Study protocol: a core outcome set for perioperative exercise clinical effectiveness trials for lung cancer patients

Wanjun Zhou (wjzhouahmu@163.com)
Anhui Medical University

Yawen Zhang
Anhui Medical University

Zhiwei Wang
Anhui Medical University

Liang Zhang
First Affiliated Hospital of Anhui Medical University

Xinqiong Zhang
Anhui Medical University

Research Article

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Abstract

Background

Outcome assessment in perioperative exercise trials of lung cancer is heterogeneous, often omitting those that are important and patient-relevant. This hinders evidence synthesis. To solve this problem, a core outcome set, an agreed standardized set of outcomes to be measured and reported to reduce heterogeneity among outcome measures, is needed. This study protocol describes the methodology, aiming to develop a core outcome set for perioperative exercise intervention trials for lung cancer in clinical practice.

Methods

The project will follow the standard methodology recommended by the Core Outcome Measures in Effectiveness Trials (COMET) initiative, which will be divided into four steps. Stage 1: Conduct a scoping review of outcomes reported in clinical trials and protocols to develop a list of potential outcome domains. Stage 2: Conduct semi-structured interviews to obtain important outcomes for patients. Stage 3: Choose the most important outcomes by conducting two-round Delphi surveys. Stage 4: Establish consensus in a face-to-face meeting to discuss the final core outcome set.

Discussion

This is the first project identified for the core outcome set of outcomes for perioperative exercise trials for lung cancer, which will improve the quality, comparability, and usability of future trials and positively impact the perioperative exercise and the care of patients with lung cancer.

Trials registration

Core Outcome Measurement in effectiveness Trials (COMET) Initiative database registration:

https://www.comet-initiative.org/Studies/Details/2091

Background

Lung cancer (LC) is the most common tumor of respiratory system disease worldwide, characterized by a low early detection rate, rapid progression, and significant burden of symptoms [1]. LC accounted for 11.4% of all new cancer cases and 18% of all cancer mortality for 36 cancers in 185 countries [2]. Surgical resection, as the most effective radical treatment of early-stage LC [3], has increased the five-year survival rates of patients to 60% [4]. Although surgery provides a chance of cure, it also immediately damages the cardiopulmonary function. And the incidence of postoperative complications will be increased, affecting the prognosis and even endangering the patient's life [4]. Perioperative exercise has been demonstrated to promote the rehabilitation of patients.
Exercise training is a subset of physical activity that is planned, structured, and repetitive, and has a final or intermediate objective, the improvement or maintenance of physical fitness [5]. Perioperative exercise, as an economical, safe, and effective treatment for lung cancer patients, has been proven to improve patients' lung function and exercise ability [6, 7]. The incidence of postoperative complications and hospitalization can be reduced through perioperative exercise, and the patient's long-term quality of life will be improved [4, 8–10]. Types of perioperative exercise comprise aerobic, resistance, and respiratory exercise. Currently, clinical trials on the effectiveness of perioperative exercise in lung cancer patients are increasing, including randomized controlled trials and quasi-randomized controlled trials. The trials can provide conclusive evidence of the safety and efficacy of intervention to minimize potential biases [11].

The selection of outcomes can affect the trials’ validity, accuracy, and clinical applicability. Only a limited number of results can be evaluated in each trial. Researchers generally choose clinical trial outcomes that are easier to measure and require fewer resources, ignoring outcomes important to patients and other stakeholders, while leading to potential bias [12]. Moreover, the number and measurement tools of outcomes are multiple, which cannot provide high-level evidence for clinical practice.

Particularly in trials evaluating the intervention of perioperative exercise in LC, outcomes are heterogeneous due to different designs and implementation of trials. The selection and use of relevant, comparable, well-defined, and patient-important outcomes are of great significance [13]. In a recent methodological scoping review, outcomes assessment and report is heterogeneity in exercise intervention trials for lung cancer patients [14]. More than 16 results were contained in the respiratory, thoracic, and mediastinal outcomes domain, while safety outcomes (adverse events) and health economics outcomes (hospitalization costs and length) were assessed in a few studies. Furthermore, significant heterogeneity was in the definition and measuring time of outcomes used to evaluate the effectiveness of the intervention. Finally, there is no agreed consensus on what outcomes clinical trials should collect and report when evaluating exercise interventions for LC. This means that when new trials are published to evaluate a perioperative exercise intervention for LC, researchers and clinicians may not be able to fully understand its potential benefit for patients, in the context of previously published research. A core outcome set allows researchers to measure consistent clinical outcomes.

A core outcome set (COS) is an agreed standardized set of outcomes that should be measured and reported in clinical trials, which aims to facilitate the synthesis of evidence and improve the consistency of reported outcomes [15]. COS promotes the homogeneity of clinical trials, increases the availability and comparability of trials, and promotes the generation of high-quality evidence [16]. The COS facilitates communication among healthcare professionals, patients, and researchers, which supports healthcare decision-making. In addition, it provides reference outcomes for health professionals to assess the effectiveness of perioperative exercise in patients. This project is the first to develop a COS for LC. A core outcome set allows researchers to measure a consistent set of clinical endpoints.

Aims and objectives
A core outcome set comprises the minimum agreed outcomes that should be measured and reported in trials for a given health condition. Therefore, establishing "what" should be measured most during perioperative exercise in lung cancer patients is vital. The study aims to develop a core outcome set with patients, health professionals and researchers to examine the benefits of perioperative exercise for adults with LC. The main objectives are:

1. To identify a list of outcomes currently reported in perioperative exercise trials for LC.
2. To evaluate consistency in outcome reporting in published trials and protocols.
3. To explore the important outcomes for stakeholders, including patients and healthcare professionals, researchers, and methodologists.
4. To reach consensus among multi-stakeholders on important outcomes in this COS.

Steering group

To oversee the development of the COS, we established an expert steering committee group of healthcare professionals, researchers, patients, and methodologists to guide the study's design, recruitment, and development.

Patient or public contribution

Patient and public representatives were involved throughout the study to obtain multi-stakeholders perspectives on perioperative exercise outcomes.

Method/design

The Core Outcome Measures in Effectiveness Trials (COMET) aims to promote COS's formation and development and develop a transparent methodology for COS. For the development and reporting of this COS, we will follow the rigorous process by COMET initiative (COMET handbook) [16] (Table 1), Core Outcome Set-STAAndards Protocol Items (COS-STAP) [17], Core Outcome Set-STAAndards for Development (COS-STAD) [18], Core Outcome Set-standards for Reporting (COS-STAR) [19], which has been successfully implemented in several high-quality COS projects [20, 21]. A mixed qualitative and quantitative, multi-stage approach will be used to develop this study protocol. Figure 1 shows an overview of the COS development steps.

Stage 1: Conduct a scoping review of outcomes reported in clinical trials and protocols to develop a list of potential outcome domains.

Stage 2: Conduct semi-structured interviews to obtain outcomes that are important to patients.

Stage 3: Choose the most important outcomes by conducting two-round Delphi surveys.

Stage 4: Establish consensus in a face-to-face meeting to discuss the final core outcome set.
Stage II: Systematic scoping review of outcomes measured and reported for perioperative exercise with lung cancer

Research question: what outcomes are measured and reported in studies of perioperative exercise with lung cancer?

Search strategy

Systematic searches were carried out in the following electronic databases: PubMed, Web of Science, EMBASE, CNKI, WanFang database, VIP, CBM, Chinese Clinical Trials Registry and Clinical Trials.gov. We included only quantitative studies, qualitative and mixed-method studies will be excluded.

Types of studies

Publications that focus on perioperative exercise intervention with lung cancer, which includes randomized controlled trials and quasi-randomized controlled trials.

Types of interventions

Any intervention exercise consisting of aerobic, resistance and respiratory training will be included.

Types of participants

The study population was lung cancer patients who underwent a perioperative exercise experience.

Exclusion criteria

1. Duplicated articles;
2. There is no full text in Chinese or English and the impossibility to access the whole text;
3. Chinese literature published in non core journals and English literature published in non SCI journals.

Data extraction

Articles were excluded if their title is not relevant. Two reviewers independently screened the results of the search. In case of discrepancies, a third reviewer was consulted. Two reviewers independently extracted data, which extracted the basic information of the study (first author, publication time, publication journal, literature title, and study type), study object information (sample size), intervention information (intervention time, intervention type) and outcome. information (outcome name, measurement time point, and measurement tool). Data extraction was performed independently by two people.

Stage II: Complementing the outcomes of perioperative exercise intervention in patients with LC

What outcomes do patients regard as potentially important when undertaking perioperative exercise for LC?
Participant eligibility and sampling

Considering patients' perspectives is essential in developing a COS because they often identify outcomes not considered by other stakeholders or in the literature. Information about experience and expectations regarding exercise and outcomes relevant to patients' attitudes were collected during the interviews. Patient interviews conducted in China. We approached patients in the thoracic surgery ward at Anhui Medical University First Affiliated Hospital. Informed consent were obtained from the patients before the interview. The questions of the semi-structured interviews are as follows:

There is no strict standard for the sample size of semi-structured interviews, and we recruited 15 patients until the interview data reaches saturation [22]. To ensure the diversity of interview data, we selected patients of different genders, ages, disease stages, education levels, and occupations for interviews. Patients may withdraw at any time during the interview if they feel uncomfortable.

Data collection

The interviews were audio-recorded. It included open-ended questions about the patient's exercise experience, desired exercise outcomes, and the impact on the patients.

Data analysis

The interview data, once transcribed and anonymized, were thematically analyzed using NVivo software for data management [23]. We classified outcomes by the COMET framework[24]. The Consolidated Criteria for Reporting Qualitative Research (COREQ) was used to report the qualitative study [25].

Review of outcome list

The results from the scoping review and interviews generated a long list of outcomes to be used in the questionnaire of the Delphi consensus study. Determine important outcomes for patients based on the frequency of the outcomes. Using the COMET taxonomy, the list was grouped into outcome domains. Patient representatives prepared and verified a definition for each outcome in simple language. The final survey has been pilot tested to ensure clarity and feasibility before data collection. Before the first Delphi surveys, a pilot test had been conducted on three types of stakeholders through email (3 patients, 3 healthcare providers, and 2 researchers). Respondents were asked to complete the questionnaire within 1 week of receiving the email, and after the questionnaire is evaluated and adjusted, 2 rounds of Delphi surveys will be conducted.

Stage Ⅱ: Delphi survey

Delphi survey is a widely agreed upon method to develop consensus, which utilizes a process of sequential questionnaire completion and feedback to establish expert consensus between a panel of experts [26, 27]. A modified Delphi approach proposed by the COMET initiative will be used in this study, involving two Delphi rounds [28].
Recruitment

Four types of stakeholders will be invited to participate in the survey to reflect the perspectives of experts in the field of perioperative exercise in lung cancer:

1. Patients with perioperative lung cancer who have received exercise experience;
2. Health professionals caring for LC patients (e.g., doctors, nurses, rehabilitation therapists);
3. Researchers who care for patients but are also involved in designing research studies;
4. Other stakeholders (methodology experts).

Sampling

There has yet to be a consensus for the optimal sample size for the Delphi, ranging from 12 to 174 for health professionals in previous studies[15]. Decisions about how many people to include in the Delphi process are pragmatic rather than based on statistical power. For the Delphi survey, we attempt to invite every eligible participant to participate in the Delphi survey, with 70 stakeholders expected to be invited to account for a 20% drop-out rate. Participants will be emailed to complete the online Delphi survey within two weeks. To explain, we will provide personalized questionnaires and use minimum waiting times between rounds 1 and 2.

Date collect

In the first round, the piloted candidate outcomes and associated description text will be presented. The order of the outcomes presented to participants will be randomly generated for each participant to eliminate the possibility of bias in the order of questions affecting the results [29]. Stakeholders will be invited to rate the importance and suggest other outcomes that they consider important. In the Delphi exercise, a 9-point Likert scale will be used to rate the importance of each item (i.e., 1-3, not important; 4-6, important but not critical; 7-9, important and critical) [15]. If it is difficult for participants to score in importance, they can also choose "not sure" for each result. An open-ended question will be at the end of the questionnaire: Which outcomes do you think are important but not included? At this stage, the panel will review the new outcomes to decide whether to include them in the second round.

All outcomes will be carried over from round one to round two. Participants' scores will be calculated for each outcome, and the results obtained for each outcome will be represented in a histogram based on the stakeholder groups' responses. The steering group will consider additional outcomes proposed by stakeholders. Those new results will be presented with the initial round one outcomes and circulated in the second round.

In the second round, we will invite the participants who completed the first round to the second round. Summary scores from all participants will be presented in the second round of the questionnaire. Participants will be invited to reflect on the feedback from the stakeholder group, re-score round one
outcomes, and score the additional outcomes suggested by participants in round one. In addition, if they change the rating, they will have the opportunity to explain their reasons.

**Miss data**

To reduce the loss of participants between Delphi survey rounds, we will send emails reminding participants to complete the Delphi survey by the end of the second week's weekend, to minimize the loss of participants. If the response rate is less than 3%, we will extend the opening time of the Delphi survey and invite other eligible individuals to participate.

**Consensus definition**

Applying standardized consensus definitions to identify core outcomes: (1) Consensus: If $\geq 70\%$ of respondents score 7-9 points, and $\leq 15\%$ of respondents score 1-3 points, the outcome will be included in the final COS. (2) No consensus reached: If $\geq 70\%$ of respondents score 1-3 points, and $\leq 15\%$ of respondents rate 7-9 points, the outcome will be excluded in the final COS. The experts will discuss outcomes not reached after the Delphi survey at the consensus meeting.

**Stage 8: consensus meeting**

This meeting may be held in person, comprising a selected group representing all stakeholders: patients with LC, health professionals, researchers, and methodology experts. These key stakeholders not only have insight into the outcomes of exercise for patients with perioperative LC but are also potential users of LC COS. After 2 rounds of e-Delphi exercise, the results of each outcome score are presented for all stakeholder groups. All participants used the same scoring mechanism as the Delphi survey. Outcomes with consensus among all stakeholder groups are prioritized, and the remains are discussed in turn according to the number of stakeholder groups. If the final COS is not reached at the end of the first consensus meeting, subsequent meetings will be considered.

**Discussion**

Perioperative exercise plays an essential role in the rehabilitation of patients with LC. Increasing research showed that perioperative exercise can reduce the adverse effects of surgery and increase lung function, exercise capacity, survival rate and overall health [8, 30]. However, there is a pronounced heterogeneity and low comparability between studies. This makes it difficult to compare and pool results, and therefore restricts the application and promotion of perioperative exercise and hinders the synthesis of evidence [31]. How effective these exercise interventions are can only be truly understood if clinical trials report the same outcomes, which are measured and defined in the same way.

COS is crucial in the synthesis and transformation of evidence. The development of this study will follow the best method guidelines provided by the COMET initiative, standardize the selection of clinical research outcomes, and enhance the value of clinical research. The COS will help improve the
standardization of reporting relevant research outcomes and reduce heterogeneity in reporting similar studies.

The program was constructed through a scoping review, semi-structured interviews, Delphi surveys, and consensus meetings to adopt multiple stakeholders' views, which ensure the feasibility and promotion of this COS in future clinical trials. The development of COS ensures consistent reporting of perioperative exercise research results for future lung cancer patients, helping to reduce reporting bias. In the future, different clinical trial results can be compared and analyzed to improve the value of clinical research and reduce research waste.

**Dissemination**

The COS will be disseminated through international publications and presented at relevant conferences to promote the implementation of this study. Study results will be reported following COS-STAP, which is designed to reduce reporting bias and heterogeneity in the development process. In addition, this study aims to improve the quality of perioperative exercise clinical trials in lung cancer patients and facilitate the generation of high-quality evidence for systematic reviews/META analysis.

**Trials status**

The outcome selection of the study has been completed and commenced in January 2022. Experts have been identified in the first Delphi round, has started on August 10 2023. The intended recruitment completion will be May 1, 2024. This protocol is version 1.0, registered in July 2022.

**Abbreviations**

LC: Lung Cancer; COMET: Core Outcome Measures in Effectiveness Trials; COS: Core Outcome Set; COS-STAP: Core Outcome Set-STAndards Protocol Items; COS-STAD: Core Outcome Set-STAndards for Development; COS-STAR: Core Outcome Set-standards for Reporting.

**Declarations**

**Acknowledgments**

Not applicable.

**Protocol checklist**

Please note that this protocol follows the recommendations of the Core Out-Come Set-STAndardised Protocol Items, the COS-STAP checklist [17].

**Author contributions**
Wanjun Zhou contributed to the study protocol’s design, method development, and preparation. Yawen Zhang, Zhiwei Wang, and Liang Zhang participated in the study design. Xinqiong Zhang took part in the study design and text revisions. All authors approved the final versions of this manuscript.

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**Conflict of interest**

The authors declare no conflict of interest.

**Ethics approval and consent to participate**

The Anhui Medical University of Ethics Committee has approved ethical approval for the project. Number: 84230050.

**Consent for publication**

All the authors of this study have agreed to its publication.

**Availability of data and materials**

The datasets used and analyzed in this study are available upon request from the corresponding author.

**References**


Controlled Trials in Inflammatory Bowel Disease[J]. Gastroenterology. 2022;163(4):950-964.


Tables

Table 1 and 2 are available in the Supplementary Files section.

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Figure 1

Flow diagram illustrating the process of developing the COS

Stage II: Conduct a scoping review of outcomes reported in clinical trials and protocols to develop a list of potential outcome domains.

Stage III: Conduct semi-structured interviews to obtain outcomes that are important to patients.
Stage II: Choose the most important outcomes by conducting two-round Delphi surveys.

Stage III: Establish consensus in a face-to-face meeting to discuss the final core outcome set.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table12.docx
- COMETchecklist.pdf.pdf