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Cost-effectiveness of prehabilitation prior to elective surgery compared to usual preoperative care: protocol for a systematic review of economic evaluations

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ABSTRACT

Introduction Preoperative functional capacity is an important predictor of postoperative outcomes. Prehabilitation aims to optimise patients' functional capacity before surgery to improve postoperative outcomes. As prolonged hospital stay and postoperative complications present an avoidable use of healthcare resources, prehabilitation might also save costs. The aim of this systematic review is to investigate the cost-effectiveness of prehabilitation programmes for patients awaiting elective surgery compared with usual preoperative care. The results will be useful to inform decisions about the implementation of prehabilitation programmes and the design of future economic evaluations of prehabilitation programmes.

Methods and analysis We will search PubMed, Embase, the Centre for Reviews and Dissemination Database, the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for full or partial economic evaluations of preoperative prehabilitation programmes conducted in any population compared with usual preoperative care. Studies will be included regardless of the type, design and perspective of the economic evaluation, and their publication year, language or status. Initial searches were performed between 30 April and 4 May 2020. Study selection, data extraction and assessment of the included studies' risk of bias and methodological quality will initially be performed by two independent reviewers and, if agreement was sufficiently high, by one reviewer. We will extract data regarding the included studies' basic characteristics, economic evaluation methods and cost-effectiveness results. A narrative synthesis will be performed. The primary endpoint will be cost-effectiveness based on cost–utility analyses. We will discuss heterogeneity between the studies and assess the risk of publication bias. The certainty of the evidence will be determined using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Ethics and dissemination Ethics approval is not required as the systematic review will not involve human participants. We plan to present our findings at scientific conferences, pass them on to relevant stakeholder organisations and publish them in a peer-reviewed journal.

PROSPERO registration number CRD42020182813

Strengths and limitations of this study

- A strength of this study is that the search strategy was developed involving an experienced information specialist using the Peer Review of Electronic Search Strategies 2015 Evidence-Based Checklist.
- Furthermore, the selection of electronic databases was based on research of the most efficient combination of healthcare databases that should be used to identify studies for systematic reviews of economic evaluations.
- The findings of this systematic review might be limited by the fact that economic evaluations are generally prone to publication bias, as they will usually only be performed if the intervention is effective.
- Furthermore, the quality of the evidence generated through this systematic review will depend on the risk of bias/methodological quality and reporting quality of the included studies.
- Lastly, as both prehabilitation programmes and economic evaluations are by nature heterogeneous, it might not be possible to draw firm conclusions from this systematic review, which are transferable to a range of health systems.

BACKGROUND

Rationale

Each year, millions of surgical procedures are performed worldwide. For example, in Germany, 17 million surgeries requiring hospitalisation were performed in 2018.[1] A major concern in the surgical context is the prevention of postoperative complications, which are devastating for patients and burdensome for health systems as they present avoidable use of healthcare resources,[2] for example, through a prolonged length of hospital stay or readmissions. Preoperative functional capacity is an important predictor of postoperative outcomes,[3–6] therefore, it can be hypothesised that prehabilitation

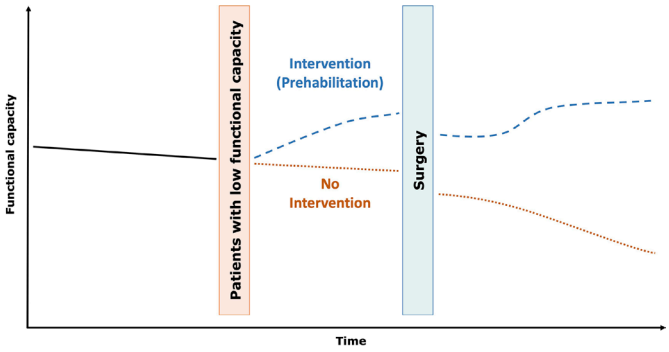

Figure 1 Events pathway diagram of patients with low functional capacity. Own figure based on Birkelbach *et al*[52] .

prior to elective surgery might prevent complications and thereby save costs.

While rehabilitation has long been an essential part of healthcare in developed countries,[7] prehabilitation has only received increased attention in the past two decades.[8] The word consists of the prefix *pre* and the noun rehabilitation and is defined as the process of 'enhancing an individual's functional capacity to enable him or her to withstand a forthcoming stressor'.[9] The idea behind prehabilitation is to begin the rehabilitation process to optimise an individual's functional capacity *before* the stressor, for example, a surgery, takes place and thus to enhance outcomes and recovery afterwards,[10] see figure 1. Prehabilitation programmes may include one or more modalities, such as medical optimisation (eg, smoking cessation or control of blood glucose), physical exercise and promotion of physical activity, nutritional support or psychological support and are usually provided by a multidisciplinary team.[9]

The first randomised controlled trial (RCT) on prehabilitation prior to elective surgery was published in 2000.[11] It investigated the effect of a multimodal preoperative intervention for low-risk patients awaiting elective coronary artery bypass graft surgery compared with usual care. The authors found that prehabilitation reduced length of hospital stay by 1 day, resulting in an approximate net saving of $C133 per patient per day.[11] Their RCT was followed by a large number of primary studies whose results have been synthesised in various systematic reviews, the majority of which looked at abdominal surgery.[12–22]

The cost-effectiveness of an intervention, that is, its value for money, is an important factor for health policy-makers deciding about the implementation of a new programme.[23] However, despite the growing interest in prehabilitation programmes by healthcare professionals and policy-makers, only a subset of studies has evaluated the cost-effectiveness of prehabilitation. To date, there is no systematic review that provides an overview of the cost-effectiveness of prehabilitation programmes across different surgical disciplines. Hence, it still needs to be determined if prehabilitation prior to elective surgery is cost-effective.[9]

This systematic review is part of a larger project that investigates prehabilitation of frail or prefrail patients before elective surgery as a new model of care in Germany.[24] An RCT enrolling more than 1400 patients and an accompanying economic evaluation is planned. Therefore, we are not only interested in the findings of previous economic evaluations of prehabilitation programmes prior to elective surgery but also in their methods to guide our own economic evaluation.

Objective

The aim of this systematic review is to answer the question: What is the cost-effectiveness of prehabilitation programmes for patients awaiting elective surgery compared with usual preoperative care?

Our objectives are to identify all eligible economic evaluations, assess their validity and systematically present their characteristics, methods and findings to inform decisions about the implementation of prehabilitation programmes and guide the design of future rigorous economic evaluations of prehabilitation programmes.

METHODS

The design of our systematic review followed the five-step approach to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions.[25] Furthermore, we consulted the Cochrane Handbook for Systematic Reviews of Interventions[26] and guidance for undertaking reviews in healthcare by the Centre for Reviews and Dissemination (CRD) of the University of York, in particular chapter 5.[27] This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement[28 29] (see online supplemental appendix 1).

Registration

After checking that there is no similar published or ongoing systematic review, we have submitted a record for our systematic review on PROSPERO on 30 April 2020 (CRD42020182813).

Eligibility criteria

The study inclusion and exclusion criteria can be found in table 1.

As we aim to provide a comprehensive overview of the available evidence on the cost-effectiveness of prehabilitation, we decided to include both full and partial economic evaluations as well as economic evaluations based on both RCTs and non-randomised studies of interventions (NRSI). While full economic evaluations should generally be preferred over partial economic evaluations,[30] partial economic evaluations might still be useful for decision-makers to understand the costs and consequences of an intervention.[31]

Information sources

We will search the following electronic databases and trial registries from their inception:

Table 1 Study inclusion and exclusion criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients from any country undergoing elective surgery	Patients undergoing emergency surgery or non-surgical treatments (eg, chemotherapy)
Intervention	A preoperative prehabilitation programme (any setting), defined as a (set of) intervention(s) aimed to optimise functioning and reduce disability in individuals awaiting surgery. The intervention(s) had to include at least one component of physiotherapy or occupational therapy and at least one in-person meeting between the patient(s) and healthcare professional(s). The programme's overall duration and the duration and frequency of individual sessions had to be sufficiently long to have an effect given the patients fully adhered to it.	Purely medical/nutritional interventions (eg, an extradose of a specific drug/nutritional supplements), an intervention consisting of prehabilitation combined with additional postoperative rehabilitation, a prehabilitation programme not containing any physiotherapy or occupational therapy components (eg, cognitive–behavioural therapy or health counselling/education only), a prehabilitation programme without any in-person meetings (eg, purely web/app based).
Control	Usual preoperative care as defined by the study authors, that is, the routine care that patients with a given condition receive in the respective hospital (extended only by the baseline measurements performed as part of the trial)	Another prehabilitation intervention
Outcome	Clinical effectiveness and costs, any time frame for follow-up	Clinical effectiveness only
Study type	Full (ie, cost–benefit, cost-effectiveness and cost–utility analyses) or partial economic evaluations (ie, cost-minimisation analysis), trial based (any design) or model based. Studies will be included regardless of their cost perspective, publication year, language and status (ie, full article, protocol/registration record, conference abstract).	Systematic reviews, mere cost analyses (ie, studies that simply calculated the costs of the intervention but did not compare it to the costs of for the control treatment), commentaries/letters, animal studies

- PubMed (via PubMed), initial search date 30 April 2020.
- Embase (via Embase), initial search date 30 April 2020.
- CRD Database (containing the Health Technology Assessment (HTA) database and archives of the Database of Abstracts of Reviews of Effects and the National Health Service Economic Evaluation Database) (via CRD Database), initial search date 4 May 2020.
- WHO International Clinical Trials Registry Platform (ICTRP), not searched yet as the ICTRP Search Portal was temporarily not accessible from outside WHO due to the heavy traffic generated by the COVID-19 outbreak[32]
- ClinicalTrials.gov (although ClinicalTrials.gov is included in the WHO ICTRP, it is recommended that it is searched separately due to additional features[26]), initial search date 4 May 2020.

The selection of electronic databases was based on recommendations by the CRD and a study by Arber *et al* who found that the most efficient combination of healthcare databases was Embase, the HTA database and PubMed.[33]

In addition, we will screen the reference lists of any relevant systematic reviews on prehabilitation identified and of the included studies, and perform a forward citation search in Web of Science (WoS), or in Google Scholar if a study was not indexed in WoS. To identify ongoing or (yet) unpublished studies (grey literature), we will search Open Access Theses and Dissertations and the DART-Europe E-theses Portal. We will also contact the authors of the included studies who we consider content experts about whether they know of any further eligible studies.

Search strategy

Following initial scoping searches, the draft search strategies for PubMed and Embase were developed by one reviewer (TR). An experienced information specialist (HE) reviewed the draft search strategies using the Peer Review of Electronic Search Strategies 2015 Evidence-Based Checklist.

The revised search strategy (see online supplemental appendix 2) consists of three sets of terms, relating to the population, intervention and study type, respectively: (1) terms to search for the population (such as preoperative), (2) terms to search for the intervention (such as exercise) and (3) terms to search for the economic evaluations (such as cost). The term prehabilitation is included in the set of terms relating to the population as well as the intervention. Both, controlled vocabulary (such as Medical Subject Headings (MeSH) terms in MEDLINE) and free-text terms (including truncations where appropriate) are used and no limits will be applied. We will report the final search strategies following the PRISMA Search Reporting Extension (PRISMA-S).[34]

To identify economic evaluations in MEDLINE, we will use the following terms: *cost[tiab] OR costs[tiab] economic*[tiab] OR budget*[tiab] OR "Costs and cost analysis"[MeSH]*

OR "Exercise/economics"[Mesh] OR "Rehabilitation/economics"[Mesh]. These terms were inspired by a filter by Wilczynski *et al*[35] that had the best optimisation of sensitivity and specificity in identifying economic evaluations in MEDLINE according to a study by Glanville *et al*.[36] To identify economic evaluations in Embase, we will use a filter (adapted for the Embase search surface) by McKinlay *et al*[37] that had the best optimisation of sensitivity and specificity in identifying economic evaluations in Embase according to Glanville *et al*[36]: *cost:ti,ab,kw OR costs:ti,ab,kw*. Analogue to the PubMed search strategy, these terms were supplemented by the following terms: *economic*:ti,ab,kw OR budget*:ti,ab,kw OR 'economic aspect'/exp*.

Once the first round of study selection has been completed, we will calculate the search strategies' relative recall (identified eligible records/all eligible records indexed in the database) for the electronic databases. If one of the search strategies' relative recall will be below 90%, we will revise it and perform a new search in that database. Weekly alerts for new studies identified with our search strategy will be activated for PubMed (using MyNCBI) and Embase. All searches will be repeated at completion of the systematic review to ensure that it is up to date and any new studies included in a second round of study selection can be incorporated before publication.

Data management

All records will be imported to EndNote X9.3.2 (Clarivate Analytics, Philadelphia, Pennsylvania USA) where they will be deduplicated and screened for eligibility. Full-text articles will also be stored in EndNote.

Selection process

Two reviewers (TR and HE) will screen a random 10% sample of all unique records based on their titles and abstracts and discuss their results until consensus has been reached. If agreement between them was sufficiently high (at least 80% raw agreement), the remaining records will be screened by one reviewer (TR). If agreement was below 80%, another 10% sample will be screened by the same two reviewers and the process will be repeated. We will mark any relevant systematic reviews on prehabilitation.

We will retrieve the full-text articles for all records deemed potentially eligible after title/abstract screening and of relevant systematic reviews on prehabilitation. Two reviewers (TR and HE) will independently screen all full-text articles of potentially eligible studies and capture reasons for exclusion. Eligible articles will then be mapped to studies (as the unit of interest). Records of ongoing studies (eg, protocol publications or registration records) will be included, as we are interested in the methods of ongoing studies, too. The references of all eligible studies and all relevant systematic reviews on prehabilitation will be screened for further eligible studies.

Results of the study selection process will be displayed in form of a flow diagram.[28] A list of articles excluded after full-text screening with reasons for exclusion will be provided.

Data collection process

All eligible studies will be checked for errata or retractions before data extraction. Data will be extracted into a standardised Excel sheet. One reviewer (TR) will pilot the extraction sheet using n=2 randomly selected studies to test its user-friendliness and completeness, then two reviewers (TR, HE/WQ) will perform a calibration exercise by independently extracting the data of a random 20%-sample of the included studies. If less than n=15 studies are included, n=3 studies will randomly be selected for independent data extraction by two reviewers. Discrepancies will be discussed until consensus has been reached and the extraction sheet will be revised where necessary. If agreement between the reviewers was sufficiently high (at least 80% raw agreement), the data of the remaining studies will be extracted by one reviewer (TR). If agreement was below 80%, the process will be repeated.

We will contact the study authors via email to obtain missing data or resolve any uncertainties regarding their data. A reminder email will be sent after 2 weeks if necessary. Missing data will not be imputed if emails remain unanswered. Unresolved uncertain data will be marked as such.

Data items

We will extract data on various items (see table 2).

In addition, we will extract details on the methods of the economic evaluations (see table 3).

This selection of items was informed by Wijnen *et al*.[30] A draft data extraction form can be found in online supplemental appendix 3.

Outcomes and prioritisation

Our primary outcome is the cost-effectiveness of prehabilitation prior to elective surgery based on results from cost–utility analyses, as these provide a cost-effectiveness measure (cost per quality-adjusted life year (QALY) gained) that is comparable across disciplines and for which willingness to pay thresholds are available for several countries. Therefore, they are most meaningful to health policy-makers.

Secondary outcomes are the clinical effectiveness- and cost outcomes of prehabilitation prior to elective surgery based on results from other types of economic evaluations. We will only consider clinical effectiveness outcomes that are patient-relevant (eg, mortality, morbidity or quality of life). Surrogates (eg, duration of surgery or laboratory parameters) will not be considered. If there are different cost outcomes (eg, costs during hospital stay, costs following hospital stay and total costs), we will only consider the total costs. If no total costs are reported, we will aim to calculate them based on the cost data provided.

Risk of bias in and methodological quality of individual studies

Trial-based economic evaluations: We will assess the risk of bias on study level using the current gold standard

Table 2 Data extraction items

Item	Specification
Study ID	Study acronym/first author's last name, publication year
Registration	Registration no (eg, NCT no)
Source of funding	Non-profit, for-profit, mixed, unclear, no funding; not stated If funded: extract name of funder
Competing interests	No, yes; not stated If yes: specify
Publication type	Full article/HTA report, protocol/ registration record, conference abstract
Location	Country and city where the investigation was performed If multicentre: Extract all cities and countries
Enrolment period	mm/yyyy to mm/yyyy
Length of follow-up	In months
Population	Description of study participants' underlying disease and type of surgery Inclusion and exclusion criteria If study has been completed: No of randomised patients (in total, per group) Age, gender, comorbidities of patients
Intervention	Description of the study intervention (setting, modality, overall duration, frequency, session duration, healthcare staff performing the intervention)
Control	Description of the control intervention (eg, description of the usual preoperative care if reported)
Outcomes	Description of the outcomes (including effects, costs and cost-effectiveness) If study has been completed: ► Results on effects in disaggregated and aggregated form (with CIs) ► Results on costs in disaggregated and aggregated form (with CIs) ► Results on cost-effectiveness (eg, incremental cost-effectiveness ratios) ► Study authors' conclusion regarding the intervention's cost-effectiveness (copied verbatim)

HTA, Health Technology Assessment; ID, Identifier; NCT, ClinicalTrials.gov identifier.

tool, which currently would be the Cochrane RoB V.2.0 tool[38] for RCTs and the ROBINS-I tool[39] for NRSI. In addition, we will assess the methodological quality of all full economic evaluations using the Consensus on Health Economic Criteria checklist.[40] For model-based studies, we will only assess the methodological quality of the economic evaluation using the International Society for Pharmacoeconomics and Outcomes Research checklist.[41]

Two reviewers (TR, HE/WQ) will independently assess a random 20%-sample of the included studies. If less than n=15 studies are included, n=3 studies will randomly be selected for assessment. If agreement between them was sufficiently high (at least 80% raw agreement), the remaining studies will be assessed by one reviewer (TR). If agreement was below 80%, another 20% sample will be assessed by the same two reviewers and the process will be repeated.

Data synthesis

We will perform a meta-analysis using standard methods[26] if we identify two or more methodologically homogenous studies reporting on the same outcome. However, as both prehabilitation programmes[9] and economic evaluations[27] are by nature rather heterogeneous, we do not expect to be able to meta-analyse the included studies' results. Thus, we will perform a narrative synthesis by comparing their results in detail in table format and summarising them in text form. We will present the included studies' basic characteristics (including details on the prehabilitation programmes) and economic evaluation methods. For completed studies, we will also present the results of our risk of bias/ methodological quality assessment and the studies' cost-effectiveness results (presented alongside their overall risk of bias/methodological quality).

Results will be presented in aggregated (eg, as an incremental cost-effectiveness ratio) and disaggregated form in natural units if possible. For example, the primary outcome (cost-effectiveness of prehabilitation based on a cost–utility analysis) will be reported as cost per QALY gained and as change in health-related quality of life, length of life, quantities of resource use and unit costs. This is to allow decision-makers to apply the results to their own context and to facilitate the reuse of these data as inputs to of future model-based economic evaluations.[42] Costs will be reported in the original monetary units as well as converted to 2020 Euros. For conversion, we will use the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre Cost Converter,[43] a free web-based tool for adjusting estimates of cost expressed in one currency and price year to a specific target currency and price year. We will not aim to rank the studies based on their cost-effectiveness results, but we may present their results in cost-effectiveness planes where common metrics were used.

Studies will be ordered alphabetically by study identifier (ID). Depending on the number of included studies, we may group studies according to their setting, population, intervention or methods. We will narratively discuss heterogeneity between the studies.

Metabias(es)

We will address selective reporting within studies by comparing study reports with their study protocols whenever such are available.

Table 3 Further data extraction items

Item	Specification
Type of analysis	Cost-minimisation analysis, cost–consequence analysis, cost–benefit analysis, cost-effectiveness analysis, cost–utility analysis; other (with description)
Design of economic evaluation	Trial based, model based If trial based: RCT or NRSI If model based: Markov, decision tree and discrete event simulation
Cost perspective	Societal perspective, healthcare payer perspective, healthcare provider perspective, patient perspective; other (with description))
Time horizon	For effects and costs; in months
Effects	Data source of effects Measurement of effects Valuation of effects
Costs	Type (direct/indirect) Approach (top-down/bottom-up) Data source of resource use Measurement of resource use Valuation (methods used to calculate unit costs)
Missing data	Handling of missing data
Discounting	No, yes (with description of discount rate for effects and costs)
Inflation rate	No, yes (with description)
Reference year and currency	State year and currency
Statistical analysis	Details of the analysis of cost-effectiveness For model-based studies: model assumptions
Uncertainty	Details of the analyses of uncertainty (eg, statistical comparison, bootstrapping, sensitivity analysis(one way, multiway), threshold analysis (eg, using a cost-effectiveness acceptability curve), analysis of extremes and best/worst case analysis) and probabilistic sensitivity analysis
Willingness-to-pay threshold	Sum per unit of health outcome (eg, 20 000 pound sterling per QALY)

NRSI, non-randomised studies of interventions; QALY, Quality-adjusted life year; RCT, randomised controlled trial.

To address publication bias across studies, we will search comprehensively for relevant trial registration records and study protocols. We will contact authors if their record/protocol implies that the study has already been completed to follow up on the study's status.

Confidence in cumulative evidence and transferability

We will determine the quality (high, moderate, low or very low) of the evidence for each cost-effectiveness outcome following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach,[44] particularly following part 10 of the GRADE Guidelines (Considering Resource Use and Rating the Quality of Economic Evidence).[45] We will summarise our assessment in form of a GRADE evidence profile and in Summary of Findings tables using disaggregated data. Furthermore, we will discuss the transferability of our results to different health systems using a checklist by Welte *et al*.[46]

Study dates

The systematic review is currently ongoing. We started with the conception and preliminary searches on 1 April 2020. The anticipated date of completion is 31 March 2021.

We plan to update this systematic review in summer 2022, as we expect that our own economic evaluation and some of the ongoing studies that we might identify in this initial systematic review will have been completed by then.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and dissemination

Our systematic review will not involve human participants or contain personal and/or medical information about an identifiable living individual. Therefore, ethics approval or consent to participate is not required.

We plan to present our findings at scientific conferences, pass them on to relevant stakeholder organisations and publish them in a peer-reviewed journal. We will report our systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[47 48] or the updated PRISMA Statement[49] if available by then. Furthermore, we will disseminate links to this protocol, the PROSPERO record

and the final publication via social media (Twitter and ResearchGate).

Amendments

Important protocol amendments will be documented in the systematic review's PROSPERO record. A (dated) new version of the record with short explanation of the amendment will then be published.

DISCUSSION

This systematic review of economic evaluations will provide its readers with a summary and synthesis of studies that have evaluated or will evaluate the cost-effectiveness of prehabilitation prior to elective surgery compared with usual preoperative care. Our systematic review will be helpful both for decision-makers who consider the implementation of a prehabilitation programme as well as for researchers aiming to perform an economic evaluation of a prehabilitation programme in the future.[50] As we will include studies on patients from all surgical disciplines without restrictions, we may be able to identify knowledge gaps for certain groups of patients, for whom no studies were found or who did not meet the studies' eligibility criteria.

We anticipate a number of limitations. First, economic evaluations are generally prone to publication bias, as many study authors will only consider performing an economic evaluation if there is conclusive evidence that the study intervention is more effective than the control intervention.[42] We will address this issue by searching comprehensively for relevant trial registration records and study protocols and following-up on any studies that are supposed to be completed but have not yet been published.

Second, as there is currently no gold-standard tool to assess the methodological quality of economic evaluations,[30] we had to choose the aforementioned tools based on their user friendliness and feasibility in the context of our systematic review. Furthermore, instead of having to use two tools for trial-based and model-based economic evaluations, a single validated tool to assess the risk of bias in both types of economic evaluations would be much welcomed. In addition, both the Cochrane RoB V.2.0 tool[38] and the ROBINS-I tool[39] are relatively new tools that still need to be validated.[51]

Third, the quality of the evidence generated through this systematic review will depend on the risk of bias/methodological quality of the included studies. For example, in case of prehabilitation, it is not usually possible to blind patients or investigators to the intervention. We will discuss the risk of bias/methodological quality of the included studies when reporting their results and make recommendations of how to improve the validity of economic evaluations' findings.

Fourth, trial-based studies that present partial economic evaluations and/or are reported alongside the trial results are likely to report their economic evaluation methods only briefly. Therefore, we might not be able to extract data in the same detail for them as for full economic evaluations/trial-based economic evaluations that were published separately. Lastly, as both prehabilitation programmes and economic evaluations are usually heterogeneous in their design, it might not be possible to draw firm conclusions from this systematic review, which are transferable to a range of health systems.

Contributors TR and WQ conceptualised the review. TR drafted the protocol. HE and WQ revised the protocol. All authors were involved in the conception of the protocol, approved the final version of the manuscript to be published and agree to be accountable for all aspects of the planned systematic review.

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