



BMJ Open Identifying relative efficacy of components of prehabilitation in adult surgical patients: protocol for a systematic review and component network meta-analysis

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ABSTRACT

Introduction Prehabilitation is a high-priority intervention for patients, the public, clinicians and health systems. However, existing knowledge syntheses are generally low quality and do not provide insights regarding the relative efficacy of different prehabilitation components (eg, exercise, nutrition, psychosocial or cognitive interventions). The objective of the planned review is to evaluate the relative efficacy of different prehabilitation components to inform current care, implementation and future research.

Methods and analysis We will perform a systematic review and component network meta-analysis (CNMA). We will use a peer-reviewed search strategy to identify all randomised trials of prehabilitation in adult surgical patients from Ovid Medline, Embase, the CINAHL, PsycINFO, Web of Science and the Cochrane Central Register of Controlled Trials, along with grey literature. All stages of the review and data extraction process will be performed in duplicate, following recommended best practices. To compare the relative efficacy of different prehabilitation components (prespecified as exercise, nutrition, psychosocial or cognitive interventions), we will use CNMA, an extension of network meta-analysis that allows estimation of the contributions to efficacy of each component of a multicomponent intervention through direct and indirect comparisons. We will use additive CNMA models for critical outcomes (postoperative complications, patient-reported recovery, physical recovery and length of stay); standard care will be the common reference condition. Pre-specified sensitivity and subgroup analyses will be conducted.

Ethics and dissemination This review of published data does not require ethical review. Results will be disseminated via scientific conferences, peer-reviewed publications, social and traditional media and via our research network to target partners and organisations.

INTRODUCTION

Globally, >300 million surgical procedures are performed each year.^{1 2} These surgeries mostly occur on a planned (also referred to as ‘elective’) basis,³ meaning that wait-times can

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A prespecified protocol based on best practices for systematic review and meta-analysis will guide conduct of the study.
- ⇒ All stages of the study will be done in collaboration with patient and knowledge user partners so that findings will be co-produced in an integrated knowledge translation framework.
- ⇒ Component network meta-analysis will allow comparison of the relative efficacy of different prehabilitation components, even when multiple components are delivered simultaneously.
- ⇒ If assumptions underlying component network meta-analysis are not met, we may be unable to estimate relative efficacy of different components.

be positively leveraged to optimise patient status prior to surgery. Patient optimisation is critical in supporting high value surgical care as adverse postoperative events that matter to patients and the healthcare system are common.⁴ Complications such as cardiopulmonary events, infections and major bleeding occur in 10%–20% of patients.^{5–7} Impaired functional recovery or new clinically significant disability develop in more than one in five surgical patients; such adverse events are even more common among older patients and those with poor baseline health.^{8–12} Effective strategies to improve outcomes for the millions of people having surgery each year are urgently needed.

Prehabilitation is a process undertaken in advance of surgery, which has the specific intent of improving an individual’s functional, physiologic, cognitive and/or mental health status through targeted interventions.^{13 14} Patients, the public and international specialty societies identify prehabilitation as a high priority intervention, including multiple James Lind

Alliance priority setting partnerships.^{15–17} However, despite the face validity and enthusiasm for prehabilitation interventions, a recently completed umbrella review of 55 prehabilitation systematic reviews found that existing evidence synthesis is insufficient to inform practice.¹⁸ Several key knowledge gaps preclude translation of current evidence into practice. First, existing systematic reviews have major methodological shortcomings; 51 of 55 prehabilitation reviews synthesised in a recent umbrella review were rated as low quality.^{18 19} Second, prehabilitation interventions are heterogeneous, as they may consist of different components, including exercise, nutrition, psychosocial and cognitive interventions, or combinations thereof.¹⁸ Existing prehabilitation reviews have typically focused only on single component interventions, or pooled all types of prehabilitation components or interventions together. This means that patients, clinicians, researchers and health system planners are unable to determine what specific components, or combinations of components, contribute the most to prehabilitation efficacy and deserve the greatest focus in implementation and future research. Understanding how the current evidence network can be leveraged to detect differences between the effects of interventions and their individual components would help to address these important gaps.

Component network meta-analysis (CNMA), an extension to network meta-analysis, allows estimation of separate effects for each component of a multicomponent intervention through direct and indirect comparison, even when these are delivered in combination.^{20 21} We propose a CNMA based on an up-to-date, high-quality systematic review, to address important knowledge gaps in the prehabilitation evidence base. Our objective is to estimate which prehabilitation components contribute the greatest efficacy in improving critical outcomes, including postoperative complication rates, patient-reported recovery, physical recovery and length of stay in adult patients preparing for surgery.

METHODS

Design

This study will be a systematic review with CNMA. The study began in March 2022 and has an anticipated end date of March 2023. This protocol has been prepared in consideration of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines, the PRISMA extension for network meta-analysis and specific considerations for CNMA.^{22–24} Methods for the review are directly informed by the Cochrane Handbook and Methodological Expectations of Cochrane Intervention Reviews.^{25 26} Findings will be reported according to PRISMA guidance.^{23 27 28} Any deviations from our prespecified methodology will be described in the final report (with rationale).²⁹ The protocol has been submitted for registration to the International Prospective Register of Systematic Reviews (PROSPERO).

Patient and public involvement

This review will be conducted and co-produced with partners using an integrated knowledge translation (IKT) framework.^{30–32} Specifically, patients who will be impacted by the research and knowledge users who will implement evidence in practice have been, and will continue to be, regularly engaged through meetings, surveys and one-on-one discussions. A start-up meeting occurred 3 June 2022; mid-study, postsynthesis and wrap up team meetings will also be held to ensure meaningful input can be obtained throughout the course of the study. Patient and public involvement will be reported according to the Guidance for Reporting Involvement of Patients and the Public-2 checklist.³³

Intervention definition

A prehabilitation intervention is intended to improve physical, physiological, cognitive or psychosocial function and to correct deficiencies in these domains in advance of surgery.^{13 14} We will define and operationalise the following working definition of prehabilitation based on consistent descriptions of prehabilitation provided in the literature: a unimodal intervention consisting of exercise (eg, aerobic, strength or flexibility focused interventions), nutrition (eg, advice, supplementation or other interventions to improve oral or enteral macro or micronutrient intake), cognitive (eg, interventions to improve or maintain cognitive function) or psychosocial (eg, interventions to improve mood, affect or motivation) training or a multimodal intervention that combines exercise, nutrition, cognitive and/or psychosocial training with or without other interventions, undertaken for seven or more days before surgery.^{13 34–36} No limitations will be placed on duration, location or supervisory approaches to the prehabilitation intervention. For the purposes of CNMA, intervention components will be classified as: exercise, nutrition, cognitive or psychosocial. The reference category will be standard care, which is the most common comparator in existing randomised trials and meta-analyses of prehabilitation.¹⁸

Inclusion criteria

Selection criteria will be informed by our population–intervention–comparator–outcome question. We will include randomised trials addressing a population of adults (≥ 18 years; provision of paediatric surgical care is substantively different from adults) undergoing major elective surgery where participants were exposed to a prehabilitation intervention prior to surgery compared with individuals receiving standard care or a different prehabilitation intervention (eg, another prehabilitation intervention consisting of different components) reporting prespecified outcomes (see the Outcomes section).

Exclusion criteria

Studies evaluating isolated preoperative risk factor management (eg, smoking cessation, anaemia treatment,

medication management in isolation) or interventions applied immediately (≤ 7 days) before surgery (a time frame consistent with enhanced recovery after surgery)^{37,38} will be excluded to be consistent with accepted definitions of prehabilitation.¹⁸ No language exclusions will be applied. Quasi-experimental and other non-randomised designs will be excluded.

Outcomes

Consultation with partners (patients, clinicians, health system leaders and scientists) and a recent umbrella review performed by our team informed prespecification of outcomes.¹⁸ This led to the choice of critical and exploratory outcomes that are prioritised by knowledge users and that will be adequately reported in prehabilitation trials. Critical outcomes include: (1) a composite of any postoperative medical or surgical complications during the index hospitalisation or within 30 days (a core outcome in surgery and perioperative medicine)^{39,40} as it is a key step on the causal pathway between prehabilitation and improved recovery after surgery,¹⁰ and is the most commonly reported outcome in prehabilitation RCTs³⁶; (2) patient-reported recovery (eg, disability or quality of life; most distal reported measure up to 90 days after surgery); (3) physical recovery (eg, 6 min walk test, short physical performance battery; most distal reported measure up to 90 days after surgery) and (4) length of hospital stay (LoS). Exploratory outcomes will be organised per the Institute for Healthcare Improvement Triple Aim domains, and will include health (non-home discharge, mortality), experience (pain, satisfaction) and resource use (costs).^{36,41,42} These exploratory outcomes will be analysed if adequate data and resources are available.

Search strategy

Our search strategy (online supplemental file 1) has been developed with our team's information specialist, and has undergone the Peer Review of Electronic Search Strategies review process with a second, independent information specialist.⁴³ Grey literature sources will be searched.^{26,44} We will translate and apply our search strategy to Ovid Medline, Embase, the CINAHL, PsycINFO, Web of Science and the Cochrane CENTRAL Register of Controlled Trials. We will assess reference lists of included trials and related reviews to identify citations missed by our search.

Study review and selection

All stages of the review will be conducted in duplicate by two independent reviewers using Distiller SR (Evidence Partners, Ottawa, Canada). At each stage of the review, the first 50 citations will be assessed, followed by a meeting of reviewers with study leads to review decisions, identify any issues related to disagreements and/or interpretation of selection criteria, and recalibrate reviewers' approaches as needed. The first stage will include title and abstract review. After full text review by two independent authors,

any conflicts will be resolved through consensus in a meeting between study leads and reviewers; reasons for exclusion at full text review will be documented and provided in the final publication.

Data extraction

Data will be extracted using a form specifically designed for this review following a piloting exercise by the review team. Key to the implementation of CNMA as our analytical approach, we will collect full descriptions of comparator conditions (eg, standard care, other prehabilitation interventions). All data will be extracted in duplicate; disagreements will be resolved by reviewers through cooperative review of the primary source with a study lead. A full description of all anticipated data points is included in online supplemental file 2. Sample size, population characteristics and missing data will be collected for each trial. For binary outcomes, we will collect the 2x2 table, event rates and/or effect measures (eg, ORs or risk ratios) along with a measure of uncertainty (eg, 95% CIs, p values). For continuous outcomes we will collect means and SD, and/or effect estimates such as mean differences along with their 95% CIs and p values. Any missing data will be sought directly from study authors.

Assessment of bias in included studies

The Cochrane Risk of Bias 2 tool will be applied in duplicate to each included RCT⁴⁵ to assess within-study bias of the included evidence. Where >10 studies are available in a meta-analysis, funnel plots and Egger's test will be used to assess for possible publication bias and small-study effects.⁴⁶

Assessment of certainty of evidence

We will use the GRADE working group classification to assess the certainty of evidence for each outcome,⁴⁷ including modifications specific to certainty assessment in network meta-analysis.⁴⁸ This will allow us to categorise evidence as high/moderate/low/very-low certainty, which will be reported using appropriate statements.⁴⁹

Intervention effect estimates

Pooled effect estimates will be reported as odds ratios (binary outcomes), mean differences (continuous outcomes on a single scale (eg, LoS)) or standardised mean differences (SMDs) (continuous outcomes on multiple scales (eg, functional recovery)); point estimates along with 95% CIs will be reported. Where SMDs are calculated from different scales that capture related conceptual outcomes (eg, patient-reported recovery via quality of life or disability scales), directionality will be standardised prior to analysis. Where multiple scales that reflect functional recovery are reported within a single included study, we will preferentially select for pooling generic (vs disease specific) scales to enhance generalisability, and quality of life (vs other concepts) scales, as our previous work demonstrates that quality of life is reported far more frequently in prehabilitation studies than related measures like disability.¹⁸ Where continuous

outcome measures are not reported as means and SD, we will use the methods of Wan and colleagues to estimate means and SD from reported measures such as medians and IQR or overall ranges.⁵⁰ Effect estimates derived from cluster randomised trials will be pooled using the reported effect adjusted for clustering, or if not available, a corrected estimate accounting for an estimated design effect.⁵¹

Data syntheses and analyses

Our approach to analysis will follow previous recommendations, whereby sequential and complimentary techniques will be used to estimate the pooled effects of prehabilitation and its components.^{20 52}

Pairwise meta-analysis

Pairwise meta-analysis will first be used to estimate whether any prehabilitation intervention, or prespecified components (exercise, nutrition, psychosocial or cognitive) improve critical outcomes compared with standard care or comparator interventions (separately). All meta-analysis models will use random effects, as existing knowledge suggests that assumptions for fixed-effect meta-analysis will not be met (in particular due to heterogeneity related to different surgical procedures).¹⁸ We will use the Hartung-Knapp-Sidik-Jonkman method to derive appropriate CIs.⁵³ Between-study variance will be estimated using the restricted maximum likelihood method and its 95% CI using the Q-profile approach.⁵⁴⁻⁵⁶ We will also calculate the I^2 statistic to quantify the percentage of variability due to between-study heterogeneity rather than random error. If substantial heterogeneity exists, sources will be explored using subgroup analysis and meta-regression, based on prespecified postulated effect modifiers (type of surgery, age, type of prehabilitation, baseline functional status).

Assessment of assumptions for NMA and CNMA

We will assess for transitivity (the assumption that two components can be validly compared via a common control condition) both visually and statistically. Visual evaluation will be conducted via assessment of the distribution of effect modifiers in tabular and graphical presentations across treatment comparisons. We will visually inspect similarity of the distribution of the following effect modifiers: type of surgery, age, baseline functional status, comorbidity or American Society of Anesthesiologists' Score, presence of cancer, presence of malnutrition. Statistical assessment of transitivity will involve a global assessment of consistency using the design-by-treatment interaction model,⁵⁷ and a local assessment through the node-splitting approach.⁵⁸ For the CNMA, we will assess the additivity assumption using the method of Rücker *et al* based on the difference in Q statistics between the additive CNMA and standard NMA model.²⁴

Network meta-analysis

Next, we will conduct a standard NMA, also referred to as a full interaction model in CNMA,²⁰ and generate network

plots to visually explore the available evidence base. We will perform a random-effects NMA assuming a common between-studies variance (τ^2) across the whole network, using the restricted maximum likelihood method.⁵⁹ We will estimate summary effect measures (ORs, mean differences, weighted mean differences) along with 95% CIs and 95% prediction intervals. To assess the magnitude of heterogeneity, we will compare the estimated τ^2 with an empirical distribution for dichotomous data.⁶⁰ We will obtain a treatment hierarchy using P-scores, which take values between 0 and 1, and which is based on the estimated treatment effects and their associated uncertainty.⁶¹

Component network meta-analysis

We will use an additive CNMA model to evaluate the influence of the individual components, where each component has its own effect, and the total effect of an intervention will be equal to the sum of the relative component effects. It should be noted that common components in comparisons of interventions cancel out (ie, *mean difference*_{A+B vs. A+C} is identical to the effect of *mean difference*_{B vs. C}).

Model implementation

All analyses will be performed in the R programming language (R Foundation for Statistical Computing, Vienna, Austria). We will fit pair-wise meta-analysis models in R using the *meta* package,⁶² and will conduct all NMA, CNMAs, design-by-treatment interaction models, node-splitting models, subgroup and sensitivity analyses in R using the *netmeta* package.⁶³

Sensitivity analyses

If adequate data are available and network geometry is not substantively changed, we will re-estimate our additive CNMA models limited to low risk of bias trials only.

While we have prespecified, based on our prior umbrella review, exercise, nutrition, psychosocial and cognitive interventions as the components that we will compare using CNMA, theoretically each component can be further subdivided. If adequate data are available, we will explore CNMA analyses by subcomponent (eg, exercise: aerobic, strength, other; nutrition: supplementation, counselling, other; psychosocial: anxiety reduction, mood stabilisation, other; although ultimately some subcomponents listed here may require further merging or disaggregation based on their distribution between studies) to further refine our understanding of intervention component efficacy. If missing data are present and unaccounted for in primary reports, we will complete sensitivity analyses using appropriate techniques to impute missing values and assess consistency between primary and imputed results.

Ethics and dissemination

Results will be disseminated through presentations at scientific conferences and submission of peer-reviewed manuscripts. Using our IKT approach, we will also perform targeted dissemination to partner organisations

and via our investigator network. Social and traditional media will also be used to spread results to a larger audience. Ethics approval was not required, as this study does not require participation of human subjects.

Limitations

CNMA requires specific assumptions and acknowledgement of limitations. Assumptions underlying CNMA are similar to those of network meta-analyses,⁶⁴ and will require assessment prior to analysis. Because network comparisons (direct and indirect) depend on a common reference condition (ie, standard care), detailed description of standard care conditions in existing trials will be described to allow meaningful clinical interpretation of results. Should assumption-violating differences between RCTs be identified, we will incorporate baseline risk meta-regression (ie, control rate meta-regression) in our analyses.⁶⁵ Some indirect (ie, via the standard care reference condition) comparisons may not be possible due to a lack of relevant RCT comparators. We have defined our components as exercise, nutrition, psychosocial and cognitive. However, we recognise that these components could be subdivided further, and have therefore prespecified exploratory investigation of subcomponents (eg, strength vs aerobic exercise) should adequate data be available. Sparse data can also limit the power to detect meaningful differences, especially in CNMA models with interactions and for meta-regression.^{20 66 67}

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