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[Intervention Protocol]

Robotic-assisted thoracoscopic surgery lobectomy versus open or video-assisted thoracoscopic surgery lobectomy for early-stage non-small cell lung cancer

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

Objective 1: to assess the effects of robotic-assisted thoracoscopic surgery lobectomy versus conventional open lobectomy or video-assisted thoracoscopic surgery lobectomy in people with early-stage non-small cell lung cancer (NSCLC).

Objective 2: to appraise full economic evaluations comparing robotic-assisted thoracoscopic surgery with open lobectomy or video-assisted thoracoscopic surgery lobectomy for early-stage NSCLC by extracting data on resource use, costs, utilities, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) from societal and healthcare perspectives.

BACKGROUND

Description of the condition

Lung cancer occurs when cells in the pulmonary tissue (in one or both lungs) develop mutations and lose their ability to regulate growth. One of the strongest risk factors for lung cancer is tobacco smoking, which is thought to cause approximately 90% of all cases. Smoking rates are higher among people from low socioeconomic backgrounds, who also often face additional barriers to accessing both smoking cessation support and preventative healthcare services [1]. Other risk factors include exposure to radon, advancing age, previous lung disease, and family history of lung cancer. Lung cancer is divided into two histologic categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [2]. NSCLC, which accounts for around 85% of all lung cancer cases, involves various subtypes, among them adenocarcinoma (AD), squamous cell carcinoma (SqCC), and large cell carcinoma (LC) [2, 3]. Most cases of NSCLC are asymptomatic in early stages and are detected as incidental findings during imaging performed for unrelated reasons [3, 4].

In 2020, lung cancer was one of the most common malignancies diagnosed globally, with more than two million new cases registered. It is still the most lethal cancer, both in terms of prevalence and mortality worldwide, with 1.8 million deaths per year [5]. Prognosis and therapeutic options depend on the stage of the disease at the time of diagnosis [6, 7, 8, 9, 10]. For an accurate and timely diagnosis, initial imaging is performed, followed by histopathologic analysis of a tissue biopsy for histologic confirmation, and clinical staging according to the TNM system (tumor-node-metastasis), which assesses tumor size (T), lymph node involvement (N), and distant metastasis (M). According to the 9th edition of the TNM classification, early-stage lung cancer corresponds to stages I and II, characterized by localized tumors without significant regional spread. In contrast, advanced stages include stages III and IV, which involve extensive local invasion, regional lymph node involvement, or distant metastases [11, 12].

Surgical resection, most typically in the form of a lobectomy with systemic lymphadenectomy, represents the standard of care for early-stage NSCLC. Traditionally, this procedure has been performed through a conventional open thoracotomy, which requires a large incision and spreading of the ribs. Over recent years, minimally invasive surgical techniques, such as video-assisted thoracoscopic surgery and robotic-assisted thoracoscopic surgery, have increasingly been adopted, with their promise of minimizing perioperative morbidity [13, 14, 15]. In people for whom surgery is unsuitable, stereotactic ablative radiotherapy (SABR) provides a promising non-invasive alternative solution [16, 17, 18].

Description of the intervention and how it might work

Robotic-assisted thoracoscopic surgery (RATS) was introduced in the early 2000s as an emerging minimally invasive approach for early-stage NSCLC, evolving as an alternative to both conventional open thoracotomy and video-assisted thoracoscopic surgery (VATS) [19]. VATS avoids the large incision of open thoracotomy, but its two-dimensional view and restricted instrument maneuverability can make some dissections technically challenging. RATS was developed to overcome these limitations. The procedure is performed using systems such as the da Vinci Surgical System, which incorporates a surgeon console and robotic arms that mimic

the surgeon's hand movements, enabling precise intrathoracic manipulation [19]. Compared to VATS, RATS provides three-dimensional HD visualization, increased magnification at the console, better wrist articulation of instrumentation and tremor filtration, and improved ergonomics, which may enable more precise dissections and make challenging resections easier [15]. These advantages may be particularly relevant for lymph node dissection, which is a key component of lung cancer surgery. These technical benefits have led to RATS being implemented in specialized thoracic centers, though its utilization varies across regions and institutions due to resource availability and surgeon expertise [20, 21].

People who undergo RATS are less likely to have their procedure aborted due to a conversion to open surgery than those treated with VATS; they also experience less intraoperative blood loss and have a shorter stay in hospital with less post-procedure pain [22, 23]. Regarding oncologic outcomes, compared to people treated with VATs, people treated with RATS may achieve similar or even better lymph node retrieval (LNR), clearer resection margins, and a higher overall survival (OS) rate [21]. However, several factors have limited the broader use of RATS, including incremental procedural costs, limited access to robotic platforms, and a steep learning curve for surgeons. Moreover, patient-specific variables (e.g. comorbidities, tumor characteristics) and institutional experience are likely to affect outcomes. Preliminary economic studies indicate that, despite potential reductions in postoperative complications and length of stay, RATS remains associated with higher operative costs than either VATS or open surgery in most settings [21]. Hence, whether RATS for lung cancer can become a standard surgical care option requires a holistic evaluation in terms of clinical effectiveness and adverse effects, along with cost-effectiveness and equity issues [19, 24].

Geographic disparities in access to thoracic surgeons have been associated with lower surgical utilization and poorer outcomes among patients with early-stage NSCLC, particularly older adults and those in underserved or rural areas [18]. These disparities may further limit the adoption of advanced techniques such as RATS, despite its technical advantages.

Current clinical guidelines, such as those from the American College of Chest Physicians and the National Comprehensive Cancer Network (NCCN), acknowledge RATS and VATS as acceptable approaches for anatomic lung resection in early-stage NSCLC. However, VATS remains more widely adopted due to cost and accessibility considerations [21, 25, 26].

Why it is important to do this review

In a time when the popularity of minimally invasive surgical approaches is growing, RATS is increasingly being considered as an alternative approach for lobectomy in NSCLC. However, as explained above, although RATS offers several technical advantages over VATS and open thoracotomy, its widespread use is hindered by high operative and maintenance costs and the need for specialized training [21].

Despite other surgical specialties providing supportive evidence on the potential benefits of robotic-assisted techniques [20, 27], cost-effectiveness and long-term clinical outcomes of RATS used in lung cancer surgery are unknown. While several studies have suggested improved perioperative outcomes with RATS, evidence

regarding long-term oncologic results remains limited, and its cost-effectiveness relative to VATS or open surgery continues to be unclear. Furthermore, economic evaluations diverge depending on whether a country has universal healthcare coverage or is funded by private insurance, which impacts cost considerations, policymaking, and resource allocation [28, 29].

Given these gaps, it is essential to integrate economic and clinical outcomes in this review to provide comprehensive information for decision-making regarding the adoption of RATS, and assessing the implications of adopting robotic surgery across different settings, particularly in light of varying healthcare funding models and access [22, 23, 29]. Therefore, we plan to explicitly integrate economic evaluations alongside clinical outcome data in this review, aiming to assess the value of RATS not only from a clinical standpoint but also from societal and healthcare system perspectives, an approach recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* [30]. This review will appraise and synthesize the relevant literature that compares surgical outcomes, complication rates, survival, and cost-effectiveness of RATS directly with those of VATS or open lobectomy, providing the best evidence for healthcare providers, policymakers, and patients. Accordingly, the review will include: (1) a clinical effects component, evaluating the benefits and harms of the intervention; and (2) an economic evaluation component, assessing costs, resource use, utilities, QALYs, and cost-effectiveness outcomes.

OBJECTIVES

Objective 1: to assess the effects of robotic-assisted thoracoscopic surgery lobectomy versus conventional open lobectomy or video-assisted thoracoscopic surgery lobectomy in people with early-stage non-small cell lung cancer (NSCLC).

Objective 2: to appraise full economic evaluations comparing robotic-assisted thoracoscopic surgery with open lobectomy or video-assisted thoracoscopic surgery lobectomy for early-stage NSCLC by extracting data on resource use, costs, utilities, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) from societal and healthcare perspectives.

METHODS

This protocol was developed in accordance with the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (hereafter *Cochrane Handbook*) [31], and we will follow the PRISMA-P guidelines to report its conduct and findings [32].

Criteria for considering studies for this review

Types of studies

Clinical effects component

We will include randomized controlled trials (RCTs), quasi-RCTs (studies with treatment allocation based on alternation, alternating medical records, date of birth, or other predictable methods), and cluster-RCTs that evaluate RATS lobectomy compared to conventional surgical treatments, such as open and VATS lobectomy, in people with early stage NSCLC. Given we are interested in comparisons of different surgical techniques, we do not anticipate finding cross-over studies or studies with multiple

intervention groups. We will include studies regardless of whether they are available as full texts, as abstracts only, or are unpublished.

Economic evaluation component

We will include full economic evaluation studies, defined as those comparing both costs and outcomes of two or more alternatives (e.g. cost-effectiveness and cost-utility analyses), that have been conducted alongside RCTs, cluster-RCTs, or quasi-RCTs meeting the eligibility criteria for this review [33]. We will consider two types of economic evaluations linked to eligible trials.

- Trial-based economic evaluations, which analyze individual participant data collected prospectively within the trial
- Model-based economic evaluations, which use data primarily derived from a single included trial to populate a decision-analytic model (such as decision trees or Markov models), are potentially supplemented by external sources to estimate long-term costs and effects.

To maintain feasibility and relevance, we will prioritize economic evaluations based on the following criteria: clinical and contextual relevance to this review, quality of reporting, appropriateness of data inputs, and analytical rigor. For model-based studies, we will accept a minimum time horizon of five years, assuming epidemiological evidence indicates minimal recurrence beyond this period. When feasible, we will prefer lifetime horizons to reflect long-term clinical and economic outcomes comprehensively. To avoid selective reporting and facilitate a valid synthesis, we have prespecified in the outcome measures section which health-related quality of life (HRQoL) measures would be prioritized, based on their relevance, psychometric properties, and frequency of use in the included studies.

Types of participants

For both the clinical effects and economic components of this review, we will include people of any age with a confirmed diagnosis of NSCLC based on imaging modalities (e.g. chest CT (computed tomography), MRI (magnetic resonance imaging), or PET-CT (positron emission tomography)) or histopathological biopsy. Given the focus on early-stage operable NSCLC, initial inclusion will be broad to ensure comprehensive identification of relevant studies; however, participants will be stratified by clinical stage for subsequent analyses. The primary comparative analysis will focus on patients with early stage (I and II) NSCLC, given that this subgroup is more clinically homogeneous and less influenced by technical confounders such as local invasion or metastatic disease. Where data are available and appropriate for synthesis, our secondary analyses may include patients with other non-metastatic or locally advanced stages, such as stage IIIA, which, although classified as locally advanced, may still be considered potentially resectable depending on tumor location and lymph node involvement.

We will consider studies reporting data from mixed-stage populations as eligible if disaggregated data for these early-stage subgroups can be extracted or obtained from the authors. In cases where such data are unavailable, we will carefully evaluate the potential for bias and limitations in synthesis, and the study may be included only in the narrative summary with appropriate caveats [34].

Types of interventions

For both the clinical effects and economic components of this review, we will include studies assessing RATS lobectomy in patients with early stage NSCLC, performed using various surgical platforms and encompassing different technical approaches. We will include two comparisons:

- RATS versus VATS lobectomy; and
- RATS versus open thoracotomy lobectomy.

Outcome measures

Critical outcomes

Clinical effects component

- In-hospital mortality
 - Defined as the number of deaths that occur during hospitalization. Mortality will be assessed up to hospital discharge; if not reported, we will extract data closest to the 30-day postoperative mortality as an alternative time point.
- Serious adverse events (SAEs)
 - Defined as the number of participants who experience at least one event that increases the risk of death, requires or prolongs hospitalization, results in persistent or significant disability, or involves any potentially harmful clinical event. SAEs will be assessed primarily during the index hospitalization; if these data are unavailable, we will extract outcomes reported closest to 30 days postoperatively.
- Disease-free survival (DFS)
 - Defined as the interval from the primary treatment to the occurrence of any of the following events: first documented recurrence of disease (local, regional, or distant), diagnosis of a second primary lung cancer, or death from any cause. People who have not experienced an event by the time of analysis will be censored at their last known follow-up. DFS will be assessed over specified time intervals, with a predefined hierarchy to guide data extraction and analysis. For meta-analysis, we will prioritize HRs as measures of effect. When only time-specific survival estimates are available (i.e. no HR can be obtained), we will prioritize survival estimates closest to five years to ensure comparability across trials and report them as risk ratios (RR). This hierarchical approach aims to preserve consistency across studies while maximizing the inclusion of relevant data.

Important outcomes

Clinical effects component

- Overall survival (OS)
 - Defined as the interval between the date of randomization and the date of death from any cause. Participants who are alive at the time of analysis will be censored at the date of their last known follow-up. We will extract OS as reported by each study (e.g. hazard ratios (HR), survival curves, or time-specific survival estimates). For meta-analysis, we will prioritize HRs as measures of effect. When only time-specific survival estimates are available (i.e. no HR can be obtained), we will prioritize survival estimates closest to five years to ensure comparability across trials and report them as risk ratios (RR).

- Length of hospital stay
 - Defined as the interval between the date of admission and the date of discharge from that hospitalization, usually expressed in days.
- Surgery-related complications
 - We will include any intraoperative or postoperative complications judged to be directly attributable to the surgical procedure. These may overlap with serious or non-serious adverse events but will be reported separately when possible. Examples include prolonged air leak, bronchopleural fistula, hemothorax, empyema, surgical site infection, atelectasis requiring bronchoscopy, conversion from video or robotic surgical access to open/conventional surgery, and other complications specifically associated with lung resection techniques. We will assess complications primarily during the index hospitalization; if these data are not reported, we will extract outcomes closest to 30 days postoperatively.
- Non-serious adverse events (NSAEs)
 - We will include any unintended medical occurrences that do not meet the criteria for seriousness. These events may require minor or no intervention, do not pose an immediate threat to life, and do not prolong hospital stay. Examples include mild or transient arrhythmias, minor wound infections, mild pneumothorax not requiring drainage, postoperative nausea and vomiting, urinary retention, low-grade fever, and other self-limited postoperative symptoms. We will assess NSAEs primarily during the index hospitalization; if these data are unavailable, we will extract outcomes reported closest to 30 days postoperatively.
- Health-related quality of life (HRQoL)
 - We will prioritize measurements using the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) [35]. If unavailable, we will include any validated instrument that can be directly converted to utilities (e.g. Health Utilities Index (HUI) [36]). When neither EQ-5D-5L nor convertible measures are reported, we will include other validated HRQoL instruments, whether generic (e.g. WHOQOL-BREF [37], SF-36 [38]) or disease-specific (e.g. EORTC QLQ-LC13 [39], FACT-L [40]). We will extract data at all reported time points. For meta-analysis, we will group assessments into short term (up to 3 months after surgery), medium term (> 3 to 12 months), and long term (> 12 months after surgery).

Economic evaluation component

- Utility values and quality-adjusted life years (QALYs)
 - We will prioritize utility values measured using the EQ-5D-5L and based on the national value sets applied in the included studies. We will use the utilities reported by the included studies to estimate QALYs. When studies do not report utilities but provide other eligible HRQoL measures, we will use validated mapping algorithms to convert these measures into EQ-5D-5L compatible utility values and subsequently estimate QALYs. We will extract all available utility values reported at any follow-up time, reflecting the changes in health-related quality of life over time and the time spent in each health state.
- Resource use and costs
 - This economic analysis will adopt both a healthcare system and a societal perspective, giving priority to the societal perspective. From the healthcare system perspective, we

will include direct medical costs such as hospitalization (including intensive care unit and ward stays), outpatient consultations, procedural resources (e.g. operating room time and surgical equipment), post-procedural treatments (e.g. prescribed medicines), and surveillance (e.g. imaging tests). High-cost items not adequately captured by per diem charges (e.g. robotic equipment, specialized instruments) will be identified separately to avoid double-counting. From the societal perspective, we will additionally include indirect costs, where reported, such as productivity losses, caregiver time, and out-of-pocket expenses (direct medical and non-medical, e.g. co-payments, transport, accommodation, informal caregiving), as well as opportunity costs (i.e. benefit foregone when resources used for one purpose instead of their best alternative use [41]) [42]. To avoid double-counting, we will clearly distinguish productivity losses from broader opportunity costs and will extract the valuation methods used (e.g. human capital or friction cost approach) when these costs are reported. Where available, we will report total costs as incremental costs per person. We will prioritize results based on a lifetime time horizon. If these data are unavailable, we will prioritize the longest time horizon, with a minimum of 5-year horizon to be accepted.

- Incremental cost-effectiveness ratio (ICER)
 - We will calculate ICERs as the ratio of incremental costs to incremental effects. For cost-effectiveness analyses, effects will be expressed in natural units (e.g. life-years gained); for cost-utility analyses, effects will be expressed as QALYs gained. We will prioritize results based on a lifetime time horizon. If lifetime estimates are not available, we will prioritize analyses with a time horizon of at least five years, using the longest available horizon when multiple are reported.

Search methods for identification of studies

We will search for all relevant studies without restrictions on language, year, or publication status.

Electronic searches

Clinical effects component

We will search the following databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL, to the latest issue), from inception to present (see [Supplementary material 2](#))
- MEDLINE accessed via PubMed (from 1946 to present) (see [Supplementary material 3](#))
- Embase accessed via Elsevier (from 1980 to present) (see [Supplementary material 4](#))

We will search all databases using both controlled vocabulary (namely, medical subject headings (MeSH) in MEDLINE and Emtree in Embase) and a wide range of free-text terms. We will perform the MEDLINE search using the Cochrane Highly Sensitive Search Strategy precision-maximizing version, as described in the *Cochrane Handbook* [43].

We will search the following trial registers.

- ClinicalTrials.gov (clinicaltrials.gov/) (see [Supplementary material 5](#))

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/clinical-trials-registry-platform) (see [Supplementary material 5](#))

We will present the full search strategies for all databases and registers, including the date when each source was last searched. We will report search methods according to the guidance provided in the *Cochrane Handbook* to ensure transparency and reproducibility, and to facilitate future updates [43]. We will also indicate in which databases the included studies were found. We will use EndNote software to manage records and remove duplicates [44].

Economic evaluation component

We will conduct a parallel search specifically for economic evidence in the following databases.

- MEDLINE accessed via Pubmed (from 1946 to present)
- Embase accessed via Elsevier (from 1980 to present)
- The Tufts Medical Center Cost-Effectiveness Analysis Registry (<https://cear.tuftsmedicalcenter.org/>) (1976 to present)
- INAHTA (International Network of Agencies for Health Technology Assessment) database (<https://database.inahta.org/>), current coverage

The economic search strategies we plan to use are presented in [Supplementary material 1](#).

Searching other resources

Clinical effects component

We will search Open Grey (<http://www.opengrey.eu/>) and ProQuest Dissertations & Theses Global (<https://search.proquest.com/pqdtglobal/dissertations/>) using the free-text terms from the MEDLINE search from inception. We will also look for surgical device reviews submitted to the US Food and Drug Administration (FDA) [45].

We will search for relevant material in the following associations and societies.

- European Society for Thoracic Surgery (ESTS)
- European Respiratory Society (ERS)
- European Association for Cardio-Thoracic Surgery (EACTS)
- Society of Thoracic Surgery (STS)
- American Association of Thoracic Surgery (AATS)
- American Thoracic Society (ATS)
- American Society of Clinical Oncology (ASCO)
- International Association for the Study of Lung Cancer (IASLC)

As part of our search strategy, we will actively monitor for any post-publication amendments concerning included or eligible studies. Specifically, we will undertake the following tasks.

- Check for expressions of concern, errata, corrigenda, and retractions by consulting relevant databases such as Retraction Watch, PubMed, and CrossMark
- Review publisher websites and journal pages for notices related to included studies
- Utilize automated alerts and database updates to identify any changes occurring after publication

We will document and report all identified amendments within the review. Furthermore, as recommended in the *Cochrane Handbook*, we will assess the potential impact of such changes on the validity and conclusions of the review [46].

Economic evaluation component

To identify economic evidence, we will also search relevant grey literature, including health technology assessments, reports, and working papers. Specifically, we will search the websites of international Health Technology Assessment (HTA) agencies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (Conitec, Brazil).

In addition to electronic database searches, we will employ forward and backward citation tracking as complementary methods for identifying additional relevant economic evaluations. We will apply forward citation tracking to all included studies to identify economic evaluations derived from or linked to these studies. Backward citation tracking will involve examining the reference lists of included economic evaluations to identify the clinical trials that underlie trial-based or model-based analyses. This approach aims to strengthen the connection between economic evaluations and their clinical evidence source, enhancing the comprehensiveness of the search, particularly where relevant studies may be poorly indexed in bibliographic databases.

Data collection and analysis

Data sharing is not applicable to this article, as it is a protocol and no datasets were generated or analyzed.

Selection of studies

Two review authors (EIL and DA) will independently screen the titles and abstracts of all potential studies identified through the search strategy. Any disagreements will be resolved through discussion or, if necessary, by consulting a third review author (HS). We will identify and remove duplicate studies, and collate multiple reports of the same study, so that the unit of inclusion is the study rather than an individual report. We will use Covidence software to facilitate duplication detection, screening, and full-text assessment [47].

As the review encompasses two distinct study types, those evaluating clinical effectiveness and those reporting economic evaluations, we will conduct study selection separately for each component. Accordingly, we will produce two PRISMA flow diagrams: one for clinical effectiveness studies and another for economic evaluations. Similarly, we will prepare two separate 'characteristics of excluded studies' tables to list the full-text articles we exclude and the reasons for their exclusion. We will document the entire selection process in sufficient detail to ensure transparency and reproducibility [48, 49].

Data extraction and management

Two review authors (EIL and AR) will independently extract outcome data from the included studies. If outcome data are not reported in a usable way, we will note this in the 'characteristics of included studies' table. We will resolve disagreements by consensus or by involving a third review author (HS). One review author (AR) will transfer data into Review Manager (RevMan) [50]. A

second review author (EIL) will 'spot check' study characteristics for accuracy against the trial report. We will use the Covidence software for data extraction [47].

Clinical effects component

We will extract the following study characteristics.

- **Methods:** study design, total duration of the study, details of any run-in period, number of study centers and locations, study setting, withdrawals, date of the study, and dates of first and last enrolled participants, and, for cluster-RCTs, the unit of randomization, the number of clusters per arm, cluster size (mean and variability), and whether analyses accounted for clustering
- **Participants:** number of participants, mean age, age range, sex distribution, diagnostic criteria, baseline lung function, smoking history, inclusion and exclusion criteria, medical history before diagnosis of NSCLC, pathological confirmation of NSCLC, tumor staging according to the IASLC (International Association for the Study of Lung Cancer) TNM classification [11, 12]
- **Interventions:** intervention, comparison, duration, same or different surgeons, bleeding, transfusion, surgical duration, and complications, need for conversion from video or robotic surgical access to open/conventional surgery (e.g. there are cases where severe complications, such as significant bleeding, prevent adequate visualization with the video optics, and there is a need for rapid control of the lesion, making an emergency thoracotomy a safer option.)
- **Outcomes:** critical and important outcomes of the study, as documented in publications or extracted from trial protocols
- **Results:** number of inclusions per arm, study flow diagram, sample size, number of and reasons for dropouts or missing data, handling of intention-to-treat and missing data, summary data per group, effect estimates with confidence intervals (CI) and P value, and subgroup analysis, and, for cluster-RCTs, intraclass correlation coefficients (ICCs) for each outcome or sufficient information to calculate them (e.g. average cluster size, number of clusters per arm, within- and between-cluster variability), as well as the statistical methods used (e.g. mixed-effects models, Generalized Estimating Equation (GEE), or cluster-robust variance estimators)
- **Notes:** funding sources, role of sponsor in the study, trial registration code, and declared conflicts of interest, including information relevant to cluster-specific risk of bias domains such as recruitment bias, baseline imbalance, loss of clusters, and contamination

Economic evaluation component

We will develop a separate data extraction form for economic evaluations, based on the NHS Economic Evaluation Database (NHS EED) format and guidance [51], adapted for this review. This form will be piloted on at least one included economic evaluation before full data extraction to ensure clarity and consistency.

We will collect the following data from the economic evaluation studies.

- Type of evaluations (e.g. cost-effectiveness analysis (CEA) and cost-utility analysis (CUA))
- Country and organizational setting

- Sources of effects data (e.g. clinical trial, observational study)
- Inputs and assumptions for model-based studies
- Outcome measures and sources (e.g. HRQoL measured using EQ-5D-5L, from which QALYs are derived)
- Source and description of health state utility values (including sample size, means, medians, and standard errors)
- Resource use and associated costs (e.g. surgical time, length of stay, equipment), cost categories (e.g. direct medical, indirect), methods and data sources, unit costs, reported currency, and price year
- Perspective of the analysis (e.g. healthcare system, societal)
- Time horizon and discount rate applied
- Study design and analytic framework (e.g. trial-based analysis; model-based approaches such as microsimulation or Markov models)
- PICO elements (population, intervention, comparator, outcomes)
- Details of study participant selection and recruitment methods, and attrition and losses to follow-up
- Source of funding and potential conflicts of interest
- Incremental Cost-Effectiveness Ratio (ICER); incremental costs, deterministic and probabilistic sensitivity analyses

When the economic evaluation is based on a specific clinical trial, we will also extract relevant methodological and participant information from the corresponding trial publication to assess consistency. If the cost data are not fully reported in the original manuscript, we will contact study authors for further information. We will document any discrepancies between economic and clinical reports and consider these in our assessment of the certainty of the evidence.

Risk of bias assessment in included studies

Clinical effects component

Two authors (EIL and ACPNP) will independently assess the risk of bias for each outcome result using the Cochrane risk of bias tool (RoB 2) [52]. We will evaluate both the impact of being assigned to the intervention ('intention-to-treat effect') and the impact of adhering to the intervention ('per-protocol effect') for each main outcome result and time point that we have specified for inclusion in the 'summary of findings tables' [53].

We will assess both effects because the review aims to evaluate the real-world effectiveness of the intervention (effect of assignment), as well as its efficacy under ideal adherence conditions (effect of adherence), in accordance with Section 8.2.2 of the *Cochrane Handbook* [49]. This dual approach allows for a more comprehensive understanding of the intervention effects.

We will assess both the effect of assignment to the intervention and the effect of adhering to the intervention for each of the main outcomes and time points that we will present in our summary of findings tables (see [Certainty of the evidence assessment](#)). We will assess the risk of bias according to the following domains.

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome

- Bias in selection of the reported result

We will judge each potential source of bias as 'low', 'some concerns', or 'high risk of bias', based on answers to the signaling questions. We will consider objective outcomes, such as mortality, at low risk of bias, regardless of whether participants, staff, and evaluators were blinded. We will use an Excel tool to record and manage RoB 2 assessments [49, 54]. We will resolve any disagreements by discussion or by involving another review author (HS).

For cluster-randomized trials, we will assess additional domains specific to the cluster design, including recruitment bias, baseline imbalances, loss of clusters, incorrect analysis, and comparability to individually randomized trials, following *Cochrane Handbook* guidance [55]. These will be incorporated into the overall RoB 2 judgment using the cluster-specific RoB 2 tool where applicable.

We will summarize the risk of bias judgments for each outcome across all domains, providing justifications for the judgments in the 'risk of bias' table [49, 54, 56]. We will use the overall RoB 2 judgments for our GRADE assessments [52, 57].

We plan to focus primarily on the effect of assignment for the main analyses and GRADE assessments, as this reflects the standard intention-to-treat principle. However, we will extract results related to the effect of adherence and present these in supplementary tables. We will discuss any differences between these effects in the review text to enhance transparency and interpretability.

Economic evaluation component

For the economic evaluation studies, we will perform a two-stage process. The first stage will involve examining the risk of bias in the sources of effectiveness data using RoB 2 [54]. We will carefully compare trials and economic evaluations to see if they agree and will consider both reports for the RoB 2 assessments. In the second stage, we will assess bias in economic evaluations using the Consensus Health Economic Criteria (CHEC) list [58], the CHEERS checklist [59, 60] for trial-based studies. For model-based studies, we will use the NICE study limitations checklist [61] and CHEERS checklist, supplemented by the Philips checklist [62].

We will consider that a study has important methodological limitations if it does not perform sensitivity analyses exploring key cost-effectiveness drivers (e.g. cost of the robotic acquisition and maintenance); if it does not consider important differences in effects (e.g. differences in length of stay/complications); if it does not report information on sources of inputs (e.g. utilities, costs); if it does not use validated measures for evaluating utilities (e.g. EQ-5D-5L); or if the duration of follow-up is not sufficient (i.e. a minimum of five years).

Measures of treatment effect

Clinical effects component

We will assess the treatment effect on time-to-event outcomes, specifically OS and DFS, using hazard ratios (HR) with 95% confidence interval (CI) for each comparison and outcome. We will extract HR and standard errors (SE) from reported data, or estimate them from alternative sources, including Kaplan-Meier curves, where feasible [33, 48, 63, 64]. For dichotomous variables, we will measure the treatment effect for treatment-related in-hospital mortality and serious adverse events using the risk ratio (RR) with 95% CI. The results for the length of hospital stay will be

reported as a mean differences (MD) with 95% CI. According to the data availability, we will consider using change-from-baseline or postintervention value scores and plan to summarize these types of results separately.

We will conduct meta-analyses only when they are appropriate, meaning when the treatments, participants, and underlying clinical questions are similar enough to justify combining data. For meta-analyses involving at least one study with zero events in both arms, we will opt for risk differences (RDs) rather than relative risks (RRs), as the Mantel-Haenszel method for RRs automatically excludes such studies [65].

Study authors often signal skewed data by presenting medians and interquartile ranges (IQRs). When we identify this, we will acknowledge the skewness, assess its implications, and choose not to pool these studies in a meta-analysis, providing a descriptive summary instead.

In cases where studies include multiple arms, we will select only the pertinent ones for analysis. If a study contributes two relevant comparisons to the same meta-analysis, we will divide the control group size by two to prevent over-representation.

Economic evaluation component

We will present point estimates for resource use and cost items, along with their associated measures of uncertainty, for both the target intervention and its comparators. We will report incremental costs and cost-effectiveness estimates, including uncertainty measures.

We will convert all costs to US dollars (USD) in 2026 using a mixed deflator approach. We will prioritize healthcare-specific deflators (e.g. the Medical Care Consumer Price Index in the USA) to best reflect sector-specific inflation trends. In cases where healthcare-specific deflators are unavailable, we will use the CCEMG-EPPI Centre Cost Converter tool (<https://eppi.ioe.ac.uk/costconversion/default.aspx>), which applies Purchasing Power Parities (PPP) and general GDP deflators.

We will conduct sensitivity analyses, where possible, to evaluate the impact of alternative deflator assumptions on cost estimates.

Unit of analysis issues

The participant will be the primary unit of analysis. We will include RCTs, quasi-RCTs, and cluster-RCTs in this review. For cluster-RCTs, we will check whether appropriate methods to account for clustering have been used in the analysis. If clustering has not been accounted for, we will adjust the data using intracluster correlation coefficients (ICCs) obtained from the trial or similar studies, as recommended in the *Cochrane Handbook* [55]. We will perform sensitivity analyses to assess the impact of these adjustments.

We do not anticipate including cross-over trials given the nature of the interventions. For trials with multiple intervention groups, we will combine or split relevant data to ensure only one pairwise comparison is included in each meta-analysis, preventing double counting of participants [66].

Dealing with missing data

We will contact the investigators or sponsors of the studies to verify the key characteristics of the studies and obtain any missing

numerical outcome data whenever possible, particularly for studies available only in abstract form. If verification is not possible and the absence of data is considered a potential source of significant bias, we will assess the impact of including such studies in the overall evaluation of results through sensitivity analysis.

In cases where numerical outcome data, such as standard deviations (SDs) or correlation coefficients, are missing and cannot be obtained from the authors, we will not perform imputation of these missing data. When studies provide medians and IQRs instead of means and SDs, we will present the data narratively and will not conduct meta-analysis.

Reporting bias assessment

We will assess reporting biases by drawing a funnel plot (trial effect versus trial size), assuming we include enough trials in the review (more than 10 for each outcome). To test for asymmetry, we will perform a regression-based method as suggested by Page and colleagues [67, 68].

Synthesis methods

Clinical effects component

We will conduct quantitative synthesis of clinical outcomes where appropriate. For outcomes reported in a sufficient number of comparable studies, we will perform meta-analyses using the random-effects model as the default approach, since clinical diversity is expected. The Restricted Maximum Likelihood (REML) estimator will be used to estimate between-trial variance (heterogeneity). When there are at least three studies and heterogeneity is greater than zero, we will apply the Hartung-Knapp-Sidik-Jonkman method to calculate CI for the pooled effect estimate. In other scenarios (e.g. meta-analyses including only two studies or where heterogeneity is zero), we will use the Wald-type method.

For each outcome, we will calculate summary effect estimates (e.g. risk ratios or mean differences) with 95% CI. We will assess statistical heterogeneity using the I^2 statistic and χ^2 test, and we will explore potential sources of heterogeneity through subgroup analyses when feasible [65].

If meta-analysis is not appropriate due to substantial heterogeneity or insufficient data, we will provide a structured narrative synthesis. This will include a tabulated summary of study characteristics and findings, grouped by intervention and outcome, and will follow guidance from the *Cochrane Handbook* [69, 70].

To assess the robustness of the results, we will perform sensitivity analyses using a fixed-effect model for the critical outcomes (i.e. in-hospital mortality, SAEs, DFS). In cases of divergence between models, we will report both results; otherwise, we will present only the results from the random-effects model [65, 70].

Economic evaluation component

We will use additional tables to summarize the characteristics, methods, and key results of the included economic evaluations. We will convert estimates to current-year USD, where possible, to enhance comparability. We will conduct a structured narrative synthesis, comparing studies in terms of study design, analytical perspective, time horizon, model structure (if applicable), data sources for costs and outcomes, and reported results (e.g. QALYs,

ICERs). We will report relevant differences across studies in terms of input data considered in the studies (i.e. unitary costs, incidence-prevalence) and in the resulting differential resource use and costs. In line with *Cochrane Handbook* guidance, we will not perform a meta-analysis of economic outcomes [71], as such results are highly context-dependent, and pooling estimates may reduce rather than enhance their relevance. Instead, we will explore and explain how and why the results differ across studies.

Investigation of heterogeneity and subgroup analysis

Assessment of heterogeneity

We will assess initial heterogeneity visually through forest plots, evaluating the overlap of CIs across studies. We will evaluate statistical heterogeneity using the χ^2 test (significant if $P < 0.1$) and quantified with the I^2 statistic, interpreted as follows [72, 73, 74].

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We will explore the potential causes of substantial and considerable heterogeneity through the prespecified subgroup analyses below [70, 73].

Subgroup analysis

We plan to conduct subgroup analyses to examine whether the effects of interventions differ across various population groups, with an emphasis on equity-related factors. These subgroup analyses aim to identify potential disparities in effectiveness and inform equitable implementation strategies. The primary comparisons for this review are surgical approaches: RATS lobectomy versus VATS lobectomy versus open thoracotomy lobectomy. Additionally, we will extract data on surgical duration, length of hospital stay, and complications, to examine time-dependent relationships and their variation across surgical approaches (RATS, VATS, open thoracotomy).

We plan the following subgroup analyses. We will test subgroup differences using the formal test provided in RevMan [50].

- Age (PROGRESS-Plus): older participants (≥ 60 years) versus younger participants (< 60 years). We hypothesize that older participants may have poorer outcomes, such as longer hospital stays and more complications [75].
- Place of residence (PROGRESS-Plus): countries categorized by Human Development Index (HDI) - low/middle versus high/very high. We expect that participants living in lower development settings may face delayed diagnosis and slower initiation of treatment [75].
- Lung cancer stage (clinical subgroup): early (stage I to II) versus advanced (stage III to IV) disease, recognizing that higher stage is associated with more complex procedures and potentially worse outcomes, independent of equity considerations. According to the 9th edition of the TNM staging system by the IASLC, stage I NSCLC includes tumors up to 4 cm in size without lymph node involvement (T1 to T2a N0 M0), while stage II encompasses tumors larger than 4 cm (T2b to T3) or any tumor up to 5 cm with ipsilateral lymph node involvement

(N1). It may also include tumors between 5 and 7 cm without lymph node involvement or distant metastases (T3 N0 M0), classified as stage IIA or IIB depending on tumor size and extent. Stage III, in turn, involves mediastinal lymph node involvement or invasion of adjacent structures (N2/N3 or T4), while stage IV is characterized by distant metastases, including malignant pleural effusion or lesions in other organs (M1a to c) [11, 12].

Equity-related assessment

There may be unequal provision, access, participation, and outcomes in robotic surgeries, mainly due to financial and social constraints and differences in awareness of rapid technological advances. As part of Cochrane's current efforts to include health equity considerations in systematic reviews, we plan to assess equity-related considerations relevant to the treatment of lung cancer with robotic surgeries [76].

Based on the participant characteristics table from PRO EDI (available at Trial Forge - Pro EDI) and the characteristics defined by the PROGRESS-Plus framework [75] (available at PROGRESS-Plus), we plan to quantify the populations in included studies according to race/ethnicity, sex/gender, educational levels, and place of residence (urban versus rural), and to describe barriers to access or participation in robotic surgeries reported in the included studies according to race/ethnicity and sex/gender, educational levels, and type of residence (urban versus rural), for example, due to lack of time to participate because of social roles, occupation, etc. We will present the results in tabulated summaries and report any baseline risk variations identified, as well as whether there are significant differences between groups in participant dropout rates during the study, based on the reasons for dropout reported in the studies.

We will also consider equity-related differences across countries of different development levels using the HDI - see relevant subgroup analysis described above.

Sensitivity analysis

Clinical effects component

To assess the robustness of the conclusions, we plan to conduct the following sensitivity analyses for the critical outcomes (i.e. in-hospital mortality, SAEs, DFS) and economic results.

- Excluding studies judged to be at high of bias in any domain of the RoB 2 tool
- Excluding clinical studies in which the sponsor was involved in the design or conduct of the trial
- Excluding unpublished results
- Repeating the analyses using the fixed-effect model (data synthesis)
- Excluding studies where cluster-RCT data have not been appropriately adjusted for clustering to assess the impact of this on the overall findings
- Assessing the impact of missing data by repeating analyses using alternative plausible assumptions for missing outcome data

We will document and report any methodological amendments made by the review authors during the conduct of the review under a section entitled 'Differences between the review and the

protocol'. We will then quantitatively assess (where feasible) or narratively discuss how these changes may affect the validity and conclusions of the review.

Economic evaluation component

- Excluding economic evaluation studies where the sponsor (especially industry) was involved in the design, conduct, analysis, or writing of the economic component [77]
- Restricting the clinical outcome analysis to trials for which an economic evaluation is available, to assess whether these studies differ systematically in effect estimates, such as greater imprecision or potential shifts in direction of effect, compared to the full set of included trials
- Recalculating economic results using healthcare-specific deflators (e.g. Medical Care Consumer Price Index, Personal Health Care Deflator), where available, to assess the impact of alternative inflation assumptions compared to general GDP-based deflators
- Excluding economic evaluation studies judged to have important methodological limitations according to CHEC (if trial-based) or NICE checklist (if model-based)

Certainty of the evidence assessment

We will prepare summary of findings tables summarizing the evidence for the two comparisons of interest (RATS versus VATS lobectomy, and RATS versus conventional open thoracotomy lobectomy), on the effect of assignment to intervention for the following outcomes [55, 57, 78].

- In-hospital mortality, assessed up to hospital discharge. When this outcome is not reported, we will use 30-day postoperative mortality as a substitute measure.
- SAEs, assessed primarily during the index hospitalization; if not reported, we will use the time point closest to 30 days postoperatively.
- DFS at five years (HR will be the preferred effect measure; prioritized as HR; if unavailable, we will use the survival estimate closest to five years and meta-analyze it as RR.)
- OS (prioritized as HR; if unavailable, we will use the estimate closest to five years and meta-analyze it as RR)
- Length of hospital stay (days from admission for the index hospitalization to discharge)
- Incremental cost per person will be assessed using a lifetime time horizon whenever possible. When a lifetime horizon is not available, we will prioritize economic evaluations with the longest reported time horizon, provided it is at least five years.
- ICER will be assessed over a lifetime horizon if possible. When a lifetime horizon is unavailable, we will use the longest reported time horizon in each economic evaluation, provided it is at least five years.

We have selected our time points and outcome definitions for clinical relevance and in accordance with *Cochrane Handbook* recommendations.

Two review authors (EIL, ACPNP) will independently assess the certainty of the body of evidence for each outcome using the GRADE approach. We will resolve any discrepancies through discussion or, if necessary, consultation with a third author (HS). We will apply the five GRADE domains (study limitations, consistency of effect,

imprecision, indirect evidence, and publication bias) to assess the certainty of the body of evidence, based on the RCTs that contribute data to the qualitative or quantitative syntheses for each outcome. We will classify the evidence's certainty as high, moderate, low, or very low [54]. We will follow the methods and recommendations outlined in the *Cochrane Handbook* [30] and use GRADEpro GDT software for the assessment [57].

We will justify all decisions to downgrade the certainty of the evidence in footnotes [79, 80, 81]. Where additional information is available for outcomes we have not included in the meta-analyses, we will describe this data in the column for comments, indicating whether it supports or contradicts the meta-analytic findings.

For economic outcomes that we will include in the summary of findings table (e.g. incremental costs and ICER estimates), we will assess the certainty of the economic evidence using an adapted GRADE approach, as outlined in published guidance for economic evaluations [82]. For incremental cost outcomes, we will apply GRADE as for continuous outcomes, except when outcomes are reported as proportions, in which case they will be treated as dichotomous outcomes. We will not assess the certainty directly for the final outputs of economic evaluations (e.g. ICERs); instead, it will be inferred from the separate GRADE assessments of incremental costs and incremental effects. For model-based economic evaluations, we will also consider factors such as the quality of the underlying clinical evidence, the relevance and quality of economic data inputs, the transparency and validity of modeling methods, model credibility, and the consistency of results across settings.

Consumer involvement

The review will be conducted without direct involvement of consumers due to limited resources. However, this protocol was commented on by a consumer reviewer. We have aimed to include and prioritize outcomes that are important to people undergoing lung cancer treatment, as identified by the Core Outcome Measures in Effectiveness Trials initiative (available at <https://www.comet-initiative.org/>) [83].

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD016158](https://doi.org/10.1002/14651858.CD016158).

Supplementary material 1 Search strategies

Supplementary material 2 Supplementary material - CENTRAL

Supplementary material 3 Supplementary material - MEDLINE (accessed via PubMed)

Supplementary material 4 Supplementary material - Embase (accessed via Elsevier)

Supplementary material 5 Supplementary material - Clinical Trials E WHO

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): John C Ruckdeschel, MD, Fox Chase Cancer Center, Philadelphia, PA, USA
- Managing Editor (provided editorial guidance to authors, edited the article): Pricivel Carrera, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments and supported editorial team): Cynthia Stafford, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Laura MacDonald, Cochrane Central Production Service
- Peer reviewers (provided comments and recommended an editorial decision): Sarah Lukeman, Patient Perspective Professional (patient and public review); Tom Patterson, Cochrane Evidence Production and Methods Directorate(methods review); Luke Vale, Professor of Health Economics, London School of Hygiene and Tropical Medicine, UK (economic review); Jo Platt, Central Editorial Information Specialist (search review)

Contributions of authors

EIL conceived and designed the protocol, drafted the manuscript, revised the content, and approved the final version.

AR contributed to drafting sections of the manuscript, revised the content, and approved the final version of the protocol.

ACPNP contributed to drafting sections of the manuscript, revised the content, and approved the final version of the protocol.

DA contributed to drafting sections of the manuscript, revised the content, and approved the final version of the protocol.

HS contributed to drafting sections of the manuscript, revised the content and methods, and approved the final version of the protocol.

Declarations of interest

EIL has no commercial or non-commercial conflicts of interest relevant to this review.

AR has no commercial or non-commercial conflicts of interest relevant to this review.

ACPNP has no commercial or non-commercial conflicts of interest relevant to this review.

DA has no commercial or non-commercial conflicts of interest relevant to this review.

HS has no commercial or non-commercial conflicts of interest relevant to this review.

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Internal sources

- None, Other

None

External sources

- None, Other

None

Registration and protocol

Cochrane approved the proposal for this review in April 2024.

Data, code and other materials

Data sharing not applicable to this article as it is a protocol, so no datasets were generated or analyzed.

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