.

Treatment complications and serious adverse events

Trial CRFs captured postoperative complications that participants experienced, including pulmonary, cardiac, renal, gastrointestinal, infective and neurological complications, and the need for reoperations. We discussed with the research team the likely resource implications of complications that were not

already being captured. Trial CRFs also captured resource use around SAEs. SAEs were individually reviewed and additional resources were costed, only if not already captured in complication costs to avoid double counting. *Appendix 3*, *Tables 29–31* and *33–35*, show all the complications, the corresponding diagnostic tests and treatments assumed and their unit costs.

Hospital readmissions and other post-discharge primary and secondary health and social care visits

The costs of hospital readmissions included all expected and unexpected thoracic surgery and chemotherapy/radiotherapy complications in terms of AEs and SAEs, but excluded all unexpected unrelated complications. For example, our analysis included the cost of readmissions for wound pain, but excluded the cost of readmissions for ophthalmology. Clinical opinion was sought to clarify whether unexpected complications were possibly related or were unrelated to the index surgery. Treatment relating to known pre-existing conditions (i.e. conditions known prior to randomisation) were excluded unless lung related. Similarly, resource use associated with lung cancer progression or recurrence was included, but resource use related to new non-lung cancer and totally unrelated cancer (e.g. prostate cancer) was excluded. The cost of an ED attendance was included if a participant was admitted via ED or referred by their general practitioner (GP) (and assumed to be admitted via ED).

We reviewed the reasons for outpatient attendance and discussed with the trial research team whether or not these were likely to be linked to the surgery to avoid costing any outpatient visits that were totally unlinked to the trial. Similarly, the reasons for ED visits and community health and social care contacts were reviewed, and any unrelated activity excluded.

Attaching unit costs to resource use

Unit costs for hospital and community health-care resource use were largely obtained from national sources, for example the National Schedule of Reference Costs[42,43] for ward costs, scans and many complications, and Unit Costs of Health and Social Care[44] for community costs. Resources were valued in 2018/19 GBP and any unit costs not in 2018/19 prices have been adjusted to 2018/19 prices using the NHS cost inflation index.[45] Where available, costs of drugs given in hospital were taken from the electronic marketing information tool (eMIT),[46] which provides the reduced prices paid for generic drugs in hospital. Otherwise, costs were obtained from the *British National Formulary*.[47] For a summary of the sources of unit cost information, see *Appendix 2*, *Table 25*. For further details on all unit costs and their source, see *Appendix 3*, *Tables 28–39*.

Measurement of health-related quality of life and quality-adjusted life-years

Measurement of health-related quality of life

The EQ-5D-5L questionnaire, advocated for use in economic evaluations by NICE,[38] was used to measure HRQoL.[39,40] The EQ-5D is a generic measure of health outcome, covering five dimensions: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort and (5) anxiety/depression. The EQ-5D-5L was completed by participants at six time points: (1) baseline (pre-randomisation), (2) 2 weeks, (3) 5 weeks, (4) 3 months, (5) 6 months and (6) 1-year post randomisation. Although data were gathered using the EQ-5D-5L (the five-level version, with five possible responses for each dimension), responses recorded on the instrument were converted into a single index value using the original three-level UK valuation set.[48] Scores were then used to facilitate the calculation of QALYs. Utility values were calculated by mapping the five-level descriptive system to the three-level valuation set using the crosswalk developed by van Hout *et al.*[49] in accordance with NICE recommendations at the time of analysis.[49,50]

Calculation of quality-adjusted life-years

The QALY profile for each participant was estimated from surgery to 1 year, and the area under the curve of utility measurements was used to calculate the number of QALYs accrued by each participant. QALYs were calculated assuming that each participant's utility changes linearly between each of the time points [i.e. that utility changes at a constant rate (in a straight line) between measurements].

For participants who died during the trial, their utility was assumed to change linearly between the preceding time point and the time of death, and to take the value of zero from death onwards.

Missing data

We first summarised the number of missing data for resource use and outcomes (EQ-5D scores) descriptively. Exploratory analyses were conducted to explore the possible mechanisms and patterns of missing data.[51] Logistic regressions were used to explore associations between missingness and baseline variables, and missingness and previously observed outcomes. If the number of missing data was small (< 1% of cases), then unconditional or conditional mean imputation was considered to be sufficient. However, we anticipated that it would be necessary to use multiple imputation to impute missing values. Multiple imputation is a flexible approach, which is valid if data are assumed to be missing at random (i.e. the probability that data are missing does not depend on the unobserved values; it is conditional on the observed data).[51,52] This assumption was assessed.

Multiple imputation uses regression to predict *m* values for each missing data cell, and enables all key variables used in the economic evaluation and demographic data (i.e. both complete and incomplete) to be used to predict the values of missing data cells. In accordance with guidelines,[51,53] multiple imputation using chained equations was conducted and the number of imputations set to be at least equal to the percentage of incomplete cases.[53] Multiple imputation was performed separately for each treatment group.

Multiple imputation can be conducted at an aggregated level of total costs, for example, or at a disaggregated level of individual resource use items or EQ-5D domains. Given that imputing large numbers of variables may make the model difficult to estimate, a balance between the two is likely to be required. The patterns of missing data for resource use/costs and outcomes were used to determine the approach to multiple imputation. For example, data collected on a patient follow-up questionnaire may have similar patterns of missing data, in which case the total costs for that follow-up can be imputed rather than individual resource use items. For each variable with missing data, individual regressions were specified and tailored to the type of data being predicted. Linear regression with prediction mean matching was used, as it is particularly flexible.

Once multiple imputation had been conducted, tabulations and summaries of the observed and imputed data were compared to check the validity of the imputations. Rubin's rule was then used to summarise data across the *m* data sets.[54] This approach accounts for the variability both within and between imputed data sets and takes uncertainty in the estimated mean into account.

Adjustment for baseline utility

Given that baseline utility directly contributes to QALY calculations, it is important to control for any potential imbalances in baseline utility in the estimation of the mean difference (MD) in QALYs between treatment groups to avoid introducing bias.[55] Regression adjustment also allows for regression to the mean and increases precision. Therefore, if there is an imbalance at baseline, we planned to adjust QALYs for baseline EQ-5D.

Within-trial statistical analysis of cost-effectiveness results

Analyses were conducted in Stata version 15 and Microsoft Excel® 2016 (Microsoft Corporation, Redmond, WA, USA).

Initially, descriptive summaries of resource use, costs and HRQoL were performed using means, SDs and standard errors around the means using the central limit theorem. Cost data are typically positively skewed; however, regardless of this, costs were summarised using the arithmetic mean, as it is this combined with the total number of patients that relates to the total budget impact of an intervention.

The ICER was derived from the average costs and QALYs gained in each trial group, producing an incremental cost per QALY gained of VATS lobectomy compared with open surgery. Non-parametric bootstrapping of costs and QALYs was used to quantify the degree of uncertainty around the ICER. Results are expressed in terms of a cost-effectiveness acceptability curve (CEAC), which indicates the likelihood that VATS lobectomy is cost-effective for different levels of willingness to pay for health gain. Although VATS lobectomy is considered cost-effective if the ICER falls below £20,000, the ICERs and CEACs presented allow decision-makers to assess cost-effectiveness at a willingness-to-pay threshold of their choice.

Discounting

Costs and effects were not discounted, as our time horizon was 12 months.

Sensitivity analysis

Univariate sensitivity analyses were used to investigate the impact on costs and cost-effectiveness results of variation in key parameters and major cost drivers, and to investigate the impact of uncertainty on the cost-effectiveness results.

Factors examined in the sensitivity analyses for costing were varying the unit costs for key cost drivers, including surgery and ward stays. The impact of any high-cost participants was also investigated. For outcomes, we examined not adjusting for baseline utility and the impact of any missing survival status.

For details of all sensitivity analyses, see *Appendix 4*.

Subgroup analysis

No subgroup analyses were pre-planned for the cost-effectiveness analyses; comparing pain scores by type of analgesia, as per the clinical analyses, would not be meaningful here.

Chapter 3 Results: trial cohort

Study sites

Five sites took part in Phase I of the trial and a further four were opened in Phase II. Sites were well spread geographically and represented a mix of university and NHS trusts that are representative of NHS practice. The study sites and the dates they opened to recruitment are given below.

Phase I: study sites and dates opened to recruitment

- Royal Brompton Hospital and Royal Brompton and Harefield NHS Foundation Trust (29 July 2015).
- Liverpool Heart and Chest Hospital NHS Foundation Trust (6 October 2015).
- Bristol Royal Infirmary and University Hospitals Bristol NHS Foundation Trust (14 October 2015).
- The James Cook University Hospital and South Tees Hospitals NHS Foundation Trust (29 October 2015).
- Harefield Hospital and Royal Brompton and Harefield NHS Foundation Trust (18 December 2015).

Phase II: study sites and dates opened to recruitment

- John Radcliffe Hospital and Oxford University Hospitals NHS Foundation Trust (25 September 2017).
- Castle Hill Hospital and Hull University Teaching Hospitals NHS Trust (12 October 2017).
- Birmingham Heartlands Hospital and University Hospitals Birmingham NHS Foundation Trust (28 September 2017).
- Royal Infirmary of Edinburgh, NHS Lothian (20 September 2018).

Patients screened and recruited

Between 23 July 2015 and 14 February 2019, a total of 2109 patients were assessed for eligibility, of whom 1606 were excluded (1110 patients were ineligible, 147 patients were not approached by the local team, 315 patients were approached but declined to take part and 34 patients agreed to take part but then withdrew their consent prior to randomisation). Therefore, 503 patients (i.e. 50% of eligible patients and 59% of patients approached) were recruited and randomised. The main reasons for screened patients not being recruited, by study site, are shown in *Appendix 5*, *Table 44*. Participant flow through the trial is shown in *Figure 2*.

Recruitment

Between 30 July 2015 and 26 February 2019, 503 participants consented to take part and were randomised (VATS group, $n = 247$; open-surgery group, $n = 256$). One participant withdrew after randomisation and before surgery and no further data were collected (see *Figure 2*). The final follow-up for the last participant was completed on 23 March 2020.

Recruitment rate

When the study was designed, the estimated recruitment rate was expressed in terms of the proportion of eligible patients recruited, rather than as a recruitment per site per month. The proposed study sites were asked to estimate the number of lobectomies performed for early-stage lung cancer each year and from this the anticipated recruitment rate was derived, allowing for a staggered opening of study sites. It was estimated that 60% of patients would be eligible for the trial and that the participating surgical

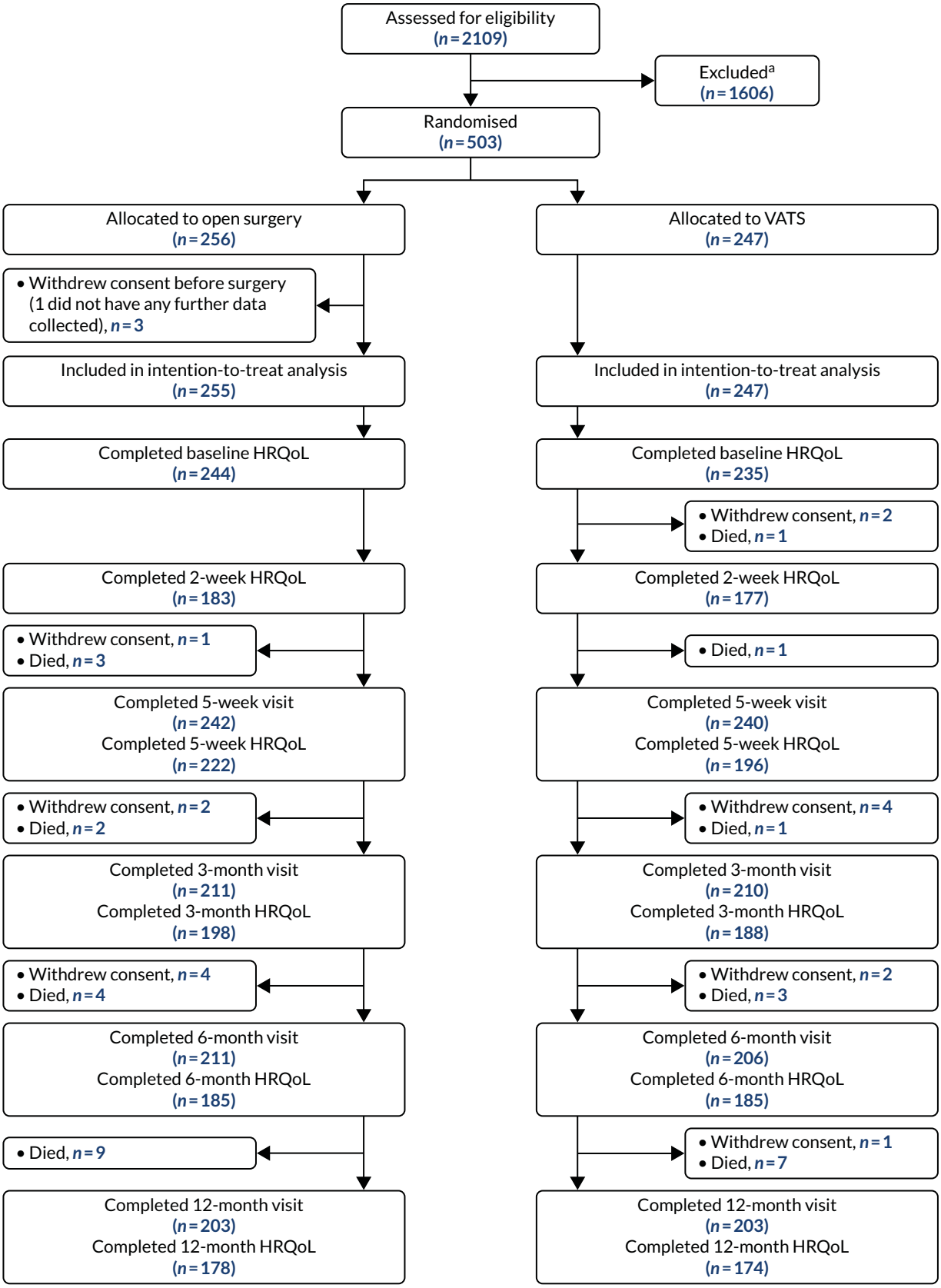

FIGURE 2 The VIOLET trial CONSORT flow diagram. a, Reasons for exclusion are provided in *Appendix 5*, *Table 44*. Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

teams would initially recruit 30% of eligible patients, but that with training and feedback provided by the QRI team this might increase to 50% after 6 months. The anticipated recruitment rate for each of the participating centres is documented in *Appendix 5*, *Table 45*.

The actual recruitment rate is illustrated in *Figure 3*. The trial was assessed for progression 18 months after the start of recruitment. Recruitment was ahead of target at that time and remained so throughout the trial, completing 2 months ahead of schedule. The trial over-recruited by five participants. The number of patients recruited by site and the rate per month at each site is given in *Appendix 5*, *Table 46*.

Progression from Phase I to Phase II

Progress against the predefined progression criteria was assessed in December 2016. Performance against the prespecified criteria is shown in *Appendix 5*, *Table 47*. The Trial Steering Committee (TSC) recommended progression to Phase II. Following review of the screening data and reasons for ineligibility, the eligibility criteria were widened to include bi-lobectomies to increase the generalisability of the trial results.

Comparison of recruited and non-recruited patients

The age of trial participants was similar to those patients who were screened but did not join the trial because they were ineligible, not approached or did not wish to take part (see *Appendix 5*, *Table 48*).

Patient withdrawals

In total, 34 participants withdrew consent prior to randomisation. Nineteen participants withdrew after randomisation (before surgery, $n = 3$; after surgery, $n = 16$). The reasons for post-randomisation withdrawal are detailed in *Table 4*. The most cited reason was that the participant 'changed their mind' about trial participation.

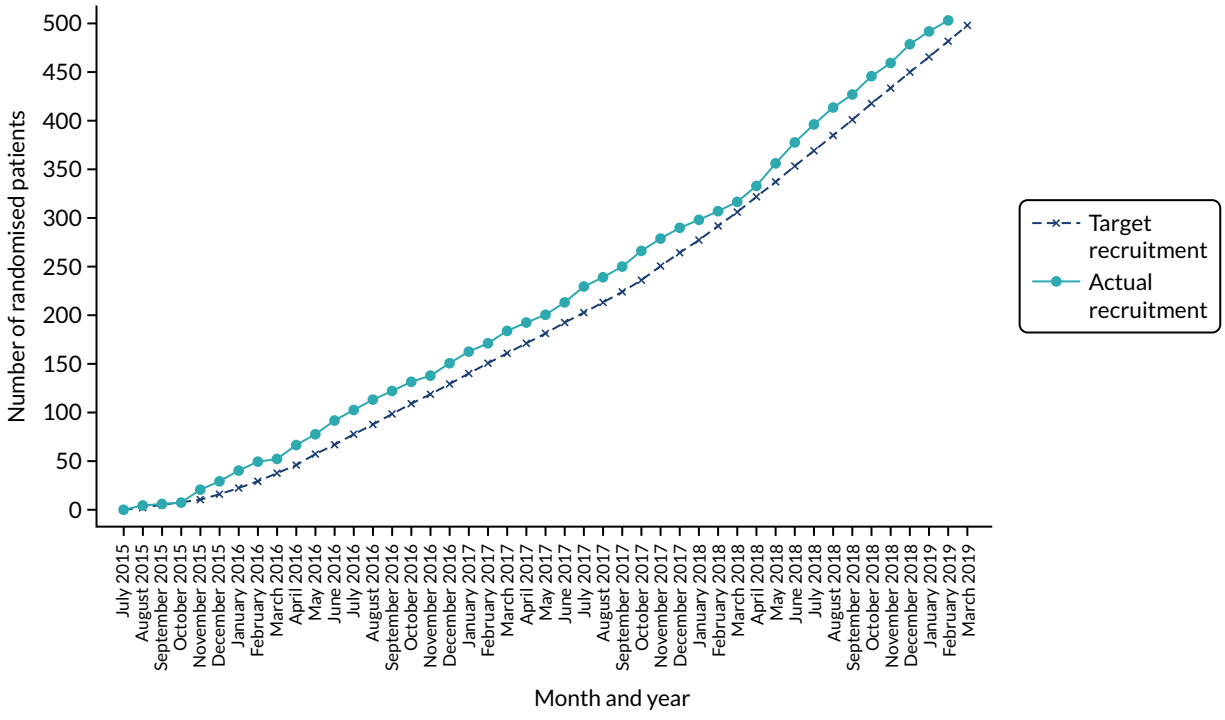

FIGURE 3 Predicted and actual recruitment.

TABLE 4 Post-randomisation withdrawals

Withdrawal detail	Participant allocation		Overall (*N* = 503), *n/N* (%)
	Randomised to VATS (*N* = 247), *n/N* (%)	Randomised to open surgery (*N* = 256), *n/N* (%)	
Any withdrawal	9/247 (3.6)	10/256 (3.9)	19/503 (3.8)
Timing of withdrawal			
Before surgery[a]	0/9 (0.0)	3/10 (30.0)	3/19 (15.8)
After surgery	9/9 (100.0)	7/10 (70.0)	16/19 (84.2)
Reason for withdrawal			
Clinician's advice	1/9 (11.1)	2/10 (20.0)	3/19 (15.8)
Surgery no longer appropriate	0/1 (0.0)	1/2 (50.0)	1/3 (33.3)
Patient no longer eligible	1/1 (100.0)	1/2 (50.0)	2/3 (66.7)
Patient's decision	8/9 (88.9)	8/10 (80.0)	16/19 (84.2)
Patient changed their mind about the study	6/8 (75.0)	2/8 (25.0)	8/16 (50.0)
Patient does not want to continue with follow-up	2/8 (25.0)	3/8 (37.5)	5/16 (31.3)
Refused to give reason	0/8 (0.0)	1/8 (12.5)	1/16 (6.3)
Other	0/8 (0.0)	2/8 (25.0)	2/16 (12.5)
Further details			
Withdrawn from follow-up	9/9 (100.0)	10/10 (100.0)	19/19 (100.0)

a Operation details were obtained for two patients withdrawn before surgery.

Protocol deviations

Eligibility and surgery

Overall, the number of protocol deviations were low at 13% (66/502) (*Table 5*). Forty-nine patients did not undergo a lobectomy (31 patients were found to have benign disease on frozen section, 11 patients underwent a wedge resection, three patients underwent a segmentectomy, two patients were found to have extensive malignancy and so no resection was performed, and two patients

TABLE 5 Protocol deviations

Protocol deviation	Participant allocation		Overall (*N* = 502), *n/N* (%)
	Randomised to VATS (*N* = 247), *n/N* (%)	Randomised to open surgery (*N* = 255), *n/N* (%)	
Protocol deviation	41/247 (16.6)	25/255 (9.8)	66/502 (13.1)
Patient ineligible but treated in the study	0/247 (0.0)	0/255 (0.0)	0/502 (0.0)
Patient did not undergo lobectomy	26/247 (10.5)	23/255 (9.0)	49/502 (9.8)
Patient received the other trial intervention to that they were allocated[a]	15/221 (6.8)	2/232 (0.9)	17/453 (3.8)

a Only includes patients who underwent a lobectomy.

underwent a pneumonectomy). A further 17 participants who underwent a lobectomy received the other trial intervention to that they were allocated [15 participants randomised to VATS received open surgery (one participant decided preoperatively to have open surgery and the remaining 14 participants were intraoperative conversions necessitated by the surgeon) and two participants randomised to open surgery had a VATS procedure (both participants decided preoperatively to have VATS)]. Reasons for conversions from VATS to open surgery can be found in *Table 6*.

Adherence to the mandated and prohibited aspects of the surgical procedure (i.e. number of ports used for a VATS procedure and use of rib spreading) and to the criteria for fitness for discharge are presented in *Baseline data and operative characteristics* and *Chapter 5*, *Exploratory analysis: length of stay*, respectively.

Success of blinding

Bang *et al.*'s Blinding Index[13] asks for individuals to guess which treatment (i.e. method of surgical access) the participant received. Results of the assessment of blinding of participants and RNs responsible for outcome data collection are presented in *Table 7*. At day 2, 159 of 442 (36.0%) participants correctly identified the surgery they had received. At discharge, 202 of 417 (48.4%) participants correctly identified the surgery they had received. A greater proportion of RNs correctly identified the surgical approach at discharge (275/440, 62.5%). This had reduced by 12 months (208/414, 50.2%).

TABLE 6 Reasons for conversion from VATS to open surgery

Reason for conversion	Total ($N = 14$), *n* (%)
Diffuse pleural adhesion	4 (28.6)
Bleeding from vascular injury	3 (21.4)
Poor visualisation	1 (7.1)
Calcified periarterial nodes	1 (7.1)
Absent or thick fissure	1 (7.1)
Margin extension	1 (7.1)
Invasion of the artery	1 (7.1)
Bleeding from vascular injury and poor visualisation	1 (7.1)
Invasion of the artery and discovery of N2 tumours	1 (7.1)

TABLE 7 Assessment of the success of blinding

Blinding assessment	Participant allocation		Total ($N = 502$), *n*/*N* (%)
	Randomised to VATS ($N = 247$), *n*/*N* (%)	Randomised to open surgery ($N = 255$), *n*/*N* (%)	
Participant			
Guessed correctly: 2 days post surgery	87/220 (39.5)	72/222 (32.4)	159/442 (36.0)
Guessed correctly: discharge	107/209 (51.2)	95/208 (45.7)	202/417 (48.4)
RN			
Guessed correctly: discharge	145/220 (65.9)	130/220 (59.1)	275/440 (62.5)
Guessed correctly: 5 weeks	150/236 (63.6)	142/239 (59.4)	292/475 (61.5)
Guessed correctly: 12 months	118/206 (57.3)	90/208 (43.3)	208/414 (50.2)

Patient follow-up

The number of patients for whom follow-up data were available is presented in *Figure 2*. Follow-up data at 1 year was available for 81% of randomised participants. Of the 50 patients not followed to 1 year, 19 had withdrawn and 31 had died.

Numbers analysed

The analysis population consisted of 502 randomised participants. One randomised participant withdrew consent prior to surgery, at which point data collection stopped. This patient was excluded from the analysis population. The numbers of participants included in the analyses of each outcome are presented in *Table 8*.

Baseline data and operative characteristics

The baseline characteristics were similar in the two groups (*Table 9* and see *Appendix 5*, *Table 49*). The mean age of participants was 69 (SD 8.8) years and 249 (49.5%) participants were men. Most participants were white (96.4%), not obese [mean body mass index of 27 (SD 5) kg/m^2] and were a past or current smoker (87.3%). Most participants were cT stage 1 (67.2%) and cN stage 0 (95.6%).

TABLE 8 Numbers analysed

Outcome	Number (%) of participants included in analysis
QLQ-C30 physical functioning (primary)	502 (100)[a]
Time from surgery to hospital discharge	502 (100)
In-hospital pain scores	502 (100)[b]
Lymph node upstaging	496 (99)
Resection completeness	439 (87)
Overall survival	502 (100)
Progression-free survival	502 (100)
Uptake of adjuvant treatment	502 (100)
Prolonged incision pain	482 (96)
QLQ-C30 questionnaire	502 (100)[c]
QLQ-LC13 questionnaire	502 (100)[d]
EQ-5D questionnaire	502 (100)[e]
Any in-hospital AE	502 (100)
Any post-discharge SAE	493 (98)

a Data available for 460 participants. Multiple imputation used to account for missing data and so 502 participants included in analysis.
b Data available for 470 participants. Multiple imputation used to account for missing data and so 502 participants included in analysis.
c Data available for at least 458 participants. Multiple imputation used to account for missing data and so 502 participants included in analysis.
d Data available for at least 452 participants. Multiple imputation used to account for missing data and so 502 participants included in analysis.
e Data available for 457 participants. Multiple imputation used to account for missing data and so 502 participants included in analysis.

Almost half (48.2%) of the participants did not have a tissue-confirmed diagnosis at recruitment. Comorbidities were common, with almost half (46.3%) of participants having a history of cardiovascular disease.

Most operations (83.6%) were consultant led. Of the 242 participants who did not have a confirmed histological diagnosis at randomisation and so underwent a biopsy first, 32 (13.2%) were confirmed benign. Of these 32 participants, 31 did not undergo a lobectomy. The team proceeded with a lobectomy for the other case because of a suspicion of cancer. All surgeons adhered to the protocol in terms of the number of ports used in a VATS procedure (between one and four ports allowed) and the use of rib spreading, which was mandated for open surgery and prohibited with VATS.

TABLE 9 Participant characteristics and surgical details

Characteristic	Participant allocation		Total (*N* = 502)
	Randomised to VATS (*N* = 247)	Randomised to open surgery (*N* = 255)	
Participant demography			
Age (years), mean (SD)	69 (8.7)	69 (9.0)	69 (8.8)
Male, *n*/*N* (%)	119/247 (48.2)	130/255 (51.0)	249/502 (49.6)
Clinical characteristics			
Clinical stage: cT, *n*/*N* (%)			
1a	24/247 (9.7)	17/255 (6.7)	41/502 (8.2)
1b	77/247 (31.2)	86/255 (33.7)	163/502 (32.5)
1c	64/247 (25.9)	70/255 (27.5)	134/502 (26.7)
2a	50/247 (20.2)	47/255 (18.4)	97/502 (19.3)
2b	13/247 (5.3)	16/255 (6.3)	29/502 (5.8)
3	19/247 (7.7)	19/255 (7.5)	38/502 (7.6)
Clinical stage: cN, *n*/*N* (%)			
0	232/247 (93.9)	238/255 (93.3)	470/502 (93.6)
1	15/247 (6.1)	17/255 (6.7)	32/502 (6.4)
ECOG performance status, *n*/*N* (%)			
0	148/244 (60.7)	172/252 (68.3)	320/496 (64.5)
1	84/244 (34.4)	75/252 (29.8)	159/496 (32.1)
2	10/244 (4.1)	5/252 (2.0)	15/496 (3.0)
3	2/244 (0.8)	0/252 (0.0)	2/496 (0.4)
Mean predicted lung function (%), mean (SD)			
FEV_1[a]	82 (19.8)	82 (21.2)	82 (20.5)
FVC[b]	95 (17.1)	95 (18.3)	95 (17.7)
TLco[c]	76 (26.3)	72 (20.4)	74 (23.5)

continued

TABLE 9 Participant characteristics and surgical details (*continued*)

Characteristic	Participant allocation		Total (*N* = 502)
	Randomised to VATS (*N* = 247)	Randomised to open surgery (*N* = 255)	
Histological type, *n*/*N* (%)			
Adenocarcinoma	80/247 (32.4)	91/255 (35.7)	171/502 (34.1)
Squamous carcinoma	33/247 (13.4)	26/255 (10.2)	59/502 (11.8)
Other NSCLC	7/247 (2.8)	7/255 (2.7)	14/502 (2.8)
SCLC	0/247 (0.0)	2/255 (0.8)	2/502 (0.4)
Carcinoid	6/247 (2.4)	8/255 (3.1)	14/502 (2.8)
Histology not confirmed	121/247 (49.0)	121/255 (47.5)	242/502 (48.2)
HRQoL			
QLQ-C30 physical functioning score, median (IQR)[d]	87 (73.3–100.0)	87 (73.3–100.0)	87 (73.3–100.0)
Surgical details*, n/N *(%)			
Biopsy outcome			
Benign disease on frozen section	15/247 (6.1)	16/255 (6.3)	31/502 (6.2)
Benign disease on frozen section and lobectomy	1/247 (0.4)	0/255 (0.0)	1/502 (0.2)
Lobectomy			
Lobectomy performed	221/247 (89.5)	232/255 (91.0)	453/502 (90.2)
Rib spreading[e]	15/221 (6.8)	228/230 (99.1)	243/451 (53.9)
VATS			
VATS performed	206/221 (93.2)	2/232 (0.9)	208/453 (45.9)
Number of VATS ports			
One port	42/206 (20.4)	0/2 (0.0)	42/208 (20.2)
Two ports	18/206 (8.7)	0/2 (0.0)	18/208 (8.7)
Three ports	119/206 (57.8)	1/2 (50.0)	120/208 (57.7)
Four ports	27/206 (13.1)	1/2 (50.0)	28/208 (13.5)
Thoracotomy			
Thoracotomy performed	15/221 (6.8)	230/232 (99.1)	245/453 (54.1)
Posterolateral thoracotomy	12/15 (80.0)	161/230 (70.0)	173/245 (70.6)
Anterior thoracotomy	3/15 (20.0)	69/230 (30.0)	72/245 (29.4)

cN, regional lymph nodes; cT, primary tumour; ECOG, Eastern Cooperative Oncology Group; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TLco, transfer capacity of the lung.

a Missing data: 12 patients (VATS group, *n* = 7; open surgery, *n* = 5).
b Missing data: 15 patients (VATS group, *n* = 8; open surgery, *n* = 7).
c Missing data: 118 patients (VATS group, *n* = 60; open surgery, *n* = 58).
d Missing data: 24 patients (VATS group, *n* = 12; open surgery, *n* = 12).
e Rib spreading in the VATS group and non-rib spreading in the open-surgery group were crossovers.

Chapter 4 Results: QuinteT Recruitment Intervention

Overview

The number of patients randomised and the QRI activities undertaken by month are presented in *Figure 4* to provide the context for the QRI findings described below.

Following the initial activities aimed at averting recruitment challenges (May–October 2015), we undertook data collection/analysis to understand the VIOLET trial recruitment processes and to identify instances of good practice and opportunities to optimise recruitment (October 2015–February 2016). Next, we collaboratively developed and implemented strategies to overcome the identified recruitment challenges (March 2016–February 2019; note that the iterative model of the QRI meant that this period also involved new data collection/analysis).

Data set

Our data set comprised interview data from 15 staff (recruiting surgeons, $n = 11$; RNs, $n = 3$; TMG members, $n = 1$) involved in VIOLET trial oversight and recruitment. A total of 451 individual patients' audio-recordings were available from six recruitment sites and a purposively selected sample of 304 individual patient recordings were analysed in detail.

Understanding recruitment processes and issues

We identified four overarching recruitment themes of importance in the VIOLET trial (strategies to address the recruitment issues are discussed in the next section). Elements of good practice and recruitment challenges in relation to each of these themes are presented below. The themes are (1) patient pathways through eligibility and recruitment, (2) recruiter equipoise, (3) patient preferences and (4) explaining the VIOLET trial. These key themes were not discrete or exclusive, and had overlapping threads that ran through them all. The findings are supported by anonymised quotations from interviews and audio-recordings, as appropriate (also see *Appendix 6*). In addition to the key recruitment themes, some findings that related to specific aspects of the trial design, such as challenges with the implementation of blinding, are summarised at the end of this section (with details further details provided in *Appendix 7*).

Patient pathways through eligibility and recruitment

A description of the standard patient pathway in VIOLET trial sites is presented, followed by pathway-related recruitment issues and recruiter perceptions regarding eligibility criteria in VIOLET (perceived to be clear and unambiguous, with some reservations expressed for specific groups of patients).

Patient pathways

The pathway for potentially eligible patients for the VIOLET trial was simple and consistent across centres. Recruiters felt that the VIOLET trial was easily integrated into standard clinical practice. Although there was some site variation, patients generally underwent similar processes to those illustrated in *Figure 5*.

Patients referred to secondary care centres received diagnostic tests and their results were discussed in MDTs. PIs screened these patients and confirmed eligibility of potential trial participants. Approaches to invite patients to take part in research occurred during patient consultation with surgeons who would perform the surgery. Surgeons were the primary information providers and recruiters in the

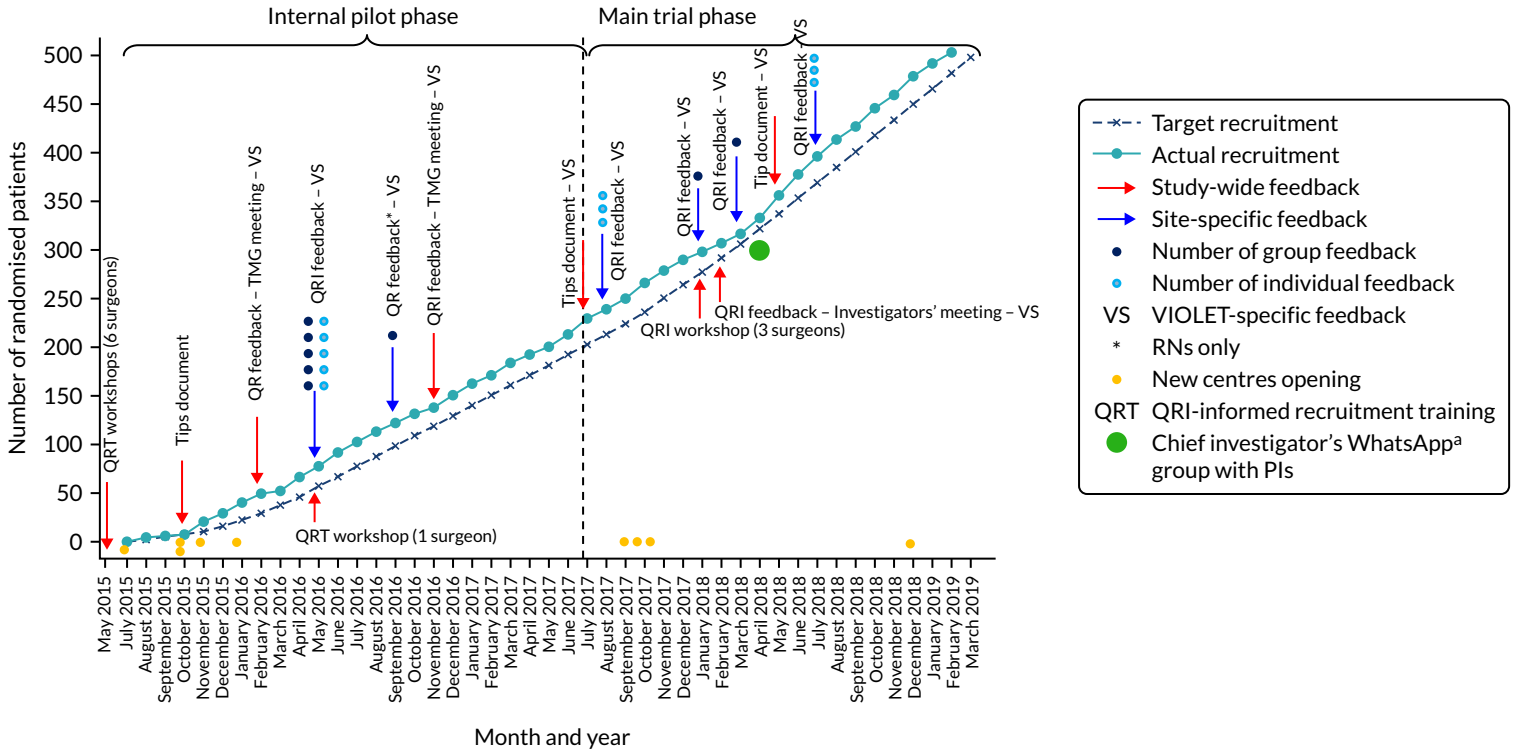

FIGURE 4 Recruitment to the VIOLET trial and QRI actions by month. a, Facebook, Inc., Menlo Park, CA, USA.

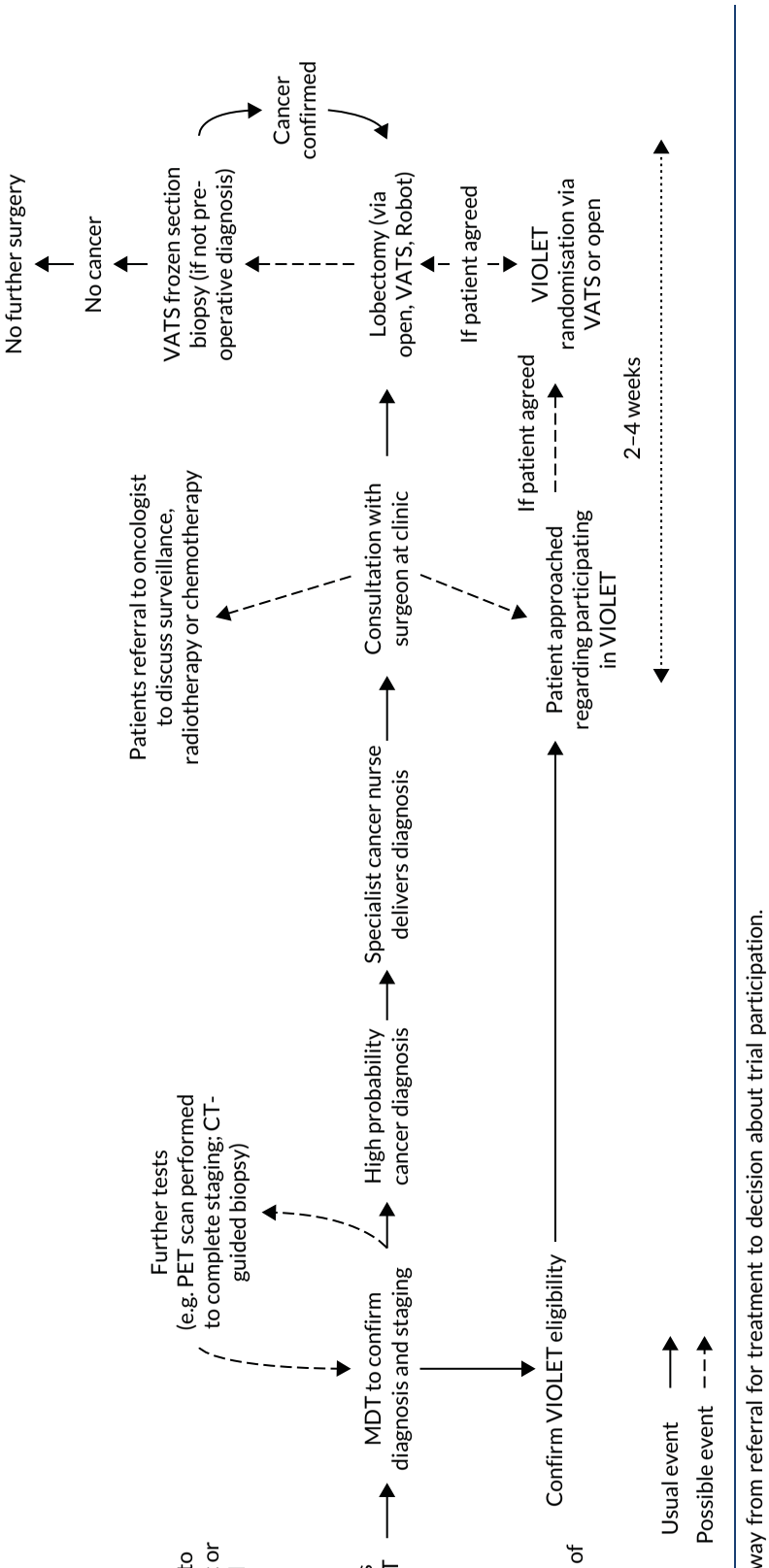

FIGURE 5 Patient pathway from referral for treatment to decision about trial participation.

VIOLET trial. RNs facilitated study-related paperwork, such as written consent for audio-recording of consultations, trial baseline assessments and follow-up questionnaires.

Recommendation for VATS by staff early in the pathway

Despite the relatively simple pathway, it was quickly discovered that treatment recommendations were made by some health-care professionals early in the patient pathway (e.g. preoperative nurses, respirologists). The recommendations, reflecting routine clinical practice, were often in favour of VATS. This was evident in the consultations:

> *We had a problem where we obviously hadn't given enough information to the preoperative nurses who came in and told a patient that they're having a VATS lobectomy just because that's what I did all the time.*
>
> *Surgeon, interview*

> *Well when I went to the [clears throat] hospital here last time and we saw the clinical nurse she said you'll be having a keyhole and I said well we're in a trial we don't know which one we're going to have. And she said, no you'll be having keyhole.*
>
> *Patient, consultation*

Subsequently, two centres had informed any potential health-care professionals in the pathway about the VIOLET trial and the importance of not stating which type of procedure the patient would be undergoing:

> *We've had to make sure that they're educated as well and everyone's kept in the loop, so generally it now seems to be very, very good.*
>
> *Surgeon, interview*

However, there was some indication of reluctance to address treatment recommendations made by respirologists (i.e. chest physicians, as opposed to nurses):

> Surgeon, interview: *There are quite a few respirologists that say 'I believe this patient is high risk and I don't think it's fair for them to have a thoracotomy', 'cause of their experience of seeing very sore thoracotomies and not seeing very many sore VATS [. . .]*
>
> QRI researcher, interview: *That's interesting. And what do you do in that circumstance?*
>
> Surgeon, interview: *If the respirologists want it by VATS, they'll give it by VATS, because they are the people that send us the cases so I have to [listen] to them.*

Eligibility criteria: pragmatic and straightforward, with some exceptions

Recruiters consistently described how patients had to be stage T1a–2b N0–1 M0 or be undergoing frozen section biopsy with the intention to proceed with lobectomy if T1a–2b N0–1 M0 was confirmed. Overall, there was agreement that the VIOLET trial eligibility criteria were 'straightforward' and 'pragmatic'. There were, however, some differences in opinion in relation to specific groups of patients (e.g. older patients, patients with poor health/lung function and those with deeper or larger tumours) and their suitability to have VATS (screening logs showed that 29.2% of patients were ineligible because they were not suitable for both open surgery and VATS):

> *The higher risk are older people with worse lung function and comorbidity, in the past we would have turned down for surgery, but now we can do it by VATS, we're sort of pushing the boat out a bit to say 'well, OK I'm happy for you to have surgery but only just happy, I wouldn't want to do a thoracotomy on this yet'.*
>
> *Surgeon, interview*

> *I would refer a patient with bad lungs to have VATS because of the pain issues and everything.*
>
> *Surgeon, interview*

Some recruiters, however, acknowledged that there was no evidence to support the view that VATS was more suitable for some groups of patients:

> *There is a feeling that a VATS approach was less traumatic, less stressful for a patient, so maybe you can get those older and less fit patients through a VATS lobectomy, you wouldn't necessarily get them through an open lobectomy, when of course we don't have any evidence for that at all . . . But we might find that as our natural prejudices come out as the trial progresses.*
>
> *Surgeon, interview*

Recruiters also described the location and size of the tumour to be important. For instance, some recruiters commented that if the tumour was 'sitting too deep', then the majority of thoracic surgeons would perform an open lobectomy. There was also a suggestion that surgeons who were less experienced with VATS may not feel comfortable to do the bigger resection through keyhole surgery. Although most surgeons commented that tumours < 7 cm were suitable for the VIOLET trial, two recruiters commented that this was < 5 cm.

Views on eligibility criteria were sometimes observed to influence whether or not patients were approached for the VIOLET trial and the way in which the trial was introduced:

> *I'm not 100% sure you are a perfect candidate for the study but if you're interested, we're here to talk about it.*
>
> *Surgeon, consultation*

Summary

Despite a simple patient pathway, there were some concerns around treatment recommendations for VATS made by some staff members who saw patients early in the patient pathway, with indication of sites addressing this issue prior to their first trial-specific feedback session. Similarly, eligibility criteria were generally considered pragmatic and easy to apply, but there were some groups of patients for whom eligibility was more contested, with some indication that views on eligibility criteria influenced how and whether or not the study was put forward to patients. These issues, once understood, were addressed in the QRI plan of actions (see *Plan of action: strategies to optimise recruitment and informed consent*).

Recruiter equipoise

In the interviews, recruiters expressed strong enthusiasm for the VIOLET trial, yet there were a number of discernible instances of recruiter biases evident in the interviews, usually in favour of VATS. In the consultations, many recruiters were adept at withholding their personal biases and carried out balanced information provision on the two operations, with an emphasis on uncertainty. There were some instances where these biases were unwittingly conveyed to patients. In addition, recruiter bias towards open lobectomy was observed in some consultations as the trial progressed (mainly from one centre). Some of these findings are detailed below.

Recruiter preference for VATS

Some surgeons questioned the need for a trial to persuade surgeons to do VATS, as 'that ship has sailed already in this country' (surgeon, interview). VATS was described as 'promising' and 'exciting', with the potential for patients to experience less pain and recover faster than with an open lobectomy. Several recruiters explicitly stated that they would opt for VATS if they were a patient:

> QRI researcher, interview: *If you were a patient would you be randomised to VIOLET?*

Surgeon, interview: *No.*

QRI researcher, interview: *You wouldn't. Why not?*

Surgeon, interview: *I would want a keyhole operation.*

Some recruiters commented that, although the oncological outcomes were likely to be similar across the two operation, patients who had VATS appeared to recover faster (which was considered particularly beneficial if adjuvant chemotherapy was needed).

Recruiter discomfort when patients were randomised to thoracotomy

Some surgeons described initial discomfort when a patient had been randomised to a thoracotomy when they would have had VATS outside the trial or noted instances where they felt their concerns regarding thoracotomy were validated when patients developed complications:

> *These days if it was straightforward, I would do a VATS, so [laugh], it was, yeah, [small pause], it was a bit strange doing an open.*
>
> *Surgeon, interview*

Surgeon, interview: *The patient was randomised to a thoracotomy and, uh, had complications. That wasn't a good start.*

QRI researcher, interview: *No, I can imagine. How did that make you feel?*

Surgeon, interview: *Mad, small . . . bad luck for the patient more than anything else. [. . .] Maybe it's because of the thoracotomy, so that's all I can say.*

Acknowledgement of lack of evidence to support preference for VATS

Recruiters described how existing research that compared the two procedures comprised primarily observational studies and that the few randomised studies were of poor quality or had small sample sizes. Recruiters appeared well aware that their views in favour of VATS were not grounded in evidence and they exhibited signs of experiencing an intellectual struggle in relation to equipoise. Many recruiters had joined the VIOLET trial intuitively believing that VATS was better, but giving due consideration to the design and purpose of the trial had enabled them to take a step back and feel more comfortable with the concept of equipoise (also see *Appendix 6*):

> *There's this implicit assumption, keyhole is just better . . . Actually, when you look critically at the world literature then we've got no evidence to show that any of these things are actually true, so it's this bias, that assumption that keyhole must be better.*
>
> *Surgeon, interview*

It is possible that the QRI-informed recruitment training that a number of surgeons attended prior to commencing recruitment in the VIOLET trial, and prior to these interviews, played a role in their increased awareness of own biases and how they overcame these during discussions with patients, as described below.

Conveying equipoise in consultations: general patterns and concerns

Analysis of the consultations showed that recruiters were relatively skilled at conveying equipoise by communicating the uncertainty around the two operations early in the consultation, presenting them in a neutral manner, stating that there was variation across the country and explaining that both

approaches were established (all of which were key aspects of the QRI-informed training sessions attended by PIs prior to recruitment):

> *We can use an open operation or a keyhole operation and they're both standard approaches for lung cancer surgery. We don't know which is better and that's why we're doing a study to compare them.*
>
> *Surgeon, consultation*

> *We don't have a clear-cut top-quality evidence that tells us which is the best approach, so we are running a study.*
>
> *Surgeon, consultation*

However, some recruiters made statements later in the consultation that went against their previously expressed neutrality, reflecting some of their views in favour of VATS expressed in the interviews. For instance, imbalanced information was provided and loaded terminology was used to describe the treatments. VATS was described with/without the mention of cuts as keyhole, whereas cuts were mentioned for open lobectomy. In addition, where cuts were mentioned in VATS, they were described as small cuts in comparison to the big cut for open lobectomy. Please see *Appendix 6*, *Table 68*, for more examples.

Similarly, personal opinions or treatment recommendations were provided to patients, which also affected recruitment, and this was usually in favour of VATS (note that, on rare occasions, especially as the trial progressed into the main phase, a bias towards open lobectomy was observed, especially in one centre) (see *Appendix 6*):

> *We need to offer patients the type of treatment which is actually beneficial. At the moment we really don't know. I'm comfortable with it, it's not a problem . . . but I believe that VATS lobectomy patients have a quicker recovery.*
>
> *Surgeon, consultation*

> *Outside of the trial, I would perform a VATS.*
>
> *Surgeon, consultation*

> Surgeon, consultation: *If you say no, I don't want the chance of having a cut on my chest, I would rather have a keyhole surgery, I will respect that, it's up to you.*
>
> Patient, consultation: *OK. That's what I want then.*
>
> Surgeon, consultation: *Keyhole surgery?*
>
> Patient, consultation: *Yes please.*
>
> Surgeon, consultation: *OK [recorder switched off].*
>
> Patient, consultation: *Let's just say you was having it done, which one would you prefer?*
>
> Surgeon, consultation: *Um . . . [patient laughs].*
>
> Surgeon, consultation: *Um personally if it was a small tumour I, I don't know I may go for the keyhole but I don't know which is better but uh I might go for the keyhole.*

Crucially, lack of recruiter equipoise had an impact on whether or not the VIOLET trial was explained to patients. This is detailed in *Explaining the VIOLET trial and related concepts*.

Summary

There was widespread support for the VIOLET trial among recruiters. A number of recruiters appeared to have a personal (i.e. for themselves) and a professional (i.e. for their patients) preference for VATS lobectomy, and may have participated in the trial while believing that VATS was better. However, recruiters' awareness of this bias and the intellectual challenges involved in overcoming this allowed for balanced discussions in many consultations, as recruiters were able to assume a position of equipoise. This may have been facilitated by the QRI-informed recruitment training received by a number of surgeons prior to recruitment commencing in the VIOLET trial. In some instances, however, these biases became evident in the consultations in the form of imbalanced treatment presentations, which involved loaded terminology, providing personal opinions and treatment recommendations, and assuming that patients would not be interested in the VIOLET study (see *Explaining the VIOLET trial and related concepts*). These issues were addressed in the QRI plan of actions (see *Plan of action: strategies to optimise recruitment and informed consent*).

Patient preferences

Responding to patient preferences

In interviews, there was a feeling among recruiters that, because the trial was not comparing two radically different interventions, most patients did not come with strong preferences as to how a lobectomy was performed. Some recruiters, however, did describe instances where patients attributed more positive connotations to keyhole surgery rather than open surgery:

> *I think in my experience 90%, 95, would want a keyhole operation, given the choice of both, 'cause it's just intuitive for the patient, makes sense.*
>
> *Surgeon, interview*

> *It's very emotive. Keyhole means minimal access means better recovery means better outcomes.*
>
> *Surgeon, interview*

As described in the previous section (see *Recruiter equipoise*), this may be a reflection of the recruiters' own biases.

There were instances where recruiters responded well to patient preferences prior to trial-specific feedback:

> Patient's son, consultation: *Can I ask about visualisation, isn't the issue with the camera that you . . . is it easier to miss something visually that's going on that you might otherwise see?*

> Surgeon, consultation: *Some people say that, some people say it's easier to see all the way round the chest with a camera. Some people say that you can't do as good an operation with the cameras so that's why they do it open, other people feel they can do the operation exactly the same. There's pros and cons and you can give arguments for one or the other hmm but the bottom line is we really don't know if one is better than the other.*

However, there were also instances where it appeared that patients' preferences (often for a keyhole procedure) were readily accepted without exploration to check the patient's understanding, introducing the VIOLET trial or stating uncertainty:

> Surgeon, consultation: *Have you had a think about things at all?*

> Patient, consultation: *I would like to go for the keyhole.*

Surgeon, consultation: *If that's what you prefer. No, that's absolutely fine. [VIOLET not discussed.]*

Patient, consultation: *Can I just have the keyhole surgery?*

Surgeon, consultation: *You would rather have keyhole surgery. OK. So, I will put down that you would not like to participate in the study.*

Summary

There was a feeling that the VIOLET trial's interventions were not entirely different from each other and, therefore, did not generate entrenched preferences among patients (as might radiotherapy vs. surgery, for example). Although recruiters appeared to be addressing preferences to some extent, there was indication of preferences being accepted at face value and without further study information provision or exploration of patient's understanding or reasons for preference. We addressed these issues in the QRI plan of actions (see *Plan of action: strategies to optimise recruitment and informed consent*).

Explaining the VIOLET trial and related concepts

In many instances, recruiters placed the study in the context of existing uncertainty and emphasised that the two operations being compared were established techniques. A number of recruiters also avoided using the word 'trial' in their consultations, opting for 'study' instead, as recommended in QRI-informed training accessed by VIOLET trial recruiters prior to recruitment (occasional use of 'trial' was noticed and was limited to specific centres or recruiters). However, recruiters sometimes presented the VIOLET trial in an apologetic manner and appeared reluctant to present the trial information when they assumed that patients would not want to consider participating in VIOLET trial and would have preferences in line with their own (i.e. a preference for VATS). These beliefs led to a tendency to close down, rather than open up, conversations and patients missing opportunities to hear about the VIOLET trial, with recruiters appearing surprised when patients were willing to consider trial participation (see *Appendix 6*):

Surgeon, consultation: *If you don't want to be part of the study, that is the other option, then you tell me which procedure you want and we will do it.*

Patient's wife, consultation: *He was thinking he'd quite like to be randomised.*

Patient, consultation: *Like you say there's no, it's toss a coin really isn't it, it's, yeah, whatever, yeah. I'm all right, yeah.*

Surgeon, consultation: *Right, so you've agreed to have the lobotomy operation, what do you think about the VIOLET study? Do you want to be part of that?*

Patient, consultation: *Yeah.*

Surgeon, consultation: *You sure?*

Surgeon, consultation: *So, coming to the study, have you got any interest in this or you, just to step out and let . . . no one will force you and, that's absolutely fine with me and then you say, OK, I'm not interested, and I . . .*

Patient, consultation: *No, I would like to do it [patient was subsequently randomised].*

Explanations of randomisation were sometimes absent or not well explained in consultations, with recruiters emphasising 'lack of choice' or implying that treatment is 'selected' or 'decided' by a computer.

Similarly, some recruiters struggled with explanations of blinding, leading to patient concerns about what the process meant for them (see *Appendix 6*):

> Surgeon: *Before that you don't know if you had keyhole surgery or surgery by thoracotomy, that's the main let's say parameter for you.*
>
> Patient: *I'm wary of that, sounds a bit like a lottery. I'm surprised that the experts don't know which is the best, especially for somebody of my age perhaps.*
>
> Surgeon: *You and the research nurse looking after you whilst you are an inpatient, the study attempts to blind you to what you had.*

Summary

Although it appeared that recruiters explained uncertainty well and avoided 'trial' in favour of 'study', likely in response to the training received prior to recruitment, there were opportunities for improvement in other areas. There were noticeable instances of reluctance from recruiters in putting the trial forward to patients, likely stemming from their own preferences for VATS. Trial concepts, namely randomisation and blinding, were particularly difficult to explain to patients. These issues were addressed in the QRI plan of actions (see *Plan of action: strategies to optimise recruitment and informed consent*).

Trial design-related issues

In addition to the above four recruitment themes, during interviews recruiters mentioned challenges they faced that were linked to aspects of the trial design. Blinding (of outcome assessors, usually RNs and patients) was particularly discussed as difficult to implement in some centres because of existing processes, and some RNs and patients disliked the concept. However, this issue resolved over time. Other issues were in relation to the availability of treatment options outside the trial, the possibility of including segmentectomy in the VIOLET trial protocol as an intervention, the standardisation of analgesia, variations in surgical expertise and the trial not accounting for recent advancements in the way open lobectomies were carried out. These issues were highlighted to the trial team, as discussed in *Plan of action: strategies to optimise recruitment and informed consent*. Further details are in *Appendix 7*.

Summary of recruitment processes and issues

Recruiters expressed high levels of support for the VIOLET trial. The patient pathway and eligibility criteria were considered straightforward, with some concerns regarding treatment recommendations for VATS made early in the pathway, which recruiters had addressed before it became overly problematic (i.e. from the prior training they received). Eligibility criteria for specific groups of patients was felt to be debatable. It appeared that a number of recruiters in the VIOLET trial had a preference for VATS and yet, for the most part, were able to overcome this, assume a position of equipoise and present balanced information on the two operations to patients (likely as a result of prior training). There were instances, however, where this was more challenging for recruiters, as they offered treatment recommendations and conveyed their own biases to patients. Patient preferences were being addressed by recruiters to some extent in the VIOLET trial, but we observed instances where patient preferences were accepted without further discussion or information. In addition, although concepts, such as the uncertainty underpinning the need for the VIOLET trial, were well presented, there were some noticeable instances of reluctance from recruiters in putting the trial forward to patients, likely stemming from their own preferences for VATS. Recruiters struggled with explanations of randomisation and blinding. Recruiters were found to follow recruitment advice from the training received prior to recruitment to use 'study' instead of 'trial'. Although the blinding component of the study had been challenging to implement at first, the process became easier in most centres over time. In summary, although upfront training helped overcome some recruitment challenges, it did not resolve all issues. A number of key recruitment issues identified through the QRI were addressed, as outlined below.

Plan of action: strategies to optimise recruitment and informed consent

The QRI identified a number of elements of good recruitment practice, as well as challenges to recruitment, in an iterative process that spanned the entire recruitment period. A plan of action that comprised strategies to optimise recruitment and informed consent was designed in collaboration with the TMG and chief investigator, and was delivered to centres as recruitment proceeded. Issues relating to the trial design that were identified through the QRI were passed on to the trial team and the QRI team focused on support and training for recruiters to address the recruitment challenges. *Table 10* outlines the key QRI findings and corresponding QRI actions/strategies recommended to optimise recruitment.

Key QRI dissemination activities are outlined in *Figure 4* and explained in detail below.

TABLE 10 Recruitment challenges in relation to key themes mapped against QRI actions and strategies

Key recruitment theme	Action and QRI strategy[a]
Patient pathway through eligibility and recruitment: • Treatment recommendations made by staff who interact with patients early in the pathway • Differences in views on eligibility for specific groups of patients (despite lack of evidence to support their exclusion) and influence on if/how the study was introduced	• Good practice disseminated among other pilot sites and to the new sites in the main phase (some sites had addressed this with respective staff members following upfront training) • Suggestion to put the study forward to all potentially eligible patients • Recruiters' views on lack of evidence to support exclusion of specific groups emphasised in feedback sessions
Recruiter equipoise: • Evidence of recruiter bias in interviews, but balanced information provision in consultations [sometimes followed by statements and terminology that went against previously expressed neutrality (often in favour of VATS)] • Providing personal opinions and recommendations	• Lists of loaded terminology used to stimulate discussion in feedback sessions and suggestions to avoid loaded terminology provided in tips document • Reminders to convey equipoise throughout the consultation in feedback sessions • Examples of balanced discussions and good explanations of uncertainty circulated through feedback sessions • Suggestions to avoid providing personal opinions or recommendations in feedback sessions and tips documents • Examples of how recruiters appropriately managed questions on which treatment they would recommend or have themselves if they were a patient circulated through feedback sessions
Patient preferences: • Accepting patient preferences without exploration or study information provision	• Suggestions on how to address patient preferences provided in tips documents • Examples of patient preferences being addressed circulated through feedback sessions as examples of good practice
Explaining the VIOLET trial: • Trial rationale (uncertainty) usually well explained, with appropriate terminology ('study' instead of 'trial'), but trial sometimes put forward apologetically, with reluctance, or in a negative manner, in the light of unfavourable assumptions made about patients' willingness to consider the trial • Randomisation and blinding explanations needed improvement	• Suggestions to not make assumptions about willingness to consider trial and to put trial forward to all potentially eligible patients • Examples of positive trial presentation, where the VIOLET trial is mentioned early in the consultation, emphasising uncertainty, the established nature of the two operations and benefits of trial participation circulated through feedback sessions • Suggested wording for randomisation and blinding provided from previous QRI work
Other: • Trial design-related issues were highlighted to the chief investigator/TMG for further action	

a These actions/strategies were disseminated in group or individual feedback sessions, presentations at TMG/investigator meetings and in tips documents.

Preventing recruitment difficulties: training and guidance prior to recruitment

Six surgeons, including PIs of all five pilot sites, attended the QRI-informed recruitment training workshops in May 2015, prior to the internal pilot phase in July 2015. A further pilot site surgeon attended the same workshop in May 2016. After the VIOLET trial moved to the main phase (July 2017), PIs of the new centres were invited to the training workshop in January 2018, which was attended by three VIOLET trial surgeons, including two PIs from two of the four new sites. This occurred in the same month that VIOLET trial-specific feedback was provided to the main phase sites.

Individual feedback

Eleven individual feedback sessions were held with nine recruiting surgeons from five centres (two surgeons received feedback on two occasions each), either face to face or over the telephone. The QRI researchers analysed each surgeon's audio-recordings of recruitment consultations and prepared a two-page report. The confidential feedback highlighted aspects of their communication that worked well in promoting informed consent and trial participation, and provided suggestions for improving aspects of communication that may benefit from using alternative approaches.

Group feedback

The QRI team conducted eight feedback sessions with six sites (internal pilot sites, $n = 5$; main phase site, $n = 1$). Note that one site had three feedback sessions, one of which was for RNs only. Three of the new sites in the main phase did not receive a group feedback session. One centre submitted only two audio-recordings, which were insufficient to provide feedback; one centre did not submit any audio-recordings and provided screening log data that were incomplete or delayed; and one centre opened 4 months before recruitment was completed. Group feedback sessions included a presentation of site-specific recruitment figures (i.e. SEAR data) and anonymised QRI findings, drawing from audio-recordings from the site and the wider findings across other centres. Interactive group discussions focused on elements of good practice and suggestions for improving recruitment practice that were developed in collaboration with recruiters at each site to ensure that strategies were tailored to address their particular recruitment issues.

Recruitment and informed consent guidance (tips) documents

The QRI team produced two tips documents. The first version, disseminated early in the internal pilot phase (October 2015), contained suggestions for recruiters on how to discuss the study purpose and procedures, including randomisation, drawing from evidence in previous QRIs and a few audio-recordings collected in the first months of recruitment. A revised version of the guidance was developed and disseminated (June 2017) when new sites came on board in the main phase of the trial. The revised version was based on VIOLET trial audio-recordings and provided more extensive communication suggestions, including tips to balance information provided about the two operations, exploring patient preferences and how best to close a recruitment appointment.

Trial Management Group, investigator and study update meetings

The QRI findings and updates were regularly discussed at all available opportunities in VIOLET trial meetings (as mentioned in *Chapter 2*). QRI researchers disseminated findings on recruitment challenges at three TMG meetings. These meetings helped shape the recruitment strategies that were then disseminated more widely to the sites. The presentations were based on the challenges faced by recruiters at the given time. For instance, the TMG organised a meeting (Birmingham; February 2018) with PIs and co-applicants mid-way through the main phase of the study, with the purpose of providing an update on the study's progress and encouraging sites to continue recruiting to the VIOLET trial after declining randomisation rates in the preceding 3 months. The QRI team's presentation, therefore, focused on strategies to ensure that the momentum gained in recruitment previously was sustained for the remainder of the recruitment period.

Rapid communication strategy

When recruitment dipped towards the target line (March 2019), the TMG and QRI teams made co-ordinated efforts to support and continue engaging with sites until recruitment target was achieved (February 2019). These activities included the following.

Monthly newsletter with tip of the month

Recruitment tips were added to the monthly update newsletter sent by the trial co-ordinator to all staff recruiting to the VIOLET trial.

'New recruitment targets' infographics

New recruitment targets' infographics were meant to provide the final push to achieve the recruitment target by encouraging site teams to increase their monthly recruitment rates to complete the study on time and within budget.

Chief investigator's virtual group with principal investigators

In response to the QRI team's concerns in April 2018, regarding achieving the recruitment target on time (at this point, the VIOLET trial had nearly 40% of the recruitment target to achieve in < 1 year), the chief investigator led a WhatsApp (Facebook, Inc., Menlo Park, CA, USA) group to encourage and support recruiting surgeons in their efforts to recruit patients to the study.

QRI evaluation

We evaluated the QRI in the VIOLET trial in three ways. First, there were many examples where QRI concepts had already been taken up because of recruiters' upfront training. A number of recruitment challenges reported in other RCTs[21,25,27–30,33] with QRIs were of lesser intensity (e.g. patient preferences) or already addressed by recruiters in the VIOLET trial. For instance, recruiters managed a potential recruitment issue caused by staff who met patients early in the patient pathway by speaking to them and requesting them to not convey a treatment recommendation to patients. Recruiters also avoided the misunderstanding caused by the term 'trial' among patients, as reported in other RCTs,[21,22] by using the term 'study'. Similarly, despite being vocal about their preference for VATS in interviews, recruiters became skilled at not conveying them to potential participants in most instances. Given that these and other similar topics were part of the QRI-informed recruitment training workshops that surgeons attended, this could be considered the first indication of prevention of recruitment difficulties in a RCT.

Second, we monitored SEAR data at site and recruiter level on a monthly basis and intervened rapidly whenever it appeared to fall towards the target line (as the VIOLET trial consistently recruited above target). The trial achieved its target sample size on time. However, it is difficult to determine the exact impact of the QRI on recruitment figures in the VIOLET trial or attribute causality between recruitment success and the QRI for the following reasons (see also *Appendix 1*). The amount of support VIOLET trial recruiters received well in advance of recruitment precludes identification of a precise 'pre-intervention' period and it is difficult to assess how much this support contributed to the excellent start to recruitment in the VIOLET trial or the momentum for the consistently above-target recruitment line in the VIOLET trial. In the absence of evidence on factors that predict good or poor recruitment to RCTs, we cannot ascertain if recruitment to the VIOLET trial would have been different if the intervention had not taken place. If the VIOLET trial had a precise pre- and post-intervention period, a causal link would still not be established because of the large number of confounding factors that may also contribute to successful recruitment. The QRI, alongside the highly committed chief investigator and PIs and efficient and supportive trials centre, all played a role in the VIOLET trial's success.

Third, we evaluated changes in recruitment practice. *Figure 4* shows the monitoring of changes to recruitment based on QRI feedback. From listening to audio-recordings, we were able to note that recruiters advanced their recruitment skills after they received VIOLET trial-specific feedback. For instance, although recruiters addressed patient preferences from the early days of recruitment, their skills were further refined and nuanced with more examples of good practice after they received tailored feedback from the QRI team (see *Appendix 8*, *Table 69*).

Chapter 5 Results: primary and secondary outcomes

Primary outcome: EORTC QLQ-C30 physical function at 5 weeks

Using the QLQ-C30 physical functioning score at 5 weeks from randomisation as a global marker of recovery, with higher scores indicating higher levels of functioning, participants allocated to VATS had a median score of 73 (IQR 60.0–86.7) compared with median score of 67 (IQR 53.3–86.7) for participants allocated to open surgery [adjusted MD (i.e. VATS – open surgery) 4.65, 95% CI 1.69 to 7.61; $p = 0.0089$]. The sensitivity analysis, excluding participants with benign disease, was consistent with the primary analysis (*Table 11*).

The target treatment effect, unpinning our sample size calculation, was 0.25 SDs (see *Chapter 2*, *Sample size*). Our observed unadjusted treatment effect was slightly lower at 0.21 SDs (i.e. an unadjusted difference of 4.62, with a pooled SD of 22.4).

Secondary outcomes

EORTC QLQ-C30 physical function over time

The EORTC QLQ-C30 physical functioning scores over time from randomisation to 1 year are shown in *Figure 6* and *Appendix 5*, *Table 50*. The improvement in physical function was more marked in the early discharge period and less pronounced after 6 months (see *Figure 6*). On average, the score was 4.22 points higher with VATS than with open surgery (95% CI 1.48 to 6.97 points; $p = 0.009$).

Complete resection

The total number of lymph node stations harvested (median, IQR 4–6) was very similar in both groups, as was the number of mediastinal nodes harvested (median 3, IQR 3–4) (*Table 12*). Complete R(0) resection was achieved in 429 of 439 (97.7%) participants and there was no difference between the groups (RR 0.999, 95% CI 0.97 to 1.26; $p = 0.94$) (see *Appendix 5*, *Figure 27*). All participants with residual disease had R1 disease.

Lymph node upstaging

Lymph node upstaging is summarised in *Table 13*. Upstaging from clinical node stage 0 (cN0) to pN1 and from clinical node stage 0 or 1 (cN0/1) to pN2 was similar in the groups (see *Appendix 5*, *Figure 28*).

TABLE 11 Primary outcome results: difference in EORTC QLQ-C30 physical function at 5 weeks

	Primary analysis		Analysis excluding benign patients	
Outcome	**MD (95% CI)**	***p*-value[a]**	**MD (95% CI)**	***p*-value[a]**
QLQ-C30 physical function at 5 weeks	4.65 (1.69 to 7.61)	0.0089	4.66 (1.71 to 7.62)	0.0089

a *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]

Notes
Multiple imputation (50 imputed data sets) was used to account for missing data. Models could not be adjusted for operating surgeon or centre.

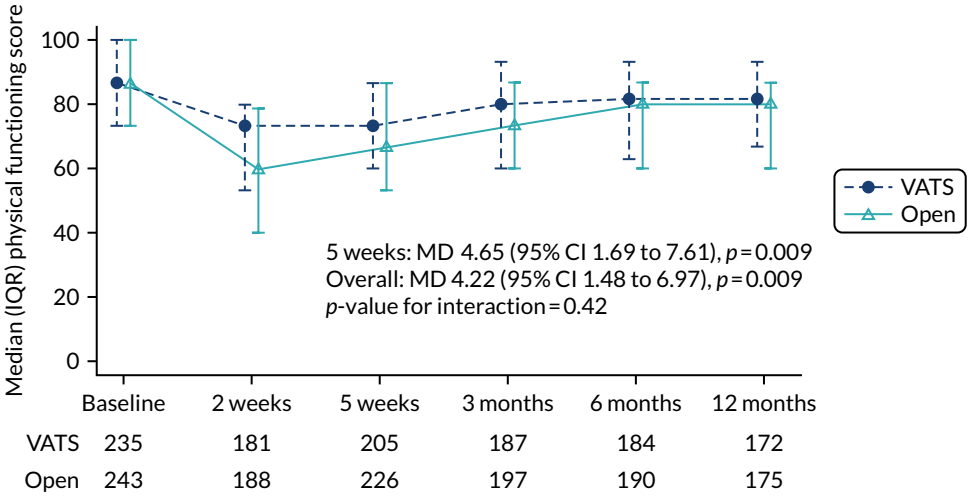

FIGURE 6 QLQ-C30 physical function over time. Higher scores indicate better physical function. Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

TABLE 12 Resection details

Outcome	Participant allocation	
	Randomised to VATS (*N* = 247)	Randomised to open surgery (*N* = 255)
Total number of lymph node stations harvested, median (IQR)	5 (4.0–6.0)	5 (4.0–6.0)
Mediastinal nodes harvested (stations 2 to 9), median (IQR)	3 (3.0–4.0)	3 (3.0–4.0)
Complete (R0) resection, *n/N* (%)	210/215 (97.7)	219/224 (97.8)
Site of residual (R1) disease, *n/N* (%)		
Bronchial margin	2/5 (40.0)	3/5 (60.0)
Vascular margin	0/5 (0.0)	1/5 (20.0)
Lung parenchymal margin	2/5 (40.0)	0/5 (0.0)
Other	1/5 (20.0)	0/5 (0.0)
No data	0/5 (0.0)	1/5 (20.0)

R0, no residual tumour; R1, microscopic residual tumour.
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Pain in the first 2 days post surgery

Visual analogue scale pain scores

In-hospital VAS pain scores in the first 2 days post surgery are shown in *Figure 7* and in *Appendix 5*, *Table 51*. Pain scores were similar in the two groups on day 1, with a median score of 4 in both groups (MD −0.02, 95% CI −0.46 to 0.41; $p = 0.913$), but participants in the VATS group had significantly lower pain scores on day 2 than participants in the open-surgery group (median 3 vs. 4, MD −0.54, 95% CI −0.99 to −0.09; $p = 0.018$). The complete-case sensitivity analysis gave consistent results (see *Appendix 5*, *Table 52*).

TABLE 13 Lymph node upstaging

Outcome	Participant allocation		RR (95% CI)	*p*-value
	Randomised to VATS (*N* = 247)	Randomised to open surgery (*N* = 255)		
cN0 to pN1, *n*/*N* (%)				
Yes	15/244 (6.2)	13/252 (5.2)	1.18 (0.54 to 2.58)	0.68
No	211/244 (86.5)	219/252 (86.9)		
Not cancer	18/244 (7.4)	20/252 (7.9)		
cN0/1 to pN2, *n*/*N* (%)				
Yes	15/244 (6.2)	12/252 (4.8)	1.31 (0.60 to 2.86)	0.50
No	211/244 (86.5)	220/252 (87.3)		
Not cancer	18/244 (7.4)	20/252 (7.9)		

Denominators differ from the total *N* in the table headings due to missing data.

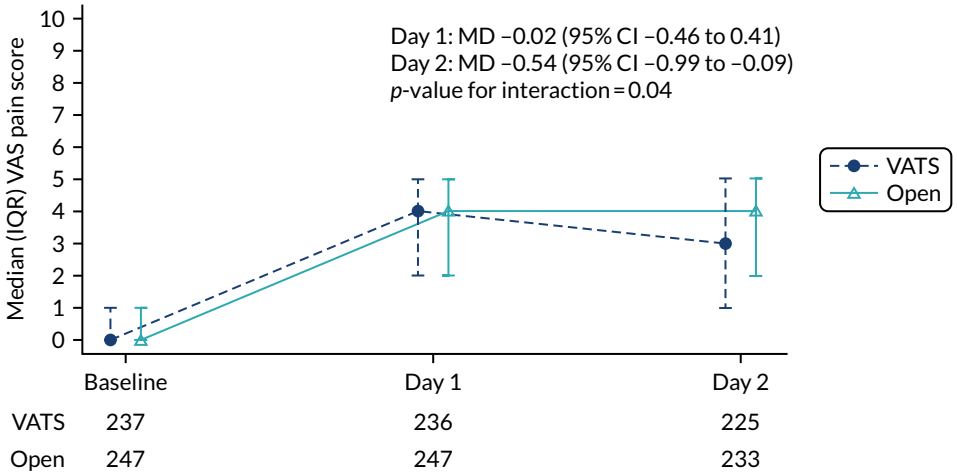

FIGURE 7 Pain scores over time. Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

Postoperative analgesia

Analgesia is used to manage pain following surgery. The most commonly prescribed analgesia during the intraoperative and postoperative hospital stay, expressed as the ratio of mean daily dose, is shown in *Figure 8*. Overall, analgesic consumption was 10% lower in the VATS group (mean ratio 0.9, 95% CI 0.80 to 1.01). Additional analgesia prescribed, which are included in the overall estimate but not depicted in *Figure 8*, are given in *Appendix 5*, *Table 53*.

Subgroup analysis: impact of type of analgesia received during surgery

Most participants received an intercostal block (315/502, 63%), with a similar proportion of participants receiving a paravertebral block (96/502, 19%) or neither (85/502, 17%). There was no evidence to suggest the difference in pain scores between VATS and open surgery differed by the type of analgesia received (test for treatment by analgesia interaction $p = 0.19$) (*Figure 9*).

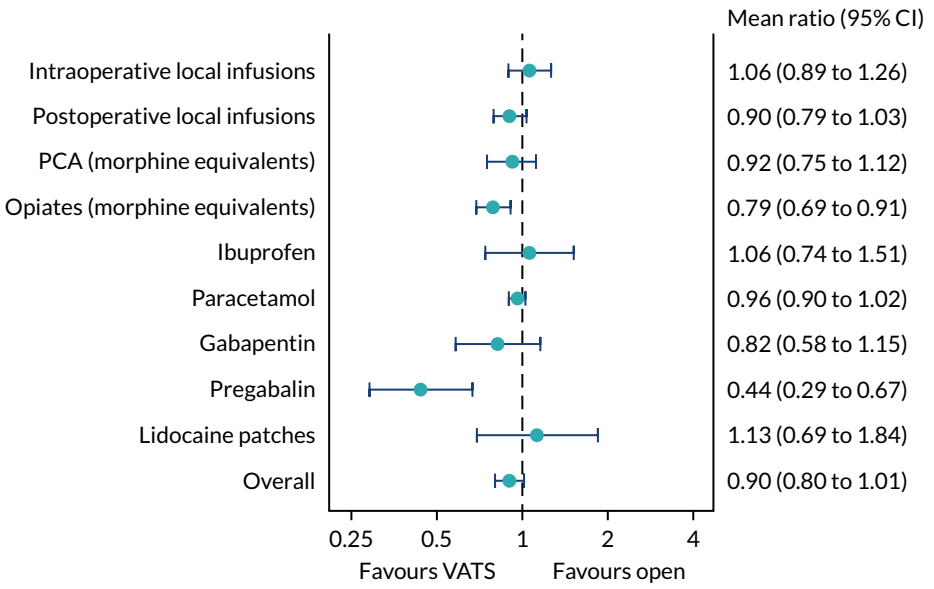

FIGURE 8 Analgesia prescribed intraoperatively and postoperatively. Data show the mean ratio (95% CI). PCA, patient-controlled analgesia. Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

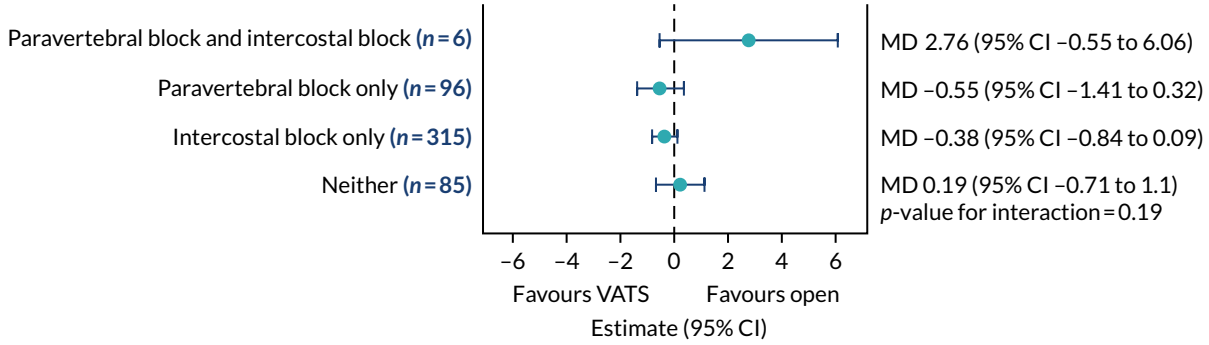

FIGURE 9 Subgroup analysis of pain scores by analgesia received.

Exploratory analyses: pain scores

Impact of type of thoracotomy, use of muscle sparing and rib resection

Differences in pain scores by type of thoracotomy performed, use of muscle sparing and rib resection are shown in *Figure 10*. In the first 2 days, pain scores did not vary significantly by type of thoracotomy, the use of muscle sparing or with rib resection.

Impact of number of port sites

Summaries of pain scores by number of port sites are presented in *Table 14*. Lower pain scores on day 1 were reported in participants receiving single-port VATS than in participants receiving multiport VATS and open surgery (median score 3 vs. 4 vs. 4, respectively). On day 2, the median pain score report by participants was the same for single-port VATS and multiport VATS (i.e. a median score of 3) and lower than open surgery (i.e. a median score of 4). The exploratory analysis comparing pain scores found no significant differences (see *Appendix 5*, *Table 54*).

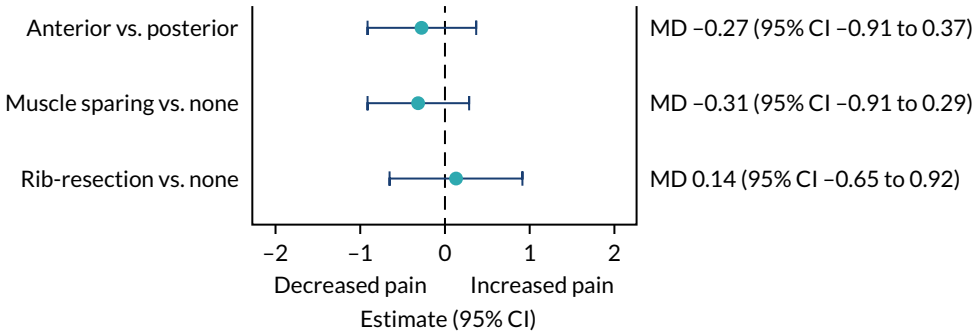

FIGURE 10 Exploratory analysis of the impact of type of thoracotomy on pain scores.

TABLE 14 Pain scores by number of port sites

Time point	Patients receiving VATS ($N = 208$)		Patients receiving open surgery ($N = 245$)
	Single-port VATS ($n = 42$)	Multiport VATS ($n = 166$)	
Baseline[a]	0 (0.0–1.0)	0 (0.0–2.0)	0 (0.0–1.0)
Day 1[b]	3 (2.0–5.0)	4 (2.0–6.0)	4 (2.0–6.0)
Day 2[c]	3 (1.0–5.0)	3 (0.0–5.0)	4 (2.0–5.0)

a Missing data: 17 patients (single-port VATS, $n = 1$; multiport VATS, $n = 7$; open surgery, $n = 9$).
b Missing data: 17 patients (single-port VATS, $n = 3$; multiport VATS, $n = 7$; open surgery, $n = 7$).
c Missing data: 33 patients (single-port VATS, $n = 6$; multiport VATS, $n = 13$; open surgery, $n = 14$).

Note
Data are presented as median (IQR).

Prolonged incision pain beyond 5 weeks

The proportion of patients with prolonged incision pain (defined as the need for analgesia after 5 weeks post randomisation) is shown in *Table 15*. A total of 143 (59.6%) patients in the VATS group experienced prolonged incision pain compared with a total of 175 (72.3%) patients in the open-surgery group. This difference was significant (RR 0.82, 95% CI 0.72 to 0.94; $p = 0.003$) (see *Appendix 5*, *Figure 29*).

Time from surgery to hospital discharge: postoperative length of hospital stay

Time from surgery to hospital discharge is presented in *Figure 11* and in *Appendix 5*, *Table 55*. Median length of stay was lower for patients in the VATS group than for patients in the open-surgery group (at 4 and 5 days, respectively). This difference was statistically significant (HR 1.34, 95% CI 1.09 to 1.65; $p = 0.006$).

TABLE 15 Prolonged incision pain

Outcome	Participant allocation		RR (95% CI)	*p*-value
	Randomised to VATS ($N = 247$), *n/N* (%)	Randomised to open surgery ($N = 255$), *n/N* (%)		
Prolonged incision pain[a]	143/240 (59.6)	175/242 (72.3)	0.82 (0.72 to 0.94)	0.0033

Analyses are adjusted for operating surgeon.
Denominators differ from the total *N* in the table headings due to missing data.

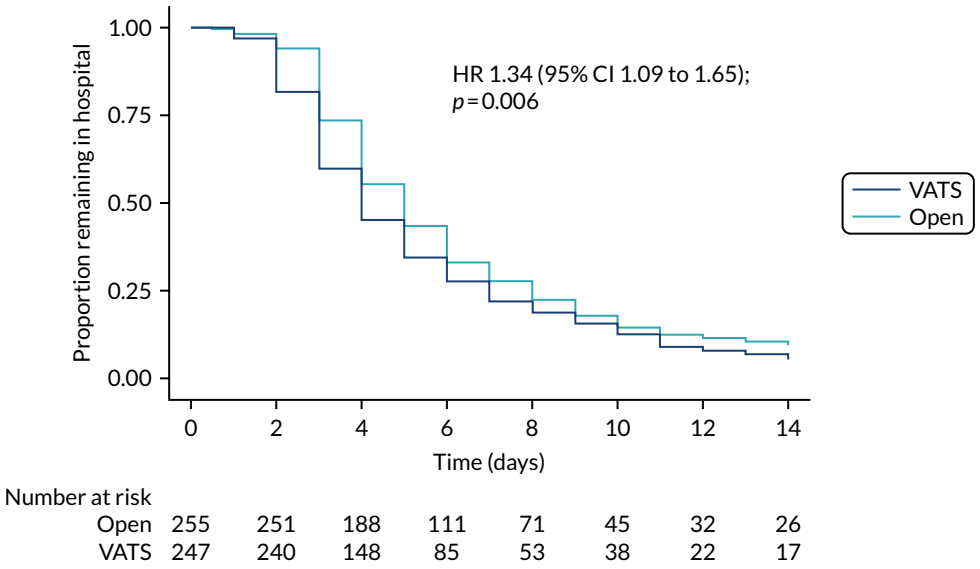

FIGURE 11 Time from surgery to hospital discharge. Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

Exploratory analysis: length of stay

Impact of number of port sites on length of stay

Summaries of length of hospital stay by number of port sites are presented in *Table 16*. The median length of stay was the same in patients who received single-port VATS and in patients who received multiport VATS (i.e. 4 days), but differed from patients who received open surgery (i.e. 5 days).

The exploratory analysis comparing length of stay confirmed this difference as statistically significant ($p = 0.017$) (see *Appendix 5*, *Table 56*).

Fitness for hospital discharge

All participants were assessed against predefined 'fit-for-discharge' criteria (see *Chapter 2*, *Fitness for discharge after surgery* for the definition). The time in days when first considered fit, and the numbers discharged before the criteria were first met, when they were first met and after they were first met are shown in *Table 17*. The median time to first meeting the fitness criteria was 1 day before the median length of stay in both groups. The proportion of patients discharged 'early' was similar in the two groups (i.e. 8.4% overall). Discharge was 'delayed' in one-quarter of participants.

Overall survival and progression-free survival to 1 year

There were 31 deaths within 1 year of randomisation, 18 in the open-surgery group and 13 in the VATS group (*Table 18*). Overall, 94.6% of participants were alive at 1 year in the VATS group compared with 92.6% of participants in the open-surgery group (HR for death 0.67, 95% CI 0.32 to 1.40; $p = 0.28$). Overall survival by group is shown in *Appendix 5*, *Figure 30*.

TABLE 16 Length of stay by number of port sites

Length of stay	Patients receiving VATS ($N = 208$)		Patients receiving open surgery ($N = 245$)
	Single-port VATS ($n = 42$)	Multiport VATS ($n = 166$)	
Time to discharge (days), median (IQR)	4 (3–8)	4 (3–7)	5 (4–8)

TABLE 17 Fitness for hospital discharge

Fitness for discharge	Participant allocation		Overall (*N* = 492)
	Randomised to VATS (*N* = 240)	Randomised to open surgery (*N* = 252)	
Time until fitness criteria first met (days), median (IQR)	3 (2.0–5.0)	4 (3.0–6.5)	4 (2.0–6.0)
Patient discharged, *n*/*N* (%)			
On first day fit	161/235 (68.5)	162/251 (64.5)	323/486 (66.5)
After first day fit	54/235 (23.0)	68/251 (27.1)	122/486 (25.1)
Before first day fit	20/235 (8.5)	21/251 (8.4)	41/486 (8.4)

TABLE 18 Causes of death in-hospital and following discharge from hospital to 1 year

Cause of death	Participant allocation	
	Randomised to VATS (*N* = 11), *n*	Randomised to open surgery (*N* = 13), *n*
Bronchopneumonia	0	1
Cardiac arrest	0	1
Disease progression	7	5
Infective exacerbation of COPD	1	0
Ischaemic brain injury, cardiac arrest, myocardial ischaemia	0	1
Pneumonia	2	0
Pseudomonas, respiratory failure	0	1
Pulmonary embolism	0	1
Respiratory/cardiac failure	0	1
Stroke, myocardial infarction	1	0
Subarachnoid haemorrhage	0	1
Unknown	0	1

COPD, chronic obstructive pulmonary disease.
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Sixteen VATS participants and 17 open-surgery participants experienced disease recurrence/progression within 1 year. Overall, 90.4% of participants were alive and disease free at 1 year in the VATS group compared with 88.0% of participants in the open group (HR for disease progression 0.73, 95% CI 0.42 to 1.27; $p = 0.26$) (*Table 19*). Progression-free survival by group is shown in *Appendix 5*, *Figure 31*.

Sensitivity analyses adjusting for pathological disease stage were carried out for survival and progression-free survival outcomes. See *Table 19* for data contrasting the results of the primary analyses for these outcomes and the results of the sensitivity analyses, which were very similar.

The locations of recurrence and new cancers are shown in *Table 20*. There were 24 cases of locoregional recurrence (VATS, $n = 11$; open surgery, $n = 13$), 17 cases of distant recurrence (VATS, $n = 7$; open surgery, $n = 10$) and 10 cases of new cancer (VATS, $n = 4$; open surgery, $n = 6$).

TABLE 19 Survival and progression-free survival to 1 year

	Primary analysis		Analysis adjusting for pathological disease stage	
Outcome	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Survival	0.67 (0.32 to 1.40)	0.283	0.71 (0.34 to 1.50)	0.366
Progression-free survival	0.73 (0.42 to 1.27)	0.262	0.75 (0.42 to 1.32)	0.312

Analyses are adjusted for operating surgeon and centre.

TABLE 20 Location of recurrence/new cancer/metastases

	Participant allocation	
Type/location	Randomised to VATS (*N* = 18)	Randomised to open surgery (*N* = 21)
Locoregional recurrence		
Lung	3/3 (16.7)	7/6 (28.6)
Mediastinal	4/4 (22.2)	1/1 (4.8)
Bronchus	0	1/1 (4.8)
Pleura and lymph nodes	1/1 (5.6)	0
Not collected[a]	3/2 (11.1)	4/4 (19)
Distant recurrence		
Adrenal gland	0	3/2 (9.5)
Adrenal gland and liver	0	1/1 (4.8)
Brain	1/1 (5.6)	2/2 (9.5)
Brain/spine	1/1 (5.6)	0
Liver	2/2 (11.1)	0
Liver, adrenal glands, intra-abdominal lymph nodes	1/1 (5.6)	0
Thoracic and lumbar spine	1/1 (5.6)	0
Not collected[a]	1/1 (5.6)	4/4 (19)
New cancer		
Prostate	1/1 (5.6)	2/2 (9.5)
Lung	1/1 (5.6)	1/1 (4.8)
Acute myeloid leukaemia	0	1/1 (4.8)
Bowel	1/1 (5.6)	0
Cholangiocarcinoma	1/1 (5.6)	0
Sarcoma	0	1/1 (4.8)
Not collected[a]	0	1/1 (4.8)

a Data collection added part-way through the study and so available for a subset of patients only.

Notes
Data are recurrences *n*/patients *n* (%).
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Uptake of adjuvant treatment

Time to uptake of adjuvant treatment was analysed in the primary intention-to-treat population and, for the subset of participants eligible for adjuvant treatment according to NICE guidelines,[57] namely participants with a postoperative disease stage of (1) N1–2 and M0 or (2) T2b to 4, N0 and M0 were deemed eligible. Overall, 73 participants had adjuvant treatment, 56 of whom met the eligibility criteria defined by NICE (see *Appendix 5*, *Table 57*). The time to uptake of adjuvant treatment was similar between the two treatment groups, both for the primary intention-to-treat population and the NICE-eligible subset of participants (*Figures 12* and *13*, see also *Appendix 5*, *Table 57*).

EORTC QLQ-C30 quality-of-life questionnaire

The EORTC QLQ-C30 comprises an overall measure of global health and a number of subscales. For all scales, higher scores indicate a higher level of functioning or symptoms or problems.

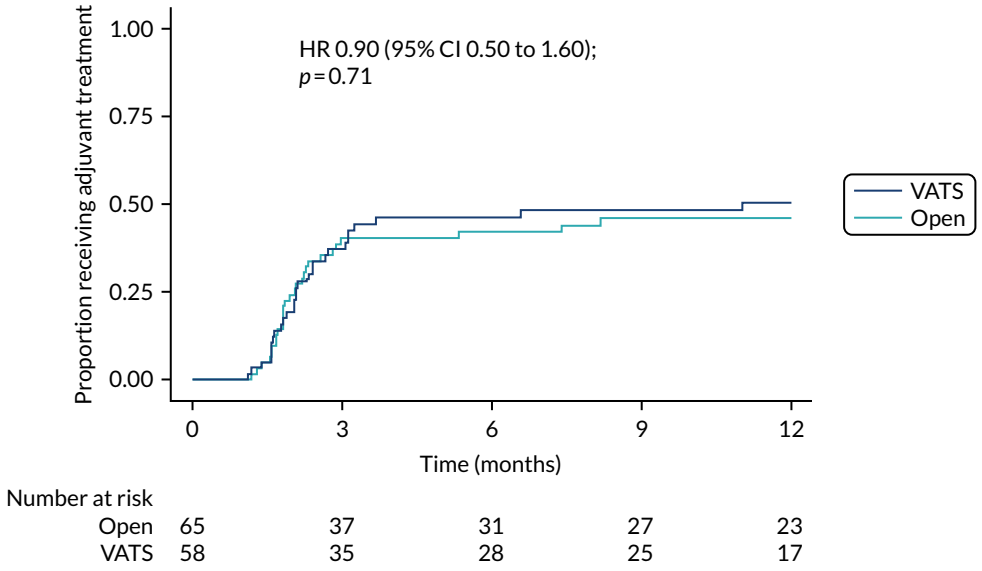

FIGURE 12 Uptake of adjuvant treatment in the primary analysis population.

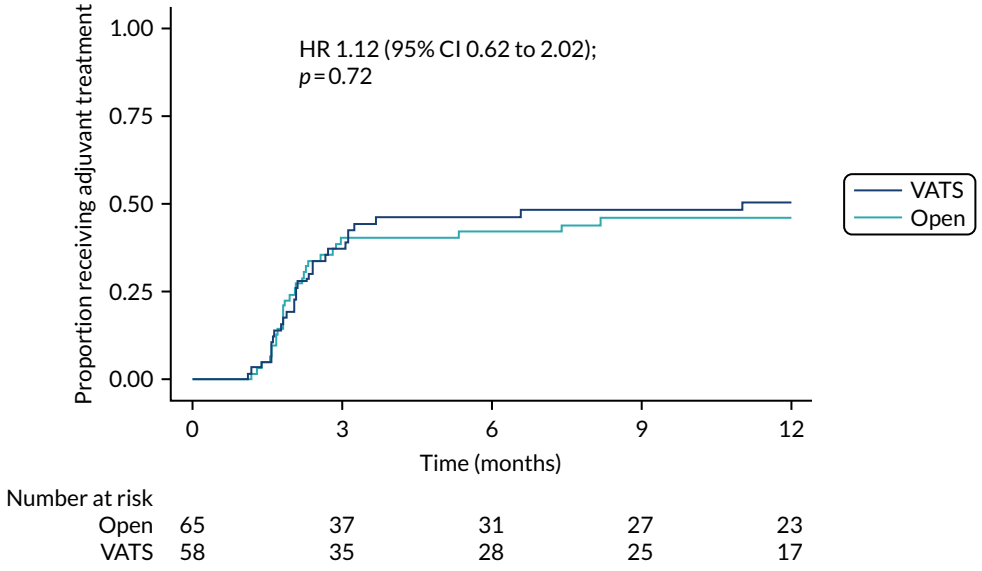

FIGURE 13 Uptake of adjuvant treatment in the NICE-eligible subset of participants.

Global health status and subscales assessing functioning

In addition to the global health status, the questionnaire measures physical, role, social, cognitive and emotional functioning. The physical function subscale was the primary outcome for the VIOLET trial and is reported in *Primary outcome: EORTC QLQ-C30 physical function at 5 weeks* and *EORTC QLQ-C30 physical function over time*. Scores for the other scales over time for participants randomised to VATS or open surgery are shown in *Appendix 5*, *Figures 32–34*. Global health status, role and social functioning were all significantly higher in the VATS group (*Figure 14*) than in the open-surgery group, and where cognitive function was impaired, the impairment was less in the VATS group than in the open-surgery group (*Figure 15*). The effect of surgery on emotional function varied over time. At 2 weeks, fewer participants in the VATS group than in the open-surgery group reported some impaired emotional function, but thereafter the results were similar in the two groups (*Figure 16*). Summary data and the estimated treatment effects for each scale are given in *Appendix 5*, *Tables 58* and *59*.

Subscales assessing symptoms and problems

Scores for scales measuring symptoms and problems over time for participants randomised to VATS or open surgery are shown in *Appendix 5*, *Figures 35–43*. Participants randomised to VATS experienced less pain and fatigue and had less difficulty sleeping in the first 2 weeks than participants randomised to open surgery. These participants were also less likely to experience appetite loss and nausea, and constipation in the early period post surgery. Other measures were similar in the two groups (*Figure 17*). Summary data and the estimated treatment effects for each subscale are given in *Appendix 5*, *Tables 60* and *61*.

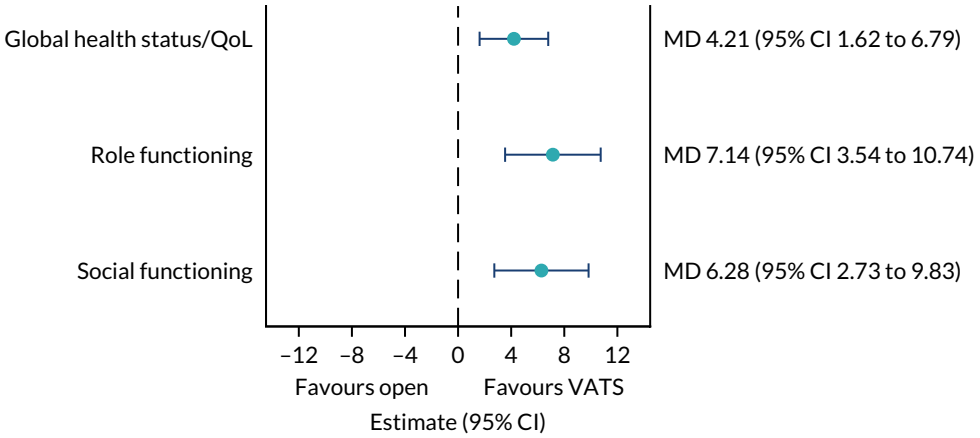

FIGURE 14 QLQ-C30 global health status and role and social functioning: treatment effects.

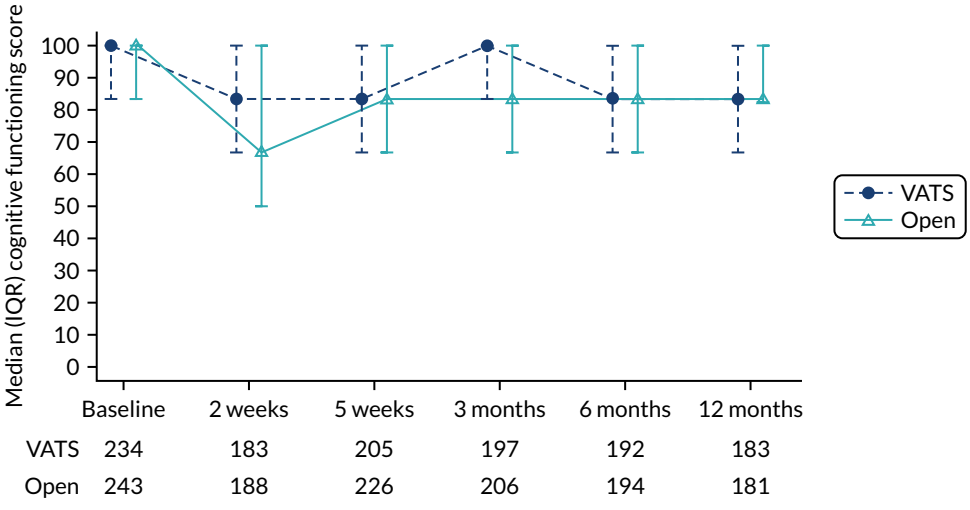

FIGURE 15 QLQ-C30 cognitive functioning over time. Higher scores indicate better health.

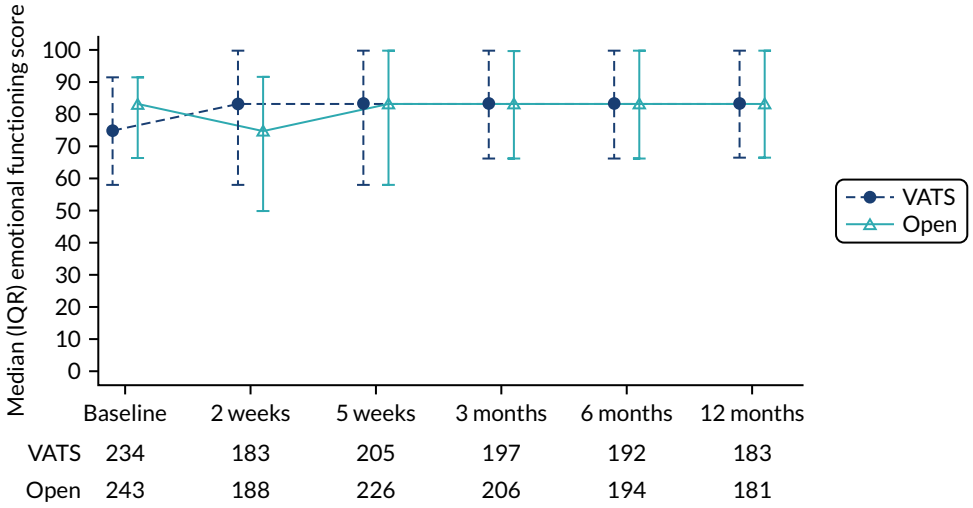

FIGURE 16 QLQ-C30 emotional functioning over time. Higher scores indicate better health.

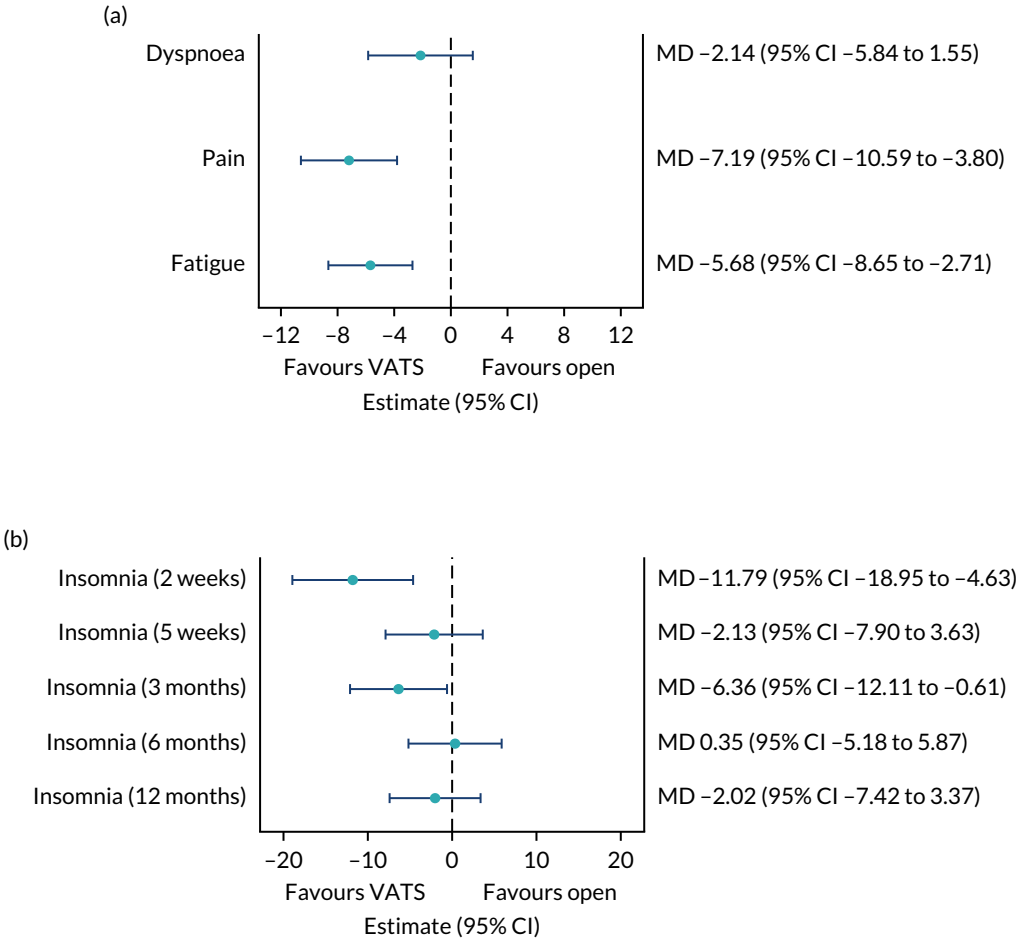

FIGURE 17 QLQ-C30 symptoms and problems subscales: treatment effects. (*continued*)

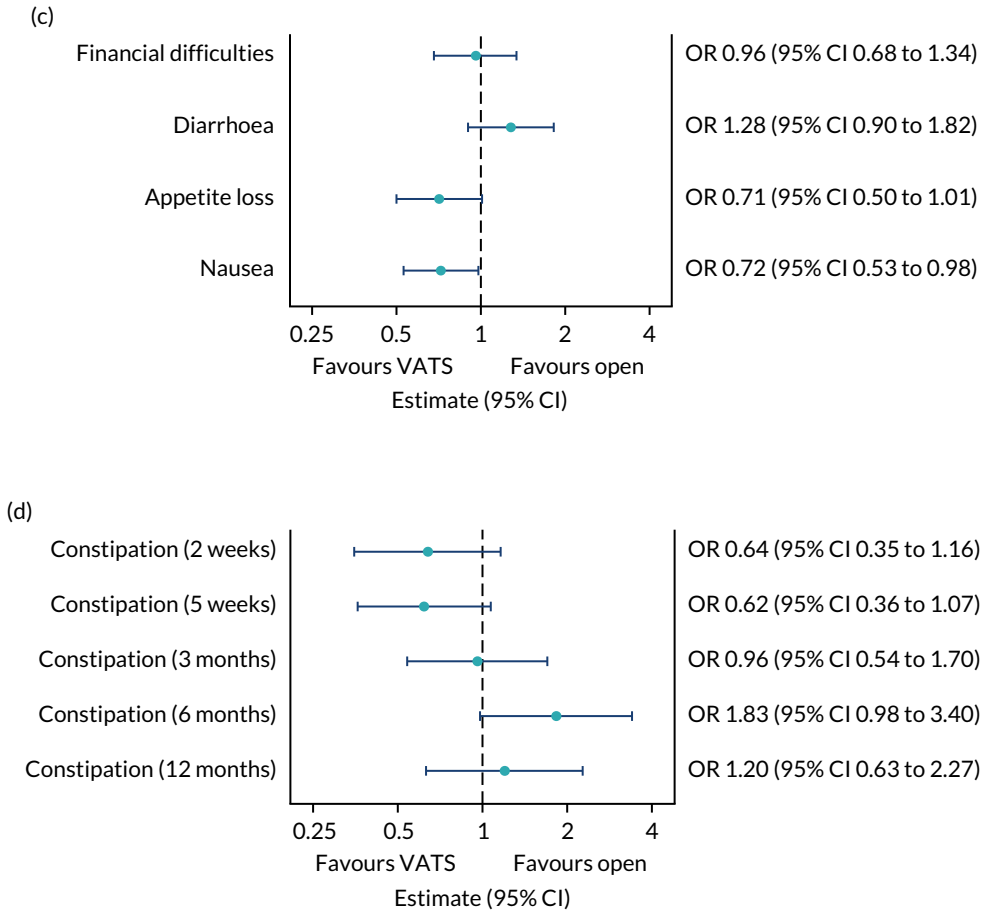

FIGURE 17 QLQ-C30 symptoms and problems subscales: treatment effects.

QLQ-C30 exploratory analysis: pain scores

Differences in pain scores to 1 year by type of thoracotomy performed, use of muscle sparing and rib resection are shown in *Figure 18*. The data show the same trend as was observed in the pain scores in the first 2 days after surgery (see *Figure 10*), with pain scores in those who had received an anterior thoracotomy being lower, on average, than those who received a posterior thoracotomy, and there being less pain with muscle sparing and significantly more pain with rib resection (MD 9.8, 95% CI 2.07 to 17.52).

EORTC QLQ-LC13 quality-of-life questionnaire

The QLQ-LC13 measures a range of cancer-related symptoms and problems. As for the QLQ-C30, higher scores indicate a higher level of symptoms or problems. Scores over time for participants randomised to VATS or open surgery are shown in *Appendix 5*, *Figures 44–53*. Participants randomised to VATS experienced significantly less pain in the chest and less pain in the arm at 5 weeks than participants randomised to open surgery, but other outcomes were similar in the two groups (*Figure 19*). Summary data and the estimated treatment effects for each subscale are given in *Appendix 5*, *Tables 62* and *63*.

EQ-5D-5L utility score

The EQ-5D-5L utility scores over time are shown in *Figure 20*. The median utility scores were higher in the VATS group than in the open-surgery group at all post-baseline time points. Participants in the VATS group were less likely to have less than perfect health (i.e. a score < 1) than participants in the open-surgery group [odds ratio (OR) 0.57, 95% CI 0.38 to 0.86; $p = 0.007$]. Of those participants with less than perfect health, participants in the VATS group had, on average, a higher score (representing better health) than those in the open-surgery group (geometric mean ratio 0.90, 95% CI 0.84 to 0.96; $p = 0.003$) (see *Appendix 5*, *Table 64*, for summary data).

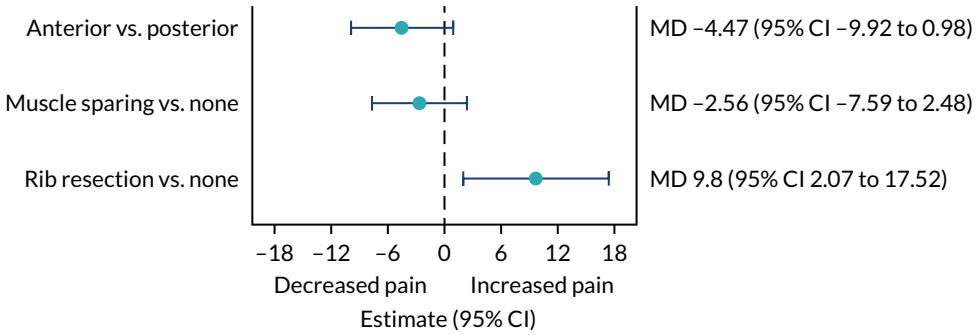

FIGURE 18 Impact of type of thoracotomy on QLQ-C30 pain scores.

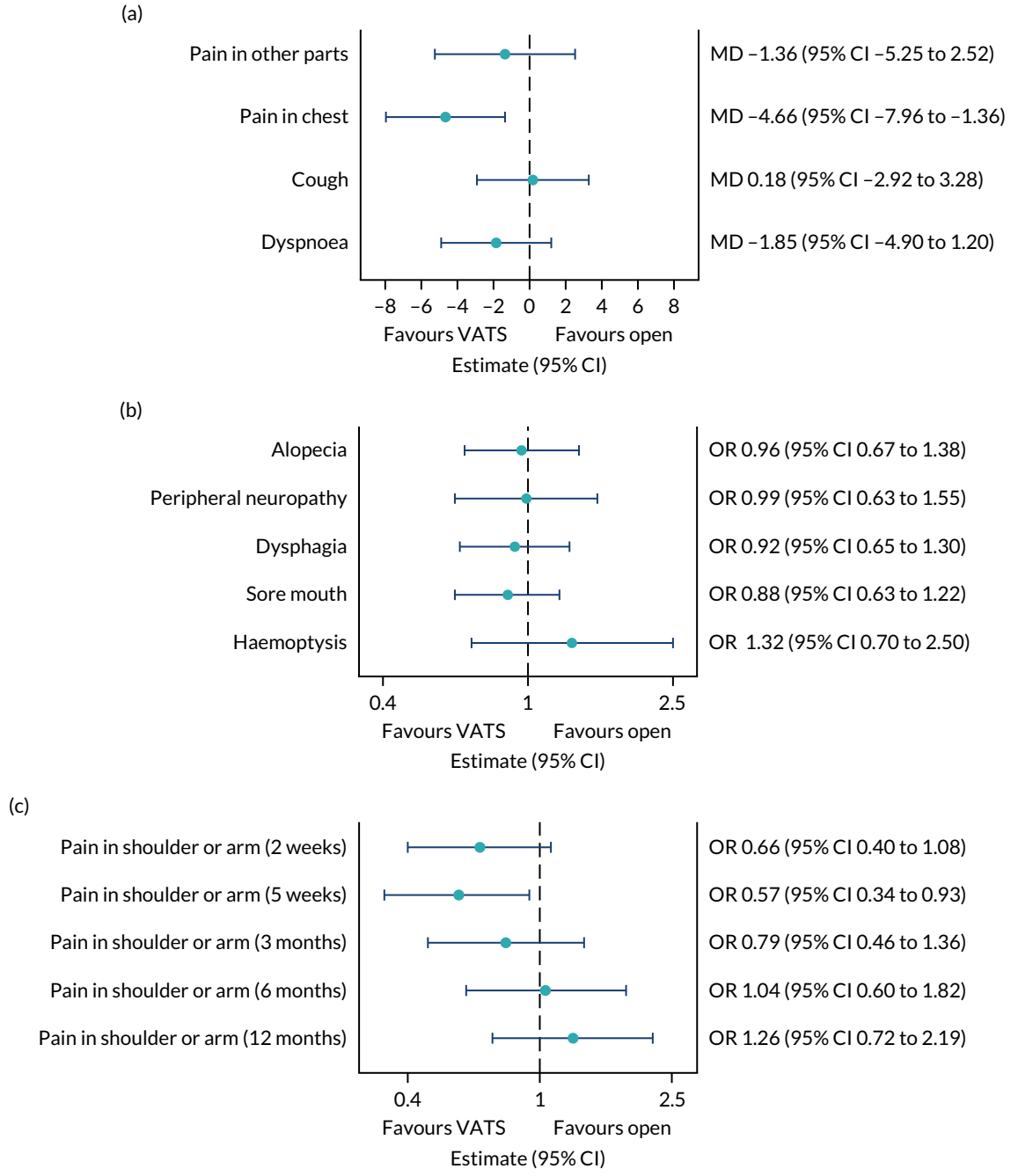

FIGURE 19 QLQ-LC13 symptoms and problems subscales: treatment effects.

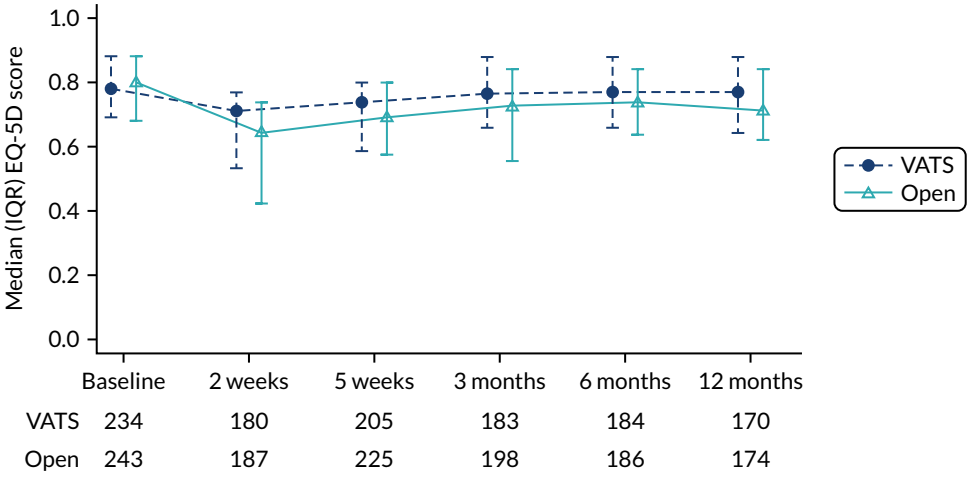

FIGURE 20 EQ-5D-5L utility scores over time.

Adverse events

Adverse events in the period from surgery to discharge from hospital following surgery

Eighty-one (32.8%) participants allocated to VATS and 113 (44.3%) participants allocated to open surgery experienced at least one AE in the period from surgery to discharge from hospital (RR 0.74, 95% CI 0.66 to 0.84; $p < 0.001$), but the number of SAEs was similar in the two groups (8.1% in the VATS group vs. 8.2% in the open group) (*Table 21*). AE and SAEs summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class are presented in *Figure 21*. Details of the events within each system organ class are given in *Appendix 5*, *Table 65*.

Infective complications were the most common in both groups, the majority of which were pneumonia or lower respiratory tract infections (see *Appendix 5*, *Table 65*). Comparing the two groups, participants in the VATS group had fewer infective (RR 0.89, 95% CI 0.84 to 0.94), psychiatric (RR 0.98, 95% CI 0.97 to 1.00) and renal (RR 0.96, 95% CI 0.91 to 1.00) complications than participants in the open-surgery group (see *Figure 21*). There were seven deaths prior to discharge from hospital (VATS group, $n = 2$; open-surgery group, $n = 5$). Causes of death for these seven participants are summarised in *Table 18*.

TABLE 21 Relative risk of AEs and SAEs following surgery

Outcome	Participant allocation		RR (95% CI)	*p*-value
	Randomised to VATS ($N = 247$), *n*/*N* (%)	Randomised to open surgery ($N = 255$), *n*/*N* (%)		
In hospital before discharge				
Any in-hospital AE	81/247 (32.8)	113/255 (44.3)	0.74 (0.66 to 0.84)	< 0.001
Any in-hospital SAE	20/247 (8.1)	21/255 (8.2)	0.98 (0.59 to 1.63)	0.948
After discharge following surgery (events/patients)				
Readmissions	117/70 (29.0)	141/88 (35.9)		
SAE	142/75 (30.7)	207/94 (37.8)	0.81 (0.66 to 1.00)	0.053

Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

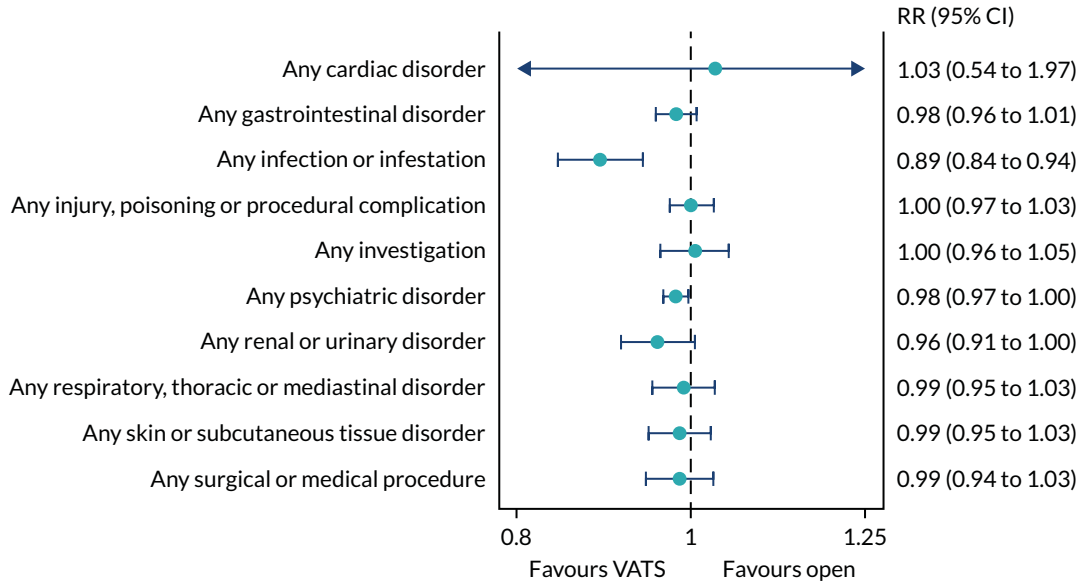

FIGURE 21 In-hospital AEs summarised by MedDRA system organ class.

Serious adverse events in the period after discharge from hospital to 1 year

Seventy-five (30.7%) participants allocated to VATS and 94 (37.8%) participants allocated to open surgery experienced at least one SAE in the period after discharge from hospital to 1 year (RR 0.81, 95% CI 0.66 to 1.00; $p = 0.053$), of which 158 (93.5%) resulted in an admission to hospital (VATS group, $n = 70$; open-surgery group, $n = 88$) (see *Table 21*). SAEs summarised by MedDRA system organ class are presented in *Figure 22*. Details of the events within each system organ class are given in *Appendix 5*, *Table 66*.

As with the early postoperative period, infective complications were the most common in both groups, the majority of which were pneumonia or lower respiratory tract infections, followed by respiratory, thoracic and mediastinal disorders (see *Appendix 5*, *Table 66*). The events that resulted in admission to hospital are summarised in *Appendix 5*, *Table 67*. There were 24 deaths after discharge from hospital (VATS group, $n = 11$; open-surgery group, $n = 13$). Causes of death for these 24 participants are summarised in *Table 18*. Half of the deaths (12/24) were due to disease progression.

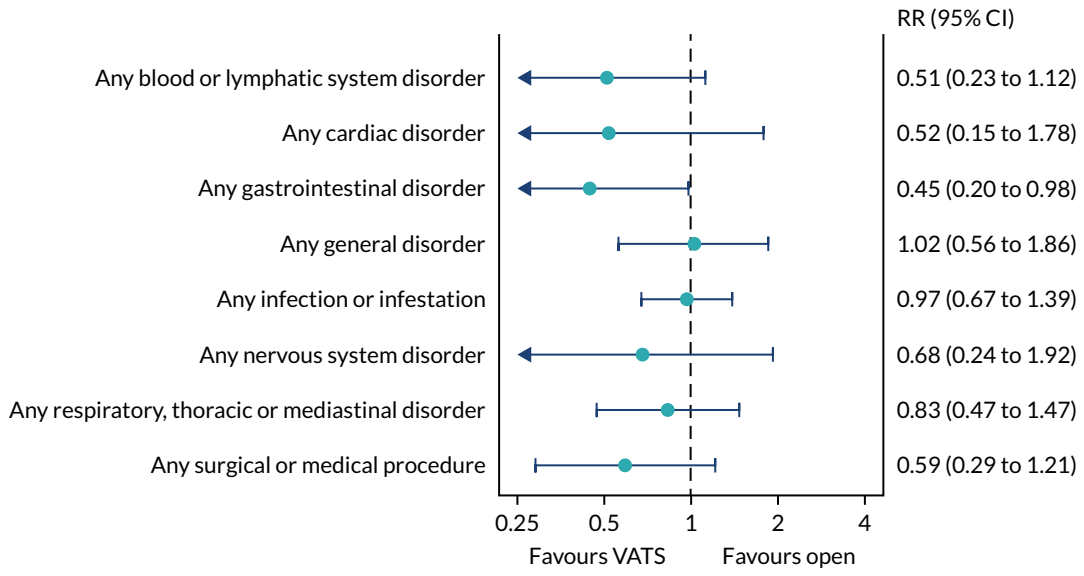

FIGURE 22 Post-discharge SAEs summarised by MedDRA system organ class.

Chapter 6 Results: economic evaluation

Analysis data set

All randomised participants were included in the health economic evaluation, except one participant who withdrew before surgery and for whom no further data were collected, and 38 participants who were found to have benign disease and who were not intended to be followed up beyond 5 weeks. Therefore, a total of 464 participants (VATS surgery, $n = 229$; open surgery, $n = 235$) were included in our analyses.

Missing data

The number of complete data for resource use and outcomes (i.e. individual EQ-5D-5L scores and QALYs) for patients in each trial group is detailed in *Appendix 2*, *Table 26*. In summary, 40% of participants in both trial groups had complete resource use data, and 49% overall (VATS, 48%; open surgery, 51%) had complete EQ-5D-5L scores across the six time points. Data collection on information related to staples used in surgery and two complications (pleural effusion and prolonged air leak) began part way through the study and were, therefore, not available for around 50% of participants. Aside from information on staples and these two complications, 460 (99%) participants had complete data for their index admission. Missing data were non-monotonic, as individuals with missing resource use or EQ-5D-5L data at 3 months, for example, may have complete resource use or EQ-5D-5L data at 6 months. Multiple imputation can handle non-monotonic missing data. There were 29 (7%) participants who had died by 12 months. Survival status was unknown for 23 (5%) participants. These participants were assumed to be alive and we examined this assumption in a sensitivity analysis.

When associations between missing total costs and QALY data and key baseline variables (i.e. age, sex, hospital site and treatment group) were assessed, hospital site was found to be a significant predictor of missing costs, and hospital site and age were significant predictors of missing QALYs, at a 5% significance level. This suggests that data were not missing completely at random. Hospital site was a significant predictor of costs and QALYs, and treatment group also predicted costs. Associations were found between missingness and previously observed EQ-5D-5L outcomes, which suggests that missing data are dependent on more than just observed baseline covariates.

These findings support a missing-at-random assumption and, therefore, multiple imputation was appropriate to be used, as this is a flexible approach for handling the missing data. Cost components for the initial index admission (i.e. time in theatre; staples; days in intensive care, high dependency and on a ward; and the complications pleural effusion and prolonged air leak combined) were imputed along with total primary and secondary care costs for hospital discharge to 5 weeks, 5 weeks to 3 months, 3 months to 6 months, and 6 months to 12 months, and the six EQ-5D-5L scores, separately by treatment group. When conducting the multiple imputation, the complete variables, costs of in-hospital complications (excluding pleural effusion and prolonged air leak), SAEs and pathology for frozen section, and an indicator variable for whether or not the patient survived to 12 months were included in regression models, as were the baseline variables of age and hospital site, as missingness may depend on them. Prediction mean matching with 10 nearest neighbours was used (i.e. based on the variables included, the 10 most similar patients were identified and the costs for one randomly selected patient assigned to the patient with missing data). Given that 80% of cases were incomplete (82% and 77% in the VATS and open-surgery arms, respectively), multiple imputation with $m = 85$ imputations was conducted.

Quality-adjusted life-years

A summary of the mean EQ-5D-5L scores at each of the follow-up time points is shown in *Appendix 2*, *Figure 26*, for participants who completed the questionnaire (or who had died by that follow-up time point and were given a score of zero). Although the mean score at baseline was slightly higher in the open-surgery group than in the VATS group at each follow-up time point, thereafter mean scores were higher in the VATS group than in the open-surgery group.

Table 22 reports EQ-5D-5L scores at each of the time points and QALYs for all participants, with missing data imputed. As in *Appendix 2*, *Figure 26*, mean EQ-5D-5L scores at baseline were slightly higher in the open-surgery group than in the VATS group, but at all other time points were higher in the VATS group than in the open-surgery group. This results in a greater gain in QALYs in the VATS group than in the open-surgery group, and this difference is statistically significant. Participants in the VATS group enjoy greater combined quantity and quality of life than participants in the open-surgery group.

Resource use and costs

Table 23 reports information on the main resource use items for the trial groups to 12 months. In the index admission, this includes time in theatre and the number of staples used in surgery, length of hospital stay by ward type and complications. Post hospital discharge, this includes hospital readmissions and other primary and secondary care resource use over the 12 months' follow-up, including hospital visits for chemotherapy and radiotherapy.

Surgery took, on average, 2.7 and 2.3 hours for participants in the VATS and open-surgery groups, respectively. Participants in the VATS group spent, on average, 19 minutes longer in theatre than those in the open-surgery group (MD in hours 0.3, 95% CI 0.2 to 0.5 hours). A mean of eight staples was used in each arm of the trial, although use was slightly less in the open-surgery group than in the VATS group.

TABLE 22 EQ-5D-5L scores and QALYs to 12 months for all participants (imputed)

Outcome	Participant allocation		
	Randomised to VATS (*N* = 229), mean (SE)	Randomised to open surgery (*N* = 235), mean (SE)	VATS vs. open surgery, MD (95% CI)
EQ-5D-5L[a]			
Baseline	0.746 (0.014)	0.762 (0.014)	–0.016 (–0.056 to 0.023)
2 weeks	0.608 (0.018)	0.544 (0.018)	0.064 (0.013 to 0.115)
5 weeks	0.658 (0.017)	0.619 (0.017)	0.039 (–0.008 to 0.086)
3 months	0.721 (0.017)	0.643 (0.017)	0.078 (0.031 to 0.126)
6 months	0.708 (0.018)	0.672 (0.018)	0.036 (–0.013 to 0.086)
12 months	0.693 (0.019)	0.637 (0.019)	0.057 (0.004 to 0.109)
QALYs to 12 months (adjusted for baseline EQ-5D-5L)	0.841 (0.017)	0.780 (0.016)	0.060 (0.025 to 0.095)

SE, standard error.
a Deaths included as zero.
Values are rounded to three decimal places.

TABLE 23 Observed resource use for participants

Resource use	Participant allocation				VATS vs. open surgery, MD (95% CI)
	Randomised to VATS (*N* = 229)		Randomised to open surgery (*N* = 235)		
	n (%)	Mean (SD)	*n* (%)	Mean (SD)	
Surgery/ward stays					
Time in theatre (hours)	228 (100)	2.7 (0.9)	235 (100)	2.3 (0.8)	0.3 (0.2 to` 0.5)
Number of staples	120 (52)	8.1 (3.6)	129 (55)	7.6 (3.4)	0.5 (−0.4 to 1.4)
Intensive care unit stay (days)[a]	227 (99)	0.5 (3.0)	234 (100)	1.0 (5.9)	−0.4 (−1.3 to 0.4)
High-dependency unit stay (days)	227 (99)	1.0 (1.4)	234 (100)	1.4 (3.5)	−0.4 (−0.9 to 0.1)
Ward stay (days)[a]	227 (99)	4.1 (5.3)	234 (100)	4.8 (4.1)	−0.7 (−1.6 to 0.2)
Total stay (days)[a]	227 (99)	5.6 (6.7)	234 (100)	7.2 (9.4)	−1.5 (−3.0 to −0.0)
Selected complications[d]					
Pulmonary collapse	229 (100)	10 (4)[b]	235 (100)	8 (3)[b]	1[c]
Surgical emphysema	229 (100)	9 (4)[b]	235 (100)	13 (6)[b]	−4[c]
Bronchoscopy	229 (100)	11 (5)[b]	235 (100)	9 (4)[b]	2[c]
Infection	229 (100)	38 (17)[b]	235 (100)	69 (29)[b]	−12[c]
Acute psychosis	229 (100)	6 (3)[b]	235 (100)	12 (5)[b]	−2[c]
Reoperation	229 (100)	3 (1)[b]	235 (100)	6 (3)[b]	−2[c]
Post hospital discharge					
Further inpatient days	187 (82)	2.4 (6.4)	192 (82)	4.2 (12.1)	−1.8 (−3.7 to 0.2)
Hospital visits	188 (82)	7.7 (7.6)	190 (81)	8.6 (7.6)	−0.9 (−2.4 to 0.6)
Community visits	187 (82)	7.2 (6.2)	191 (81)	7.3 (6.3)	−0.1 (−1.4 to 1.1)

a Includes length of stay at another hospital if discharged there after surgery.
b Frequency (%).
c Percentage difference.
d Selected complications are those with high associated costs or the most frequently occurring.

Participants spent a mean of 5.6 and 7.2 days in hospital after surgery in the VATS and open-surgery groups, respectively. Participants in the VATS group spent less time in intensive care, in high dependency and on a ward than participants in the open-surgery group. The overall difference in length of stay was statistically significantly lower in the VATS group than in the open-surgery group. Only a few selected complications are shown here (those with high associated costs and those most frequently occurring), but overall complications were lower in the VATS group than in the open-surgery group. Resource use post hospital discharge follows a similar pattern. The mean number of days readmitted to hospital, and the number of hospital and community visits, are lower in the VATS group than in the open-surgery group.

A breakdown of total costs for all participants is provided in *Figure 23* (with missing data imputed). The key cost drivers are surgery, time in critical care and on a ward, and costs post discharge. Costs are clearly lower in the VATS group than in the open-surgery group. Greater detail on these costs is provided in *Appendix 2*, *Table 27*.

Although costs associated with time in theatre are statistically significantly higher in the VATS group than in the open-surgery group, costs associated with length of stay are statistically significantly lower, and these cost savings more than outweigh the higher costs associated with surgery. Costs post hospital

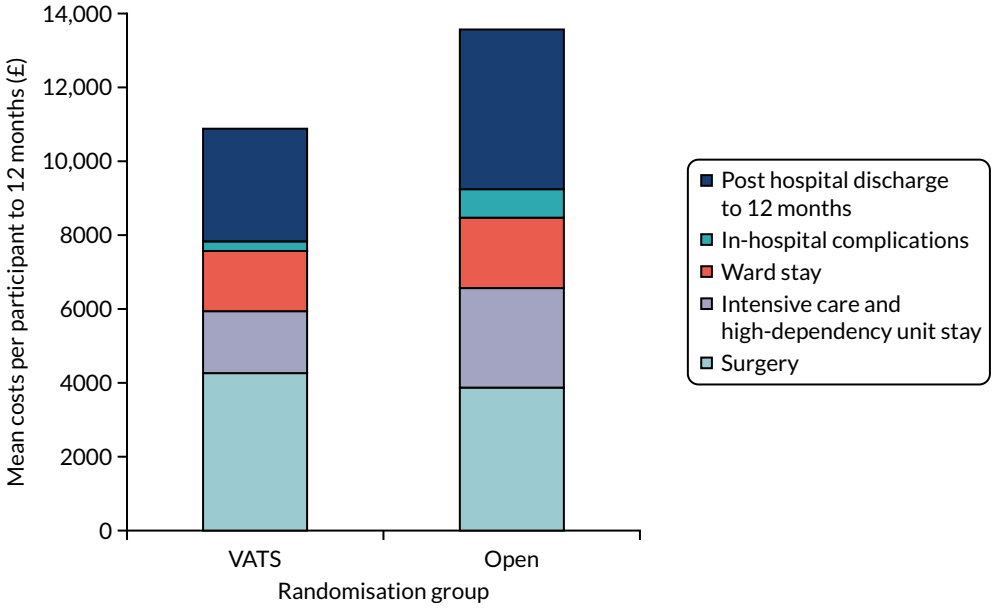

FIGURE 23 Total costs to 12 months for all participants.

discharge are also statistically significantly lower in the VATS group than in the open-surgery group, driven by smaller numbers of days readmitted to hospital and fewer hospital visits. Discharge to 5-week costs do not follow this trend because of a couple of high-cost outliers for this time point in the VATS group. Total costs to 12 months are, on average, £10,879 in the VATS group and £13,581 in the open-surgery group (MD −£2702, 95% CI −£5624 to £221).

Base-case cost-effectiveness results

Table 24 combines the cost and outcome results and presents the cost-effectiveness. The difference in costs favours the VATS group and is close to statistical significance. The difference in QALYs favours the VATS group and is statistically significant. Based on the point estimates of the cost and QALY differences and on the point estimate of the ICER (−£44,908), VATS is considered cost-effective. VATS surgery is dominant over open surgery, as it is both more effective (more QALYs) and less costly. However, it is important to consider the uncertainty around this result. *Figure 24* shows the cost-effectiveness plane, with the bootstrap replicates of the cost and QALY differences. The black dot is the point estimate of the cost and QALY difference. Virtually all the bootstrap replicates are in the south-east quadrant where costs are lower and QALYs are higher in the VATS group, indicating that we can be very certain that VATS is cost-effective.

TABLE 24 Base-case cost-effectiveness results

	Participant allocation		
Cost-effectiveness element	**Randomised to VATS (*N* = 229), mean (95% CI)[a]**	**Randomised to open surgery (*N* = 235), mean (95% CI)[a]**	**VATS vs. open surgery, MD (95% CI)[a]**
Total costs (£)	10,879 (10,021 to 11,738)	13,581 (10,793 to 16,369)	−2702 (−5632 to 228)
QALYs	0.841 (0.811 to 0.870)	0.780 (0.746 to 0.815)	0.060 (0.029 to 0.092)
ICER (£) (cost/QALY)			VATS dominant (−£44,908)

a CIs are based on 5100 bootstraps (i.e. 60 bootstraps for each of the 85 imputed data sets).
Costs are rounded to the nearest pound and QALYs are rounded to three decimal places.

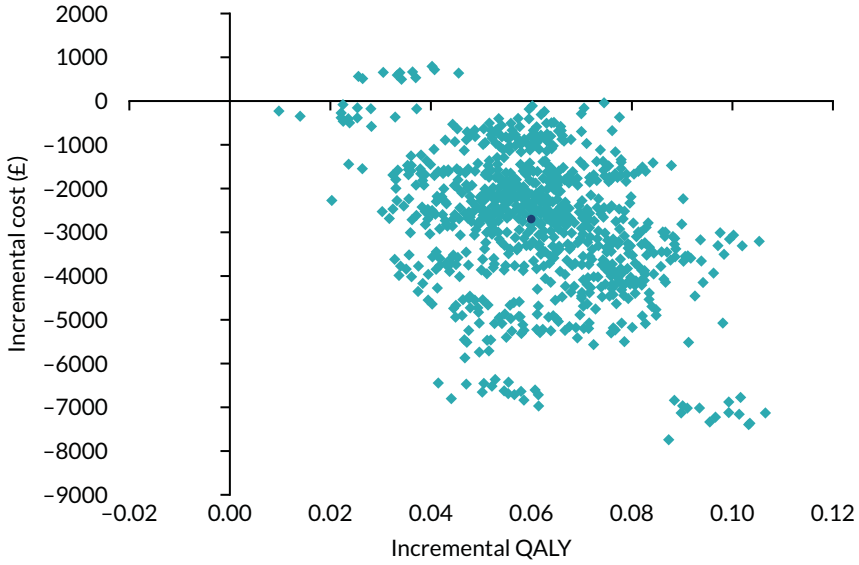

FIGURE 24 Cost-effectiveness plane. For points to be seen, a random sample of 1000 of the 5100 bootstrap replicates were plotted.

The CEAC in *Figure 25* shows the probability that VATS surgery is cost-effective for a range of willingness-to-pay thresholds. Even at a willingness-to-pay threshold of £0, the probability that VATS is cost-effective is 0.98 (equivalent to the probability that VATS is less costly than open surgery). At a willingness-to-pay threshold of £20,000 per QALY, which is generally considered as the threshold that NICE adopts for considering an intervention to be cost-effective, the probability that VATS surgery is cost-effective is 1 (0.996). Indeed, at any willingness-to-pay threshold, VATS surgery is considered cost-effective and there is negligible uncertainty around this finding.

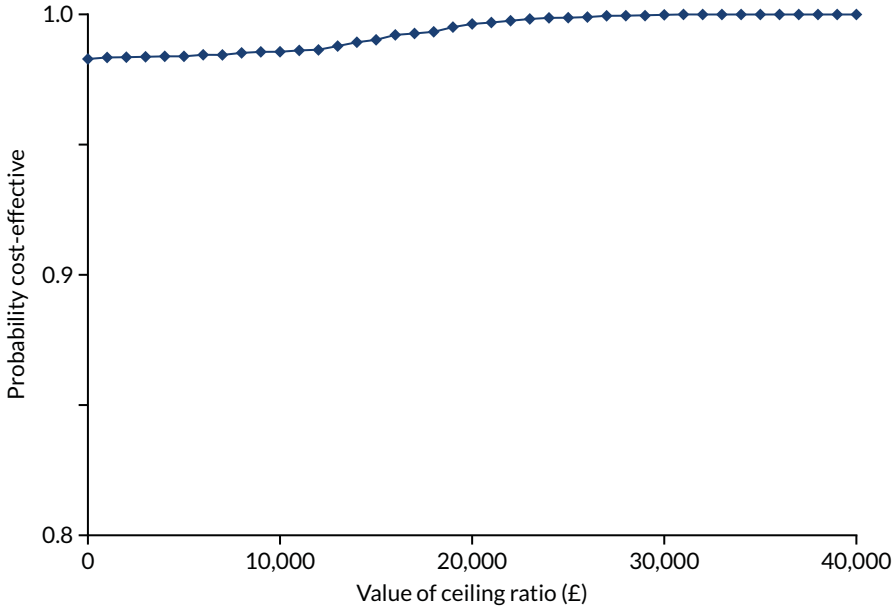

FIGURE 25 Cost-effectiveness acceptability curve.

Sensitivity analyses

The results of the sensitivity analyses conducted around costs and outcomes are provided in full in *Appendix 4*, *Tables 40–43*, and key findings are summarised here. None of the sensitivity analyses varying unit costs had a great impact on the cost difference between the groups. Several high-cost participants, who exert a significant impact on the cost results but do not alter conclusions, were identified.

Sensitivity analyses around outcomes (assuming patients with missing survival data died at 12 months, and no adjustment for baseline utility) did not impact on the differences between the groups, nor on the cost-effectiveness conclusions.

Summary

There were differences in costs and QALYs in favour of the VATS group and, when combined, the VATS group was clearly cost-effective. The mean QALYs to 12 months were 0.841 and 0.780 in the VATS and open-surgery groups, respectively, resulting in a statistically significant MD of 0.060 (95% CI 0.029 to 0.092). The total costs of care from surgery to 12 months were £10,879 in the VATS group and £13,581 in the open-surgery group, creating a MD of –£2702 (95% CI –£5632 to £228). When combined, the cost-effectiveness results clearly indicated that VATS is cost-effective across all willingness-to-pay thresholds we examined. Results were robust to all the sensitivity analyses performed.

Chapter 7 Discussion

Main findings

Trial conduct

With the support of the QRI to optimise recruitment, the trial successfully recruited to time and target. Average recruitment rates at study sites ranged from 0.5 participants randomised per month in Hull to 3.4 participants randomised per month in Bristol. The lead study site (Brompton) was the second highest recruiting site, with an average of 2.5 participants randomised per month.

Recruitment was paused in Bristol for 3 months in early 2016 (i.e. 5 January 2016 to 29 March 2016) because of issues in the postoperative recruitment pathway that were unblinding the researcher responsible for data collection, which had the potential to bias the cost-effectiveness analysis. During late 2015, it became apparent that the Bristol research team were experiencing difficulties integrating the VIOLET trial into their local practice. These difficulties stemmed from historical hospital guidelines that specified that patients undergoing thoracotomy should recover in a high-dependency unit, whereas patients undergoing VATS should go to a general ward for their recovery. Recruitment was paused while the Bristol PI and colleagues liaised with the policy-makers to encourage the hospital to adopt a more patient-focused, risk-based approach to patient management. These discussions were protracted, but, on 29 March 2016, the hospital agreed to change the guidelines and adopt a risk-based approach to patient management, allowing recruitment to restart immediately. Following this, recruitment at the Bristol site progressed well. Bristol was the highest recruiting site in the VIOLET trial, with 136 participants.

The study sites were engaged with the trial throughout and data completion rates were good. There was one change that related to the transition to TNM8[13] of the TNM staging system, which had a significant impact on study sites and the trials centre. Following approval of an amendment to the protocol to reflect this change in June 2017, the screening log and CRFs were revised to collect the clinical staging in accordance with TNM8.[13] Subsequent to this, the trials centre became aware that TMN8[13] was not mandated for clinical use until January 2018, and that at least one study site was still using TMN7,[14] which meant that there was not a clear transition from TMN7[14] to TNM8[13] in line with the change to the CRF. In addition, there was not a clear mapping from TNM7[14] to TNM8.[13] Following discussion at a study investigator meeting, it was agreed that all participants recruited before January 2018 would be restaged using TNM8[13] to ensure that we had consistent data for the full trial. A 'restaging' CRF and associated page in the study database were created to facilitate this data collection exercise.

During a regular review of the study data, it also became apparent that the CRF for collecting data on 'ward movements' (i.e. length of stay in the intensive care unit/high-dependency unit/ward) was being misinterpreted by some sites. The CRF was redesigned to maximise the accuracy of the data and sites were asked to reconfirm the data submitted for participants recruited before the change. To minimise the burden for study sites, this was carried out at the same time the participant staging was reviewed.

QRI

We applied a range of QRI methods to optimise recruitment and informed consent in the VIOLET trial, focusing on prevention of recruitment challenges and the identification and resolution of potential recruitment issues. Recruitment to the VIOLET trial commenced and progressed well, completing to target and on time. Although examples of good practice were seen (e.g. expressing uncertainty and avoiding the term 'trial' in favour of the term 'study'), the QRI also identified and addressed a number

of recruitment challenges (e.g. recruiters recommending a treatment, using imbalanced/loaded terminology to explain the two operations and explaining the study apologetically). QRI actions included upfront training, followed by trial-specific group and individual feedback sessions, tips documents and a rapid communication strategy. These actions were aimed at helping recruiters present the study to all eligible patients, balance information provision on the two operations, provide clearer explanations of randomisation and blinding, and avoid loaded terminology, treatment recommendations or assumptions regarding patients' views on the trial.

The recruitment issues reported in the VIOLET trial have been previously identified in other RCTs with QRIs.[25–27,30,33] However, the VIOLET trial recruited above target from the very beginning and throughout the recruitment period. Although it is difficult to prove cause and effect, it is plausible that the QRI training contributed towards the good start to recruitment. It is also plausible that the QRI training sustained the momentum thereafter, including when new centres joined the study, and helped recruitment pick up when it dipped towards the target line in the last year of recruitment. An observational study[58] that evaluated five QRIs showed that randomisation improved in three of the five RCTs in the post-intervention period. The two RCTs that showed no difference in recruitment after the QRI were similar to the VIOLET trial in that it had completed recruitment on target following training and support before recruitment began and then throughout the recruitment period.[58]

It is important to note, however, that the prior training and support received by recruiters did not resolve all challenges in advance of recruitment, with many being identified and addressed later with the help of the QRI, which contributed towards sustaining the recruitment momentum gained early on. The most crucial aspect of QRI evaluation is the change in recruitment practice observed qualitatively. Despite some healthy recruitment practices, there was scope for improvement, and we observed noticeable changes in how recruiters addressed patient preferences, expressed uncertainty or explained the trial following VIOLET trial-specific training.

Trial results

The results of the VIOLET trial suggest that for patients with early-stage lung cancer a VATS approach to lobectomy was associated with less pain, fewer complications and a shorter length of hospital stay, without any compromise to oncologic outcome. The benefits of a VATS approach extended beyond the in-hospital period. The primary outcome of physical function was significantly improved at the 5-week point and improved recovery was consistent for all secondary measures of quality-of-life outcomes up to 1 year. In addition, there were fewer post-discharge readmissions for care and no difference in the measures of oncologic outcome of recurrence-free and overall survival up to 1 year.

Prior to the conduct of the VIOLET trial, the benefit of VATS lobectomy was widely considered to be 'better recovery' (i.e. a readily understandable but nebulous term with multifactorial and time-dependent components). When challenged to consider one single most relevant outcome that encompasses all the potential benefits of better 'recovery' at a single most relevant time point, physical function at 5 weeks was chosen by our patient and public involvement (PPI) group and unanimously agreed by the Trial Management Committee. With this global composite measure, our results revealed a striking 13-point improvement between the observed median scores in favour of VATS at 2 weeks, which reduced to a modelled difference of approximately 5-point difference at 5 weeks. It took a further 6 months for participants in the open-surgery group to reach similar levels of physical function as the participants in the VATS group. The results shed light on the duration of functional recovery provided by a VATS approach, as a 9-point difference has been proposed to correspond to a 1-point difference in performance status.[16] On a World Health Organization performance scale, 1 unit of change would correspond to a difference from performance status 0 (i.e. 'able to carry out all normal activity without restriction') to performance status 1 (i.e. 'restricted in strenuous activity but ambulatory and able to carry out light work'). Our earliest assessment was undertaken at 2 weeks and, therefore, we may not have captured the full effects, which we now know to be most prominent within the first 2 weeks.

Pain is a near universal trade-off for surgery and one of the most important considerations for improvement. The open-surgery approach requires rib spreaders (metal retractors) to splay the ribs apart. The result is inevitable compression of the intercostal nerves and is considered the main source of pain after open lobectomy. Results from a Danish trial[9] reported a lower proportion of patients randomised to VATS with severe pain (38% vs. 63%), but the trial did not report a direct comparison of pain scores between the two groups.[9] On a linear scale, we noted similar pain scores on day 1 and less pain (by 1 point in the VAS) on day 2. The lack of difference on day 1 can be attributed to the effective local anaesthetic blocks that were administered (often taken down on days 1 or 2 to allow patients to mobilise). Having adjusted for total analgesic use, patients randomised to VATS had approximately 10% lower composite analgesic use, with an adjusted estimate of a half-point lower pain score, surmising that a VATS approach is (modestly) less painful. We analysed the different forms of local anaesthetic block (i.e. paravertebral and intercostal block), subtypes of thoracotomy (i.e. posterior and anterior), use of rib resection and number of port sites, and found no evidence of interaction with the surgical approach (similarly effective). After discharge, however, we noted that prolonged incision pain, defined as the need for analgesia after 5 weeks, was lower in the VATS group than in the open-surgery group (59.6% vs. 72.3%), suggesting better recovery with VATS when measured by the cessation for the need of analgesics (at 5 weeks). Pain scores using QLQ-C30 and QLQ-LC13 were consistent in the direction of the estimates in favour of VATS out to 1 year. In addition, we noted that patients who underwent rib resection as part of a thoracotomy experienced significantly more pain, with a 9.8-point difference out to 1 year (an observation that has not been previously described).

Another important consideration when evaluating a new procedure is a demonstration of safety (i.e. if the new procedure can be performed without increasing harm). When we observed the in-hospital AEs, we noted that the RR of harm was in fact lower with VATS (i.e. a 26% reduction in AEs with no difference in SAEs). One specific complication that was noted was that the proportion of patients experiencing intraoperative bleeding (often attributed to blood vessel injury when using a keyhole approach) was similar in the two groups (VATS group, 6.2%; open-surgery group, 3.9%). The main benefits for VATS during the in-hospital phase was a notable reduction in kidney and infective complications. There are a number of hypotheses to be offered for this, including less analgesic use, which may reduce renal complications and improve mobility for lower chest infections, and smaller incisions, resulting in fewer wound infections.

The benefits of a less painful and safer operation culminated in a shorter length of hospital stay, an additional global outcome for 'better recovery'. The results were consistent in both fitness for hospital discharge (based on discharge criteria) and actual measured time to discharge in favour of VATS by 1 day. The benefits of a better recovery persisted in the year after discharge, with benefits from global scales (e.g. QLQ-C30 and EQ-5D-5L) and individual scales (e.g. dyspnoea, fatigue, appetite loss) broadly consistent in direction in favour of VATS or no difference between the two groups. There was no single measure that was consistently, or was of a clinically important magnitude, in favour of open surgery. AEs after discharge continued in favour of VATS, with fewer readmissions (29.0% vs. 35.9%) and a 19% reduction in the number of SAEs ($p = 0.053$) up to 1 year.

Perhaps the most important contribution of the VIOLET trial is the study of oncologic outcomes, which, to date, and to the best of our knowledge, has not been comprehensively reported in any RCT. One concern for keyhole surgery has been the ability to perform a cancer operation without the surgeon's hands entering the chest through small incisions (without direct tactile feedback), using a video camera and television monitor (without direct visualisation) through fixed positions in the skin (without a full range of movement of the instruments). We assessed the quality of the lymph node harvesting both in terms of the number and position of the nodes assessed, and found no difference in between the two groups (five stations harvested and three mediastinal stations for both arms), indicating that the VATS techniques and instruments used were able to effectively access the same extent of lymph node harvesting. Lymph node upstaging is often considered to be a more discriminating assessment of quality of lymph node dissection, with the premise that a more thorough dissection would yield

more positive lymph nodes (upstaging). When we assessed lymph node upstaging, we found 6.2% in the VATS group compared with 5.2% in the open-surgery group (cN0 to pN1) and 6.2% in the VATS group compared with 4.8% in the open-surgery group (cN0/1 to pN2). In addition, there was no difference in the ability to achieve complete pathologic resection (97.7% vs. 97.8%) between the VATS and open-group groups, respectively, confirming that there was no difference in the completeness of the cancer operation. After discharge, the uptake of chemotherapy was similar in both groups, at 50.9% in the VATS group and 45.9% in the open-surgery group, indicating that the improvement in time to recovery with VATS did not translate to an important difference in uptake of adjuvant chemotherapy. After discharge to 1 year, the HR for disease-free survival and overall survival was 0.67 ($p = 0.366$) and 0.74 ($p = 0.312$), respectively, in favour of VATS, giving assurance on the longer-term oncologic safety of a VATS approach. Our trial was not powered for long-term survival and this is an important area for further research clarification, as systematic review of (mainly) non-randomised studies indicated the possibility of a VATS approach leading to better overall survival.[4] Given that the main oncologic outcomes are similar in both groups in the VIOLET trial, we hypothesise any difference in survival to be more likely associated with secondary improvement in quality of life, rather than technical oncologic surgery.

Health economic evaluation

In the economic evaluation, differences in costs and QALYs favoured the VATS group, and when combined VATS proved to be a cost-effective option for the NHS. The mean QALYs to 12 months were 0.841 and 0.780 in the VATS and open-surgery groups, respectively, resulting in a statistically significant MD of 0.060. The mean total cost from surgery to 12 months was £10,879 in the VATS group and £13,581 in the open-surgery group (i.e. a MD of −£2702, although this was not statistically significant). This cost difference is largely driven by less time in critical care in the index admission and fewer days readmitted to hospital in the VATS group. Results were robust to all the sensitivity analyses performed.

The cost-effectiveness results clearly indicate that VATS is cost-effective across any willingness-to-pay threshold. Based on the point estimates of the cost and QALY differences and on the point estimate of the ICER (−£44,908), VATS is considered cost-effective. VATS surgery is dominant over open surgery as it is both more effective and less costly. The probability that VATS is cost-effective at a willingness-to-pay threshold of £20,000 per QALY, which is generally considered as the threshold that NICE adopts for considering an intervention to be cost-effective, is 1. Indeed, at any willingness-to-pay threshold, VATS surgery is considered cost-effective, and there is negligible uncertainty around this finding so we can be confident of this result.

Our cost-effectiveness results are consistent with the Danish study,[11] in which 103 patients were randomised to VATS and 103 patients were randomised to thoracotomy, which concluded that VATS was cost-effective compared with thoracotomy following lobectomy for stage 1 lung cancer. VATS provided a larger number of QALYs and generated lower costs. Specifically, the mean cost per patient for VATS was 103,108 kr (£11,857) and the mean cost per patient for thoracotomy was 134,945 kr (£15,518), making the costs for VATS 31,837 kr (£3661) lower than thoracotomy ($p < 0.001$). In terms of HRQoL, the difference between the two surgery types for QALYs gained over 1 year of follow-up was 0.021 ($p = 0.048$). The CEAC presented clearly showed that VATS was superior to thoracotomy more or less regardless of the willingness-to-pay threshold for a QALY, just as was shown here. Results of a French study by Pagès *et al.*[12] were not available at the time that our report was written.

Patient and public involvement

The Royal Brompton Hospital Cancer Consortia PPI group was fully engaged in the initial trial design and during the set-up phase of the trial. The PPI group comprised four patients who had undergone surgery for cancer and one carer. The PPI group advised the study team on trial design and identification of the choice and timing of the primary outcome, and secondary outcomes that were considered to be important.

The PPI group was consulted between August 2012 and September 2013. One member of the PPI group remained a member of the TSC throughout the trial.

The PPI group was also consulted before the study commenced in 2014. The group was asked for its feedback on the patient documents, and it advised that the PIL should be shortened and suggested edits on how to do this. The PPI group also encouraged the use of a flow chart to show how the main study and information study by the QRI interact. All of the PPI group's feedback was incorporated into the trial documents and the group's feedback was invaluable in producing a clear and understandable PIL for patients.

We consulted Chris Hall (the TSC PPI member) for feedback on the *Plain English summary* of this report, who commented that it was presented simply, was comprehensive and clearly worded. Furthermore, Chris Hall provided further comments about his involvement in the study:

> *I felt I was an integral part of the team whose opinions were respected, and I was fully able to contribute to the study and protocol as it applied to patients. Meeting face to face with the authors and participants enabled me to understand the many problems involved. The conclusion of the study gives an opportunity no doubt for publicity and perhaps provision of a further patient information leaflet.*

We also plan to consult the PPI group for advice on the dissemination of the research and its findings to the public.

Strengths and limitations

Strengths

Trial conduct

One of the strengths of the VIOLET trial was the ability to minimise by surgeon to ensure that the same surgeon would perform approximately equal numbers of VATS and open-surgery operations. This is an important consideration to negate surgeon effect, as VATS surgeons are usually considered to be better skilled and more forward-thinking regarding postoperative patient management. The ability to successfully mask the procedure (using large dressings) to patients and researchers in the early postoperative phase allowed a more unbiased assessment of outcome. An important secondary strength of the VIOLET trial was the ability to train research-active thoracic surgeons in the communication skills required to successfully randomise patients into a clinical trial. Strong camaraderie was also instilled among the participating surgeons and trial centres. We achieved worldwide acknowledgement and accolade, earning the UK a newfound reputation regarding the ability to conduct and deliver thoracic surgery RCTs.

QRI

Qualitative research methods and its applied nature are the main strengths of the QRI. A key strength of the QRI in the format that it was applied in the VIOLET trial is that it adopted a multifaceted approach to optimising recruitment and began by aiming to prevent recruitment challenges with upfront training, followed by investigations and actions to identify and address new challenges. This holistic approach to optimising recruitment, especially the use of a preventative component, needs to be further refined and formalised in future QRIs.

Limitations

Trial participants

Although there was good coverage across England in terms of the study sites and there was a site in Scotland, the study did not recruit from Wales or Northern Ireland. At the last census, in 2011, 14% of the population of England and Wales[59] were classified as non-white (i.e. from an ethnic minority group);

however, in the VIOLET trial, < 5% of participants were from the ethnic minority community, which is a limitation. Patient information was provided in only English and it is unknown if providing the information in other languages would have increased participation and resulted in a study more reflective of the diversity of the UK population. Nevertheless, the proportion of non-white participants is reflective of people diagnosed with lung cancer in the UK.[60]

Blinding

Blinding of participants and research staff was successful in most sites. In some sites, blinding of research staff was less successful because of the limited pool of research staff available to support the study. There were insufficient numbers of available to separate the elements of the study that necessitated unblinding and data collection that was intended to be conducted by a blinded member of the team.

QRI

The QRI could not be applied to the main trial phase in the same way as in the internal pilot. Only one of the four sites in the main trial phase engaged with the QRI and received feedback. We received minimal audio-recordings from two of the sites and one site opened towards the close of recruitment. In addition, we did not conduct interviews with the new centres in the main trial phase because saturation had been achieved in the internal pilot phase and recruitment rates remained high. Given that the QRI interviews in the internal pilot phase in VIOLET had helped with the PIs and site staff engaging with the QRI, it is possible that interviews with new site staff would have been similarly beneficial.

Patient and public involvement

The PPI group's input into the VIOLET trial was effective, insofar as patient-facing documentation was greatly improved with their input; however, we had limited engagement with the PPI group during the conduct of the trial. In addition, although there were few participant withdrawals and 88% of survivors attended the 1-year follow-up, HRQoL response rates at 1 year were lower at 76%. It is possible that this response rate, although good, could have been improved with more engagement with the PPI group. Wider engagement with the PPI group may also have facilitated wider uptake of the trial among the ethnic minority community.

Missing data for the economic evaluation

There were high levels of data completeness for resource use items and EQ-5D-5L data [aside from information on staples used in surgery and two complications (i.e. pleural effusion and prolonged air leak), for which data collection began part way through the study]. Despite this, overall, 80% of participants had some missing data, which is a limitation, but does reflect the large number of variables included in analyses. For each variable with missing data that required some imputation, on average, only 13% of cases were missing.

Future research

An important outcome that needs further clarification is the effect of a VATS approach on overall survival. All existing trials do not have sufficient power to detect any meaningful difference in overall survival, and the chief investigators of the Danish,[9] Chinese[10] and French[12] (ongoing) trials have agreed, in principle, to conduct an individual patient data meta-analysis of approximately 1800 randomised participants on the completion of the French trial.[12]

Currently, there is a world-wide movement towards robotic surgery, which (in essence) is VATS surgery undertaken with robotic arms. There is a current moratorium of NHS funding for robotic surgery, considering the huge expense, lack of any high-quality evidence of clinical efficacy and documentation of harm. Despite this, many hospitals across the UK are currently offering thoracic surgery undertaken with robotic assistance and a randomised trial comparing outcomes to VATS is likely to be useful in determining future management.

Chapter 8 Conclusion

For patients with early-stage lung cancer in whom a lobectomy is proposed, the results of the VIOLET trial suggest that VATS should be the approach of choice. The clinical benefits include less pain and fewer complications, leading to better recovery when measured by shorter hospital stay, and better physical function at 5 weeks. The benefits of a VATS approach extended well into the first year, with continuing better recovery, fewer AEs and improved general quality of life. This was achieved without any compromise to important oncologic markers of complete resection, lymph node upstaging, disease-free survival and overall survival up to 1 year. VATS was found to be cost-effective and to provide excellent value for money for the NHS. Prior to this study, to the best of our knowledge, no high-quality comparative data on physical function, hospital readmissions, uptake and timing of chemotherapy, nor cancer recurrence, were available. Therefore, the VIOLET trial makes a substantial contribution to the evidence base. Although the majority of surgery for UK patients with lung cancer is performed by VATS access, this has been a result of a trend, rather than a concerted effort to increase uptake of minimal invasive lobectomy.

In the light of the clinical effectiveness and cost-effectiveness results from the VIOLET trial, we recommend that patients with lung cancer requiring lobectomy should have access to VATS and that the UK provides appropriate training for the existing and next generation of thoracic surgeons in minimal access techniques.

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Eric Lim (https://orcid.org/0000-0002-9078-3226) (Chief Investigator, Professor of Thoracic Surgery) had full access to all data in the trial and takes responsibility for the integrity of the data and the accuracy of the data analysis; conceived the trial; was involved in obtaining funding and designing the trial; managed the trial with the TMG; interpreted the data; and co-authored the first draft of report.

Rosie A Harris (https://orcid.org/0000-0002-2405-667X) (Medical Statistician) was responsible for data management and preparation of reports for the study team and independent oversight committees during the trial; wrote the SAP; analysed the data; and co-authored the first draft of the report.

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Sangeetha Paramasivan (https://orcid.org/0000-0001-7329-9574) (Research Fellow) was the QRI lead and contributed towards the study design, funding application, ethics approval, study documentation and initial study site set-up; analysed audio-recordings and provided feedback to centres/recruiters; and wrote the QRI sections of this report, informed by descriptive accounts from Alba Realpe and Daisy Elliott, and from other extensive QRI documentation maintained by Daisy Elliott, Alba Realpe and Sangeetha Paramasivan.

Alba Realpe (https://orcid.org/0000-0001-9502-3907) (Senior Research Associate) carried out the QRI in the last year of the VIOLET trial's recruitment; analysed audio-recordings; monitored SEAR data; contributed to the rapid communication strategy developed in the final year of recruitment; wrote sections of the first draft of this report; drew together previous descriptive accounts to inform this report; and contributed towards the final QRI sections.

Daisy Elliott (https://orcid.org/0000-0001-8143-9549) (Research Fellow) led and carried out the QRI (in Sangeetha Paramasivan's absence) in the initial year of the study; carried out all the interviews; analysed interviews and audio-recordings; monitored SEAR data and provided feedback to centres/recruiters; wrote an initial descriptive account of the QRI findings in the internal pilot phase; and contributed towards the final QRI sections.

Jane Blazeby (https://orcid.org/0000-0002-3354-3330) (Professor of Surgery) was involved in trial concept and design and in obtaining funding; provided expert input on the trial; interpreted the data; and critically revised this manuscript.

Chris A Rogers (https://orcid.org/0000-0002-9624-2615) (Professor of Medical Statistics and Clinical Trials, Director of Bristol Trials Centre) had full access to all data in the trial and takes responsibility for the integrity of the data and the accuracy of the data analysis; was involved in trial concept and design; obtained funding; interpreted the data; co-authored the first draft of the report; and oversaw the statistical analysis and reporting of the trial.

Publications

Peer-reviewed publications

Lim E, Batchelor T, Shackcloth M, Dunning J, McGonigle N, Brush T, *et al*. Study protocol for VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a UK multicentre randomised controlled trial with an internal pilot (the VIOLET study). *BMJ Open* 2019;**9**:e029507.

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Rogers CA, Paramasivan S, Elliott D, Whybrow P, Kanavou S, Harris RA, *et al*. *Audio-Recording Recruitment Consultations – An Exploratory Study in Two RCTs to Investigate the Impact on Randomisation Rates*. 4th International Clinical Trials Methodology Conference and the 38th Annual Meeting of the Society for Clinical Trials, Liverpool, UK, 7–10 May 2017.

Lim E, Batchelor T, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al*. PL02.06 in hospital clinical efficacy, safety and oncologic outcomes from violet: a UK multi-centre RCT of VATS versus open lobectomy for lung cancer. *J Thorac Oncol* 2019;**14**:S6.

Lim E, Begum S, Batchelor T, Krishnadas R, Shackcloth M, Dunning J. S23 optimum diagnostic pathway and pathologic confirmation rate of early stage lung cancer: results from VIOLET. *Thorax* 2019;**74**:A15.

Press release

International Association for the Study of Lung Cancer. *Video Assisted Lung Surgery Reduces Complications and Hospital Stays Compared to Open Surgery*. Press release, 9 September 2019.

Data-sharing statement

Following publication, anonymised individual patient data will be made available on request to the corresponding author for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethics requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available prespecified protocol describing the purpose, methods and analysis of the secondary research (e.g. a protocol for a Cochrane systematic review, approved by a UK Research Ethics Committee or other similar approved ethics review body). Patient identifiers will not be passed on to any third party.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe

and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Evolution of the QRI

The QRI protocol published in 2016[19] describes how its primary aim of optimising recruitment and informed consent in RCTs can be achieved through a flexible two-phased iterative study design to understand recruitment challenges (Phase I) and collaboratively develop and implement strategies to overcome the challenges (Phase II), followed by an evaluation component. Since then, and throughout the recruitment period of the VIOLET trial, the QRI has continued to evolve and adapt to the requirements of each RCT, guided by two broader advancements. First, a substantial body of empirical research from QRIs across multiple RCTs now exists on clear, hidden[27] and specific recruitment challenges[26,28,30–33] (e.g. conveying equipoise) and strategies to overcome them. Second, this evidence base led to the development of QRI-informed recruitment training workshops to address generic and trial- and site-specific recruitment issues, tailored to recruiters from different disciplines, including surgeons, across the UK,[28] and delivered at the University of Bristol [partly funded by the MRC's Hubs for Trials Methodology Research ConDuCT II hub]. These advancements have meant that the QRI team have been able to provide upfront training and guidance prior to recruitment commencing for recruiters in RCTs with integrated QRIs. This training included activities such as QRI-informed recruitment training workshops, training during trial launch events and SIVs, and recruitment tips documents circulated to sites to share good practice and to guide revisions to patient-facing documentation. In this way, the boundaries between Phase I and Phase II of the QRI are now blurred in many RCTs, including the VIOLET trial, bringing recruiter training/guidance upfront rather than delaying it until Phase II.

Appendix 2 Additional tables and figures for the economic evaluation

TABLE 25 Resource use categories and sources of unit cost information

Resource	CRF[a]	Sources of unit cost information
Initial thoracic surgery	CRFs C1, C2, C4	ISD Scotland;[61] Medtronic plc (Medtronic plc, 2020, personal communication); Johnson & Johnson (Johnson & Johnson, 2020, personal communication)
Initial stay in hospital post surgery by ward type	CRF D6	*National Schedule of Reference Costs 2018–19*[42]
Complications, including reoperations and SAEs	CRFs C3, D1–D3, E5, S0–S4	*National Schedule of Reference Costs 2018–19*;[42] eMIT[46]
Adjuvant therapy	CRFs E4	*National Schedule of Reference Costs 2018–19*[42]
Imaging	CRFs F1 and I1	*National Schedule of Reference Costs 2018–19*[42]
Recurrence/progression of cancer	CRF G1	*National Schedule of Reference Costs 2018–19*[42]
Hospital readmissions	CRFs E1 and E5	*National Schedule of Reference Costs 2018–19*[42]
Outpatient and ED attendances	CRFs E1 and E6	*National Schedule of Reference Costs 2018–19*[42]
Community health and social care contacts	CRFs E1 and E7	*Unit Costs of Health and Social Care 2019*[44]

a C1–S4 are labels used to distinguish CRFs.

TABLE 26 Number of participants with complete data by trial group

Category	Participant allocation	
	Randomised to VATS ($N = 229$), *n* (%)	Randomised to open surgery ($N = 235$), *n* (%)
Resource use		
Index admission		
Time in theatre	228 (100)	235 (100)
Staples	120 (52)	129 (55)
Pathology for biopsy/frozen section	228 (100)	235 (100)
Intensive care unit stay	227 (99)	234 (100)
High-dependency unit stay	227 (99)	234 (100)
Ward stay	227 (99)	234 (100)
In-hospital complications and SAEs (excluding pleural effusion and prolonged air leak)	229 (100)	235 (100)
Pleural effusion and prolonged air leak	131 (57)	134 (57)
Index admission total	119 (52)	123 (52)

continued

TABLE 26 Number of participants with complete data by trial group (*continued*)

Category	Participant allocation	
	Randomised to VATS (*N* = 229), *n* (%)	Randomised to open surgery (*N* = 235), *n* (%)
Primary and secondary care post-hospital discharge		
Hospital discharge to 5 weeks	222 (97)	225 (96)
5 weeks to 3 months	208 (91)	216 (92)
3–6 months	206 (90)	212 (90)
6–12 months	206 (90)	210 (89)
Post-hospital discharge total	189 (83)	195 (83)
All	91 (40)	94 (40)
Outcomes		
EQ-5D-5L		
Baseline	217 (95)	225 (96)
2 weeks	173 (76)	180 (77)
5 weeks	191 (83)	211 (90)
3 months	186 (81)	203 (86)
6 months	190 (83)	195 (83)
12 months	182 (79)	191 (81)
QALYs	109 (48)	119 (51)
All costs and QALYs	42 (18)	53 (23)

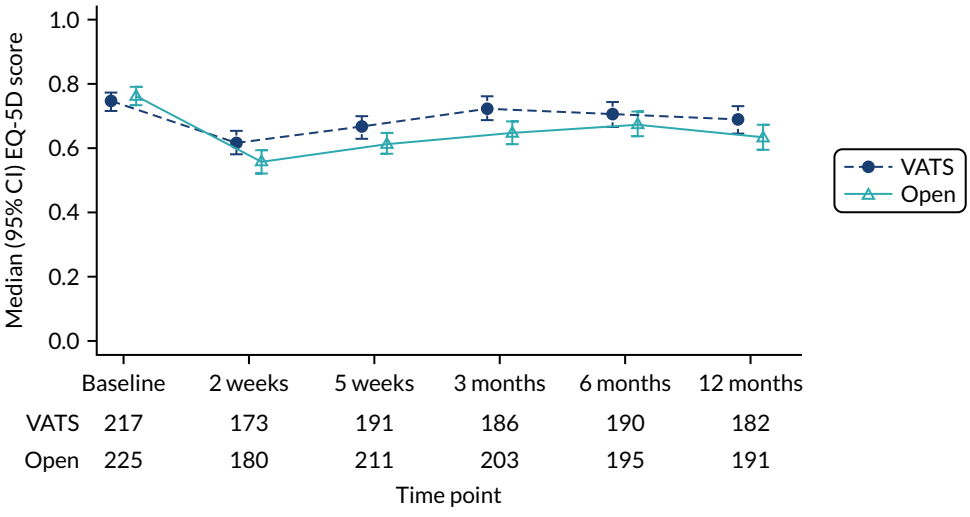

FIGURE 26 Observed mean (95% CI) EQ-5D-5L scores at each time point.

TABLE 27 Costs for all participants to 12 months

Resource	Participant allocation		VATS vs. open surgery, mean cost difference (£) (95% CI)
	Randomised to VATS ($n = 229$), mean (SE) costs (£)	Randomised to open surgery ($n = 235$), mean (SE) costs (£)	
Index admission			
Surgery			
Time in theatre	2328 (48)	2051 (47)	277 (146 to 409)
Staples	1921 (49)	1816 (47)	104 (–31 to 240)
Pathology for biopsy/frozen section	21 (2)	21 (2)	–0 (–7 to 7)
Hospital stay[a]			
Intensive care unit	764 (448)	1400 (444)	–636 (–1877 to 605)
High-dependency unit	922 (164)	1300 (166)	–379 (–838 to 81)
Ward	1614 (121)	1905 (120)	–291 (–626 to 43)
Total	3299 (546)	4605 (542)	–1305 (–2818 to 207)
In-hospital complications and SAEs	259 (272)	739 (269)	–480 (–1232 to 273)
Index admission total	7829 (771)	9232 (763)	–1403 (–3536 to 729)
Post-discharge care (primary and secondary care)			
Discharge to 5 weeks	875 (120)	740 (117)	135 (–195 to 465)
5 weeks to 3 months	595 (317)	1378 (314)	–783 (–1659 to 92)
3–6 months	601 (139)	1002 (143)	–401 (–791 to –11)
6–12 months	980 (181)	1229 (178)	–248 (–745 to 248)
Post-discharge total	3051 (443)	4349 (438)	–1298 (–2522 to –75)
Total costs	10,879 (1057)	13,581 (1046)	–2702 (–5624 to 221)

SE, standard error.
a Includes length of stay at another hospital if discharged there after surgery.

Appendix 3 Unit costs used in the economic evaluation

The majority of hospital unit cost estimates were sourced from *National Schedule of Reference Costs 2018–19*.[42] However, *National Schedule of Reference Costs 2017–18*[43] was used when it was necessary to make use of 'excess bed-day costs', as these are not available in the 2018/19 data.[42] 'Excess bed-day costs' are estimates of the daily cost for patients who stay in hospital beyond a nationally set length of stay, and were used as a proxy for the 'hotel' costs associated with admissions. Costs of additional treatments were added separately. These are the best national estimates of ward costs available in England.

For complications, reference costs include the cost of treating the complication and time on a ward. As time on a ward was collected for each patient and costed separately, 'excess bed-day costs' were used to strip out the average cost of time on a ward to provide an estimate of the cost of treating the complication only. This prevented double counting.

Note that unit costs not in 2018/19 prices have been adjusted to 2018/19 prices using the NHS Cost Inflation Index (*Tables 28–39*).[45]

TABLE 28 Unit costs associated with surgery and inpatient stays in the index admission

Resource	Unit cost (£)	Source
Surgery		
Theatre (per hour)	876	ISD Scotland[61]
Staplers per surgery	533	Average of the cost for a standard handle and vascular handle from Johnson & Johnson, and a handler from Medtronic plc; NHS Supply Chain catalogue costs provided by the companies for 2018/19
Staple	168	Average of the cost for relevant staples from Johnson & Johnson and Medtronic plc; NHS Supply Chain catalogue costs provided by the companies for 2018/19
Pathologist time per frozen section (15 minutes)[a]	27	*Unit Costs of Health and Social Care 2019*:[44] 14. Hospital-based doctors. Consultant: medical/surgical. Cost per working hour: £109
Biomedical scientist time per frozen section (70 minutes)[a]	57	*Unit Costs of Health and Social Care 2019*:[44] 12. Hospital-based scientific and professional staff. Band 6. Cost per working hour: £49
Inpatient stay		
Ward day (thoracic)	396	*National Schedule of Reference Costs 2017–18*:[43] weighted average of elective inpatient excess bed-day costs for relevant HRGs (DZ02H, DZ02J, DZ02K complex thoracic procedures, 19 years and over)
High-dependency unit day	917	*National Schedule of Reference Costs 2018–19*:[42] critical care. CCU07 thoracic surgical adult patients predominate. XC07Z adult critical care, 0 organs supported
Intensive care day	1445	*National Schedule of Reference Costs 2018–19*:[42] critical care. CCU07 thoracic surgical adult patients predominate. Weighted average of XC01Z–XC06Z, adult critical care, 1–6 organs supported
Ward day at another hospital	354	*National Schedule of Reference Costs 2017–18*:[43] weighted average of elective and non-elective inpatient excess bed-day costs across all activities

HRG, Healthcare Resource Group
a Expert opinion.
NHS Supply Chain Catalogue prices for 2018/19 were provided by Medtronic plc (Medtronic plc, 2020, personal communication) and Johnson & Johnson (Johnson & Johnson, 2020, personal communication).

TABLE 29 Resource use assumed for complications and total costs

Complication	Treatment/action	Cost (£)	Assumptions
Pulmonary complications			
Acute respiratory failure	No additional treatment	0	Captured in intensive care and ward length of stay
Pulmonary collapse (requiring intervention: CPAP)	CPAP; chest X-ray	570	
Empyema (requiring antibiotics or drainage)	Average of chest X-ray and antibiotics (piperacillin/tazobactam, 4.5 g i.v. three times per day for 5 days) and chest X-ray and chest drain	423	Return to theatre captured separately
Surgical emphysema (requiring intervention)	Chest X-ray; chest drain reinsertion	786	
Bronchopleural fistula	No additional treatment	0	Captured in return to theatre
Post-drain pneumothorax requiring intervention	Chest X-ray; chest drain	786	
Chylothorax	No additional treatment	0	Captured in return to theatre or increased length of stay
Acute respiratory distress syndrome	No additional treatment	0	Captured in intensive care unit admission
Acute lung injury	No additional treatment	0	Captured in intensive care unit admission
Pulmonary embolus	Transthoracic echocardiogram, CT chest, i.v. heparin for 5 days (initial 5000 units, then 15,000 units every 12 hours for 5 days)	210.81	
Insertion of a mini-tracheostomy tube	Mini-tracheostomy	1122	
Bronchoscopy	Bronchoscopy	540	
Pleural effusion	Chest X-ray; chest drain	786	
Prolonged air leak	Chest X-ray	31	
Cardiac complications			
Myocardial infarction	No additional treatment	0	Captured in increased length of stay
Arrhythmia (requirement treatment)	Two ECGs, amiodarone (1.2 g i.v., then oral 200 mg three times per day for 1 week, then twice per day for 1 week)	101.49	
Renal complications			
Acute kidney injury	i.v. fluids	4.59	
Haemofiltration (per day)	Haemofiltration	214	
Gastrointestinal complications			
Peptic ulcer/gastrointestinal bleed/perforation	No additional treatment	0	Reoperations captured separately
Pancreatitis	CT; parenteral nutrition for 5 days; i.v. fluids (1500 ml)	328.59	Reoperations captured separately
Other: abdominal pain	CT	108	

TABLE 29 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Other: constipation	Laxatives; enemas (bisacodyl, 5 mg; sodium citrate, assume for 5 days)	1.99	
Other: ileus/paralytic ileus	CT	108	
Other: melena/upper gastrointestinal haemorrhage	Endoscopy; omeprazole (i.v. omeprazole 40 mg for 3 days, then 40 mg oral daily for 5 days)	311.78	
Other: bowel ischaemia	CT	108	Reoperations captured separately
Other: small bowel infection	Antibiotics (cefuroxime and metronidazole for 3 days)	6.25	
Other: small bowel obstruction	CT	108	Reoperations captured separately
Infective complications			
Infection (requiring antibiotic treatment for suspected infection)	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]	28.13	
Site: pneumonia/chest infection	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray; CT	167.13	
Site: wound infection	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray	59.13	
Site: other infection – drain site infection	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray; CT	167.13	
Site: other infection – epidural site	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray; CT	167.13	
Site: other infection – pleural fluid growth group B *streptococcus*	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray; CT	167.13	
Site: other infection – *haemophilus influenza* in sputum	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray	59.13	
Site: other infection – respiratory tract infection	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; chest X-ray	59.13	
Site: other infection – sepsis (of unknown origin)	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; CT	136.13	
Site: other infection – urinary tract infection	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]; urine test	36.13	
Site: other infection – non-specific high inflammatory markers	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]	28.13	
Site: other infection – kidney	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]	28.13	

continued

TABLE 29 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Site: other infection – pancreatitis	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]	28.13	
Site: other infection – superadded infection	Antibiotics [assume piperacillin/tazobactam (4.5 g i.v. three times per day for 5 days)]	28.13	
Neurological complications			
Transient ischaemic attack	CT	108	
Stroke	Rehabilitation; CT	531	
Acute psychosis	CT	108	
Other complications			
Wound dehiscence requiring dressing		151	
Laryngeal nerve damage	Review by ear, nose and throat for vocal cord medialisation procedure after hospital discharge	107	
Deep-vein thrombosis	Duplex scan of leg veins, i.v. heparin (initial 5000 units, then 15,000 units every 12 hours for 5 days)	131.81	
Haematoma	No additional treatment	0	
Reoperation for			
Bleeding		3627	
Pleural effusion		1308	
Right VATS drainage of empyema		1571	
Sputum retention		2082	

CPAP, continuous positive airway pressure; ECG, electrocardiogram; i.v., intravenous.

TABLE 30 Unit costs of treatments/actions associated with complications (see *Table 29*)

Treatment/action	Unit cost (£)	Source
Amiodarone (1.2 g i.v., then oral 200 mg three times per day for 1 week, then twice per day for 1 week)	3.49	eMIT[46]
Antibiotics (piperacillin/tazobactam, 4.5 g i.v. three times per day for 5 days)	28.13	eMIT[46]
Antibiotics (cefuroxime and metronidazole for 3 days)	6.25	eMIT[46]
Bronchoscopy	540	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedures. Service code 340 respiratory medicine. DZ69A Diagnostic bronchoscopy, 19 years and over

TABLE 30 Unit costs of treatments/actions associated with complications (see *Table 29*) (*continued*)

Treatment/action	Unit cost (£)	Source
Chest drain	755	*National Schedule of Reference Costs 2017–18*:[43] average of the costs of two codes – 1. Non-elective long stay. DZ16N pleural effusion with single intervention, with CC score 0–5, with costs associated with the average length of stay reported subtracted at the corresponding excess bed-day cost 2. Non-elective long stay. DZ26L pneumothorax or intrathoracic injuries, with single intervention, with CC score 0–2, with costs associated with the average length of stay reported subtracted at the corresponding excess bed-day cost
Chest X-ray	31	*National Schedule of Reference Costs 2018–19*:[42] directly accessed diagnostic services. Direct access plain film
CPAP	539	Gray *et al.*[62]
CT	108	*National Schedule of Reference Costs 2018–19*:[42] Diagnostic imaging – outpatient. RD21A computerised tomography scan of one area, with post-contrast only, 19 years and over
Duplex scan of leg veins	105	*National Schedule of Reference Costs 2018–19*:[42] diagnostic imaging – outpatient. RD22Z computerised tomography scan of one area, with pre and post contrast
ECG	49	*National Schedule of Reference Costs 2018–19*:[42] directly accessed diagnostic services. EY51Z electrocardiogram monitoring or stress testing
Echocardiogram: transthoracic	76	*National Schedule of Reference Costs 2018–19*:[42] diagnostic imaging – outpatient. RD51A simple echocardiogram, 19 years and over
Endoscopy	308	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedure. FE22Z Diagnostic endoscopic upper gastrointestinal tract procedures, 19 years and over for service code 301 gastroenterology
Ear, nose and throat review	107	As outpatient cost
Haemofiltration	214	*National Schedule of Reference Costs 2018–19*:[42] renal dialysis. LE01A haemodialysis for acute kidney injury, 19 years and over
i.v. fluids (sodium chloride 0.9%, 1500 ml)	4.59	*British National Formulary*[47]
i.v. heparin (initial 5000 units, then 15,000 units every 12 hours for 5 days)	26.81	eMIT[46]
Laxatives; enemas (bisacodyl, 5 mg; sodium citrate, assume for 5 days)	1.99	eMIT[46]
Mini-tracheostomy	1122	NHS Reference *National Schedule of Reference Costs 2017–18*:[43] day case. CA63Z tracheostomy, with bed-day cost excluded by subtracting the overall elective inpatients excess bed-day cost

continued

TABLE 30 Unit costs of treatments/actions associated with complications (see *Table 29*) (*continued*)

Treatment/action	Unit cost (£)	Source
Minor treatment for wound dehiscence	151	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedures. Service code 330 dermatology. JC43C minor skin procedures, 19 years and over
Omeprazole (i.v. 40 mg for 3 days, then 40 mg oral daily for 5 days)	3.78	eMIT[46]
Parenteral nutrition (assume 5 days)	216	NICE[63]
Rehabilitation for stroke	423	*National Schedule of Reference Costs 2018–19*:[42] rehabilitation. REHABL3. Non-specialist rehabilitation services level 3. Admitted patient care. VC04Z. Rehabilitation for stroke
Reoperation for bleeding	3627	*National Schedule of Reference Costs 2017–18*:[43] non-elective long stay. DZ63A/B/C major thoracic procedures, 19 years and over, with CC score 0–6+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Reoperation for pleural effusion	1308	*National Schedule of Reference Costs 2017–18*:[43] non-elective long stay. DZ16H/J, Pleural Effusion with multiple interventions, with CC score 6–11+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Reoperation for right VATS drainage of empyema	1571	*National Schedule of Reference Costs 2017–18*:[43] non-elective long stay. DZ10H/J/K lung abscess-empyema with interventions, with CC score 0–9+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Reoperation for sputum retention	2082	*National Schedule of Reference Costs 2017–18*:[43] elective inpatients. DZ67Z major therapeutic bronchoscopy, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Urine test	8	*National Schedule of Reference Costs 2018–19*:[42] directly accessed pathology services. DAPS07 microbiology

CPAP, continuous positive airway pressure; ECG, electrocardiogram; i.v., intravenous.

TABLE 31 Costs for resource use associated with SAEs during the index admission (not previously presented)

Treatment/action	Unit cost (£)	Source
Anaphylactic reaction [500 µg adrenaline 1 : 1000 solution (0.5 ml)]	6.56	eMIT[46]
Blood transfusion (red blood cells)	128.99	NHS Blood and Transplant[64]
Cardiac arrest	574	*National Schedule of Reference Costs 2018–19*:[42] non-elective short stay. EB05C cardiac arrest with CC score 0–4
Cardioversion	696	*National Schedule of Reference Costs 2018–19*:[42] day case. EB07E. Arrhythmia or conduction disorders with CC score 0–3
Extracorporeal membrane oxygenation per day	3112	Krishnamoorthy *et al.*[65]
Fibrin patch used in theatre	93.13	HEMOPATCH® Bicarb Medium (Baxter Healthcare). 2018/19 product list prices confirmed by Baxter Healthcare (Baxter Healthcare, 2021, personal communication)
Inotropes (noradrenaline 1 mg/hour for 2 days)	18.78	eMIT[46]
Laparotomy for bleeding gastric ulcer	3590	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. FF04A/B/C/D, major oesophageal, stomach, or duodenum procedures, 19 years and over, with CC score 0–7+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Ultrasound scan	52	*National Schedule of Reference Costs 2018–19*:[42] imaging: direct access RD40Z ultrasound scan with duration of less than 20 minutes, without contrast

TABLE 32 Unit costs for reattending hospital

Resource	Unit cost (£)	Source
Ward day for readmissions	354	*National Schedule of Reference Costs 2017–18*:[43] weighted average of elective and non-elective inpatient excess bed-day costs across all activities
Intensive care day for readmissions	1436	*National Schedule of Reference Costs 2018–19*:[42] critical care. CCU07 thoracic surgical adult patients predominate. Weighted average of XC01Z–XC07Z, 0–6 organs supported
Accident and emergency attendance, leading to admission	261	*National Schedule of Reference Costs 2018–19*:[42] accident and emergency. Weighted average of all admitted codes
Accident and emergency attendance, not leading to admission	144	*National Schedule of Reference Costs 2018–19*:[42] accident and emergency. Weighted average of all non-admitted codes
Ambulance to hospital	257	*National Schedule of Reference Costs 2018–19*:[42] ambulance. ASS02 see and treat and convey

TABLE 33 Resource use assumed for prespecified readmission complications (CRF E5) and total costs (if not previously reported)

Complication	Treatment/action	Cost (£)
Atelectasis	Chest X-ray; chest physiotherapy	167
Bleeding	Chest X-ray; blood transfusion (reoperations already captured)	159.99
Sepsis	CT; antibiotics (piperacillin/tazobactam)	136.13
Infection (other)		
Cellulitis	Antibiotics (piperacillin/tazobactam)	28.13
Removal of PICC line	Antibiotics (piperacillin/tazobactam)	28.13
Bronchoscopy (reason: stent insertion)	Therapeutic bronchoscopy	887
Recurrence/progression/new cancer	Specific treatments captured and costed in hospital admissions and visits as occurred	Various
Anaemia	Blood transfusion (readmission length of stay already captured)	128.99
Neutropenia/febrile neutropenia	Antibiotics (teicloplanin and piperacillin/tazobactam)	66.12
Nausea	Antinausea medication (ondanestron)	1.01
Vomiting	Antinausea medication	1.01
Vomiting (ileus specified)	Antinausea medication; CT	109.01
Diarrhoea	i.v. fluids	4.59
Headaches	No additional treatment	0
Reoperation: left VATS mediastinal lymphadenectomy		2557

i.v., intravenous; PICC, peripherally inserted central catheter line.

TABLE 34 Unit costs associated with prespecified readmission complications and other free-text events (not previously presented)

Treatment/action	Unit cost (£)	Source
Surgery and procedures		
Right VATS segmentectomy	6060	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. DZ02H/J/K complex thoracic procedures, 19 years and over, with CC score 0–6+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Lung wedge resection/surgical lung biopsy/ left VATS mediastinal lymphadenectomy	2557	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. DZ64A/B/C intermediate thoracic procedures, 19 years and over, with CC score 0–6+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Surgery for brain metastases	7868	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. AA53A/B/C/D major intracranial procedures, 19 years and over, with CC score 0–12+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost

TABLE 34 Unit costs associated with prespecified readmission complications and other free-text events (not previously presented) (*continued*)

Treatment/action	Unit cost (£)	Source
Therapeutic bronchoscopy	887	*National Schedule of Reference Costs 2018–19*:[42] day case. DZ68Z therapeutic bronchoscopy
Haemorrhoidectomy	1375	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. FF41A/B/C, intermediate anal procedures, 19 years and over, with CC score 0–3+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Hysterectomy	3517	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. MA06A/BC major, open or laparoscopic, upper or lower genital tract procedures for malignancy, with CC score 0–4+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Ileostomy reversal	3366	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. FF22A/B/C/D major small intestine procedures, 19 years and over, with CC score 0–7+, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Laparoscopic resection with ileostomy formation	6374	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. FF31A/B/C/D complex large intestine procedures, 19 years and over, with CC score 0–9+, with costs of average length of stay reported subtracted at the corresponding excess bed-day cost
Parathyroidectomy	2796	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. KA03C/D parathyroid procedures with CC score 0–2+, with costs of average length of stay reported subtracted at the corresponding excess bed-day cost
Polypectomy	642	*National Schedule of Reference Costs 2018–19*:[42] day case. FE30Z therapeutic colonoscopy, 19 years and over
Excision of anterior abdominal wall necrosis	1068	*National Schedule of Reference Costs 2018–19*:[42] day case. JC42C intermediate skin procedures, 19 years and over
Intercostal nerve block for post thoracotomy pain	721	*National Schedule of Reference Costs 2018–19*:[42] day case. DZ71Z minor thoracic procedures
Other		
Antibiotics (teicoplanin, i.v. 400 mg twice per day first day, then 400 mg once per day for 2 days)	37.99	eMIT[46]
Antinausea medication (ondanestron, 4 mg i.v. for 5 days)	1.01	eMIT[46]
Chest physiotherapy	136	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedures. DZ30Z chest physiotherapy. 340 respiratory medicine
Colonoscopy	521	*National Schedule of Reference Costs 2018–19*:[42] day case. FE32Z diagnostic colonoscopy, 19 years and over

continued

TABLE 34 Unit costs associated with prespecified readmission complications and other free-text events (not previously presented) (*continued*)

Treatment/action	Unit cost (£)	Source
MRI	143	*National Schedule of Reference Costs 2018–19*:[42] imaging: outpatient RD01A magnetic resonance imaging scan of one area, without contrast, 19 years and over
Physiotherapy rehabilitation and ongoing care	351	*National Schedule of Reference Costs 2018–19*:[42] rehabilitation. non-specialist rehabilitation services level 3. Admitted patient care. VC40Z rehabilitation for respiratory disorders

i.v., intravenous.

TABLE 35 Costs for resource use associated with SAEs post hospital discharge (not previously presented)

Treatment/action	Unit cost (£)	Source
Surgery		
Bowel resection for diverticulitis	4316	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. FF33A/B distal colon procedures, 19 years and over, with CC score 0–3, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Traumatic hip fracture repair	1786	*National Schedule of Reference Costs 2017–18*:[43] non-elective long stay. HE11C/D hip fracture with single intervention, with CC score 0–8, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Surgery for lower leg ischaemia	4885	*National Schedule of Reference Costs 2017–18*:[43] elective inpatient. YQ12D. Single open procedure on blood vessel of lower limb with CC score 0–3, with costs of average length of stay reported, subtracted at the corresponding excess bed-day cost
Other		
Atrial fibrillation (amiodarone)	3.49	As reported in *Table 30*
Bone marrow aspirate carried out to investigate immune suppression	587	*National Schedule of Reference Costs 2018–19*:[42] day case. SA33Z diagnostic bone marrow extraction
Coronary angiogram	1005	*National Schedule of Reference Costs 2018–19*:[42] day case. EY43F standard cardiac catheterisation with CC score 0–1
Discharged home on ambulatory oxygen	463 for first month, then 73 per month	Dretzke *et al.*:[66] non-invasive ventilation
Gastroscopy	308	As reported in *Table 30* (endoscopy)
Nasogastric tube	160	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedure. FF05Z. Intermediate upper gastrointestinal tract procedures, 19 years and over for 301 gastroenterology
Psychiatric liaison nurse	70	*National Schedule of Reference Costs 2017–18*:[43] community health services. Nursing N29AF other specialist nursing, adult, face to face

TABLE 36 Unit costs for outpatient appointments

Specialty	Service code	Unit cost (£)
General surgery	100	134
Urology	101	108
Breast surgery	103	147
Colorectal surgery	104	121
Hepatobiliary and pancreatic surgery	105	209
Vascular surgery	107	145
Trauma and orthopaedics	110	120
Ear, nose and throat	120	107
Neurosurgery	150	183
Plastic surgery	160	107
Cardiac surgery	172	259
Thoracic surgery	173	206
Anaesthetics	190	141
Pain management	191	157
General medicine	300	167
Gastroenterology	301	141
Endocrinology	302	161
Clinical haematology	303	167
Hepatology	306	196
Rehabilitation service	314	156
Palliative medicine	315	176
Cardiology	320	139
Anticoagulant service	324	37
Stroke medicine	328	197
Transient ischaemic attack	329	197
Respiratory medicine	340	157
Respiratory physiology	341	120
Nephrology	361	164
Medical oncology	370	187
Neurology	400	177
Clinical neurophysiology	401	235
Rheumatology	410	147
Geriatric medicine	430	253
Gynaecology	502	141
Gynaecological oncology	503	127
Physiotherapy	650	58
Occupational therapy	651	71

continued

TABLE 36 Unit costs for outpatient appointments (*continued*)

Specialty	Service code	Unit cost (£)
Speech and language therapy	652	100
Clinical psychology	656	199
Clinical oncology (previously radiotherapy)	800	143
Interventional radiology	811	93

Costs are all sourced from *National Schedule of Reference Costs 2018–19*[42] and are all average costs for each specialty (from the 'total outpatient attendances' page, 'total activity').

TABLE 37 Unit costs for chemotherapy and radiotherapy

Resource	Unit cost (£)	Source
Chemotherapy		
First chemotherapy administration	385	*National Schedule of Reference Costs 2018–19*:[42] chemotherapy. Day case. SB14Z deliver complex chemotherapy, including prolonged infusional treatment, at first attendance
Subsequent chemotherapy administration	223	*National Schedule of Reference Costs 2018–19*:[42] chemotherapy. Outpatient. SB15Z deliver subsequent elements of a chemotherapy cycle
Chemotherapy drugs (average per visit, assuming cisplatin 145 mg on day 1 of cycle and vinorelbine 55 mg on days 1 and 8 of cycle)	21.91	eMIT[46]
Radiotherapy		
Define volume for radiation therapy	380	*National Schedule of Reference Costs 2018–19*:[42] radiotherapy. Outpatient. SC45Z preparation for simple radiotherapy with imaging and dosimetry
First radiotherapy administration	127	*National Schedule of Reference Costs 2018–19*:[42] radiotherapy. Outpatient. SC23Z deliver a fraction of complex treatment on a megavoltage machine
Subsequent radiotherapy administration	109	*National Schedule of Reference Costs 2018–19*:[42] radiotherapy. Outpatient. SC22Z deliver a fraction of treatment on a megavoltage machine

TABLE 38 Unit costs for other hospital attendances

Resource	Unit cost (£)	Source
Day case unit	752	*National Schedule of Reference Costs 2018–19*:[42] average across all day case activity
Biopsy	659	*National Schedule of Reference Costs 2018–19*:[42] day case. YD03Z Percutaneous biopsy of lesion of lung or mediastinum
Cardiac MRI	332	*National Schedule of Reference Costs 2018–19*:[42] diagnostic imaging. Weighted average of outpatient costs for RD08Z/09Z/10Z cardiac magnetic resonance imaging scan
CT biopsy	742	*National Schedule of Reference Costs 2018–19*:[42] day case. YD03Z Percutaneous biopsy of lesion of lung or mediastinum; and diagnostic imaging. RD20A computerised tomography scan of one area, without contrast, 19 years and over
Direct access blood test	4	*National Schedule of Reference Costs 2018–19*:[42] directly accessed pathology services. DAPS08 phlebotomy
Electroencephalogram monitor	204	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedure. AA33C conventional EEG, EMG or nerve conduction studies, 19 years and over for 401 clinical neurophysiology
Endobronchial ultrasound	728	*National Schedule of Reference Costs 2018–19*:[42] Day Case. DZ70Z Endobronchial Ultrasound Examination of Mediastinum
Full pulmonary function testing	164	*National Schedule of Reference Costs 2018–19*:[42] outpatient procedure. DZ52Z full pulmonary function testing for 340 respiratory medicine
PET with CT scan	549	*National Schedule of Reference Costs 2018–19*:[42] nuclear medicine. Imaging: outpatient. RN01A Positron emission tomography with computed tomography (PET-CT) of one area, 19 years and over
Vascular ultrasound scan	66	*National Schedule of Reference Costs 2018–19*:[42] diagnostic imaging. RD47Z vascular ultrasound scan

EEG, electroencephalogram; EMG, electromyography.

TABLE 39 Unit costs for post-discharge community health and social care contacts

Resource	Unit cost (£)	Source
Residential home (1 week)	620	*Unit Costs of Health and Social Care 2019*:[44] 1.2 private sector residential care for older people (age 65 + years). Mean per person weekly PSS contributions to residential care
Hospice (per day)	144	Cost per day in hospice and estimate of proportion paid for by government (one-third) sourced from Georghiou and Bardsley[67]
GP or out-of-hours GP at surgery or walk-in centre	28	*Unit Costs of Health and Social Care 2019*:[44] 10.3b, general practitioner – unit costs. Per surgery consultation contact lasting 9.22 minutes. Excluding qualification costs and direct care staff costs
GP at home	50	*Unit Costs of Health and Social Care 2019*:[44] 10.3b, general practitioner – unit costs. Assumes 9.22 minutes of patient contact and 12 minutes of travel time. Excluding qualification costs and direct care staff costs
GP by telephone	28	*Unit Costs of Health and Social Care 2019*:[44] 10.3b, general practitioner – unit costs. Assumes 9.22 minutes of patient contact. Excluding qualification costs and direct care staff costs
Nurse at GP surgery or walk-in centre	12.43	*Unit Costs of Health and Social Care 2019*:[44] 10.6, nurse (general practice). £37 per hour, excluding qualification costs. (Assumes average contact of 15.5 minutes and a ratio of direct : indirect time of 1 : 0.3, from previous edition)

continued

TABLE 39 Unit costs for post-discharge community health and social care contacts (*continued*)

Resource	Unit cost (£)	Source
Nurse at home	40	*National Schedule of Reference Costs 2018–19*:[42] community health services. N02AF district nurse, adult, face to face
Nurse by telephone	16	*National Schedule of Reference Costs 2018–19*:[42] community health services. N02AN district nurse, adult, non face to face
Health-care assistant	7.64	*Unit Costs of Health and Social Care 2017*:[68] 14. hospital-based nurses. Band 2. Cost per working hour £22. (Assume average contact of 15.5 minutes and a ratio of direct : indirect time 1 : 0.3, as nurse above)
Respiratory nurse	91	*National Schedule of Reference Costs 2018–19*:[42] community health services. Nursing N08AF specialist nursing, asthma and respiratory nursing/liaison, adult, face to face
Cardiac clinical nurse specialist by telephone	59	*National Schedule of Reference Costs 2018–19*:[42] community health services. Nursing. N11AN specialist nursing, cardiac nursing/liaison, adult, non-face to face
Clinical nurse specialist by telephone	38	*National Schedule of Reference Costs 2018–19*:[42] community health services. Nursing N29AN other specialist nursing, adult, non-face to face
Doctor at a community hospital	83	*National Schedule of Reference Costs 2018–19*:[42] non-consultant led. WF01A/B non-admitted face-to-face attendance, weighted average of first and follow-up for all service codes except those for paediatrics
Hospital doctor by telephone	66	*National Schedule of Reference Costs 2018–19*:[42] non-consultant led. WF01C/D non-admitted non-face-to-face attendance, weighted average of first and follow-up for all service codes except those for paediatrics
Dietitian	90	*National Schedule of Reference Costs 2018–19*:[42] community health services. Allied health professionals. A03 dietitian
Dietitian by telephone	48	*National Schedule of Reference Costs 2018–19*:[42] non-consultant led. 654 dietetics WF01C/D non-admitted non-face-to-face attendance, weighted average of first and follow-up
Occupational therapy	83	*National Schedule of Reference Costs 2018–19*:[42] community health services. Allied health professionals. A06A1 occupational therapist, adult, one to one
Physiotherapist	63	*National Schedule of Reference Costs 2018–19*:[42] community health services. Allied health professionals. A08A1 physiotherapist, adult, one to one
Physiotherapist: pulmonary rehabilitation class	54	*National Schedule of Reference Costs 2018–19*:[42] community health services. Allied health professionals. A08AG physiotherapist, adult, group
Physiotherapist by telephone	42	*National Schedule of Reference Costs 2018–19*:[42] non-consultant led. 650 physiotherapy WF01C/D non-admitted non-face-to-face attendance, weighted average of first and follow-up
Speech and language therapist	107	*National Schedule of Reference Costs 2018–19*:[42] community health services. Allied health professionals. A13A1 speech and language therapist, adult, one to one
Pharmacist	15	*Unit Costs of Health and Social Care 2019*:[44] 9 scientific and professional staff. Band 6. Cost per working hour: £45. Assume 20 minutes
Cognitive–behavioural therapist	96	*Unit Costs of Health and Social Care 2019*:[44] 2.1 NHS reference costs for mental health services; mental health specialist teams (per care contact); improving access to psychological therapies (IAPT), adult and elderly
Paramedic	209	*National Schedule of Reference Costs 2018–19*:[42] ambulance ASS01, see and treat or refer
Call to 111	13.77	Pope *et al.*[69]

PSS, Personal Social Services.

Appendix 4 Sensitivity analyses for the economic evaluation

Sensitivity analyses for costing were conducted to examine the impact of varying key unit costs and the impact of any high-cost participants on overall costing results. Sensitivity analyses around outcomes explored the robustness of results to the missing survival data and the impact of not adjusting for baseline EQ-5D-5L. Each of these sensitivity analyses is considered in turn.

Sensitivity analyses around unit costs

Table 40 describes the unit costs around time in theatre, staples and inpatient stay, which were varied in sensitivity analyses. Variables investigated were high-cost items used by many (or all) patients. *Table 41* reports the results. Although these resources were all key cost drivers, varying these costs by

TABLE 40 Sensitivity analyses performed around unit costs

Sensitivity analysis	Resource	Unit costs used in base-case analysis	Alternative strategy for sensitivity analysis
1	Time in theatre	£876 per hour	± 50%
2	Staples	£533 per stapler and £168 per staple	± 50%
3	Intensive care and high-dependency bed-days in index admission	£1445 for intensive care and £917 for high dependency	± 50%
4	Ward stay in index admission	£396	± 50%

TABLE 41 Results of sensitivity analyses around unit costs

	Participant allocation		
Sensitivity analysis	Randomised to VATS ($n = 229$), mean cost (£) (SE)	Randomised to open surgery ($n = 235$), mean cost (£) (SE)	VATS vs. open surgery, mean cost (£) difference (95% CI)
Base case	10,879 (1057)	13,581 (1046)	−2702 (−5624 to 221)
1: theatre			
+50%	12,043 (1059)	14,606 (1048)	−2563 (−5491 to 365)
−50%	9715 (1055)	12,556 (1044)	−2840 (−5758 to 77)
2: staples			
+50%	11,840 (1058)	14,489 (1047)	−2649 (−5576 to 278)
−50%	9919 (1056)	12,673 (1045)	−2754 (−5673 to 165)
3: critical care			
+50%	11,720 (1286)	14,931 (1273)	−3210 (−6767 to 347)
−50%	10,037 (845)	12,231 (836)	−2194 (−4530 to 141)
4: ward stay			
+50%	11,686 (1072)	14,533 (1060)	−2848 (−5811 to 116)
−50%	10,072 (1045)	12,628 (1034)	−2556 (−5446 to 334)

SE, standard error.

± 50% did not have a great impact on the cost difference between groups. The cost differences across the sensitivity analyses ranged from −£3210 to −£2194, bracketing and not substantially different from the base-case cost difference of −£2702.

Sensitivity analyses around high-cost participants

The distribution of total costs per participant is positively skewed in both surgery groups. Therefore, it is possible that a few high-cost outliers are exerting significant influence on the overall findings. Accordingly, we examined the existence of outliers and their effects. There were five participants with costs > £60,000 (VATS group, n =2; open-surgery group, n =3). Three of these participants had costs in the order of £60,000–70,000, but two open-surgery participants had costs of £113,000 and £294,000. These participants had long stays in hospital, with significant time spent in intensive care, and one participant had 3 weeks of extracorporeal membrane oxygenation. There are no grounds for excluding these participants from the analyses. Nevertheless, it is instructive to investigate the impact these participants are having on the cost results, as an imbalance across groups of these outliers could easily have arisen by chance.

Table 42 shows the effects on costs in each treatment group of excluding the two highest-cost participants and of excluding the five highest-cost participants. In both cases, the mean cost difference between groups halves and uncertainty reduces, resulting in a significant difference in costs when the five highest-cost participants are excluded. Although these participants exert a significant impact on the cost results, they do not alter conclusions.

Sensitivity analyses around outcomes

Two sensitivity analyses were conducted around outcomes. In the base-case analysis, participants missing survival status were assumed to be alive at 12 months. In a sensitivity analysis, we have assumed that these participants died at 12 months. A second sensitivity analysis compares results without adjustment for baseline utility. Results are shown in *Table 43*. Neither sensitivity analysis alters conclusions and under each scenario QALYs are statistically significantly higher in the VATS group than in the open-surgery group.

TABLE 42 Sensitivity analyses around high-cost patients

Sensitivity analysis	Participant allocation		VATS vs. open surgery, mean cost (£) difference (95% CI)
	Randomised to VATS (n = 229), mean cost (£) (SE)	Randomised to open surgery (n = 235), mean cost (£) (SE)	
Base case (all participants)	10,879 (1057)	13,581 (1046)	−2702 (−5624 to 221)
Excludes two highest-cost participants (> £100,000)	10,879 (525)	11,950 (524)	−1071 (−2530 to 388)
Excludes five highest-cost participants (> £60,000)	10,435 (445)	11,701 (445)	−1266 (−2502 to −29)

SE, standard error.

TABLE 43 Results of sensitivity analyses around outcomes

Sensitivity analysis: QALYs to 12 months	Participant allocation		VATS vs. open surgery, MD (95% CI)
	Randomised to VATS (*N* = 229), mean (SE)	Randomised to open surgery (*N* = 235), mean (SE)	
Base case	0.841 (0.017)	0.780 (0.016)	0.060 (0.025 to 0.095)
Unknown survivors died	0.827 (0.017)	0.769 (0.017)	0.057 (0.021 to 0.094)
No adjustment for baseline utility	0.695 (0.015)	0.644 (0.015)	0.051 (0.009 to 0.092)

SE, standard error.
Values are rounded to three decimal places.

Appendix 5 Additional tables and figures

TABLE 44 Reasons why screened patients were excluded

	Site								
Exclusion reason	Brompton	Liverpool	Bristol	Middlesbrough	Harefield	Oxford	Hull	Birmingham	Edinburgh
Excluded, *n*	182	311	662	85	183	121	41	21	0
Ineligible, *n*	120	219	484	62	121	68	35	1	0
Age < 16 years	0	0	0	0	0	0	0	0	0
Unable to give informed consent	2	3	8	2	4	1	1	0	0
Disease not suitable for VATS and open surgery	34	61	95	25	53	28	28	0	0
Not undergoing lobectomy/bi-lobectomy or frozen section biopsy with option to proceed to lobectomy/bi-lobectomy	45	21	117	22	73	15	2	0	0
Not known or suspected primary lung cancer beyond lobar orifice	3	100	45	16	18	7	5	0	0
Not TNM8[13] stage cT1–3, N0–1, M0	68	149	143	27	58	16	9	1	0
Planned wedge resection	19	23	72	5	34	7	11	0	0
Planned segmentectomy	15	9	64	6	10	3	1	0	0
Planned pneumonectomy	9	14	23	4	4	4	2	0	0
Planned robotic surgery	0	18	3	9	1	1	1	0	0
Previous malignancy that influences life expectancy	3	97	166	4	34	8	1	0	0
Serious concomitant disorder that would compromise patient safety during surgery	3	15	82	5	20	15	3	0	0

Exclusion reason	Site								
	Brompton	Liverpool	Bristol	Middlesbrough	Harefield	Oxford	Hull	Birmingham	Edinburgh
Not approached, *n*	13	59	36	7	14	13	3	2	0
Not sent PIL	2	45	11	3	12	3	3	1	0
Clinical reason	3	3	15	2	0	1	0	1	0
Declined surgery/wants alternative treatment	8	2	3	0	0	0	0	0	0
Logistics	0	1	4	1	1	6	0	0	0
Declined/no reason given	0	2	1	1	0	2	0	0	0
Patient preference	0	4	1	0	0	0	0	0	0
Personal reasons	0	1	1	0	1	0	0	0	0
Other	0	1	0	0	0	1	0	0	0
Did not consent, *n*	46	33	122	12	44	37	3	18	0
Patient preference	25	17	30	4	20	5	1	1	0
Declined	4	10	31	8	1	20	2	9	0
Personal reasons	1	3	31	0	3	9	0	0	0
Unwilling to be randomised/wants to know surgery	2	1	8	0	17	2	0	2	0
Logistics	3	2	5	0	3	1	0	3	0
Clinical reason	4	0	9	0	0	0	0	3	0
Wants alternative treatment	5	0	7	0	0	0	0	0	0
Surgery cancelled	2	0	1	0	0	0	0	0	0
Other reason, *n*	**3**	0	20	4	4	3	0	0	0
Patient withdrew post consent, but pre randomisation	3	0	20	4	4	3	0	0	0

TABLE 45 Anticipated recruitment at each study site

Site	Lobectomies/year		Recruitment rate/month in first 6 months[a]		Recruitment rate/month from month 7 onwards patients recruited[b]	
	2015	2016 onwards	2015	2016 onwards	2015	2016 onwards
Phase I sites						
Brompton	120	150	1.8	2.25	3	3.75
Liverpool	100	100	1.5	1.5	2.5	2.5
Bristol	50	70	0.75	1.05	1.25	1.75
Middlesbrough	70	90	1.05	1.35	1.75	2.25
Harefield	40	50	0.6	0.75	1	1.25
Phase II sites						
Birmingham		80		1.2		2
Hull		101		1.5		2.5
Oxford		67		1		1.67
Edinburgh		Not provided				

a Assumes that 60% of patients are eligible and 30% of eligible patients are recruited.
b Assumes that 60% of patients are eligible and 50% of eligible patients are recruited.

TABLE 46 Randomisations by centre

Site	Total randomised, *n*	Randomisation rate per month
Brompton	106	2.5
Liverpool	59	1.4
Bristol	136	3.4
Middlesbrough	98	2.5
Harefield	34	0.9
Oxford	25	1.5
Hull	9	0.5
Birmingham	30	1.8
Edinburgh	6	1.1

TABLE 47 Assessment of the trial performance against the progression criteria

Criterion	Target	Achieved, *n/N* (%) [95% CI]
Eligible	At least 60%	281/513 (54.8%) [50.3% to 59.2%]
Consented	50% after 6 months[a]	149/281 (53.0%) [47.0% to 59.0%]
Failure to receive allocated treatment	< 5%	3/119 (2.5%) [1.4% to 7.2%]
Lost to follow-up	< 5%	0
Confirmed benign disease	< 5%	1/115 (0.8%) [0.02% to 4.7%]

a Target 30% if eligible in the first 6 months rising to 50% thereafter.

TABLE 48 Age of non-randomised patients and trial participants

Characteristic	Non-randomised patients			
	Ineligible ($n = 1110$)	Not approached ($n = 147$)	Did not consent ($n = 315$)	Randomised ($n = 503$)
Age (years), median (IQR)[a]	70.3 (63.1–75.7)	71.6 (65.6–77.0)	69.3 (62.7–75.9)	69.9 (63.5–75.6)

a Four patients with missing data (ineligible, $n = 3$; not approached, $n = 1$).

TABLE 49 Participant characteristics and surgical details: additional information

Characteristic	Participant allocation		
	Randomised to VATS ($N = 247$)	Randomised to open surgery ($N = 255$)	Total ($N = 502$)
Participant demography			
Ethnicity, *n*/*N* (%)			
White	239/247 (96.8)	245/255 (96.1)	484/502 (96.4)
Black	2/247 (0.8)	3/255 (1.2)	5/502 (1.0)
Mixed	1/247 (0.4)	1/255 (0.4)	2/502 (0.4)
Asian	4/247 (1.6)	3/255 (1.2)	7/502 (1.4)
Other	1/247 (0.4)	3/255 (1.2)	4/502 (0.8)
BMI (kg/m^2), mean (SD)	27 (5.1)	27 (4.8)	27 (5.0)
Smoking status (ever smoked), *n*/*N* (%)	212/247 (85.8)	226/255 (88.6)	438/502 (87.3)
Comorbidities*, n/N *(%)			
Respiratory[a]	87/247 (35.2)	88/255 (34.5)	175/502 (34.9)
Neurological dysfunction[b]	9/247 (3.6)	9/255 (3.5)	18/502 (3.6)
Diabetes mellitus	29/247 (11.7)	32/255 (12.5)	61/502 (12.2)
Alcoholism[c]	19/247 (7.7)	15/255 (5.9)	34/502 (6.8)
Previous lung surgery	4/247 (1.6)	5/255 (2.0)	9/502 (1.8)
CVA and/or TIA	24/247 (9.7)	21/255 (8.2)	45/502 (9.0)
Cardiovascular[d]	109/247 (44.1)	124/255 (48.6)	233/502 (46.4)
Chronic pain syndrome[e]	31/247 (12.6)	28/255 (11.0)	59/502 (11.8)
Deep-vein thrombosis	11/247 (4.5)	9/255 (3.5)	20/502 (4.0)
Previously treated malignancy	26/247 (10.5)	35/255 (13.7)	61/502 (12.2)
Surgical details			
First operator classification, *n*/*N* (%)[f]			
Consultant surgeon	194/220 (88.2)	177/224 (79.0)	371/444 (83.6)
Trainee surgeon	26/220 (11.8)	47/224 (21.0)	73/444 (16.4)
Resection extent, *n*/*N* (%)			
Lobectomy	216/247 (87.4)	225/255 (88.2)	441/502 (87.8)
Lobectomy and wedge resection	3/247 (1.2)	7/255 (2.7)	10/502 (2.0)
Lobectomy and resection of airway	1/247 (0.4)	0/255 (0.0)	1/502 (0.2)
Segmentectomy	1/247 (0.4)	2/255 (0.8)	3/502 (0.6)

continued

TABLE 49 Participant characteristics and surgical details: additional information (*continued*)

Characteristic	Participant allocation		Total (*N* = 502)
	Randomised to VATS (*N* = 247)	Randomised to open surgery (*N* = 255)	
Pneumonectomy	2/247 (0.8)	0/255 (0.0)	2/502 (0.4)
Wedge resection	8/247 (3.2)	3/255 (1.2)	11/502 (2.2)
Open and close (inoperable/extensive malignancy)	0/247 (0.0)	2/255 (0.8)	2/502 (0.4)
Lobectomy			
Location of resection, *n*/*N* (%)			
Right-upper lobe	76/221 (34.4)	90/232 (38.8)	166/453 (36.6)
Right-middle lobe	14/221 (6.3)	9/232 (3.9)	23/453 (5.1)
Right-lower lobe	39/221 (17.6)	40/232 (17.2)	79/453 (17.4)
Left-upper lobe	54/221 (24.4)	52/232 (22.4)	106/453 (23.4)
Left-lower lobe	34/221 (15.4)	39/232 (16.8)	73/453 (16.1)
Right-upper and right-middle lobe	1/221 (0.5)	0/232 (0.0)	1/453 (0.2)
Right-middle and right-lower lobe	3/221 (1.4)	2/232 (0.9)	5/453 (1.1)
Muscle-sparing approach used, *n*/*N* (%)	6/15 (40.0)	124/229 (54.1)	130/244 (53.3)
Serratus sparing[b]	4/4 (100.0)	56/81 (69.1)	60/85 (70.6)
Latissimus sparing[b]	0/4 (0.0)	34/81 (42.0)	34/85 (40.0)

CVA, cerebrovascular accident; TIA, transient ischaemic attack.
a Any history of treated chronic obstructive pulmonary disease, asthma, interstitial lung disease or bronchiectasis.
b Any history of persistent disease of the central or peripheral nervous system diagnosed by a medical practitioner.
c As defined by the daily consumption of > 10 units for men and > 5 units for women.
d Any history of treated angina, myocardial infarction, heart failure, heart valve disease, hypertension, pulmonary embolism or peripheral vascular disease.
e As defined by chronic pain experienced > 6 months after the onset of the initial acute injury or illness.

TABLE 50 QLQ-C30 physical functioning over time

Time point	QLQ-C30 physical functioning score, median IQR	
	Randomised to VATS (*n* = 247)	Randomised to open surgery (*n* = 255)
Baseline[a]	87 (73.3–100.0)	87 (73.3–100.0)
2 weeks[b]	73 (53.3–80.0)	60 (40.0–78.9)
5 weeks[c]	73 (60.0–86.7)	67 (53.3–86.7)
3 months[d]	80 (60.0–93.3)	73 (60.0–86.7)
6 months[e]	82 (63.3–93.3)	80 (60.0–86.7)
12 months[f]	82 (66.7–93.3)	80 (60.0–86.7)

a Missing data: 24 patients (VATS, *n* = 12; open surgery, *n* = 12).
b Missing data: 129 patients (VATS, *n* = 65; open surgery, *n* = 64).
c Missing data: 58 patients (VATS, *n* = 21; open surgery, *n* = 37).
d Missing data: 72 patients (VATS, *n* = 33; open surgery, *n* = 39).
e Missing data: 66 patients (VATS, *n* = 31; open surgery, *n* = 35).
f Missing data: 83 patients (VATS, *n* = 39; open surgery, *n* = 44).

Notes
Higher scores indicate higher levels of functioning.
Missing data imputed using 50 imputed data sets.

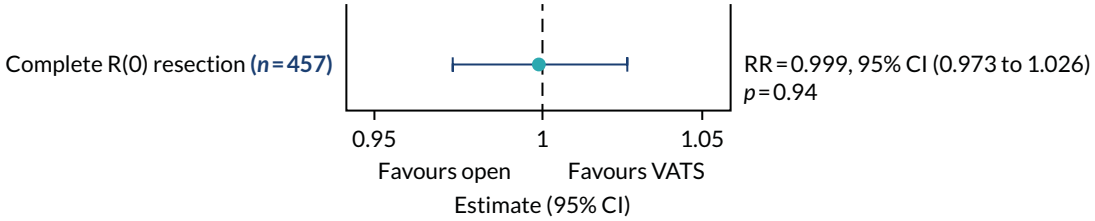

FIGURE 27 Relative risk for complete R(0) resection.

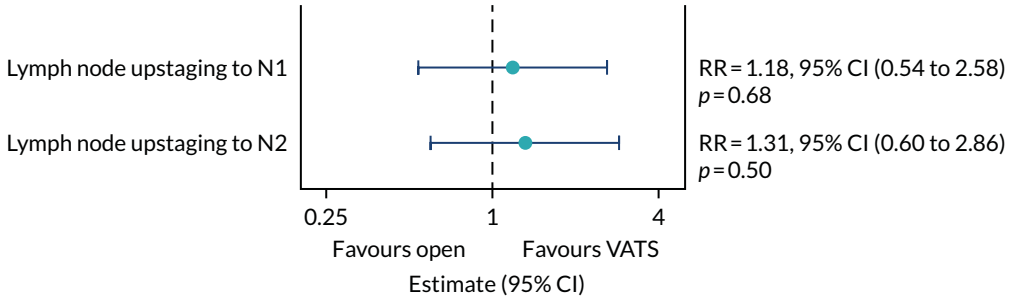

FIGURE 28 Relative risks for upstaging to N1 and upstaging to N2.

TABLE 51 Pain scores

Outcome	Participant allocation		MD (95% CI)	*p*-value
	Randomised to VATS (*n* = 247)	Randomised to open surgery (*n* = 255)		
VAS pain score, median (IQR)				
Baseline[a]	0 (0.0–1.0)	0 (0.0–1.0)		
Day 1[b]	4 (2.0–5.0)	4 (2.0–5.0)	−0.024 (−0.463 to 0.414)	0.913
Day 2[c]	3 (1.0–5.0)	4 (2.0–5.0)	−0.539 (−0.986 to −0.092)	0.018
Test for treatment-by-time interaction				0.044

a Missing data: 19 patients (VATS, *n* = 10; open surgery, *n* = 9).
b Missing data: 20 patients (VATS, *n* = 11; open surgery, *n* = 9).
c Missing data: 45 patients (VATS, *n* = 22; open surgery, *n* = 23).

Note
Missing data imputed using 100 imputed data sets.
Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

TABLE 52 Pain scores: complete-case sensitivity analysis

Outcome	Participant allocation		MD (95% CI)	*p*-value
	Randomised to VATS (*n* = 218)	Randomised to open surgery (*n* = 221)		
VAS pain score, median (IQR)				
Baseline[a]	0 (0.0–1.0)	0 (0.0–1.0)		
Day 1[b]	4 (2.0–5.0)	4 (2.0–5.0)	−0.12 (−0.56 to 0.32)	0.591
Day 2[c]	3 (1.0–5.0)	4 (2.0–5.0)	−0.55 (−1.01 to −0.10)	0.017
Test for treatment-by-time interaction				0.086

a Missing data: 19 patients (VATS, *n* = 10; open surgery, *n* = 9).
b Missing data: 20 patients (VATS, *n* = 11; open surgery, *n* = 9).
c Missing data: 45 patients (VATS, *n* = 22; open surgery, *n* = 23).

Note
Analyses are adjusted for operating surgeon and centre.

TABLE 53 Additional analgesics prescribed

Analgesia	Participant allocation	
	Randomised to VATS (*N* = 247), *n*/*N* (%)	Randomised to open surgery (*N* = 254), *n*/*N* (%)
Epidural	2/247 (0.8)	6/254 (2.4)
Diclofenac	6/247 (2.4)	11/254 (4.3)
Alfentanil	4/247 (1.6)	6/254 (2.4)
Clonidine[a]	12/247 (4.9)	16/254 (6.3)
Ketamine	2/247 (0.8)	6/254 (2.4)
Parecoxib	6/247 (2.4)	12/254 (4.7)
Magnesium	9/247 (3.6)	13/254 (5.1)

a Not included in *Figure 8* because of high variation in dose, leading to unreliable mean ratios.

TABLE 54 Exploratory analysis comparing pain scores in first 2 days post surgery by number of port sites

Outcome	MD (95% CI)	*p*-value
Single-port VATS vs multiport VATS	−0.25 (−1.07 to 0.56)	0.524
Single-port VATS vs. open surgery	−0.71 (−1.94 to 0.51)	
Multiport VATS vs. open surgery	−0.46 (−1.50 to 0.58)	

Multiple imputation (50 imputed data sets) used to account for missing data.

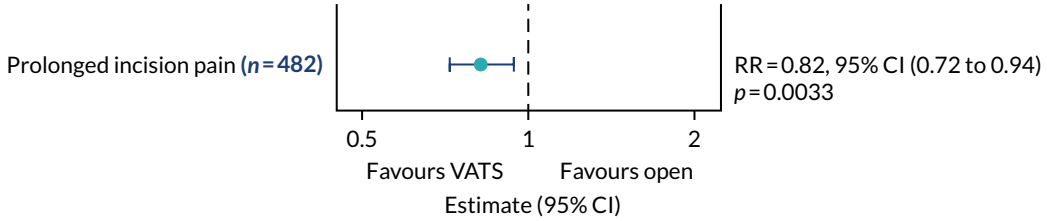

FIGURE 29 Relative risk for prolonged incision pain.

TABLE 55 Time from surgery to hospital discharge

Outcome	Participant allocation		HR (95% CI)	*p*-value
	Randomised to VATS (*n* = 247)	Randomised to open surgery (*n* = 255)		
Time to discharge (days), median (IQR)	4 (3–7)	5 (3–8)	1.34 (1.09 to 1.65)	0.0059

Analyses are adjusted for operating surgeon and centre.
Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

TABLE 56 Exploratory analysis comparing length of stay by number of port sites

Outcome	HR (95% CI)	*p*-value
Single-port VATS vs. multiport VATS	0.91 (0.56 to 1.49)	0.017
Single-port VATS vs. open surgery	2.00 (1.02 to 3.91)	
Multiport VATS vs. open surgery	2.19 (1.25 to 3.85)	

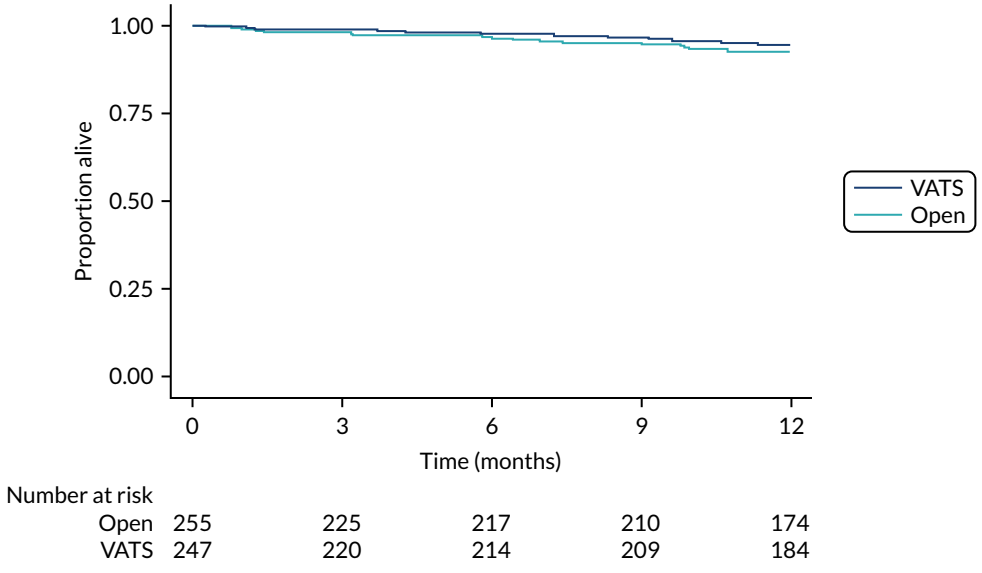

FIGURE 30 Overall survival.

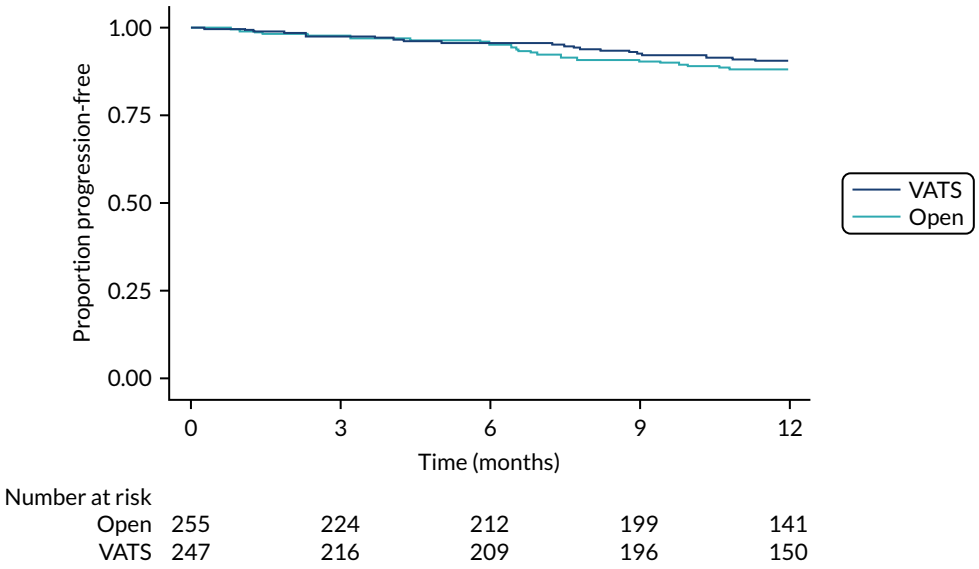

FIGURE 31 Progression-free survival.

TABLE 57 Uptake of adjuvant treatment

Outcome	Participant allocation		HR (95% CI)	*p*-value
	Randomised to VATS (*N* = 247)	Randomised to open surgery (*N* = 255)		
Received adjuvant treatment, *n*/*N* (%)	34/216 (15.7)	39/216 (18.1)		
Received adjuvant treatment (eligible subset[a]), *n*/*N* (%)	28/55 (50.9)	28/61 (45.9)		
Time to uptake of adjuvant treatment (months)			0.90 (0.50 to 1.61)	0.716
Time to uptake of adjuvant treatment (eligible subset[a]) (months)	11.0 (2.1, –)	– (2.0, –)	1.12 (0.62 to 2.02)	0.716

a Eligible if (1) N1–2 disease and M0 disease after surgery or (2) T2b to 4, N0 and M0 after surgery.

Note
Analyses are adjusted for operating surgeon.

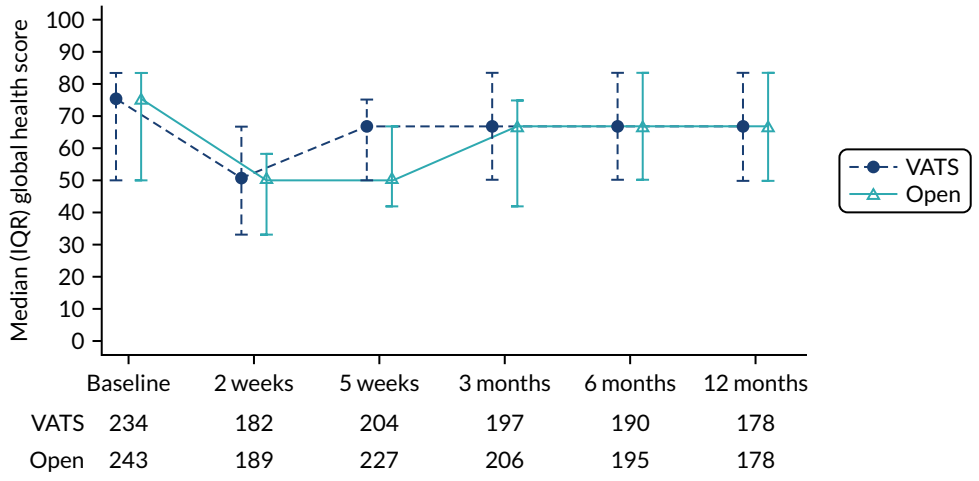

FIGURE 32 QLQ-C30 global health status over time. Higher scores indicate better health.

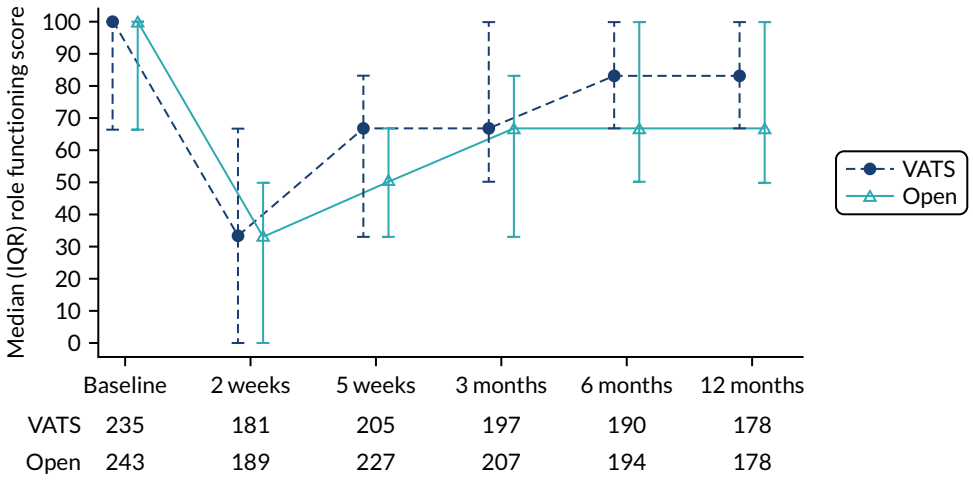

FIGURE 33 QLQ-C30 role functioning over time. Higher scores indicate better health.

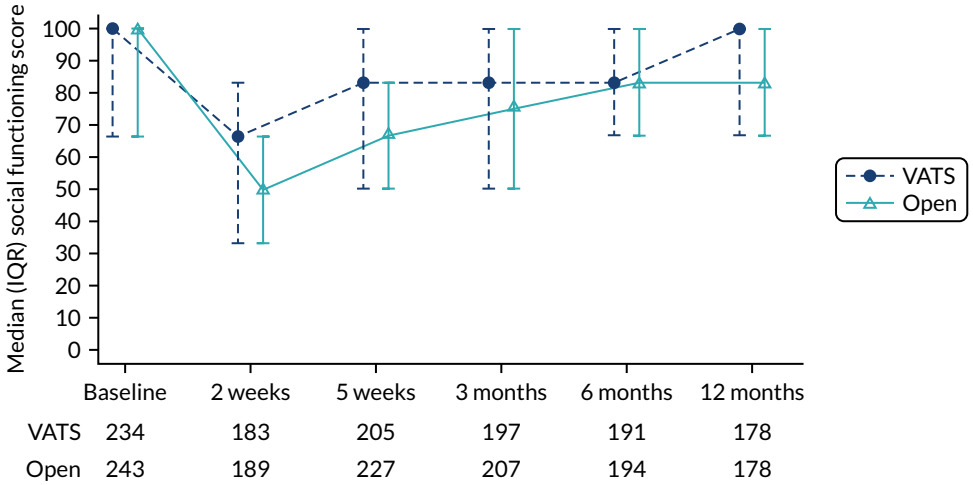

FIGURE 34 QLQ-C30 social functioning over time. Higher scores indicate better health.

TABLE 58 QLQ-C30 global health status, role and social functioning scale scores

Outcome	Participant allocation: Randomised to VATS ($n = 247$), median (IQR)	Participant allocation: Randomised to open surgery ($n = 255$), median (IQR)	MD (95% CI)	*p*-value
Global health status/quality of life				
Time point				
Baseline[a]	75.0 (50.0–83.3)	75.0 (50.0–83.3)		
2 weeks[b]	50.0 (33.3–66.7)	50.0 (33.3–58.3)		
5 weeks[c]	66.7 (50.0–75.0)	50.0 (41.7–66.7)		
3 months[d]	66.7 (50.0–83.3)	66.7 (41.7–75.0)		
6 months[e]	66.7 (50.0–83.3)	66.7 (50.0–83.3)		
12 months[f]	66.7 (50.0–83.3)	66.7 (50.0–83.3)		

continued

TABLE 58 QLQ-C30 global health status, role and social functioning scale scores (*continued*)

Outcome	Participant allocation: Randomised to VATS (*n* = 247), median (IQR)	Participant allocation: Randomised to open surgery (*n* = 255), median (IQR)	MD (95% CI)	*p*-value
Test for time-by-treatment interaction				0.29
Overall treatment effect			4.21 (1.62 to 6.79)	0.0088[g]
Role functioning				
Time point				
Baseline[h]	100.0 (66.7–100.0)	100.0 (66.7–100.0)		
2 weeks[i]	33.3 (0.0–66.7)	33.3 (0.0–50.0)		
5 weeks[j]	66.7 (33.3–83.3)	50.0 (33.3–66.7)		
3 months[k]	66.7 (50.0–100.0)	66.7 (33.3–83.3)		
6 months[l]	83.3 (66.7–100.0)	66.7 (50.0–100.0)		
12 months[f]	83.3 (66.7–100.0)	66.7 (50.0–100.0)		
Test for time-by-treatment interaction				0.18
Overall treatment effect			7.14 (3.54 to 10.74)	0.0019[g]
Social functioning				
Time point				
Baseline[a]	100.0 (66.7–100.0)	100.0 (66.7–100.0)		
2 weeks[m]	66.7 (33.3–83.3)	50.0 (33.3–66.7)		
5 weeks[j]	83.3 (50.0–100.0)	66.7 (50.0–83.3)		
3 months[k]	83.3 (66.7–100.0)	75.0 (50.0–100.0)		
6 months[n]	83.3 (66.7–100.0)	83.3 (66.7–100.0)		
12 months[f]	100.0 (66.7–100.0)	83.3 (66.7–100.0)		
Test for time-by-treatment interaction				0.32
Overall treatment effect			6.28 (2.73 to 9.83)	0.0049[g]

a Missing data: 25 patients (VATS, *n* = 13; open surgery, *n* = 12).
b Missing data: 128 patients (VATS, *n* = 63; open surgery, *n* = 65).
c Missing data: 59 patients (VATS, *n* = 38; open surgery, *n* = 21).
d Missing data: 72 patients (VATS, *n* = 39; open surgery, *n* = 33).
e Missing data: 66 patients (VATS, *n* = 35; open surgery, *n* = 31).
f Missing data: 82 patients (VATS, *n* = 43; open surgery, *n* = 39).
g *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]
h Missing data: 24 patients (VATS, *n* = 12; open surgery, *n* = 12).
i Missing data: 129 patients (VATS, *n* = 64; open surgery, *n* = 65).
j iMissing data: 58 patients (VATS, *n* = 37; open surgery, *n* = 21).
k Missing data: 71 patients (VATS, *n* = 39; open surgery, *n* = 32).
l Missing data: 67 patients (VATS, *n* = 35; open surgery, *n* = 32).
m Missing data: 127 patients (VATS, *n* = 62; open surgery, *n* = 65).
n Missing data: 66 patients (VATS, *n* = 34; open surgery, *n* = 32).

Notes
Higher scores represent higher levels of functioning.
Missing data imputed using 50 imputed data sets.

TABLE 59 QLQ-C30 cognitive and emotional functioning scale scores

Outcome	Participant allocation		Occurrence model		Intensity model		Test for time-by-treatment interaction[d]
	Randomised to VATS ($n = 247$), median (IQR)	Randomised to open surgery ($n = 255$), median (IQR)	OR[a] (95% CI)	p-value[b]	GMR[c] (95% CI)	p-value[b]	
Emotional functioning							
Time point							
Baseline[e]	75.0 (58.3–91.7)	83.3 (66.7–91.7)					
2 weeks[f]	83.3 (58.3–100.0)	75.0 (50.0–91.7)	0.51 (0.31 to 0.85)	0.023	0.93 (0.81 to 1.07)	0.441	
5 weeks[g]	83.3 (58.3–100.0)	83.3 (58.3–100.0)	0.76 (0.49 to 1.19)	0.343	1.05 (0.90 to 1.22)	0.618	
3 months[h]	83.3 (66.7–100.0)	83.3 (66.7–100.0)	0.67 (0.42 to 1.07)	0.185	0.98 (0.84 to 1.15)	0.804	
6 months[i]	83.3 (66.7–100.0)	83.3 (66.7–100.0)	0.91 (0.56 to 1.47)	0.736	0.96 (0.82 to 1.13)	0.706	
12 months[j]	83.3 (66.7–100.0)	83.3 (66.7–100.0)	1.48 (0.91 to 2.42)	0.208	0.88 (0.75 to 1.05)	0.246	0.016

continued

TABLE 59 QLQ-C30 cognitive and emotional functioning scale scores (*continued*)

Outcome	Participant allocation		Occurrence model		Intensity model		Test for time-by-treatment interaction[d]
	Randomised to VATS ($n = 247$), median (IQR)	Randomised to open surgery ($n = 255$), median (IQR)	OR[a] (95% CI)	*p*-value[b]	GMR[c] (95% CI)	*p*-value[b]	
Cognitive functioning							
Time point							
Baseline[e]	100.0 (83.3–100.0)	100.0 (83.3–100.0)					
2 weeks[f]	83.3 (66.7–100.0)	66.7 (50.0–100.0)					
5 weeks[g]	83.3 (66.7–100.0)	83.3 (66.7–100.0)					
3 months[h]	100.0 (83.3–100.0)	83.3 (66.7–100.0)					
6 months[i]	83.3 (66.7–100.0)	83.3 (66.7–100.0)					
12 months[j]	83.3 (66.7–100.0)	83.3 (83.3–100.0)					
Overall treatment effect			0.87 (0.65 to 1.17)	0.452	0.91 (0.84 to 0.99)	0.047	0.352

GMR, geometric mean ratio.
a Outcome is less than perfect functioning vs. perfect functioning.
b *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]
c Outcome is 100 – (score) and conditional on non-perfect functioning score.
d From occurrence model. Higher scores represent higher levels of functioning.
e Missing data: 25 patients (VATS, $n = 13$; open surgery, $n = 12$).
f Missing data: 127 patients (VATS, $n = 62$; open surgery, $n = 65$).
g Missing data: 58 patients (VATS, $n = 37$; open surgery, $n = 21$).
h Missing data: 71 patients (VATS, $n = 39$; open surgery, $n = 32$).
i Missing data: 66 patients (VATS, $n = 34$; open surgery, $n = 32$).
j Missing data: 82 patients (VATS, $n = 43$; open surgery, $n = 39$).

Note
Missing data imputed using 50 imputed data sets.

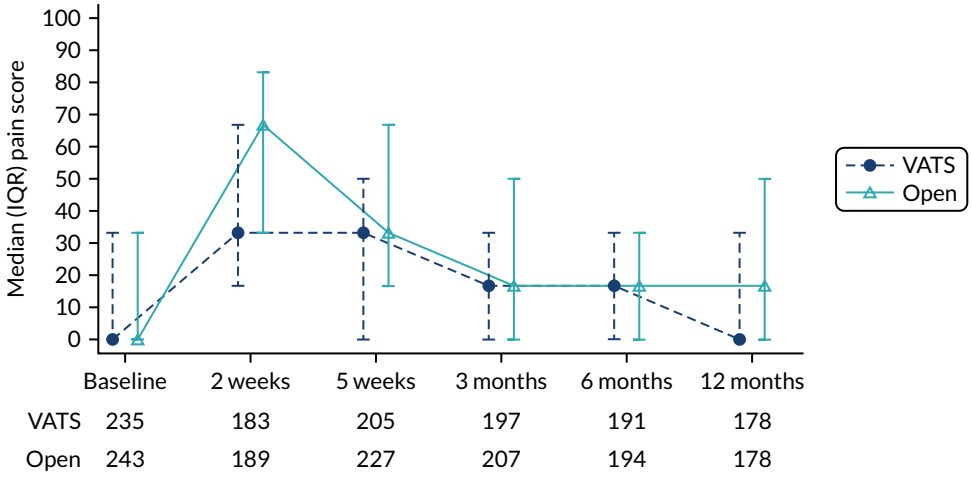

FIGURE 35 QLQ-C30 pain scores over time. Higher scores indicate more symptoms.

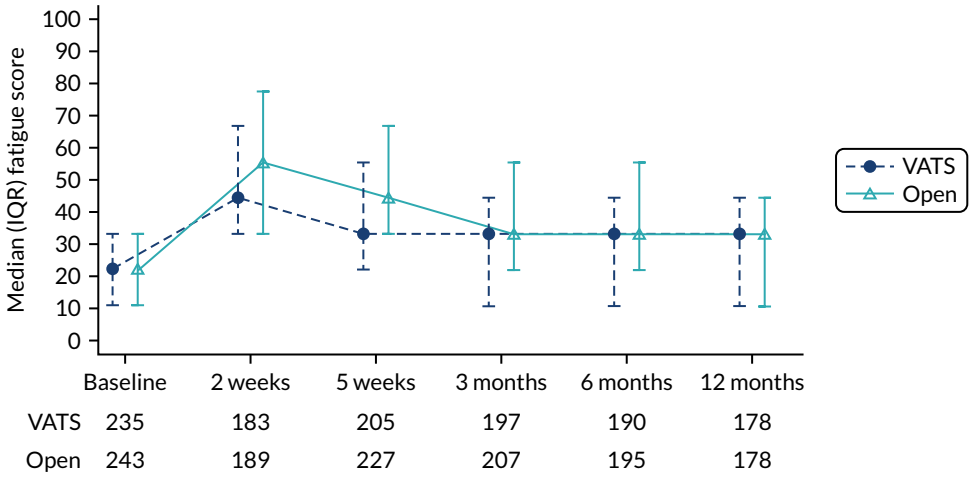

FIGURE 36 QLQ-C30 fatigue scores over time. Higher scores indicate more symptoms.

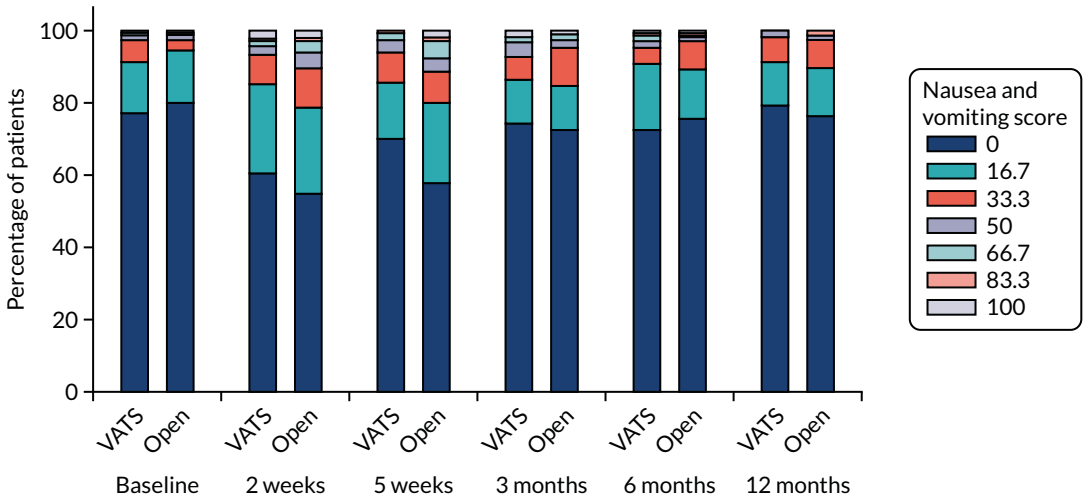

FIGURE 37 QLQ-C30 nausea symptoms over time. Higher scores indicate more symptoms.

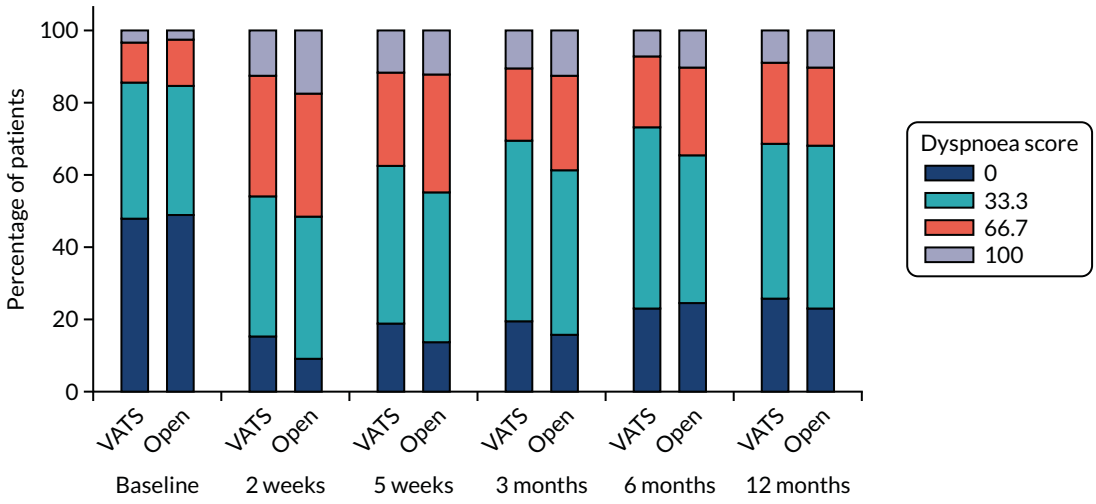

FIGURE 38 QLQ-C30 dyspnoea symptoms over time. Higher scores indicate more symptoms.

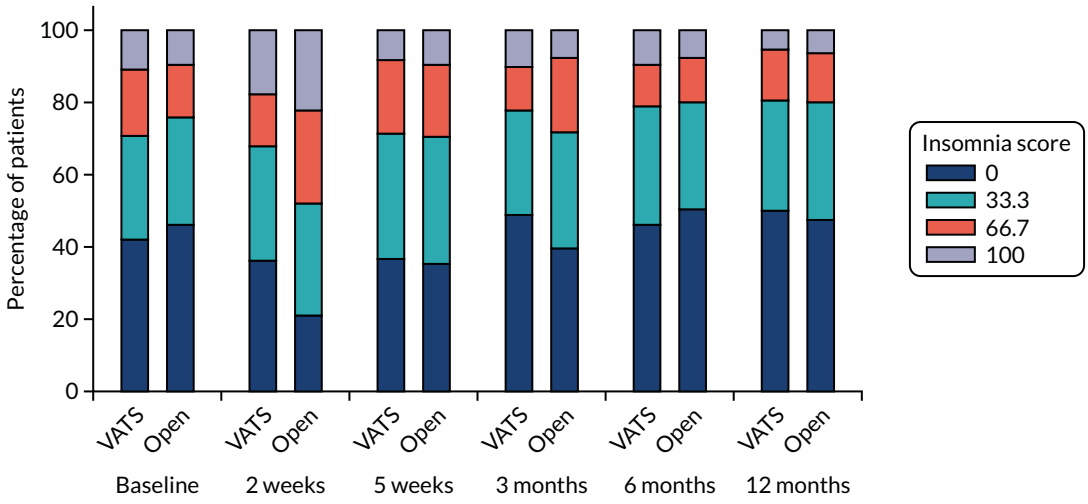

FIGURE 39 QLQ-C30 insomnia symptoms over time. Higher scores indicate more symptoms.

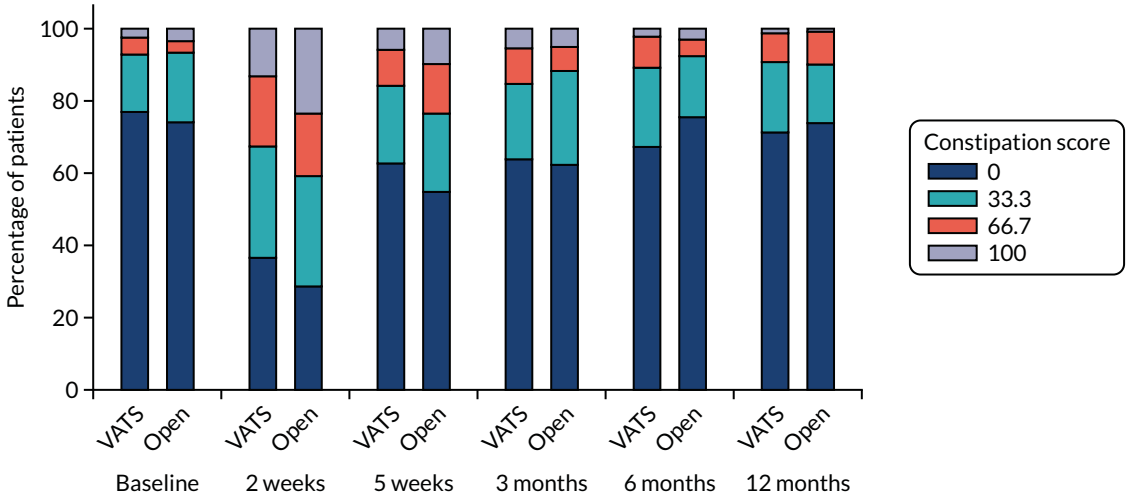

FIGURE 40 QLQ-C30 constipation symptoms over time. Higher scores indicate more symptoms.

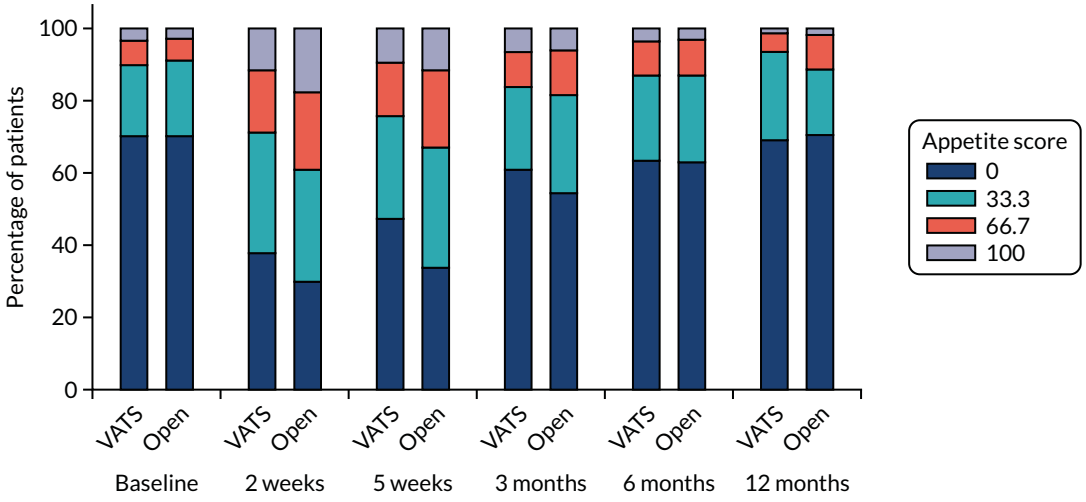

FIGURE 41 QLQ-C30 loss of appetite symptoms over time. Higher scores indicate more symptoms.

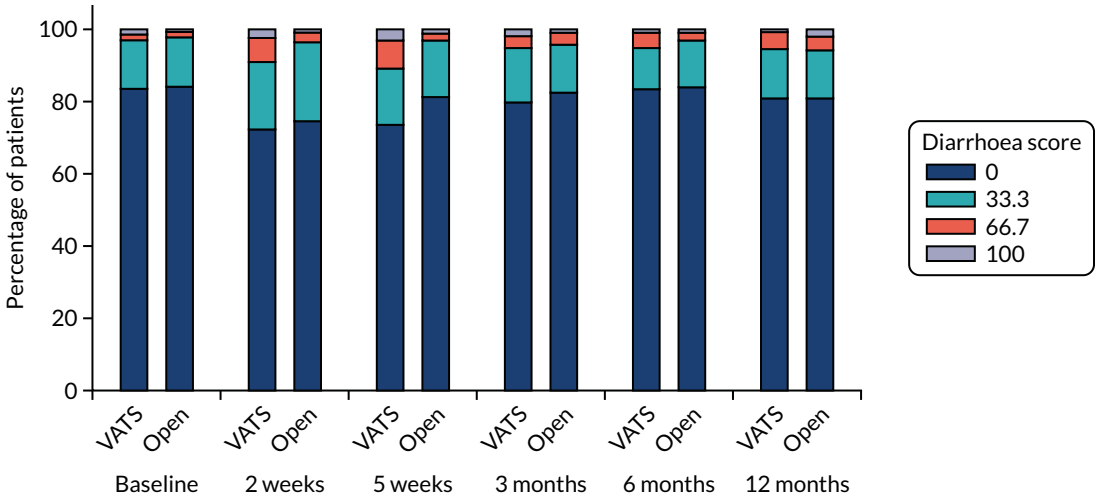

FIGURE 42 QLQ-C30 diarrhoea symptoms over time. Higher scores indicate more symptoms.

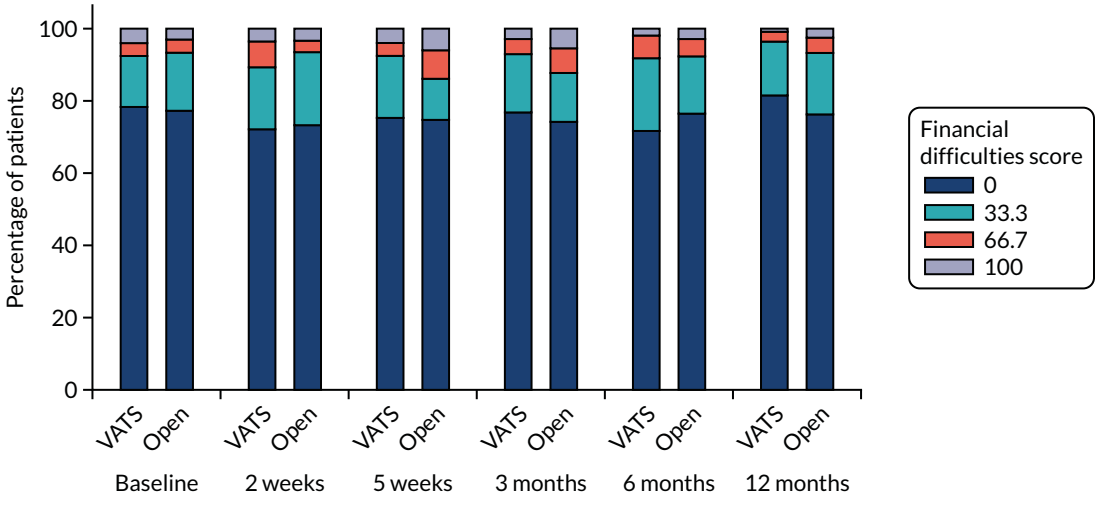

FIGURE 43 QLQ-C30 financial difficulties over time. Higher scores indicate more symptoms.

TABLE 60 QLQ-C30 fatigue, nausea, pain, dyspnoea, insomnia and constipation symptom scale scores

Outcome	Participant allocation		MD/OR (95% CI)	*p*-value
	Randomised to VATS (*n* = 247), median (IQR) or *n/N* (%)	Randomised to open surgery (*n* = 255), median (IQR) or *n/N* (%)		
Fatigue				
Time point				
Baseline[a]	22.2 (11.1–33.3)	22.2 (11.1–33.3)		
2 weeks[b]	44.4 (33.3–66.7)	55.6 (33.3–77.8)		
5 weeks[c]	33.3 (22.2–55.6)	44.4 (33.3–66.7)		
3 months[d]	33.3 (11.1–44.4)	33.3 (22.2–55.6)		
6 months[e]	33.3 (11.1–44.4)	33.3 (22.2–55.6)		
12 months[f]	33.3 (11.1–44.4)	33.3 (11.1–44.4)		
Test for time-by-treatment interaction				0.41
Overall treatment effect			MD −5.68 (−8.65 to −2.71)	0.0015[g]
Nausea and vomiting				
Time point				
Baseline	54/235 (23.0)	48/243 (19.8)		
2 weeks	72/183 (39.3)	84/187 (44.9)		
5 weeks	61/205 (29.8)	96/226 (42.5)		
3 months	47/187 (25.1)	54/198 (27.3)		
6 months	50/184 (27.2)	46/190 (24.2)		
12 months	35/173 (20.2)	41/175 (23.4)		
Test for time-by-treatment interaction[h]				0.20
Overall treatment effect			OR 0.72 (0.53 to 0.98)	0.128[g]
Pain				
Time point				
Baseline[a]	0.0 (0.0–33.3)	0.0 (0.0–33.3)		
2 weeks[b]	33.3 (16.7–66.7)	66.7 (33.3–83.3)		
5 weeks[c]	33.3 (0.0–50.0)	33.3 (16.7–66.7)		
3 months[d]	16.7 (0.0–33.3)	16.7 (0.0–50.0)		
6 months[i]	16.7 (0.0–33.3)	16.7 (0.0–33.3)		
12 months[f]	0.0 (0.0–33.3)	16.7 (0.0–50.0)		
Test for time-by-treatment interaction				0.12
Overall treatment effect			MD −7.19 (−10.59 to −3.80)	0.0006[g]
Dyspnoea				
Time point				
Baseline[j]	33.3 (0.0–33.3)	33.3 (0.0–33.3)		
2 weeks[b]	33.3 (33.3–66.7)	66.7 (33.3–66.7)		
5 weeks[c]	33.3 (33.3–66.7)	33.3 (33.3–66.7)		

TABLE 60 QLQ-C30 fatigue, nausea, pain, dyspnoea, insomnia and constipation symptom scale scores (*continued*)

Outcome	Participant allocation: Randomised to VATS (*n* = 247), median (IQR) or *n/N* (%)	Participant allocation: Randomised to open surgery (*n* = 255), median (IQR) or *n/N* (%)	MD/OR (95% CI)	*p*-value
3 months[k]	33.3 (33.3–66.7)	33.3 (33.3–66.7)		
6 months[l]	33.3 (33.3–66.7)	33.3 (33.3–66.7)		
12 months[m]	33.3 (0.0–66.7)	33.3 (33.3–66.7)		
Test for time-by-treatment interaction				0.16
Overall treatment effect			MD −2.14 (−5.84 to 1.55)	0.40[g]
Insomnia				
Time point				
Baseline[a]	33.3 (0.0–66.7)	33.3 (0.0–33.3)		
2 weeks[b]	33.3 (0.0–66.7)	33.3 (33.3–66.7)	MD −11.79 (−18.95 to −4.63)	0.007[g]
5 weeks[c]	33.3 (0.0–66.7)	33.3 (0.0–66.7)	MD −2.13 (−7.90 to 3.63)	0.66[g]
3 months[n]	33.3 (0.0–33.3)	33.3 (0.0–66.7)	MD −6.36 (−12.11 to −0.61)	0.13[g]
6 months[o]	33.3 (0.0–33.3)	0.0 (0.0–33.3)	MD 0.35 (−5.18 to 5.87)	0.95[g]
12 months[f]	33.3 (0.0–33.3)	33.3 (0.0–33.3)	MD −2.02 (−7.42 to 3.37)	0.66[g]
Test for time-by-treatment interaction				0.0059
Constipation				
Time point				
Baseline	54/235 (23.0)	63/243 (25.9)		
2 weeks	115/182 (63.2)	133/187 (71.1)	OR 0.64 (0.35 to 1.16)	0.27[g]
5 weeks	76/205 (37.1)	102/226 (45.1)	OR 0.62 (0.36 to 1.07)	0.18[g]
3 months	67/186 (36.0)	74/197 (37.6)	OR 0.96 (0.54 to 1.70)	0.95[g]
6 months	60/183 (32.8)	46/189 (24.3)	OR 1.83 (0.98 to 3.40)	0.15[g]
12 months	49/173 (28.3)	45/173 (26.0)	OR 1.20 (0.63 to 2.27)	0.70[g]
Test for time-by-treatment interaction[h]				0.012

a Missing data: 24 patients (VATS, *n* = 12; open surgery, *n* = 12).
b Missing data: 127 patients (VATS, *n* = 62; open surgery, *n* = 65).
c Missing data: 58 patients (VATS, *n* = 37; open surgery, *n* = 21).
d Missing data: 71 patients (VATS, *n* = 39; open surgery, *n* = 32).
e Missing data: 66 patients (VATS, *n* = 35; open surgery, *n* = 31).
f Missing data: 82 patients (VATS, *n* = 43; open surgery, *n* = 39).
g *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]
h From complete-case model.
i Missing data: 66 patients (VATS, *n* = 34; open surgery, *n* = 32).
j Missing data: 25 patients (VATS, *n* = 12; open surgery, *n* = 13).
k Missing data: 72 patients (VATS, *n* = 40; open surgery, *n* = 32).
l Missing data: 68 patients (VATS, *n* = 36; open surgery, *n* = 32).
m Missing data: 83 patients (VATS, *n* = 44; open surgery, *n* = 39).
n Missing data: 72 patients (VATS, *n* = 39; open surgery, *n* = 33).
o Missing data: 67 patients (VATS, *n* = 35; open surgery, *n* = 32).

Notes
Higher scores represent a higher level of symptoms.
Missing data imputed using 50 imputed data sets.

TABLE 61 QLQ-C30 appetite, diarrhoea and financial difficulties scale scores

Outcome	Time point	Score	Participant allocation		OR (95% CI)	*p*-value
			Randomised to VATS (*N* = 247), *n/N* (%)	Randomised to open surgery (*N* = 255), *n/N* (%)		
Appetite loss	Baseline	0	163/233 (70.0)	170/243 (70.0)		
		33.3	47/233 (20.2)	51/243 (21.0)		
		66.7	15/233 (6.4)	15/243 (6.2)		
		100	8/233 (3.4)	7/243 (2.9)		
	2 weeks	0	69/182 (37.9)	56/187 (29.9)		
		33.3	61/182 (33.5)	58/187 (31.0)		
		66.7	31/182 (17.0)	40/187 (21.4)		
		100	21/182 (11.5)	33/187 (17.6)		
	5 weeks	0	97/205 (47.3)	77/226 (34.1)		
		33.3	59/205 (28.8)	75/226 (33.2)		
		66.7	29/205 (14.1)	47/226 (20.8)		
		100	20/205 (9.8)	27/226 (11.9)		
	3 months	0	113/186 (60.8)	108/198 (54.5)		
		33.3	43/186 (23.1)	54/198 (27.3)		
		66.7	18/186 (9.7)	24/198 (12.1)		
		100	12/186 (6.5)	12/198 (6.1)		
	6 months	0	117/184 (63.6)	120/190 (63.2)		
		33.3	43/184 (23.4)	46/190 (24.2)		
		66.7	18/184 (9.8)	18/190 (9.5)		
		100	6/184 (3.3)	6/190 (3.2)		
	12 months	0	119/172 (69.2)	124/175 (70.9)		
		33.3	42/172 (24.4)	31/175 (17.7)		
		66.7	9/172 (5.2)	17/175 (9.7)		
		100	2/172 (1.2)	3/175 (1.7)		
	Test for time-by-treatment interaction[a]					0.22
	Overall treatment effect				0.71 (0.50 to 1.01)	0.15[b]
Diarrhoea	Baseline	0	196/234 (83.8)	205/243 (84.4)		
		33.3	31/234 (13.2)	33/243 (13.6)		
		66.7	4/234 (1.7)	4/243 (1.6)		
		100	3/234 (1.3)	1/243 (0.4)		
	2 weeks	0	132/182 (72.5)	141/188 (75.0)		
		33.3	34/182 (18.7)	40/188 (21.3)		
		66.7	12/182 (6.6)	6/188 (3.2)		
		100	4/182 (2.2)	1/188 (0.5)		

TABLE 61 QLQ-C30 appetite, diarrhoea and financial difficulties scale scores (*continued*)

Outcome	Time point	Score	Participant allocation: Randomised to VATS (*N* = 247), *n*/*N* (%)	Participant allocation: Randomised to open surgery (*N* = 255), *n*/*N* (%)	OR (95% CI)	*p*-value
	5 weeks	0	151/205 (73.7)	184/226 (81.4)		
		33.3	32/205 (15.6)	35/226 (15.5)		
		66.7	16/205 (7.8)	5/226 (2.2)		
		100	6/205 (2.9)	2/226 (0.9)		
	3 months	0	147/184 (79.9)	161/195 (82.6)		
		33.3	28/184 (15.2)	26/195 (13.3)		
		66.7	6/184 (3.3)	7/195 (3.6)		
		100	3/184 (1.6)	1/195 (0.5)		
	6 months	0	152/182 (83.5)	160/190 (84.2)		
		33.3	21/182 (11.5)	24/190 (12.6)		
		66.7	8/182 (4.4)	5/190 (2.6)		
		100	1/182 (0.5)	1/190 (0.5)		
	12 months	0	140/173 (80.9)	142/175 (81.1)		
		33.3	24/173 (13.9)	23/175 (13.1)		
		66.7	8/173 (4.6)	7/175 (4.0)		
		100	1/173 (0.6)	3/175 (1.7)		
	Test for time-by-treatment interaction[a]					0.35
	Overall treatment effect				1.28 (0.90 to 1.82)	0.29[b]
Financial difficulties	Baseline	0	184/234 (78.6)	189/243 (77.8)		
		33.3	32/234 (13.7)	38/243 (15.6)		
		66.7	9/234 (3.8)	9/243 (3.7)		
		100	9/234 (3.8)	7/243 (2.9)		
	2 weeks	0	132/183 (72.1)	138/188 (73.4)		
		33.3	32/183 (17.5)	38/188 (20.2)		
		66.7	13/183 (7.1)	6/188 (3.2)		
		100	6/183 (3.3)	6/188 (3.2)		
	5 weeks	0	154/205 (75.1)	169/226 (74.8)		
		33.3	36/205 (17.6)	26/226 (11.5)		
		66.7	7/205 (3.4)	17/226 (7.5)		
		100	8/205 (3.9)	14/226 (6.2)		
	3 months	0	143/186 (76.9)	147/198 (74.2)		
		33.3	30/186 (16.1)	27/198 (13.6)		
		66.7	8/186 (4.3)	13/198 (6.6)		
		100	5/186 (2.7)	11/198 (5.6)		

continued

TABLE 61 QLQ-C30 appetite, diarrhoea and financial difficulties scale scores (*continued*)

Outcome	Time point	Score	Participant allocation: Randomised to VATS (*N* = 247), *n/N* (%)	Participant allocation: Randomised to open surgery (*N* = 255), *n/N* (%)	OR (95% CI)	*p*-value
	6 months	0	133/185 (71.9)	145/189 (76.7)		
		33.3	37/185 (20.0)	30/189 (15.9)		
		66.7	12/185 (6.5)	8/189 (4.2)		
		100	3/185 (1.6)	6/189 (3.2)		
	12 months	0	141/173 (81.5)	134/175 (76.6)		
		33.3	26/173 (15.0)	30/175 (17.1)		
		66.7	5/173 (2.9)	7/175 (4.0)		
		100	1/173 (0.6)	4/175 (2.3)		
	Test for time-by-treatment interaction[a]					0.35
	Overall treatment effect				0.96 (0.68 to 1.34)	0.91[b]

a From complete-case model.
b *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]

Notes
Higher scores represent a higher level of symptoms.
Multiple imputation (50 imputed data sets) was used to account for missing data.

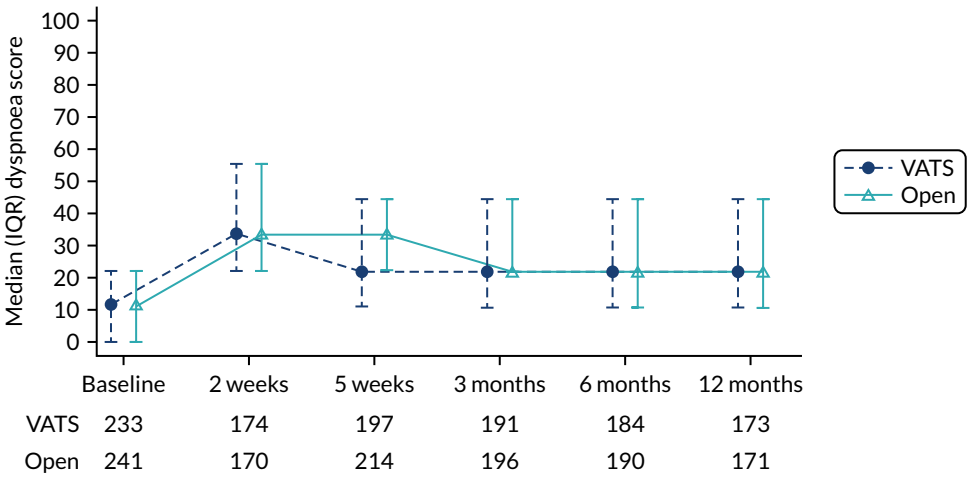

FIGURE 44 QLQ-LC13 dyspnoea symptoms over time. Higher scores indicate more symptoms.

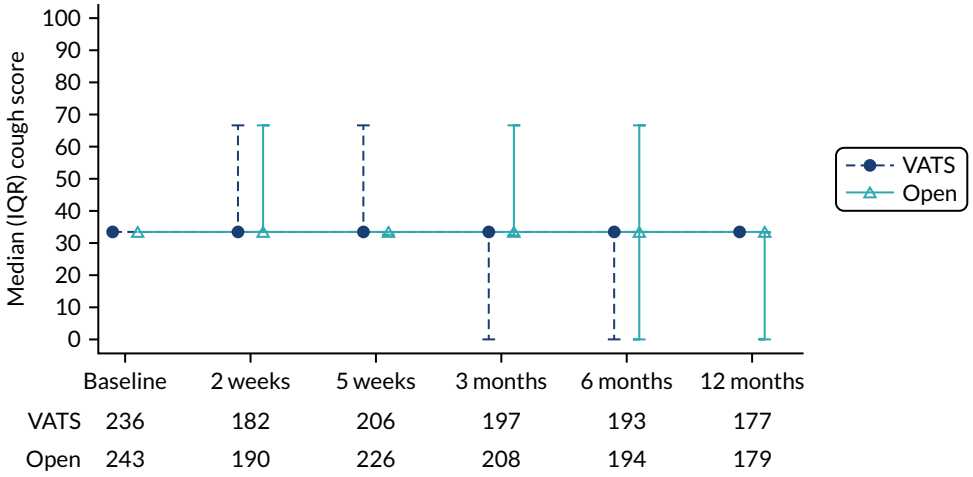

FIGURE 45 QLQ-LC13 scores for cough over time. Higher scores indicate more symptoms.

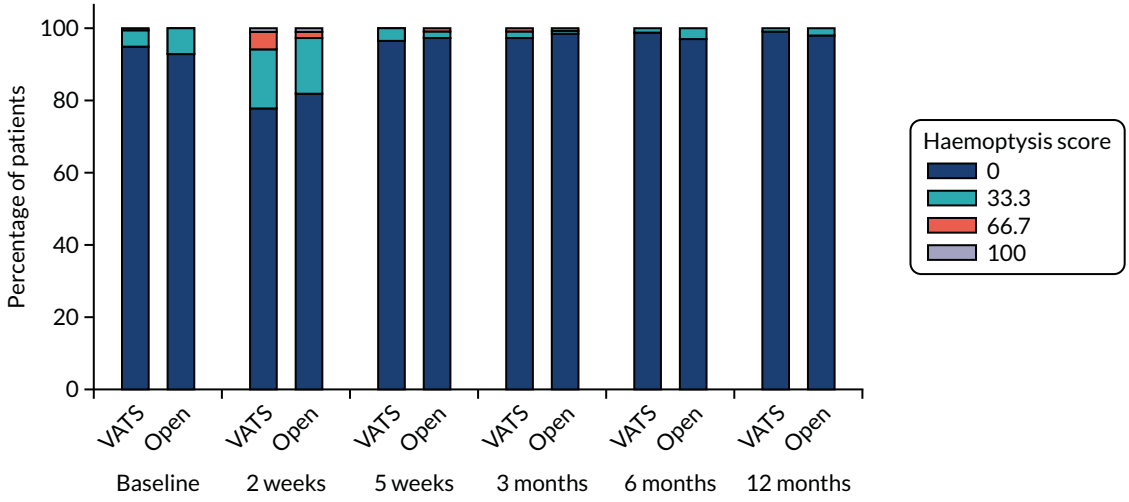

FIGURE 46 QLQ-LC13 scores for haemoptysis over time. Higher scores indicate more symptoms.

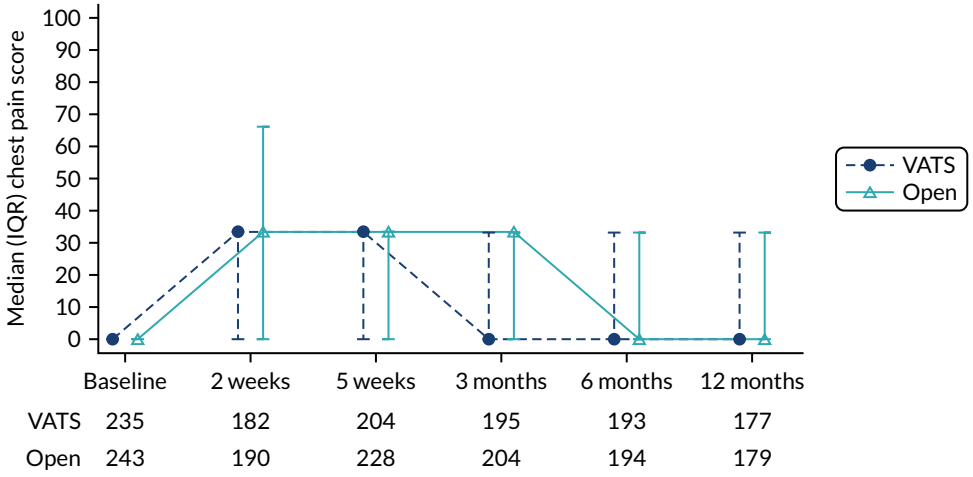

FIGURE 47 QLQ-LC13 scores for pain in the chest over time. Higher scores indicate more symptoms.

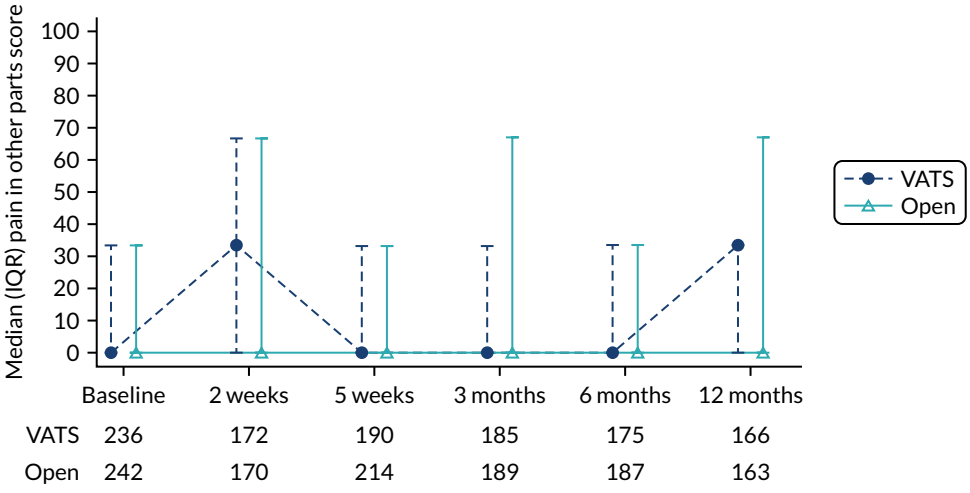

FIGURE 48 QLQ-LC13 scores for pain in other parts (not chest, arm or shoulder) over time. Higher scores indicate more symptoms.

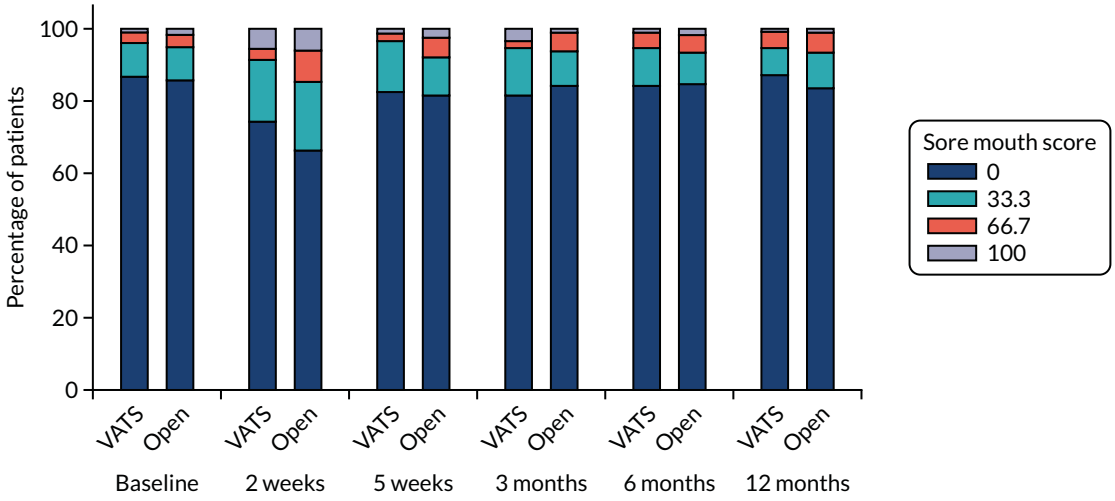

FIGURE 49 QLQ-LC13 scores for sore mouth over time. Higher scores indicate more symptoms.

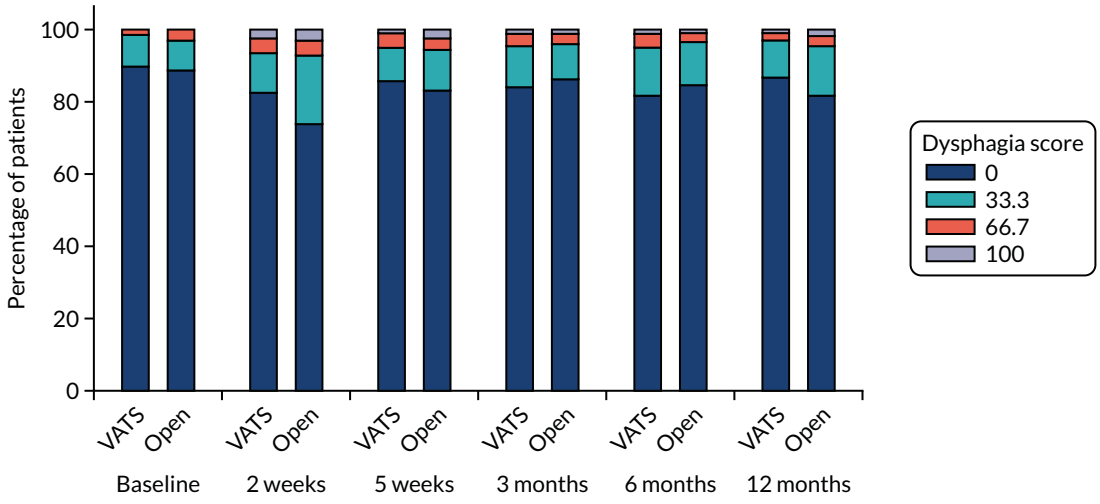

FIGURE 50 QLQ-LC13 scores for dysphagia over time. Higher scores indicate more symptoms.

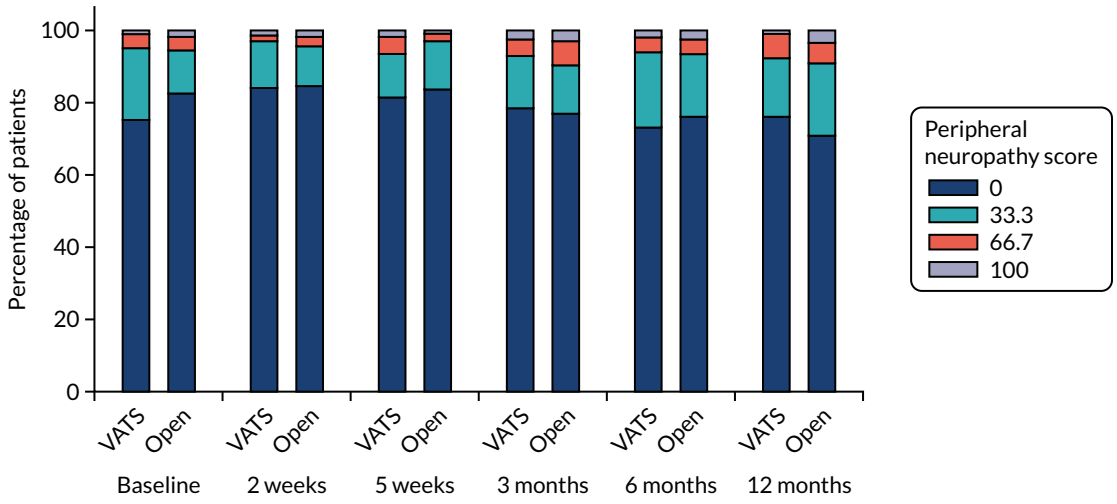

FIGURE 51 QLQ-LC13 scores for peripheral neuropathy over time. Higher scores indicate more symptoms.

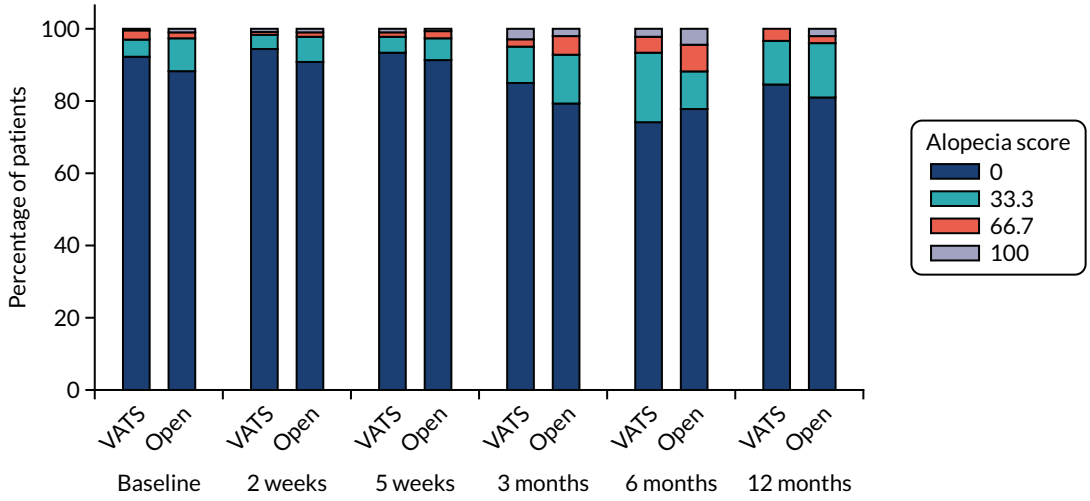

FIGURE 52 QLQ-LC13 scores for alopecia over time. Higher scores indicate more symptoms.

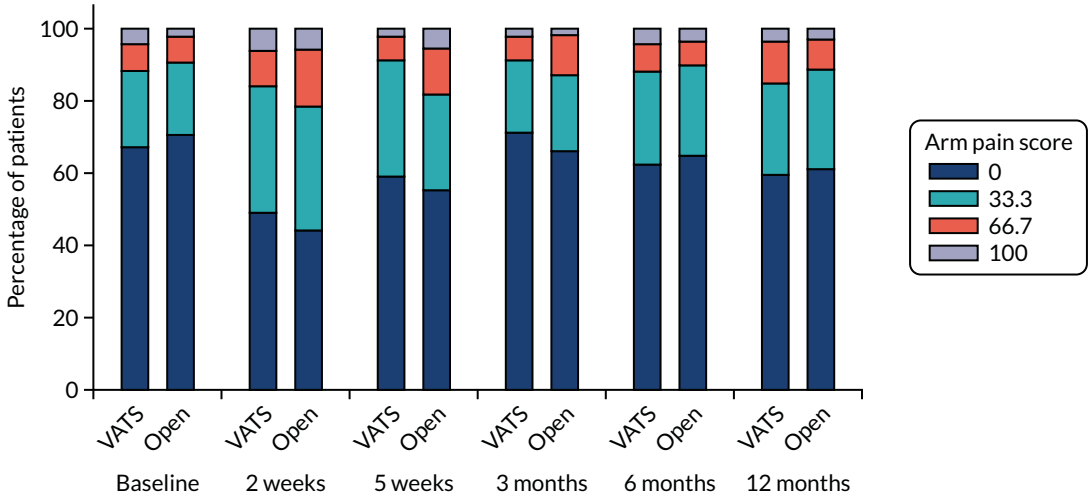

FIGURE 53 QLQ-LC13 scores for pain in the arm over time. Higher scores indicate more symptoms.

TABLE 62 QLQ-LC13 scores for dyspnoea, cough, haemoptysis, pain in chest and pain in other parts (not chest, arm or shoulder)

Outcome	Participant allocation		MD/OR (95% CI)	*p*-value
	Randomised to VATS (*n* = 247), median (IQR) or *n/N* (%)	Randomised to open surgery (*n* = 255), median (IQR) or *n/N* (%)		
Dyspnoea				
Time point				
Baseline[a]	11 (0.0–22.2)	11 (0.0–22.2)		
2 weeks[b]	33 (22.2–55.6)	33 (22.2–55.6)		
5 weeks[c]	22 (11.1–44.4)	33 (22.2–44.4)		
3 months[d]	22 (11.1–44.4)	22 (22.2–44.4)		
6 months[e]	22 (11.1–44.4)	22 (11.1–44.4)		
12 months[f]	22 (11.1–44.4)	22 (11.1–44.4)		
Test for time-by-treatment interaction				0.69
Overall treatment effect			MD −1.85 (−4.90 to 1.20)	0.82[g]
Cough				
Time point				
Baseline[h]	33 (33.3–33.3)	33 (33.3–33.3)		
2 weeks[i]	33 (33.3–66.7)	33 (33.3–66.7)		
5 weeks[j]	33 (33.3–66.7)	33 (33.3–33.3)		
3 months[k]	33 (0.0–33.3)	33 (33.3–66.7)		
6 months[l]	33 (0.0–33.3)	33 (0.0–66.7)		
12 months[m]	33 (33.3–33.3)	33 (0.0–33.3)		
Test for time-by-treatment interaction				0.99
Overall treatment effect			MD 0.18 (−2.92 to 3.28)	1.00[g]
Haemoptysis				
Time point				
Baseline	12/236 (5.1)	17/243 (7.0)		
2 weeks	40/181 (22.1)	34/190 (17.9)		
5 weeks	7/205 (3.4)	6/227 (2.6)		
3 months	4/187 (2.1)	3/199 (1.5)		
6 months	2/187 (1.1)	6/189 (3.2)		
12 months	1/172 (0.6)	3/176 (1.7)		
Test for time-by-treatment interaction				0.23
Overall treatment effect			OR 1.32 (0.70 to 2.50)	1.00[g]

TABLE 62 QLQ-LC13 scores for dyspnoea, cough, haemoptysis, pain in chest and pain in other parts (not chest, arm or shoulder) (*continued*)

Outcome	Participant allocation: Randomised to VATS (*n* = 247), median (IQR) or *n/N* (%)	Participant allocation: Randomised to open surgery (*n* = 255), median (IQR) or *n/N* (%)	MD/OR (95% CI)	*p*-value
Pain in chest				
Time point				
Baseline[n]	0.00 (0.00–0.00)	0.00 (0.00–0.00)		
2 weeks[i]	33.33 (0.00–33.33)	33.33 (0.00–66.67)		
5 weeks[o]	33.33 (0.00–33.33)	33.33 (0.00–33.33)		
3 months[p]	0.00 (0.00–33.33)	33.33 (0.00–33.33)		
6 months[l]	0.00 (0.00–33.33)	0.00 (0.00–33.33)		
12 months[m]	0.00 (0.00–33.33)	0.00 (0.00–33.33)		
Test for time-by-treatment interaction				0.97
Overall treatment effect			MD −4.66 (−7.96 to −1.36)	0.08[g]
Pain in other parts (not chest, arm of shoulder)				
Time point				
Baseline[q]	0 (0.0–33.3)	0 (0.0–33.3)		
2 weeks[r]	33 (0.0–66.7)	0 (0.0–66.7)		
5 weeks[s]	0 (0.0–33.3)	0 (0.0–33.3)		
3 months[t]	0 (0.0–33.3)	0 (0.0–66.7)		
6 months[u]	0 (0.0–33.3)	0 (0.0–33.3)		
12 months[v]	33 (0.0–33.3)	0 (0.0–66.7)		
Test for time-by-treatment interaction				0.93
Overall treatment effect			MD −1.36 (−5.25 to 2.52)	1.00[g]

a Missing data: 28 patients (VATS, *n* = 14; open surgery, *n* = 14).
b Missing data: 155 patients (VATS, *n* = 71; open surgery, *n* = 84).
c Missing data: 79 patients (VATS, *n* = 45; open surgery, *n* = 34).
d Missing data: 88 patients (VATS, *n* = 45; open surgery, *n* = 43).
e Missing data: 77 patients (VATS, *n* = 41; open surgery, *n* = 36).
f Missing data: 94 patients (VATS, *n* = 48; open surgery, *n* = 46).
g *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]
h Missing data: 23 patients (VATS, *n* = 11; open surgery, *n* = 12).
i Missing data: 127 patients (VATS, *n* = 63; open surgery, *n* = 64).
j Missing data: 58 patients (VATS, *n* = 36; open surgery, *n* = 22).
k Missing data: 70 patients (VATS, *n* = 39; open surgery, *n* = 31).
l Missing data: 64 patients (VATS, *n* = 32; open surgery, *n* = 32).
m Missing data: 82 patients (VATS, *n* = 44; open surgery, *n* = 38).
n Missing data: 24 patients (VATS, *n* = 12; open surgery, *n* = 12).
o Missing data: 58 patients (VATS, *n* = 38; open surgery, *n* = 20).
p Missing data: 76 patients (VATS, *n* = 41; open surgery, *n* = 35).
q Missing data: 24 patients (VATS, *n* = 11; open surgery, *n* = 13).
r Missing data: 157 patients (VATS, *n* = 73; open surgery, *n* = 84)
s Missing data: 86 patients (VATS, *n* = 52; open surgery, *n* = 34)
t Missing data: 101 patients (VATS, *n* = 51; open surgery, *n* = 50)
u Missing data: 89 patients (VATS, *n* = 50; open surgery, *n* = 39)
v Missing data: 108 patients (VATS, *n* = 56; open surgery, *n* = 52).

Notes
Higher scores represent a higher level of symptoms.
Missing data imputed using 50 imputed data sets.

TABLE 63 QLQ-LC13 scores for sore mouth, dysphagia, peripheral neuropathy, alopecia and pain in the arm/shoulder

Outcome	Time point	Score	Participant allocation: Randomised to VATS (*N* = 247), *n/N* (%)	Participant allocation: Randomised to open surgery (*N* = 255), *n/N* (%)	OR (95% CI)	*p*-value
Sore mouth	Baseline	0	205/236 (86.9)	209/243 (86.0)		
		33.3	22/236 (9.3)	22/243 (9.1)		
		66.7	7/236 (3.0)	8/243 (3.3)		
		100	2/236 (0.8)	4/243 (1.6)		
	2 weeks	0	136/183 (74.3)	124/187 (66.3)		
		33.3	31/183 (16.9)	35/187 (18.7)		
		66.7	6/183 (3.3)	17/187 (9.1)		
		100	10/183 (5.5)	11/187 (5.9)		
	5 weeks	0	170/206 (82.5)	184/226 (81.4)		
		33.3	29/206 (14.1)	24/226 (10.6)		
		66.7	4/206 (1.9)	13/226 (5.8)		
		100	3/206 (1.5)	5/226 (2.2)		
	3 months	0	153/187 (81.8)	167/198 (84.3)		
		33.3	24/187 (12.8)	19/198 (9.6)		
		66.7	3/187 (1.6)	10/198 (5.1)		
		100	7/187 (3.7)	2/198 (1.0)		
	6 months	0	157/187 (84.0)	160/189 (84.7)		
		33.3	20/187 (10.7)	17/189 (9.0)		
		66.7	8/187 (4.3)	9/189 (4.8)		
		100	2/187 (1.1)	3/189 (1.6)		
	12 months	0	151/173 (87.3)	147/176 (83.5)		
		33.3	13/173 (7.5)	18/176 (10.2)		
		66.7	8/173 (4.6)	9/176 (5.1)		
		100	1/173 (0.6)	2/176 (1.1)		
	Test for time-by-treatment interaction[a]					0.48
	Overall treatment effect				OR 0.88 (0.63 to 1.22)	1.00[b]
Dysphagia	Baseline	0	212/236 (89.8)	216/243 (88.9)		
		33.3	21/236 (8.9)	20/243 (8.2)		
		66.7	3/236 (1.3)	7/243 (2.9)		
		100	151/183 (82.5)	139/188 (73.9)		
	2 weeks	0	20/183 (10.9)	36/188 (19.1)		
		33.3	8/183 (4.4)	7/188 (3.7)		
		66.7	4/183 (2.2)	6/188 (3.2)		
		100	177/206 (85.9)	188/226 (83.2)		

TABLE 63 QLQ-LC13 scores for sore mouth, dysphagia, peripheral neuropathy, alopecia and pain in the arm/shoulder (*continued*)

Outcome	Time point	Score	Participant allocation: Randomised to VATS (*N* = 247), *n*/*N* (%)	Participant allocation: Randomised to open surgery (*N* = 255), *n*/*N* (%)	OR (95% CI)	*p*-value
	5 weeks	0	19/206 (9.2)	26/226 (11.5)		
		33.3	8/206 (3.9)	7/226 (3.1)		
		66.7	2/206 (1.0)	5/226 (2.2)		
		100	156/185 (84.3)	172/199 (86.4)		
	3 months	0	21/185 (11.4)	19/199 (9.5)		
		33.3	6/185 (3.2)	6/199 (3.0)		
		66.7	2/185 (1.1)	2/199 (1.0)		
		100	152/186 (81.7)	161/190 (84.7)		
	6 months	0	25/186 (13.4)	22/190 (11.6)		
		33.3	7/186 (3.8)	6/190 (3.2)		
		66.7	2/186 (1.1)	1/190 (0.5)		
		100	149/172 (86.6)	144/176 (81.8)		
	12 months	0	18/172 (10.5)	24/176 (13.6)		
		33.3	4/172 (2.3)	5/176 (2.8)		
		66.7	1/172 (0.6)	3/176 (1.7)		
		100	212/236 (89.8)	216/243 (88.9)		
	Test for time-by-treatment interaction[a]					0.14
	Overall treatment effect				OR 0.92 (0.65 to 1.30)	1.00[b]
Peripheral neuropathy	Baseline	0	178/236 (75.4)	201/243 (82.7)		
		33.3	47/236 (19.9)	29/243 (11.9)		
		66.7	9/236 (3.8)	9/243 (3.7)		
		100	2/236 (0.8)	4/243 (1.6)		
	2 weeks	0	152/181 (84.0)	160/189 (84.7)		
		33.3	24/181 (13.3)	21/189 (11.1)		
		66.7	3/181 (1.7)	5/189 (2.6)		
		100	2/181 (1.1)	3/189 (1.6)		
	5 weeks	0	167/205 (81.5)	187/224 (83.5)		
		33.3	25/205 (12.2)	31/224 (13.8)		
		66.7	9/205 (4.4)	4/224 (1.8)		
		100	4/205 (2.0)	2/224 (0.9)		
	3 months	0	146/186 (78.5)	153/199 (76.9)		
		33.3	27/186 (14.5)	27/199 (13.6)		
		66.7	9/186 (4.8)	13/199 (6.5)		
		100	4/186 (2.2)	6/199 (3.0)		

continued

TABLE 63 QLQ-LC13 scores for sore mouth, dysphagia, peripheral neuropathy, alopecia and pain in the arm/shoulder (*continued*)

Outcome	Time point	Score	Participant allocation: Randomised to VATS (*N* = 247), *n/N* (%)	Participant allocation: Randomised to open surgery (*N* = 255), *n/N* (%)	OR (95% CI)	*p*-value
	6 months	0	136/186 (73.1)	144/189 (76.2)		
		33.3	39/186 (21.0)	33/189 (17.5)		
		66.7	8/186 (4.3)	7/189 (3.7)		
		100	3/186 (1.6)	5/189 (2.6)		
	12 months	0	131/172 (76.2)	124/175 (70.9)		
		33.3	28/172 (16.3)	35/175 (20.0)		
		66.7	12/172 (7.0)	10/175 (5.7)		
		100	1/172 (0.6)	6/175 (3.4)		
	Test for time-by-treatment interaction[a]					0.41
	Overall treatment effect				OR 0.99 (0.63 to 1.55)	1.00[b]
Alopecia	Baseline	0	217/235 (92.3)	215/243 (88.5)		
		33.3	11/235 (4.7)	22/243 (9.1)		
		66.7	6/235 (2.6)	4/243 (1.6)		
		100	1/235 (0.4)	2/243 (0.8)		
	2 weeks	0	172/182 (94.5)	172/189 (91.0)		
		33.3	7/182 (3.8)	13/189 (6.9)		
		66.7	2/182 (1.1)	3/189 (1.6)		
		100	1/182 (0.5)	1/189 (0.5)		
	5 weeks	0	192/205 (93.7)	208/227 (91.6)		
		33.3	9/205 (4.4)	14/227 (6.2)		
		66.7	2/205 (1.0)	4/227 (1.8)		
		100	2/205 (1.0)	1/227 (0.4)		
	3 months	0	159/187 (85.0)	157/197 (79.7)		
		33.3	19/187 (10.2)	26/197 (13.2)		
		66.7	4/187 (2.1)	10/197 (5.1)		
		100	5/187 (2.7)	4/197 (2.0)		
	6 months	0	139/187 (74.3)	148/190 (77.9)		
		33.3	36/187 (19.3)	20/190 (10.5)		
		66.7	8/187 (4.3)	14/190 (7.4)		
		100	4/187 (2.1)	8/190 (4.2)		
	12 months	0	146/172 (84.9)	143/176 (81.3)		
		33.3	20/172 (11.6)	26/176 (14.8)		
		66.7	6/172 (3.5)	4/176 (2.3)		
		100	0/172 (0.0)	3/176 (1.7)		

TABLE 63 QLQ-LC13 scores for sore mouth, dysphagia, peripheral neuropathy, alopecia and pain in the arm/shoulder (*continued*)

Outcome	Time point	Score	Participant allocation: Randomised to VATS (*N* = 247), *n/N* (%)	Participant allocation: Randomised to open surgery (*N* = 255), *n/N* (%)	OR (95% CI)	*p*-value
	Test for time-by-treatment interaction[a]					0.73
	Overall treatment effect				OR 0.96 (0.67 to 1.38)	1.00[b]
Pain in shoulder or arm	Baseline	0	159/236 (67.4)	172/243 (70.8)		
		33.3	49/236 (20.8)	48/243 (19.8)		
		66.7	18/236 (7.6)	18/243 (7.4)		
		100	10/236 (4.2)	5/243 (2.1)		
	2 weeks	0	89/182 (48.9)	84/189 (44.4)		
		33.3	64/182 (35.2)	64/189 (33.9)		
		66.7	18/182 (9.9)	30/189 (15.9)		
		100	11/182 (6.0)	11/189 (5.8)	OR 0.66 (0.40 to 1.08)	0.45[2]
	5 weeks	0	121/205 (59.0)	125/226 (55.3)		
		33.3	66/205 (32.2)	60/226 (26.5)		
		66.7	14/205 (6.8)	29/226 (12.8)		
		100	4/205 (2.0)	12/226 (5.3)	OR 0.56 (0.34 to 0.93)	0.17[2]
	3 months	0	131/184 (71.2)	129/195 (66.2)		
		33.3	37/184 (20.1)	41/195 (21.0)		
		66.7	12/184 (6.5)	21/195 (10.8)		
		100	4/184 (2.2)	4/195 (2.1)	OR 0.79 (0.46 to 1.36)	1.00[2]
	6 months	0	116/185 (62.7)	123/189 (65.1)		
		33.3	47/185 (25.4)	47/189 (24.9)		
		66.7	14/185 (7.6)	12/189 (6.3)		
		100	8/185 (4.3)	7/189 (3.7)	OR 1.04 (0.60 to 1.82)	1.00[2]
	12 months	0	103/172 (59.9)	106/173 (61.3)		
		33.3	43/172 (25.0)	48/173 (27.7)		
		66.7	20/172 (11.6)	14/173 (8.1)		
		100	6/172 (3.5)	5/173 (2.9)	OR 1.26 (0.72 to 2.19)	1.00[b]
	Test for time-by-treatment interaction[a]					0.09

a From complete-case model.
b *p*-values have been adjusted for multiple testing using the Benjamini–Hochberg method.[37]

Notes
Higher scores represent a higher level of symptoms.
Missing data are imputed using 50 imputed data sets.

TABLE 64 EQ-5D-5L scores over time

Time point	Participant allocation		Occurrence model		Intensity model		
	Randomised to VATS (*N* = 247), median (IQR)	Randomised to open surgery (*N* = 255), median (IQR)	OR[a] (95% CI)	*p*-value	GMR[b] (95% CI)	*p*-value	Test for time-by-treatment interaction[c]
Baseline[d]	0.78 (0.69–0.88)	0.80 (0.68–0.88)					
2 weeks[e]	0.71 (0.53–0.77)	0.64 (0.42–0.74)					
5 weeks[f]	0.74 (0.58–0.80)	0.69 (0.57–0.80)					
3 months[g]	0.76 (0.65–0.88)	0.72 (0.55–0.84)					
6 months[h]	0.77 (0.65–0.88)	0.74 (0.63–0.84)					
12 months[i]	0.77 (0.64–0.88)	0.71 (0.62–0.84)					
Overall treatment effect			0.57 (0.38 to 0.86)	0.0071	0.90 (0.84 to 0.96)	0.0027	0.20

GMR, geometric mean ratio.
a Outcome is less than perfect health vs. perfect health.
b Outcome is 1 – (EQ-5D utility), conditional on non-perfect health score.
c From occurrence model.
d Missing data: 25 patients (VATS, *n* = 13; open surgery, *n* = 12).
e Missing data: 131 patients (VATS, *n* = 65; open surgery, *n* = 66).
f Missing data: 59 patients (VATS, *n* = 37; open surgery, *n* = 22).
g Missing data: 75 patients (VATS, *n* = 43; open surgery, *n* = 32).
h Missing data: 70 patients (VATS, *n* = 35; open surgery, *n* = 35).
i Missing data: 86 patients (VATS, *n* = 46; open surgery, *n* = 40).

Note
Missing data imputed using 50 imputed data sets.

TABLE 65 In-hospital AEs and SAEs

Event	Participant allocation			
	Randomised to VATS (*N* = 247)		Randomised to open surgery (*N* = 255)	
	All events, *n*/*N* (%)	SAE,[a] *n*/*N* (%)	All events, *n*/*N* (%)	SAE,[b] *n*/*N* (%)
Any event	81/247 (32.8)	20/247 (8.1)	113/255 (44.3)	21/255 (8.2)
Cardiac disorders	24/247 (9.7)	4/247 (1.6)	24/255 (9.4)	3/255 (1.2)
Arrhythmia	23/247 (9.3)	3/247 (1.2)	22/255 (8.6)	1/255 (0.4)
Atrial fibrillation	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Bradycardia	1/247 (0.4)	1/247 (0.4)	0/255 (0.0)	0/255 (0.0)
Cardiac arrest	2/247 (0.8)	2/247 (0.8)	2/255 (0.8)	2/255 (0.8)
Myocardial infarction	1/247 (0.4)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Gastrointestinal disorders	4/247 (1.6)	1/247 (0.4)	9/255 (3.5)	4/255 (1.6)
Abdominal pain	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Constipation	1/247 (0.4)	0/247 (0.0)	0/255 (0.0)	0/255 (0.0)
Ileus	1/247 (0.4)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)

TABLE 65 In-hospital AEs and SAEs (*continued*)

Event	Participant allocation			
	Randomised to VATS (*N* = 247)		Randomised to open surgery (*N* = 255)	
	All events, *n/N* (%)	SAE,[a] *n/N* (%)	All events, *n/N* (%)	SAE,[b] *n/N* (%)
Intra-abdominal bleeding	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Melaena	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Pancreatitis	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Pancreatitis necrotising	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Peptic ulcer/gastrointestinal haemorrhage/ gastrointestinal perforation	2/247 (0.8)	1/247 (0.4)	3/255 (1.2)	1/255 (0.4)
Small intestinal obstruction	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Upper gastrointestinal haemorrhage	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
General disorders and administration site conditions	1/247 (0.4)	1/247 (0.4)	2/255 (0.8)	2/255 (0.8)
Organ failure	1/247 (0.4)	1/247 (0.4)	1/255 (0.4)	1/255 (0.4)
Systemic inflammatory response syndrome	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Immune system disorders	1/247 (0.4)	1/247 (0.4)	0/255 (0.0)	0/255 (0.0)
Anaphylactic reaction	1/247 (0.4)	1/247 (0.4)	0/255 (0.0)	0/255 (0.0)
Infections and infestations	40/247 (16.2)	9/247 (3.6)	71/255 (27.8)	5/255 (2.0)
Empyema	1/247 (0.4)	0/247 (0.0)	2/255 (0.8)	0/255 (0.0)
Gastrointestinal infection	1/247 (0.4)	0/247 (0.0)	0/255 (0.0)	0/255 (0.0)
Haemophilus infection	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Kidney infection	1/247 (0.4)	1/247 (0.4)	0/255 (0.0)	0/255 (0.0)
Pneumonia/lower respiratory tract infection	37/247 (15.0)	9/247 (3.6)	53/255 (20.8)	5/255 (2.0)
Sepsis	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Superinfection	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Urinary tract infection	4/247 (1.6)	1/247 (0.4)	6/255 (2.4)	0/255 (0.0)
Wound infection	4/247 (1.6)	0/247 (0.0)	9/255 (3.5)	0/255 (0.0)
Unknown infection	0/247 (0.0)	0/247 (0.0)	6/255 (2.4)	0/255 (0.0)
Injury, poisoning and procedural complications	10/247 (4.0)	7/247 (2.8)	10/255 (3.9)	4/255 (1.6)
Bleeding from vascular injury[b]	8/129 (6.2)	6/129 (4.7)	5/127 (3.9)	1/127 (0.8)
Fall	1/247 (0.4)	1/247 (0.4)	0/255 (0.0)	0/255 (0.0)
Laryngeal nerve dysfunction	0/247 (0.0)	0/247 (0.0)	2/255 (0.8)	0/255 (0.0)
Overdose	0/247 (0.0)	0/247 (0.0)	2/255 (0.8)	2/255 (0.8)
Tracheal injury	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Wound dehiscence	1/247 (0.4)	0/247 (0.0)	0/255 (0.0)	0/255 (0.0)
Investigations	11/247 (4.5)	6/247 (2.4)	10/255 (3.9)	2/255 (0.8)
Bronchoscopy	11/247 (4.5)	6/247 (2.4)	9/255 (3.5)	1/255 (0.4)
Endoscopy upper gastrointestinal tract	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)

continued

TABLE 65 In-hospital AEs and SAEs (*continued*)

Event	Participant allocation			
	Randomised to VATS (N = 247)		Randomised to open surgery (N = 255)	
	All events, *n/N* (%)	SAE,[a] *n/N* (%)	All events, *n/N* (%)	SAE,[b] *n/N* (%)
Metabolism and nutrition disorders	1/247 (0.4)	1/247 (0.4)	1/255 (0.4)	1/255 (0.4)
Hypokalaemia	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Hyponatremia	1/247 (0.4)	1/247 (0.4)	1/255 (0.4)	1/255 (0.4)
Nervous system disorders	0/247 (0.0)	0/247 (0.0)	2/255 (0.8)	2/255 (0.8)
Syncope	0/247 (0.0)	0/247 (0.0)	2/255 (0.8)	2/255 (0.8)
Psychiatric disorders	7/247 (2.8)	0/247 (0.0)	12/255 (4.7)	0/255 (0.0)
Acute psychosis	7/247 (2.8)	0/247 (0.0)	12/255 (4.7)	0/255 (0.0)
Renal and urinary disorders	5/247 (2.0)	1/247 (0.4)	16/255 (6.3)	2/255 (0.8)
Acute kidney injury	5/247 (2.0)	1/247 (0.4)	15/255 (5.9)	1/255 (0.4)
Oliguria	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Respiratory, thoracic and mediastinal disorders	18/247 (7.3)	6/247 (2.4)	21/255 (8.2)	7/255 (2.7)
Acute lung injury	2/247 (0.8)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Acute respiratory distress syndrome	0/247 (0.0)	0/247 (0.0)	3/255 (1.2)	2/255 (0.8)
Acute respiratory failure	12/247 (4.9)	6/247 (2.4)	12/255 (4.7)	6/255 (2.4)
Atelectasis	11/247 (4.5)	5/247 (2.0)	8/255 (3.1)	2/255 (0.8)
Chylothorax	0/247 (0.0)	0/247 (0.0)	3/255 (1.2)	1/255 (0.4)
Hypoxia	1/247 (0.4)	1/247 (0.4)	2/255 (0.8)	2/255 (0.8)
Pleural effusion[b]	3/135 (2.2)	0/135 (0.0)	4/146 (2.7)	1/146 (0.7)
Pneumothorax	4/247 (1.6)	0/247 (0.0)	9/255 (3.5)	2/255 (0.8)
Pulmonary air leakage[b]	20/135 (14.8)	0/135 (0.0)	11/146 (7.5)	0/146 (0.0)
Skin and subcutaneous tissue disorders	9/247 (3.6)	1/247 (0.4)	13/255 (5.1)	1/255 (0.4)
Subcutaneous emphysema	9/247 (3.6)	1/247 (0.4)	13/255 (5.1)	1/255 (0.4)
Surgical and medical procedures	9/247 (3.6)	4/247 (1.6)	12/255 (4.7)	4/255 (1.6)
Central venous catheterisation	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Extracorporeal membrane oxygenation	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Hemofiltration	2/247 (0.8)	1/247 (0.4)	3/255 (1.2)	1/255 (0.4)
Laparotomy	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Mini-tracheostomy	5/247 (2.0)	3/247 (1.2)	6/255 (2.4)	0/255 (0.0)
Reoperation for bleeding	2/247 (0.8)	1/247 (0.4)	2/255 (0.8)	1/255 (0.4)
Reoperation for pleural effusion	1/247 (0.4)	0/247 (0.0)	0/255 (0.0)	0/255 (0.0)
Reoperation for drainage of empyema	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Reoperation for haemothorax	0/247 (0.0)	0/247 (0.0)	2/255 (0.8)	0/255 (0.0)
Reoperation for sputum retention	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Tracheostomy	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)
Transfusion	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	1/255 (0.4)

TABLE 65 In-hospital AEs and SAEs (*continued*)

Event	Participant allocation			
	Randomised to VATS (*N* = 247)		Randomised to open surgery (*N* = 255)	
	All events, *n/N* (%)	SAE,[a] *n/N* (%)	All events, *n/N* (%)	SAE,[b] *n/N* (%)
Vascular disorders	2/247 (0.8)	2/247 (0.8)	4/255 (1.6)	3/255 (1.2)
Deep-vein thrombosis	0/247 (0.0)	0/247 (0.0)	1/255 (0.4)	0/255 (0.0)
Haematoma[b]	0/129 (0.0)	0/129 (0.0)	3/141 (2.1)	0/141 (0.0)
Hypotension	1/247 (0.4)	1/247 (0.4)	2/255 (0.8)	2/255 (0.8)
Ischaemia	1/247 (0.4)	1/247 (0.4)	1/255 (0.4)	1/255 (0.4)

a SAE that prolonged the hospital stay, resulted in persistent or significant disability or incapacity, was life-threatening or resulted in death (or CTCAE grade 4 or 5).
b Added partway through the study and so collected for only a subset of patients. SAEs are a subset of total events reported. AEs were coded according to the MedDRA system organ class.
Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

TABLE 66 Post-discharge SAEs

Event	Participant allocation	
	Randomised to VATS (*n* = 244)[a]	Randomised to open surgery (*n* = 249)[a]
Total events	142/75 (30.7)	207/94 (37.8)
Blood and lymphatic system disorders	10/5 (2.0)	10/10 (4.0)
Anaemia	1/1 (0.4)	1/1 (0.4)
Neutropenia	9/5 (2.0)	8/8 (3.2)
Pancytopenia	0/0 (0.0)	1/1 (0.4)
Cardiac disorders	5/4 (1.6)	9/8 (3.2)
Atrial fibrillation	2/2 (0.8)	3/3 (1.2)
Atrial flutter	0/0 (0.0)	1/1 (0.4)
Cardiac arrest	0/0 (0.0)	2/2 (0.8)
Cardiac failure	0/0 (0.0)	2/2 (0.8)
Intracardiac thrombus	1/1 (0.4)	0/0 (0.0)
Myocardial infarction	2/2 (0.8)	0/0 (0.0)
Myocardial ischaemia	0/0 (0.0)	1/1 (0.4)
Eye disorders	1/1 (0.4)	0/0 (0.0)
Vision blurred	1/1 (0.4)	0/0 (0.0)
Gastrointestinal disorders	9/7 (2.9)	27/16 (6.4)
Abdominal pain	1/1 (0.4)	0/0 (0.0)
Constipation	0/0 (0.0)	2/2 (0.8)

continued

TABLE 66 Post-discharge SAEs (*continued*)

Event	Participant allocation	
	Randomised to VATS ($n = 244$)[a]	Randomised to open surgery ($n = 249$)[a]
Diarrhoea	1/1 (0.4)	5/4 (1.6)
Dyschezia	0/0 (0.0)	1/1 (0.4)
Gastro-oesophageal reflux disease	0/0 (0.0)	1/1 (0.4)
Gastrointestinal haemorrhage	1/1 (0.4)	2/2 (0.8)
Ileus	0/0 (0.0)	2/2 (0.8)
Nausea	1/1 (0.4)	4/3 (1.2)
Oesophageal obstruction	1/1 (0.4)	0/0 (0.0)
Oesophagitis	0/0 (0.0)	1/1 (0.4)
Pancreatitis	1/1 (0.4)	0/0 (0.0)
Small intestinal obstruction	0/0 (0.0)	1/1 (0.4)
Vomiting	3/3 (1.2)	8/6 (2.4)
General disorders	12/12 (4.9)	14/12 (4.8)
Chest pain (unknown cause)	0/0 (0.0)	2/2 (0.8)
Death (unknown cause)	0/0 (0.0)	1/1 (0.4)
Disease recurrence/disease progression	11/11 (4.5)	9/7 (2.8)
Organ failure	1/1 (0.4)	1/1 (0.4)
Pain	0/0 (0.0)	1/1 (0.4)
Hepatobiliary disorders	1/1 (0.4)	0/0 (0.0)
Cholecystitis	1/1 (0.4)	0/0 (0.0)
Immune system disorders	1/1 (0.4)	0/0 (0.0)
Anaphylaxis/hypersensitivity reaction	1/1 (0.4)	0/0 (0.0)
Infections and infestations	51/35 (14.3)	48/37 (14.9)
Cellulitis	1/1 (0.4)	0/0 (0.0)
Diverticulitis	1/1 (0.4)	0/0 (0.0)
Empyema	6/6 (2.5)	5/5 (2.0)
Encephalitis	0/0 (0.0)	1/1 (0.4)
Respiratory tract infection/pneumonia	29/24 (9.8)	34/27 (10.8)
Sepsis	4/4 (1.6)	1/1 (0.4)
Unknown infection	1/1 (0.4)	1/1 (0.4)
Urinary tract infection	8/7 (2.9)	5/4 (1.6)
Wound infection	1/1 (0.4)	1/1 (0.4)
Injury poisoning and procedural complications	2/2 (0.8)	2/2 (0.8)
Fall	1/1 (0.4)	1/1 (0.4)
Hip fracture	1/1 (0.4)	0/0 (0.0)
Wound dehiscence	0/0 (0.0)	1/1 (0.4)

TABLE 66 Post-discharge SAEs (*continued*)

Event	Participant allocation	
	Randomised to VATS ($n = 244$)[a]	Randomised to open surgery ($n = 249$)[a]
Investigations	1/1 (0.4)	5/4 (1.6)
Biopsy lung	0/0 (0.0)	1/1 (0.4)
Bronchoscopy	0/0 (0.0)	3/2 (0.8)
Colonoscopy	0/0 (0.0)	1/1 (0.4)
Cystoscopy	1/1 (0.4)	0/0 (0.0)
Metabolism and nutrition disorders	3/3 (1.2)	3/2 (0.8)
Decreased appetite	0/0 (0.0)	2/1 (0.4)
Hyperglycaemia	1/1 (0.4)	0/0 (0.0)
Hypoglycaemia	1/1 (0.4)	0/0 (0.0)
Hyponatraemia	1/1 (0.4)	1/1 (0.4)
Musculoskeletal and connective tissue disorders	0/0 (0.0)	4/3 (1.2)
Arthralgia	0/0 (0.0)	2/1 (0.4)
Musculoskeletal chest pain	0/0 (0.0)	2/2 (0.8)
Neoplasms benign, malignant and unspecified	3/3 (1.2)	3/3 (1.2)
Adenocarcinoma	1/1 (0.4)	0/0 (0.0)
Brain neoplasm	0/0 (0.0)	1/1 (0.4)
Endometrial cancer	1/1 (0.4)	0/0 (0.0)
Gastrointestinal carcinoma	1/1 (0.4)	0/0 (0.0)
Lung neoplasm malignant	0/0 (0.0)	1/1 (0.4)
Sarcoma	0/0 (0.0)	1/1 (0.4)
Nervous system disorders	4/4 (1.6)	6/6 (2.4)
Cerebral ischaemia	0/0 (0.0)	1/1 (0.4)
Cerebrovascular accident	1/1 (0.4)	2/2 (0.8)
Headache	1/1 (0.4)	0/0 (0.0)
Subarachnoid haemorrhage	0/0 (0.0)	1/1 (0.4)
Transient ischaemic attack	1/1 (0.4)	2/2 (0.8)
White matter ischaemia	1/1 (0.4)	0/0 (0.0)
Psychiatric disorders	0/0 (0.0)	1/1 (0.4)
Alcohol withdrawal syndrome	0/0 (0.0)	1/1 (0.4)
Renal and urinary disorders	0/0 (0.0)	5/4 (1.6)
Acute kidney injury	0/0 (0.0)	5/4 (1.6)
Respiratory, thoracic and mediastinal disorders	25/22 (9.0)	39/27 (10.8)
Acute lung injury	2/2 (0.8)	1/1 (0.4)
Atelectasis/pulmonary collapse	1/1 (0.4)	5/4 (1.6)
Bronchopleural fistula	0/0 (0.0)	2/2 (0.8)
Chronic obstructive pulmonary disease	2/2 (0.8)	3/2 (0.8)

continued

TABLE 66 Post-discharge SAEs (*continued*)

Event	Participant allocation	
	Randomised to VATS ($n = 244$)[a]	Randomised to open surgery ($n = 249$)[a]
Chylothorax	0/0 (0.0)	1/1 (0.4)
Dyspnoea	1/1 (0.4)	2/2 (0.8)
Haemothorax	1/1 (0.4)	0/0 (0.0)
Interstitial lung disease	0/0 (0.0)	1/1 (0.4)
Pleural effusion	9/8 (3.3)	8/7 (2.8)
Pulmonary air leakage/pneumothorax	7/6 (2.5)	9/7 (2.8)
Pulmonary embolism	2/2 (0.8)	6/6 (2.4)
Respiratory arrest	0/0 (0.0)	1/1 (0.4)
Surgical and medical procedures	12/11 (4.5)	25/19 (7.6)
Colectomy	1/1 (0.4)	0/0 (0.0)
Empyema drainage	0/0 (0.0)	2/1 (0.4)
Femoral hernia repair	0/0 (0.0)	1/1 (0.4)
Haemorrhoid operation	0/0 (0.0)	1/1 (0.4)
Haematoma evacuation	0/0 (0.0)	1/1 (0.4)
Hip arthroplasty	1/1 (0.4)	2/2 (0.8)
Hysterectomy	2/2 (0.8)	0/0 (0.0)
Ileostomy	0/0 (0.0)	1/1 (0.4)
Ileostomy closure	0/0 (0.0)	1/1 (0.4)
Intestinal resection	0/0 (0.0)	1/1 (0.4)
Knee arthroplasty	0/0 (0.0)	2/2 (0.8)
Limb operation	0/0 (0.0)	1/1 (0.4)
Lymphadenectomy	1/1 (0.4)	0/0 (0.0)
Parathyroidectomy	1/1 (0.4)	0/0 (0.0)
Peripheral artery bypass	1/1 (0.4)	0/0 (0.0)
Polypectomy	1/1 (0.4)	0/0 (0.0)
Proctectomy	0/0 (0.0)	1/1 (0.4)
Prostatic operation	0/0 (0.0)	1/1 (0.4)
Pulmonary resection	1/1 (0.4)	1/1 (0.4)
Radioactive iodine therapy	0/0 (0.0)	1/1 (0.4)
Rehabilitation therapy	2/1 (0.4)	2/2 (0.8)
Removal of foreign body	0/0 (0.0)	1/1 (0.4)
Salpingo-oophorectomy	0/0 (0.0)	1/1 (0.4)
Stent placement	0/0 (0.0)	2/2 (0.8)
Stent removal	0/0 (0.0)	1/1 (0.4)
Thyroidectomy	1/1 (0.4)	1/1 (0.4)

TABLE 66 Post-discharge SAEs (*continued*)

Event	Participant allocation	
	Randomised to VATS ($n = 244$)[a]	Randomised to open surgery ($n = 249$)[a]
Vascular disorders	2/1 (0.4)	6/5 (2.0)
Deep-vein thrombosis	1/1 (0.4)	1/1 (0.4)
Haematoma	0/0 (0.0)	1/1 (0.4)
Haemorrhage	0/0 (0.0)	2/1 (0.4)
Hypotension	0/0 (0.0)	1/1 (0.4)
Peripheral ischaemia	0/0 (0.0)	1/1 (0.4)
Phlebitis	1/1 (0.4)	0/0 (0.0)

a Data are events, *n*/patients, *n* (%).

Notes
SAEs were coded according to the MedDRA system organ class.
Adapted with permission from *NEJM Evidence*, Lim E, Batchelor TJP, Dunning J, Shackcloth M, Anikin V, Naidu B, *et al.*, Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer, Volume 1, Copyright © 2022 Massachusetts Medical Society.[56]

TABLE 67 Reasons for readmission to hospital

Reason	Participant allocation	
	Randomised to VATS ($N = 70$), *n/N* (%)	Randomised to open surgery ($N = 88$), *n/N* (%)
Infection	32/22 (31.4)	29/25 (28.4)
Medical procedure	21/20 (28.6)	30/25 (28.4)
Chemotherapy toxicities	11/7 (10)	11/10 (11.4)
Shortness of breath	16/15 (21.4)	12/11 (12.5)
Gastrointestinal disorder	4/4 (5.7)	13/11 (12.5)
Pain	8/8 (11.4)	9/8 (9.1)
Pneumothorax/surgical emphysema	6/5 (7.1)	4/3 (3.4)
Physiotherapy/rehabilitation/recovery	5/4 (5.7)	4/4 (4.5)
Cardiovascular	1/1 (1.4)	6/4 (4.5)
Neurological	3/3 (4.3)	5/5 (5.7)
Bleeding	1/1 (1.4)	5/4 (4.5)
Thromboembolism	3/3 (4.3)	4/4 (4.5)
Monitoring	0	3/3 (3.4)
Pleural effusion	2/2 (2.9)	0
Pyrexia	1/1 (1.4)	1/1 (1.1)
Metabolism and nutrition disorder	2/2 (2.9)	0
Other	1/1 (1.4)	5/5 (5.7)

Appendix 6 Additional QRI quotations and table demonstrating imbalanced information provision/loaded terminology

Additional QRI quotations

Acknowledgement of lack of evidence to support bias towards VATS

> *If you go to, if you've been to the big conferences there's so much about VATS lobectomy, why it's better, and so there's been this incredible lack of equipoise, and I think a study like this is required to try and readdress the balance a bit, yeah. You can get carried away by the evangelists.*
>
> *Surgeon, interview*

Conveying equipoise in consultations: general patterns and concerns – expressing uncertainty

> *Of course we don't know what the best way, it may well be that keyhole is better, it may well be that open is better, it may well be that they're exactly the same and that's what was found in a similar study with bowel cancer that it's been very similar.*
>
> *Surgeon, consultation*

Conveying equipoise in consultations: general patterns and concerns – statements later in the consultation that went against their previously expressed neutrality

In favour of VATS

> Surgeon, consultation: *There are two ways of doing this, 70% of these operations in the country are done through big cuts round the side of your chest and spreading your ribs apart. Nowadays more of, some people such as myself are doing more of these with keyhole surgery. Because we think it might be better, we don't know for certain that it's better, but we think it may be better than making a bigger cut.*
>
> Patient, consultation: *Be better wouldn't it? [Conversation continues along similar lines. Patient declines study and opts for VATS.]*

In favour of open surgery

> Surgeon, consultation: *So that's [open lobectomy] the way we're all taught how to do it and it's the that's the standard against which everything else is measured, so if you develop a new way of doing something it has to be measured against that.*
>
> Patient, consultation: *And you can see what you're doing presumably.*
>
> Surgeon, consultation: *Yes so with an open operation you're seeing things with your own eyes and you got conventional instruments, and if you need to then you've got your fingers and thumbs to get in there as well so a lot of people are very comfortable doing it that way so it's a straightforward operation to do.*

Explaining the VIOLET study and related concepts: apologetic study presentation, making assumptions regarding patient's willingness to consider study, closing down conversation and not presenting study to all potentially eligible patients

Surgeon, consultation: *So, if you say you are interested to hear more about this then I will go ahead. If you say well not I've mind up my mind I want this, or I want that then we just stop that, and we carry on with the consultation.*

Patient, consultation: *I'm quite happy for you to go on and explain.*

Surgeon, consultation: *We are running a nationwide study. You can say yes, I'm interested, or say no. And then if you say no we just turn that off and we just carry on with your consultation, or you can even say well I want more time to think about it, tell me more about it and I'll make up my mind later. What is your answer?*

Patient, consultation: *Well . . . I didn't really mind this part [recording], but I didn't really want to carry on with it.*

Surgeon, consultation: *You don't?*

Patient, consultation: *No.*

Surgeon: *OK. That's fine, we can turn this off and just carry on with the consultation. OK, thank you.*

Blinding

Where, whenever the patient was to participate, goes in the study and basically what happens is that we don't know until the very last minute if you will have the thoracotomy or the keyhole surgery, it's going to be decided the very day in order for the whole procedure and the postoperative recovery to be exactly the same for the two. So, is this something you would be interested to participate in?

Surgeon, consultation

Table demonstrating imbalanced information provision and loaded terminology used in consultations to describe the two operations

TABLE 68 Imbalanced information provision and loaded terminology used in consultations to describe the two operations

VATS lobectomy[a]	Open lobectomy[a]
. . . keyhole [sometimes no mention of cuts]	*. . . open cut*
. . . small cuts or small incisions	*. . . big cut or big incision*
. . . we don't know for certain that it's better, but we think it may be better than making a bigger cut	*. . . these operations are done through big cuts round the side of your chest and spreading your ribs apart*
. . . we are big advocates of keyhole surgery 'cause we enjoy doing keyhole surgery	*. . . doing it the traditional way [. . .] the way that we were originally trained to do; most common way; gold standard; extremely well established*
. . . faster, early recovery	*. . . better at taking lymph nodes out*

a Each row is information taken from one consultation to demonstrate information imbalance within a consultation.

Appendix 7 Summary of issues related to trial design identified through QRI

Treatment options outside the trial

In the consultations, most surgeons described how there were several options for early-stage lung cancer. These options included the 'main' and 'gold-standard' option, that is, a lobectomy (via thoracotomy, VATS or robot). Two recruiters told patients that a lobectomy would 'cure' them and few recruiters discussed the possibility of patients needing chemotherapy after a lobectomy. This may suggest that patients might not be expecting any potential adjuvant treatment:

> *[Describes procedure] . . . we're doing it to give you a long-term cure of cancer.*
>
> *Surgeon, consultation*

In addition, recruiters also described how patients could have active surveillance, radiotherapy, radiofrequency ablation and/or chemotherapy. The audio-recorded consultations demonstrated that there was recruiter variation within this. Many patients expressed a preference to have surgery and 'get the cancer out' (patient, consultation).

Robot-assisted lobectomy

Other than via VATS and a thoracotomy, some recruiters described how a lobectomy could also be conducted by robotic-assisted surgery (note that, in the interviews, this was not discussed in the consultations provided). Middlesbrough was the only recruiting centre that had access to a robot. There were mixed feelings as to whether or not robotic surgeries would increase in the future. One recruiter described how NHS England were carrying out a review into robotic thoracic surgery, but stated that this had been delayed. Several likened this to a prostatectomy for prostate cancer, whereby robotic surgery had become the 'gold standard'. Three recruiters commented that the robot was the 'future' for lobectomies:

> *The next step from keyhole is the robot, and people instinctively think that the robot is better, and if you talk to robotic surgeons, and they say I can't believe you're still doing keyhole surgery, the robot is so much better, my patients go home on day 1 or day 2, so there's this incredible bias now.*
>
> *Surgeon, interview*

Other recruiters were less convinced and it was described as being a 'steep learning curve' for surgeons in comparison with VATS, and substantially more costly:

> *[Sighs] A lot of expense is involved, they'll be about five or six cuts in the chest . . . I'm not convinced with this yet. It's an expensive learning curve, I wouldn't get too excited with this.*
>
> *Surgeon, interview*

Radiotherapy

There were discrepancies if and in how radiotherapy was presented to patients. The quotes below demonstrate this:

> *As I say alternative treatment would be to treat this with some radiotherapy but that, although it has lower risks it doesn't give you as good a chance of cure as the surgery.*
>
> *Surgeon, consultation*

> *There are two small studies which suggest that the outcomes of radiotherapy is better, has better overall survival, but those two studies were stopped because they couldn't complete, and the results are considered to be not very conclusive.*
>
> *Surgeon, consultation*

In the interviews, several recruiters also described an ongoing randomised study in Leeds (SABRTooth;[70] 13029788). The feasibility study is currently recruiting and aims to randomise 54 patients to either surgery or stereotactic ablative radiotherapy. Middlesbrough was the only centre in the VIOLET trial to also recruit to the SABRTooth trial,[70] although three other PIs described it as a 'promising' and 'emerging' procedure:

> *SABRE [stereotactic ablative radiotherapy] is very promising and might even be as good as surgery in some cases, whereas radical radiotherapy is far inferior to surgery.*
>
> *Surgeon, interview*

Two (4%) of the patients in the recordings patients opted for radiotherapy. In these recordings, patients commented that they were concerned about their lung function if they were to have a lobectomy. These patients tended to be in poorer health:

> *I think if my breathing gets any worse going uphill I won't be able to go uphill at all, you know . . . I think I shall go for the radiotherapy.*
>
> *Patient, consultation*

Active surveillance

Patients were informed that they could also choose not to undergo any intervention, and some patients appeared anxious at the potential risks of surgery. From the recordings provided, 6% of patients opted for active surveillance:

> *You said you would take the top third of my lung away which frightened me. I'm sorry I'm a wimp [. . .] I don't know, I'm, [–] I'm a bit scared of the big operation, I'm not a spring chicken anymore I'm quite . . . I'm getting on, hmm . . .*
>
> *Patient, consultation*

Segmentectomy

Recruiters described how a segmentectomy could be performed via VATS and open surgery. Although a lobectomy was described as the more effective procedure, there was a feeling that this tended to be more suitable for a small number of patients who were too high risk for a lobectomy:

> *There's a group of patients who, if you did a lobectomy on them and that's taken away too much lung so it would affect their quality of life, would they be breathless afterwards, or they would be at risk of death in hospital, death because it was just too much to take.*
>
> *Surgeon, interview*

The screening logs showed that 6.3% of patients underwent a segmentectomy. Following on from a TMG meeting where there was a discussion regarding whether or not a segmentectomy should be included in the protocol, the QRI researcher asked the recruiters their perspective on the trial design. Two recruiters felt that it should be included in the study:

> Surgeon, interview: *I think it should be included, I don't see really how come we've excluded that. I think that was a weird decision. I understand the reasoning for excluding it, it's a lot cleaner to just go for lobectomies. I would have put it in myself really.*

QRI researcher, interview: *Do you see many patients?*

Surgeon, interview: *Yeah, you see quite a few, that's the thing, 'cause impaired lung function patients with a small tumour, you want to preserve as much lung tissue as possible, so we're probably losing 20% of patients for people that you'd want to reserve the right to do a segmentectomy on. If you don't want to take absolutely everybody to the study then that's probably not too much of a problem.*

Two recruiters also described how it would be considerably more difficult to perform a segmentectomy via VATS. Overall, there was a feeling that including the procedure would 'overcomplicate' a simple study and the potential patient numbers would only be small:

> *VIOLET is a lobectomy study. A segmentectomy to me is possible an inferior operation to lobectomy, and also it's very small numbers as well. So I didn't think there was much to gain, it just confuses, confuses the study, so it's much cleaner if we just keep it to one operation which is the gold standard operation for lung cancer.*
>
> *Surgeon, interview*

In addition, one recruiter described how it would be technically difficult to distinguish between a segmentectomy and a wedge resection:

> *So segmentectomy is just taking a bit of the lobe, but you're still disconnecting blood vessels, and I suspect one little issue may have had is that some people cheat at doing a segmentectomy. What some people call a segmentectomy, others would call something called a wedge resectomy, just get your stapler out and cut round it, with no identification of the vessels. And you can do little cheat ways of doing it where, 'cause there's an artery vein and a bronchus to every lobe and there's an artery vein and a bronchus to every segment, so a segment you should be taking the artery vein and bronchus for that segment. You can cheat a bit, just take the artery and then use a staple gun to just chop through the rest without identifying the rest, though, but then the line becomes a bit blurred between a wedge resection, which everybody thinks is a very bad operation 'cause the recurrence rate's a lot higher, and a segmentectomy which people think is a pretty good operation. So there is a bit of blurring where there's no blurring in a lobectomy. A lobectomy's a lobectomy, there is no blurred lines.*
>
> *Surgeon, interview*

Completion of outcome measures

In some circumstances, patients' planned surgery had been cancelled because of lack of available beds. One recruiter described how the cancellation of scheduled procedures had implications for data collection:

> *We randomise the day before surgery normally, and then get everybody up on the notes ready for surgery to come, and all your file is done from date of randomisation, so, yeah, so your 5-week follow-up, if they then don't get operated on from that date for 2 weeks, then you're stuck, you're sort of, your 5 weeks date won't be a 5-week post-surgery, it will be 3 weeks. So someone, yes, which will be very different data that you're collecting at 3 weeks, post surgery, just because they were randomised. 'cause their pain will be very different, all the questions that you're asking them will be very different from someone that's actually got to the 5-week post-surgery. 'Cause your day 1 and your day 2, obviously you do post-surgery date, but your actual visits are all deemed from the randomisation.*
>
> *Surgeon, interview*

Double blinding

One recruiting site (Bristol) reported difficulties in the blinding component in that patients who usually had a thoracotomy went to a high-dependency unit, whereas VATS patients went to the general ward. Although this made blinding impossible, the alternatives were to send all patients to the general ward (therefore breaching trust guidelines) or all patients to the high-dependency unit (consequently placing a burden on the high-dependency unit's capacity). Recruitment was suspended from December 2015 to January 2016. Most other recruiters described the process of ensuring that the RNs remained blinded as challenging, and one that had been a learning curve. At the beginning, there were several instances where the nurses had quickly become unblinded. This was mostly due to electronic records, patients' notes and handover processes:

> *I just went to look, erm, after the first patient had been in I went to see where he was, whether he was in ITU [intensive care unit] or on the ward, so on the system you've got a thing called e-handover, where all the patients are put on each of the wards, and there's a little spiel about them when they came in, when they were admitted and what was wrong with them, and it just said, really nicely, 'this patient has had an open lobectomy, entered the VIOLET study' and in brackets it said 'the patient is unaware of the approach', so they were OK with that side of it but forgot that we weren't meant to know [laughter].*
>
> *RN, interview*

> *At the beginning of the study it was quite difficult for the research nurse to be blinded, you know, if I go on our electronic system to check which drugs patients have during the surgery for intercostal block, the name of the surgery is there straight away, so it takes me 10 seconds to be unblinded.*
>
> *Surgeon, interview*

> *We've had a slight issue with the fact that we have to put what the operation is on the operation list, because theatres don't want us to, they're desperate to know and they can't accept me just telling them in an e-mail, and want to know in advance. So we're kind of putting it on the op list and so one of the nurses who was going to be in the perioperative management, sort of just saw it on the list by accident looking for another patient.*
>
> *Surgeon, interview*

Most recruiters felt that, having overcome these initial issues, the double blinding process was now 'working well':

> *Apart from that, erm, the others have all managed to stay blinded at the moment, yeah.*
>
> *Surgeon, interview*

> *It's much easier now.*
>
> *RN, interview*

Patients were thought to have been successfully blinded, although surgeons at one site commented that patients became unblinded after having a shower and feeling the size of the incision:

> *Well the patients I think are relatively blinded, they can't see the site of the operation.*
>
> *Surgeon, interview*

> *They say, you gonna tell me what I've had [laugh] and they keep changing their mind what they think they've had. Initially they all think they've had open so far. Because they feel pain they think they must have had it.*
>
> *Surgeon, interview*

The patients have, they've done fairly well in staying blinded.

Surgeon, interview

Some nurses stated that, although they sometimes had 'gut instincts' as to what patients had really had, they did not truly know:

You think you do, but you . . . It's one of those things isn't it, I suppose you know because you have a gut feeling that, what they've had done, but you don't really know, so it's a guess.

RN, interview

I would say that you can try to, you can try to guess . . . But if everything is done according to the protocol it's a bit hard to know which kind of surgery they have. The thoracic is there in the same way, you know, the drain is there in the same way, so, only for looking, no, you would not say definitely which kind of surgery they had.

RN, interview

There were, however, two nurses who commented that it created unnecessary work to an otherwise straightforward study:

What's the point of it, really? It just creates extra work. It serves no function. If I were a patient, I would have a lot to say about why I'm not allowed to know.

RN, interview

One surgeon also said that a patient had declined study because they had wanted to know which procedure they were having.

Standardisation of analgesia

A key component of the VIOLET trial protocol was that patients would be prescribed the same analgesia, regardless of their treatment allocation. When asked about this, the recruiters discussed that this was working well in practice. One centre had also added recovery drinks and mobilisation aids to ensure that everything was standardised between the two groups:

We've been doing the same for both procedures for the last few years already, so it's not going to be an issue for us, it was a very straightforward thing to do.

Surgeon, interview

. . . it's worked brilliantly for us.

Surgeon, interview

Several surgeons commented that there had initially been some reluctance from a minority of anaesthetists:

There have been . . . a couple of old-school people who are still not very happy.

Surgeon, interview

Yes, it's been fine. Everyone's very happy. With the exception of a few. But that's been sorted now.

Surgeon, interview

Level of expertise of surgeon performing the procedure

One recruiter expressed concerns that as VATS were more technically difficult, consultants – rather than registrars – would perform them. This was perceived to have implications in how the findings of the study were interpreted:

> *What's going to happen is that 80% of the opens, which is a very easy operation, are going to be thrown to the registrars, and so only 20% of the VATS, which are difficult, are going to the registrars, 'cause you just have to be a lot better to do it by VATS, and you have to be a VATS trained, or you have to be in a VATS training programme. So I don't really let anybody do a VATS lobectomy who isn't a thoracic trainee, and we get cardiac trainees quite a lot of the time, whereas an open lobe, anyone can do that, piece of cake. So I do have a worry that if I was an open surgeon, and the outcome, and finally I look at the lobectomy studies, and I go 'Wait a second, 80% of registrars did open and only 10% of registrars did VATS, this is a study of registrars versus consultants'. So I think that's a big problem.*
>
> *Surgeon, interview*

The development of VATS and open lobectomies

All of the PIs performed both VATS and open lobectomies. As PIs described the history of VATS, they discussed how the technique had evolved:

> *There was probably a lot of variability for what was called lobectomy in that people were using big spreaders and putting their hands inside the chest for smaller incision or just peeking through a smaller wound rather than looking into the screen so I think it took a while to kind of understand what actually was VATS lobectomy as compared to a small thoracotomy open procedure.*
>
> *Surgeon, interview*

One recruiter voiced concerns that a thoracotomy had also developed in recent years, and that there was a possibility that this had not been captured in the study:

> *I think quite a big thing in the study, is that sort of we haven't thought enough about the open group, and that at the moment I think we're all the VATS evangelists in the study, and we all thought initially we were just going to do 1980s huge thoracotomies, because that's what maybe we were taught a bit as registrars. But actually talking to some American open surgeons they said basically 'God, that's not what a modern thoracotomy surgeon does', and what a modern thoracotomy surgeon does is the best thoracotomy they can do as well. So not all thoracotomies are the same is my discovery, and what most of the study's probably going to end up doing is very large thoracotomies, cutting all the muscles on the chest wall, when actually you can do quite a bit smaller thoracotomy and not cut any of the muscles on the chest wall, and it is, I think, considerably less painful for a patient. I kind of have a, a view that we should actually be trying to do the 2015 most modern thoracotomies we can do as well as the most modern VATS, rather than us all doing the massive posterolateral thoracotomies that they did in the eighties.*
>
> *Surgeon, interview*

Appendix 8 Good practice in addressing preferences as the trial progressed (quotations from the main phase)

TABLE 69 Examples of good practice in addressing patient preference and concerns

Patient preference or concern	Examples of good practice in addressing patient preferences and concerns
Patient's (possible) preference for keyhole because: • keyhole is less invasive • everybody thinks keyhole is the best • keyhole is carried out more frequently	Patient: *'Cause I always feel that the keyhole is less invasive than the open surgery* Surgeon: *So some people believe that the keyhole surgery as you say is less invasive because there's smaller scars, and we're not spreading the ribs and looking directly in, and some people believe that that operation you might recover from more quickly. Or maybe [it] has advantages in terms of pain. Other people believe that the open surgery is better because you are not limited by the angles of your ports, you are free to move and maybe you take more of the lymph glands and maybe that's better in cancer operations. We don't know the answer to that, I don't know the answer to that. I'm not sure, that's why I'm happy to enter the trial as a surgeon* Patient: *Well everybody seems to think that keyhole surgery is the best don't they? I'm no expert* Surgeon: *At the moment the majority of these operations in this country are going through open* Patient: *Yeah* Surgeon: *Erm, and only about a third of them are done by keyhole surgery. So the majority of people in this country prefer to do it through open. Erm, some people say that they can do a better operation through open. Some people say they can do it better through keyhole. So we don't know* Patient: *Am I right in thinking that um [city] does slightly more keyhole operations than open?* Surgeon: *We are one of the centres which do a lot of both* Patient: *It's hard for you maybe to answer this question but I'll ask it anyway do you feel that in [name of hospital] there would be a preference amongst the surgeons?* Surgeon: *I don't think that* Patient: *No* Surgeon: *We wouldn't take part in the study*
Patient's concern about lobectomy because: • open lobectomy is painful	Patient: *OK . . . So I imagine that's [open lobectomy] quite painful* Surgeon: *Well, we don't know, I mean sometimes I have patients, in fact not unusually I have patients who need an operation on both sides. And sometimes because of the way I need to perform the operation I've had to do it open on one side and keyhole on another, and I mean in one patient in particular actually he'd insisted the keyhole surgery was more painful than the open, but pain is a very individual response in all patients. We don't know is the answer* Patient: *Yeah. I don't know either [laughter]*

continued

TABLE 69 Examples of good practice in addressing patient preference and concerns (*continued*)

Patient preference or concern	Examples of good practice in addressing patient preferences and concerns
Patient's (possible) preference for open lobectomy because: • open surgery is tried and tested • open surgery provides better view of, and access to, the tumour	Surgeon: *We discussed in clinic the two ways of doing it, and I think you've got a preference. OK, how would you prefer to . . .* Patient: *The open* Surgeon: *Why's that?* Patient: *Why? Because it's tried and tested, right? That's what you've been doing for a long time. The other one hasn't been going for that long, maybe 6 years or something* Surgeon: *It's been, was done 20 years ago* Patient: *Was it? See I read up that it had only been, 2010 was the first time it was done. But also, you know you're going in with a camera in one bit and something else in the other bit and, how can, you might miss something, you know? This way you can see what you're doing, and I prefer you to see what you're doing [. . .]* Surgeon: *You also mentioned about it's better if you have a look down through the cuts, 'cuz you can see everything inside. Well I would argue that through a small cut I'm seeing sort of that part of your chest, I can't see properly right up the top, or I struggle to see up the top, and I struggle to see right down the bottom. When I put a camera in, I get a good panoramic view of all the, the whole of your chest. So you may actually be able to see better inside, and that's something that we don't know, and that's why we're doing the trial [. . .]* Patient: *No you're giving me the information now that I didn't have* Surgeon: *I want to just give you the information that you didn't have beforehand* Patient: *Yeah I didn't have that you see* Patient: *OK but I'm a lay person obviously one of the things that I, kind of, it was sorted of reflected in some of the notes and when I read that afterwards but I sort of instinctively feel that if you open it up you really can see that little rascal completely, you can see its contexts, you can see where to get the knife and really make sure you get the rascal . . .* Surgeon: *The keyhole gives you a more magnified vision* Patient: *Right* Surgeon: *So it's all on the screen and that's like, like a small problem glove will [unclear] not detect because it's all –* Patient: *Right so you get it magnified* Surgeon: *Magnified, magnified yes*

Appendix 9 Trial committee membership

Independent Trial Steering Committee members

Professor Ruth Langley (chairperson), Professor of Oncology and Clinical Trials; Professor Joy Adamson, Professor of Applied Health Research and Ageing; Mr Ian Hunt, Consultant Thoracic Surgeon; Professor Peter Licht, Professor of Cardiothoracic Surgery; Dr Arjun Nair, Consultant Radiologist; Mr Chris Hall, patient representative; and Mr Mike Cowen, Consultant Cardiothoracic Surgeon (from study start to January 2017).

Independent Data Monitoring and Safety Committee members

Ms Susan J Dutton (chairperson since May 2017, previously a member of the committee), University Research Lecturer and Oxford Clinical Trials Research Unit Lead Statistician; Mr Alan Kirk, Consultant Thoracic Surgeon; Professor Keith Kerr, Professor of Pulmonary Pathology; Mr Rajesh Shah, Consultant Thoracic Surgeon; Dr Nagmi Qureshi, Consultant Radiologist; and Professor Tom Treasure, Professor of Cardiothoracic Surgery (chairperson from study start to March 2017).

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