Cost analysis and cost-effectiveness of open versus laparoscopic versus robot-assisted versus transanal total mesorectal excision in patients with rectal cancer: a protocol for a systematic review

Ritchie T J Geitenbeek, Thijs A Burghgraef, Mark Broekman, Bram P A Schop, Tom G F Lieverse, Roel Hompes, Klaas Havenga, Maarten Postma, Esther C J Consten

ABSTRACT
Introduction Nowadays, most rectal tumours are treated open or minimally invasive, using laparoscopic, robot-assisted or transanal total mesorectal excision. However, insight into the total costs of these techniques is limited. Since all three techniques are currently being performed, including cost considerations in the choice of treatment technique may significantly impact future healthcare costs. Therefore, this systematic review aims to provide an overview of evidence regarding costs in patients with rectal cancer following open, laparoscopic, robot-assisted and transanal total mesorectal excision.

Methods and analysis A systematic search will be conducted for papers between January 2000 and March 2022. Databases PubMed/MEDLINE, EMBASE, Scopus, Web of Science and Cochrane Library databases will be searched. Study selection, data extraction and quality assessment will be performed independently by four reviewers and discrepancies will be resolved through discussion. The Consensus Health Economic Criteria list will be used for assessing risk of bias. Total costs of the different techniques, consisting of but not limited to, theatre, inhospital and postoperative costs, will be the primary outcome.

Ethics and dissemination No ethical approval is required, as there is no collection of patient data at an individual level. Findings will be disseminated widely, through peer-reviewed publication and presentation at relevant national and international conferences.

Trial registration number CRD42021261125.

INTRODUCTION
The primary treatment for extraperitoneal rectal adenocarcinoma consists of surgical resection according to the total mesorectal excision (TME) principle, often preceded by (chemo)radiotherapy. This procedure can be performed using open TME, laparoscopic TME (L-TME), robot-assisted TME (R-TME) and transanal TME (TaTME). As of yet, no clear differences regarding intraoperative, postoperative or oncological outcomes have been described between the three minimally invasive techniques. Currently all three minimally invasive techniques are performed as standard of care. As treatment of rectal cancer is primarily focused on oncological outcomes, less attention has been paid to the costs of the four TME techniques, consisting of all theatre, in-hospital and postoperative costs. However, cost-effectiveness of open TME, L-TME, R-TME and TaTME is of significant importance, particularly as robot-assisted surgery is said to be associated with significant implementation costs.
Some authors suggest costs of R-TME are higher compared with L-TME as a result of high implementation costs and longer operating times.\(^{3-10}\) Contrastingly, recent studies suggested that operating times may be equal between these techniques. TaTME was reported to be associated with shorter operating times compared with L-TME, when performed by two surgical teams.\(^{37,11,12}\) However, it is important to consider that two teams working, that is often used in TaTME surgery, yield higher costs.\(^{13}\) There are no studies comparing costs of R-TME and TaTME and the level of evidence of literature comparing the cost-effectiveness of the minimal invasive techniques is limited.

Currently, insight into the costs of the different procedures and level of evidence of cost-analysis studies is limited. An analysis and overview of the evidence on costs is, therefore, needed in order to assess the (minimal) invasive TME techniques. This systematic review aims to create an overview of the existing literature regarding the costs for open TME, L-TME, R-TME and TaTME and may provide recommendations for use and future cost-effectiveness studies. This is particularly important regarding the cost-containment discussion. Since all techniques are currently being performed, including cost considerations in the choice of treatment technique may significantly impact future healthcare costs.

**METHODS**

**Patients, interventions, control, outcome and research question**

Patients: patients with rectal cancer.

Interventions: open TME, L-TME, R-TME and TaTME

Control: -

Outcome: total costs, consisting of but not limited to theatre costs, in-hospital costs and postoperative costs.

Research question: What are the total costs, consisting of but not limited to theatre costs, in-hospital costs and postoperative costs, of open, laparoscopic, robot-assisted and TaTME for the surgical treatment of patients with rectal cancer?

**Search strategy**

This review will be performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (online supplemental file 1). A systematic search will be conducted on PubMed/ MEDLINE, EMBASE, Scopus, Web of Science and Cochrane Library databases, using a predefined search strategy consisting of a combination of standard search headings and medical subject headings related to open TME, L-TME, R-TME and TaTME for treatment of rectal cancer (online supplemental file 2). The search will be supported by an experienced librarian. No limits based on study design or setting will be imposed on the search. For literature saturation, reference lists of included studies and the function ‘related article’ in PubMed will also be used to identify articles.

Additionally, databases of ongoing (unpublished) trials (ie, WHO Registry Network (including ClinicalTrials.gov), PROSPERO, EMBASE) will be searched. Should the available data presented in primary studies be insufficient for analysis or specifics on treatment details or outcomes of interest be missing, the corresponding authors of the study will be requested for additional data.

**Study eligibility criteria**

Studies will be selected if they meet the following eligibility criteria: (1) studies reporting on total costs, which includes, but is not limited to, theatre costs (personnel, consumables, conversions), in-hospital costs (ward, laboratory, imaging, pharmacy, Post Anesthesia Care Unit (PACU), Intensive Care Unit (ICU) and postoperative costs (complications, reinterventions), after open TME, L-TME, R-TME or TaTME for rectal cancer; (2) prospective studies or retrospective cohort studies with prospective collection of cost data; (3) studies with a minimal follow-up time of 3 months; (4) were published between January 2000 and March 2022 and finally and (5) studies published in English, French, German and Spanish.

Excluded will be: (1) reviews, (conference) abstracts, commentaries, letters (however, not randomized controlled trials (RCTs) published as ‘letters to the editor’), editorials, case series and case reports; (2) studies including only patients with recurrent rectal carcinoma; (3) studies including less than 10 patients and finally (4) studies without full text available.

Retrospective studies with retrospectively collected data will be excluded, as these are associated with recall bias and, therefore, result in low evidence in term of cost evaluation. However, retrospective studies that collected cost data prospectively will be included. As substantial progression has been made during the first years following introduction of R-TME and TaTME, arguments could be made to opt for omitting early studies (ie, start the search from 2005 onwards). However, since it has been assumed that articles on costs of R-TME and TaTME are relatively scarce, we will include studies published between January 2000 and March 2022. As follow-up is essential for determining costs, a minimal follow-up time of 3 months is required. Studies reporting various follow-up lengths will be evaluated on a case-by-case basis for eligibility for inclusion.

**Outcomes**

The primary outcome of this systematic review will be total costs, consisting of but not limited to, theatre, in-hospital and postoperative costs. Due to potential variation in definition of total costs, this variable will be extracted and reported as described in individual studies. Different reporting outcomes will be evaluated for inclusion on a case-by-case basis.

**Data management**

The results from the literature search will be uploaded in Rayyan QCRI, a web-based software management programme that helps facilitate the screening and study
selection process of authors of systematic reviews. Duplicates will be removed and abstracts and full-text articles will be uploaded as Portable Document Formats. In studies reporting from the same sample of patients in different years, the study with the largest sample size and longest length of follow-up will be included.

**Study selection process**

Potentially eligible records will be identified through title and abstract screening by four independent review authors (RTJG, MB, BPAS and TGFL). Articles will receive scores based on the predefined eligibility criteria. Studies will then be selected for final inclusion through full-text screening. A flow diagram describing the screening process will be made.

**Data collection process**

A standardised data extraction form will be developed in Microsoft Excel. Review authors (RTJG, MB, BPAS, TGFL) will extract data from eligible studies independently. Instructions on the extraction form will be provided to increase consistency between authors. Extracted data will consist of study details, patient demographics, details of interventions used, methodology and relevant outcomes. Study characteristics will be tabulated in detail.

**Data items and outcomes**

The following data will be extracted from eligible studies: reference and title details (first author, journal, year of publication, country, study type, funding received), characteristics of study population (gender, age, number of patients, minimal invasive technique used), characteristics of disease (cT/cN/cM stage, neoadjuvant therapy, tumour types (colon vs rectal), characteristics of surgery (number of surgeons performing treatment, surgeon experience, type of procedure), methodological characteristics (economic evaluation type, perspective, length of follow-up, discount rate, costs, model assumptions, primary economic outcomes and sensitivity analyses), cost-effectiveness outcomes used (ie, complications, readmission rate, local recurrence, systematic recurrence, disease-free survival, overall survival) and main findings. The following cost components (if present) will be extracted from the individual studies: total costs, total theatre costs, conversion costs, instrumentation costs, consumable costs, personnel costs, costs for theatre per hour, costs of interventions, total in-hospital non-theatre costs, ward costs, complication costs, lab costs, imaging costs, pharmacy costs, PACU costs, ICU costs, rehabilitation costs, costs of community services and loss of productivity costs.

**Risk of bias and quality assessment**

Review authors (RTJG, MB, BPAS, TGFL) will independently assess the quality of included studies. All eligible studies will be assessed for quality using The Consensus Health Economic Criteria (CHEC) list. Criteria of the CHEC checklist will be modified to fit this systematic review. All disagreements between review authors will be resolved through discussion, in which three additional authors were involved, all with expertise in minimal invasive techniques for treatment of rectal cancer (TAB, ECJC, and KH).

**Statistical analysis**

Statistical analysis will be performed using R statistical software. Categorical variables reported as numbers and percentages will be analysed using the $\chi^2$ test. Continuous data will be analysed using the Analysis of Variance/Kruskal-Wallis test. Statistical significance will be defined as $p<0.050$ (two sided). Overall effects will be determined using the Z score. In case of a meta-analysis, the following will be done. For continuous outcome measures, standardised mean differences with basic descriptive statistics will be used to summarise patients and outcome data. Heterogeneity will be assessed by the $I^2$ statistics. $I^2$ values of 25%, 50% and 75% will be considered as low, moderate and high, respectively. In case of moderate or high heterogeneity, the pooled estimates of mean differences will be calculated using random effects models to consider potential interstudy heterogeneity and to adopt a more conservative approach. In case a random effects model is used, the robustness of the results and the potential sources of heterogeneity will be assessed by performing sensitivity analyses. Sensitivity analyses will consist of, but not limited to, comparison of RCTs versus non-randomised studies, in-hospital versus total costs and government versus private healthcare systems.

**Data synthesis**

A narrative synthesis will be provided presenting the findings of the included studies in text and tables, structured around the type of intervention and outcome. Data presented within and between the included studies will be assessed. Findings of studies comparing different minimal invasive techniques head-to-head will be prioritised. A meta-analysis will be performed if more than three studies use the same type of intervention with the same outcome measure. We do not expect to perform a meta-analysis due to expected high heterogeneity of studies caused by differences in range of cost components included, primary effect measures and statistical methods used across the small number of existing studies.

**Meta-bias(es)**

Reporting bias among studies will be assessed. Study protocols will be assessed for publication before the start of patient inclusion. Studies will be assessed for outcome reporting bias through comparing outcomes reported in the published protocol with those reported in the published journal article. Small sample bias will be assessed through comparing the fixed effect estimate against the random effects model.

**Confidence in cumulative evidence**

The Grading of Recommendations Assessment, Development and Evaluation working group approach (GRADE) will be used to assess the quality of evidence for the cost outcomes. The cost outcomes will be assessed using the GRADE tool. The quality of evidence will be reported as high, moderate, low or very low.
Patient and public involvement

The protocol for this systematic review was written in accordance with the Guidance for reporting Involvement of Patients and the Public 2 reporting guidelines. Patients and patient organisations were involved as research partners throughout the development of this study protocol and actively contributed to identifying the lack of insight into total costs of the different techniques. Patients will remain involved and provide feedback during the systematic review. Results of this study will be dissemination adjusted for a non-specialist audience through collaboration with respective patient organisations.

Ethics and dissemination

This study is considered, according to Dutch law, a non-WMO (Medical Research Involving Human Subjects Act) study. No ethical approval is required, as this is a systematic review without collection of patient data at an individual level. Findings will be disseminated widely, through peer-reviewed publication and presentation at relevant conferences.

Study planning

Studies will be assessed and selected from 1 April 2022 till May 2022. Data will be collected, analysed and risk of bias assessed from 1 May 2022 till 1 June 2022. Writing of the manuscript will be performed from 1 June 2022 till 1 July 2022.

Amendments

In the event of protocol amendments, the date of amendment and rationale for deviation will be provided.

Author affiliations

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Acknowledgements

We kindly thank Karin Sijtsma of University Medical Center Groningen for her support with the development of the search strategy.

Contributors

Substantial contributions to the conception and design of the work: RTJG, TAB, MB, BPAS, TFFL, RH, KH, MP, ECJC. Drafting the article: RTJG, TAB, MB, BPAS, TFFL. Revising the article critically for important intellectual content: RH, KH, MP, ECJC. Final approval of the version to be published: RTJG, TAB, MB, BPAS, TFFL, RH, KH, MP, ECJC. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests

EC is a proctor for Intuitive Surgical but no (financial) support from this organisation has been received for the submitted manuscript. Neither have there been any other activities or relations that could appear to have influenced the submitted work. All other authors declare: no support from any organisation for the submitted work; no financial relationships with organisations that may have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.
**Supplementary file 1**

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol**

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Page and section where item is reported</th>
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<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
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<td>Title:</td>
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<tr>
<td>Identification 1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>Page 1, “Study title”</td>
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<tr>
<td>Update 1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>Not applicable</td>
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<tr>
<td>Registration 2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
<td>Page 2, “Registration details”</td>
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<tr>
<td>Authors:</td>
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<tr>
<td>Contact 3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>Page 1, “Authors”</td>
<td></td>
</tr>
<tr>
<td>Contributions 3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>Page 7 “Authors’ contribution”</td>
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<tr>
<td>Amendments 4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>Page 1, “Amendments”</td>
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<td>Support:</td>
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<tr>
<td>Sources 5a</td>
<td>Indicate sources of financial or other support for the review</td>
<td>Page 7, “Funding statement”</td>
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<tr>
<td>Sponsor 5b</td>
<td>Provide name for the review funder and/or sponsor</td>
<td>Not applicable</td>
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<tr>
<td>Role of sponsor or funder 5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
<td>Not applicable</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<tr>
<td>Rationale 6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
<td>Page 3, “introduction”, paragraph 1 and 2</td>
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</table>
Objectives 7  Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)  Page 3, “introduction”, paragraph 3

<table>
<thead>
<tr>
<th>Methods</th>
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<tbody>
<tr>
<td>Eligibility criteria 8 Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review  Page 4, “Study eligibility criteria”</td>
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<tr>
<td>Information sources 9 Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage  Page 4, “Search strategy”</td>
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<tr>
<td>Search strategy 10 Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated  Page 4, “Search strategy” Supplementary file II</td>
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<th>Study records:</th>
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<tr>
<td>Data management 11a Describe the mechanism(s) that will be used to manage records and data throughout the review  Page 5, “Data management”</td>
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<tr>
<td>Selection process 11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)  Page 5, “Study selection process”</td>
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</tr>
<tr>
<td>Data collection process 11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators  Page 5, “Data collection process”</td>
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<tr>
<td>Data items 12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications  Page 5, “Data items and outcome”</td>
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</table>

| Outcomes and prioritization 13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale  Page 5, “Data items and outcome”  |

| Risk of bias in individual studies 14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis  Page 5, “Risk of bias and quality assessment”  |

| Data synthesis 15a Describe criteria under which study data will be quantitatively synthesised  Page 6, “Statistical analysis”  |
| --- | --- |
| 15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s t)  Page 6, “Data synthesis”  |
| 15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)  Not applicable  |
| 15d If quantitative synthesis is not appropriate, describe the type of summary planned  Page 6, “Data synthesis”  |

| Meta-bias(es) 16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)  Page 6, “Meta-bias(es”  |
Confidence in cumulative evidence 17 Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 6, “Confidence in cumulative evidence

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

Supplementary file II

PubMed

("Rectal Neoplasms"[Mesh] OR (Rect*[tiab] AND cancer*[tiab]) OR (Rect*[tiab] AND neoplasm*[tiab]) OR (Rect*[tiab] AND tumo*[tiab]))

AND

((total mesorect*[tiab] AND (excision*[tiab] OR removal*[tiab] OR surger*[tiab]))
OR TME*[tiab] OR tatme*[tiab] OR transanal mesorectal excision*[tiab])

AND

"Transanal Endoscopic Surgery"[Mesh] OR Transanal*[tiab] OR Open*[tiab])

Embase

('rectum tumor'/exp OR (Rect*:ab,ti AND cancer*:ab,ti) OR (Rect*:ab,ti AND neoplasm*:ab,ti) OR (Rect*:ab,ti AND tumo*:ab,ti))

AND

((total mesorect*:ab,ti AND (excision*:ab,ti OR removal*:ab,ti OR surger*:ab,ti))
OR TME:ab,ti OR tatme:ab,ti OR transanal mesorectal excision*:ab,ti)

AND

('laparoscopy'/exp OR laparoscop*:ab,ti OR 'robotics'/exp OR robot*:ab,ti OR 'Transanal Endoscopic Surgery'/exp OR Transanal*:ab,ti OR Open*:ab,ti)
Web of Science

("Rectal neoplasms" OR (Rect* AND cancer*) OR (Rect* AND neoplasm*) OR (Rect* AND tumo*))

AND

((total mesorect* AND (excision* OR removal* OR surger*)) OR TME OR tatme OR transanal mesorectal excision*)

AND

("Laparoscopy" OR Laparo* OR "Robotics" OR Robot* OR "Transanal Endoscopic Surgery" OR Transanal* OR Open)

Scopus

("Rectal neoplasms" OR (Rect* AND cancer*) OR (Rect* AND neoplasm*) OR (Rect* AND tumo*))

AND

((total mesorect* AND (excision* OR removal* OR surger*)) OR TME OR tatme OR transanal mesorectal excision*)

AND

("Laparoscopy" OR Laparo* OR "Robotics" OR Robot* OR "Transanal Endoscopic Surgery" OR Transanal* OR Open)
Cochrane Library

ID Search

#1 MeSH descriptor: [Rectal Neoplasms] explode all trees
#2 (rect*):ti,ab,kw (Word variations have been searched)
#3 (cancer*):ti,ab,kw (Word variations have been searched)
#4 (tumo*):ti,ab,kw (Word variations have been searched)
#5 (total mesorect*):ti,ab,kw (Word variations have been searched)
#6 (excision*):ti,ab,kw (Word variations have been searched)
#7 (removal*):ti,ab,kw (Word variations have been searched)
#8 (surger*):ti,ab,kw (Word variations have been searched)
#9 (TME):ti,ab,kw (Word variations have been searched)
#10 (tatme):ti,ab,kw (Word variations have been searched)
#11 (transanal mesorectal excision*):ti,ab,kw (Word variations have been searched)
#12 MeSH descriptor: [Laparoscopy] explode all trees
#13 (laparo*):ti,ab,kw (Word variations have been searched)
#14 MeSH descriptor: [Robotics] explode all trees
#15 (robot*):ti,ab,kw (Word variations have been searched)
#16 MeSH descriptor: [Transanal Endoscopic Surgery] explode all trees
#17 (transanal*):ti,ab,kw (Word variations have been searched)
#18 (open*):ti,ab,kw (Word variations have been searched)
#19 (#1 OR (#2 AND #3) OR (#2 AND #4)) AND ((#5 AND (#6 OR #7 OR #8)) OR #9 OR #10 OR #11) AND (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

Filters and limits

Limits will only be imposed for date of publication. This review will include only studies published between January 2000 and March 2022 in the search strategy.