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Interrupted versus continuous suturing for vesicourethral anastomosis during radical prostatectomy: protocol for a systematic review and meta-analysis.

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Interrupted versus continuous suturing for vesicourethral anastomosis during radical prostatectomy: protocol for a systematic review and meta-analysis.

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Abstract

Introduction

Radical prostatectomy is the mainstay of treatment for prostate cancer. The vesicourethral anastomosis is a critical step, which most likely impacts urinary continence and urethral stenosis. To date, it still remains unclear whether interrupted and continuous suturing for the anastomosis have different outcomes. Therefore, the aim of this systematic review and meta-analysis is to compare different suture techniques for vesicourethral anastomosis in terms of surgical and functional parameters.

Methods and Analysis

A comprehensive literature search will be conducted covering MEDLINE, Embase, Web of Science, the Cochrane Central Register of Controlled Trails (CENTRAL) and ClinicalTrials.gov. Studies comparing interrupted versus continuous suturing will be included in the analyses. No language restrictions will be applied. Screening, data extraction, statistical analysis and reporting will be done in line with the PRISMA guidelines. Quality assessment will be performed with the help of the Cochrane Collaboration's tool for assessing risk of bias and the Newcastle-Ottawa Scale for assessing quality of nonrandomized studies. The quality of evidence will be evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The primary outcome will be the time until removal of the urinary catheter. Secondary outcomes include rate of extravasation, length of hospital stay, time needed to perform the anastomosis, continence level at defined postoperative intervals and development of urethral strictures. Quantitative analysis will be calculated if meaningful.

Ethics and dissemination

In order to meet the highest ethical and methodological standards we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)-2015 Checklist. Each item was answered appropriately. For systematic reviews the ethical issues are strictly methodological as only data which was published earlier will be used. The full manuscript will be submitted to a peer-reviewed journal. Furthermore, the results will be presented on national and international congresses.

PROSPERO registration number: CRD42017076126

Strengths and limitations of this study:

- Radical prostatectomy is one of the most commonly performed procedures in urological oncology thus affecting a tremendous amount of patients.
- To our best knowledge, this will be the first systematic review and meta-analysis comparing interrupted versus continuous suturing for vesicourethral anastomosis during radical prostatectomy.
- Subgroup analysis will differentiate between different surgical approaches in order to address a holistic but detailed overview for the individual patient.
- The reporting of outcome parameters might be variable among studies. Therefore, it remains to be determined what outcomes are feasible for pooling of the data.
- Quality assessment of included studies will provide an overview of the strength of evidence for each outcome.

Background

Prostate cancer (PCa) is the most frequently-occurring cancer among men worldwide [1, 2], with a cancer-specific mortality of about two to three percent in the western world [3, 4]. The mainstay of curative treatment, besides radiotherapy, is radical prostatectomy (RP). RP is chosen as primary treatment in about 50 percent of patients, compared to 25 percent who choose some kind of radiotherapy [5].

During the last two decades different surgical approaches to RP including open, laparoscopic (LRP) and robotic-assisted prostatectomy (RARP) were established. These have been shown to be comparable with regards to oncological outcome, postoperative complications and continence [6-8]. Despite its effectiveness, RP remains a challenging procedure with a high impact on the patient's life including continence, erectile function and quality of life.

The vesicourethral anastomosis (VUA) is a crucial and challenging step of RP even in the hands of experienced surgeons [9, 10]. Although the quality of the VUA is unlikely to have an impact on oncological outcome, it strongly affects functional outcome and thus quality of life [11]. Notably, VUA leakage was found to be the predominant risk factor for postoperative incontinence [12]. Furthermore, VUA quality possibly influences the development of postoperative vesicourethral anastomotic stenosis (VUAS), which occurs in around 2.1-7.5 percent of patients [13-15].

The suture technique, specifically interrupted (IS) versus continuous suturing (CS), might influence the outcome of the VUA. In general, CS is usually faster and associated with a lower leakage rate [16, 17]. On the other side, CS raises concerns for a higher incidence of strictures [18].

Currently, there is a lack of clear evidence concerning a conceivable superiority of IS or CS for VUA. Therefore, the aim of this systematic review and potential meta-analysis will be to compare different suture techniques for VUA in patients undergoing RP.

Methods/design

The protocol of the planned systematic review and potential meta-analysis is written in line with the PRISMA-P 2015 checklist [19]. Additionally, the systematic review and meta-analysis was registered with the international prospective register of systematic reviews PROSPERO (CRD42017076126)[20].

Search methodology

A systematic literature search will be conducted according to the PICO criteria [21]. In order to retrieve as much evidence as possible, the search will include MESH terms and free text combined with Boolean operators. The search will include synonyms of the following terms: single suture / continuous suture / vesicourethral / anastomosis / prostatectomy / barbed. A previous screening of relevant articles will help to identify synonyms for suture techniques and further relevant key words (e.g. vesicourethral vs. urethrovesical or single suture vs. interrupted suture).

The combined search term will be modified for each database and applied to MEDLINE (via PubMed), Embase, Web of Science and the Cochrane Central Register of Controlled Trails (CENTRAL) and ClinicalTrials.gov. By this approach, published, unpublished, and ongoing trails will be detected. After removing all duplicates, the remaining articles will be uploaded to convidence.org [22]. Furthermore, the reference section of all included articles and previous reviews will be searched manually, and experts will be consulted to identify additional literature. In case of missing data, the corresponding authors will be contacted directly.

Study selection and data extraction

Two researchers will independently screen title and abstract of each article. If considered eligible, the full text will be retrieved and reviewed for eligibility again. Potential disagreement in one of those steps will be solved by consensus and, if necessary, with the help of a third reviewer. This process will be documented in detail in order to create a PRISMA flow diagram.

Eligibility criteria

Studies are considered eligible if they compare IS versus CS. All types of studies will be included (RCT, non-RCT, observational studies). No language restrictions will be applied. If needed, studies will be translated by professional translators.

Exclusion criteria

Studies which focus on experiments and operations on animals, models or cadavers will be excluded. Additionally, if a posterior reconstruction was done previously to the VUA in one study group only, these studies or groups will be excluded from analysis. Posterior reconstruction has a potential impact on the operative outcome which was investigated elsewhere [23]. Furthermore, studies with no

comparison group or none of the defined outcome measures analyzed will be excluded. Studies reporting a perineal approach for RP, an indication for RP other than PCa, or salvage RP will be excluded.

Data extraction

All extracted data will be filled in a dedicated data sheet (Microsoft Excel™, Redmond, Washington, USA). The data sheet will then be tested on five studies to prove its suitability. Two reviewers will extract the data independently from each other. The following information will be retrieved:

1) Methods: authors, year of publication, journal, type of study, country, registration of trial
2) Patients: mean age, cancer stage, PSA level, Gleason score, body mass index,
3) Interventions: intervention technique (open / laparoscopic / robotic prostatectomy), suture technique (continuous / interrupted), suture material (Vicryl / monofilament)
4) Outcome: primary and secondary outcome of each study including but not limited to
    a. catheterization time
    b. anastomotic time
    c. urinary incontinence at reported intervals
    d. leakage / extravasation
    e. VUAS
    f. hospital stay
    g. prostate size / specimen weight

Endpoints

The primary endpoint will be catheterization time. Secondary endpoints will include rate of extravasation, urinary incontinence at 3, 6 and 12 months postoperatively, development of VUAS, length of hospital stay and time to perform the VUA intraoperatively.

Subgroup analysis

In order to evaluate the best surgical option for VUA, various comparisons of suture techniques and surgical approach will be performed. The following subgroup analysis will be done if the extracted data appears suitable:

1) interrupted suture vs. continuous suture
    a. in minimally invasive approaches
    b. in LRP
    c. in RARP
    d. in open surgery

e. in open surgery vs. minimally invasive approaches

f. in LRP vs. RARP

Quality assessment

Quality assessment of RCTs will be done with the help of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [24]. This tool incorporates the following seven domains: a) Random sequence generation, b) Allocation concealment, c) Blinding of participants and personnel, d) Blinding of outcome assessment, e) Selective reporting and f) Anything else, ideally prespecified (e.g. funding). All these domains can be rated as either high, low or unclear.

Quality assessment of all non-RCTs will be done with the Newcastle-Ottawa Scale for assessing quality of nonrandomized studies in meta-analyses [25]. Three domains a) selection, b) comparability and c) exposure will be rated with a maximum total score of nine stars.

Congress abstracts and further material which can be considered as 'grey literature', will be rated with the lowest possible quality. This literature will be reported separately and not included in statistical testing.

Quality of evidence

The strength of the body of evidence for relevant endpoints will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[26]. According to GRADE the quality of evidence can be rated as high, moderate, low and very low.

Statistical analysis

In case the extracted data is appropriate for pooled analyses (e.g. similar techniques and patients) a meta-analysis will be performed. Dichotomous data will be analyzed using the Mantel-Haenszel model and reported as odds ratio. In case of continuous data, inverse variance models will be used and reported as mean difference. Forest plots will be used for visualization of the results.

The heterogeneity of studies will be calculated using the I^2 index. An I^2 value of 0 - 25 % represents insignificant heterogeneity; > 25 % - 50 % low heterogeneity; > 50 % - 75 % moderate heterogeneity; and > 75 % high heterogeneity [27]. Insignificant heterogeneity will be calculated using a fixed-effects model and with a low or moderate heterogeneity using a random-effects model. If concerns for high heterogeneity exist, a sensitivity analysis will be performed. In case of a different reporting pattern, mean and standard deviation values (e.g. trials reporting median and range/interquartile range) will be transformed according to Hozo et al. and Higgins et al. [28, 29]. Funnel plots will be used to visualize publication bias. For other bias, a risk of bias assessment figure will be used. For all calculations, the Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) will be used.

A p-value of less than 0.05 will be considered as statistically significant.

Discussion

Over 90,000 RPs are performed per year in the U.S. [30] and about 25,500 in Germany [31]. Due to this high volume, even small differences in surgical outcomes can possibly affect a great number of patients. Therefore, we aim to increase the level of evidence concerning the optimal suture techniques for VUA. Our results might help to further standardize the procedure and to optimize functional outcome of patients undergoing RP for PCa.

In our analyses, the time until removal of the urinary catheter will be used as the primary outcome, as it is also a direct indicator for length of hospital stay and might has a positive influence in continence [32]. Furthermore, it is likely to be stated in the majority of studies, as its assessment is simple and thus little differences between the included studies are expected. In contrast, continence level or quality of life are commonly measured by different scores making comparison more difficult [33, 34].

Whereas the prevailing aim of the study is to assess differences between IS and CS for VUA in general, subgroup analysis might help to identify the optimal combinations of technique and surgical approach (open vs. LRP/RARP). In case of low sample sizes, the studies will be cumulated and subgroup analysis will only be performed if meaningful.

Following the “best evidence approach” and in order to gather all existing literature, we chose to include not only RCTs but also non-RCTs and observational studies. Whether non-RCTs should be included in systematic reviews and meta-analyses is controversial. Some argue that only RCTs provide the highest scientific quality [35]. Without appropriate randomization, studies are prone to confounding bias and to over- or underestimate the effect of interest [29]. In contrast, randomization is not feasible for some research questions [36, 37]. Besides, observational studies might reflect daily clinical work in a more realistic way [38]. Moreover, grey literature (e.g. congress presentations, registered trials) is generally considered as poor quality because detailed information on methodology and randomization are often impossible to reconstruct. Nonetheless, grey literature can be important because it often contains results which were not published since they did not show significant findings and could therefore address publication bias [39, 40]. In order to provide a holistic overview, grey literature will be included but marked as such. In addition, it will not be part of the meta-analysis, and conclusions will be drawn extremely carefully. Finally, the comprehensive literature search will also help to detect alternative surgical strategies which are not commonly used and could be of interest for future research.

In summary, the systematic review and meta-analysis will help to determine if there is any difference in CS or IS for VUA and if one technique is superior to the other. Furthermore, quality assessment of the included studies will yield if further well-designed studies are necessary.

Trial status:

Preliminary searches: started

Piloting of the study selection process: started

Formal screening: not started

Date extraction: not started

Risk of bias assessment: not started

Data analysis: not started

Abbreviations:

CS: continuous suturing; IS: interrupted suturing; LRP: laparoscopic radical prostatectomy; PCa: prostate cancer; RARP: robotic-assisted radical prostatectomy; RCT: randomized controlled trial; RP: radical prostatectomy; VUA: vesicourethral anastomosis; VUAS: vesicourethral anastomotic stenosis

Competing interests:

The authors have no competing interests to declare.

Authors' contributions:

KFK and CT drafted the manuscript and created the study concept. FN and PM gave methodological advice. SH provided statistical advice and will perform statistical analysis. MR provided supervision and guidance during the study. MK helped to concept the study and is the guarantor of the review. All authors reviewed and approved the manuscript in its current form.

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Draft of search strategy for MEDLINE

("Prostatectomy"[Mesh]) OR (vesicourethral) OR (vesico AND urethral) OR (urethrovesical) OR (urethro* AND vesical) OR (VUA) OR (prostatectomy))*

AND

((running) OR (running AND sutur*) OR (running* AND knot*) OR (interrupted) OR (interrupted* AND sutur*)*

OR (interrupted AND knot*) OR (single) OR (single* AND sutur*) OR (single* AND knot*) OR (velthoven)*

OR (barbed AND sutur*) OR (barbed) OR (sutur*) OR (knot*))*

AND

(("Anastomosis, Surgical"[Mesh]) OR (anastomo) OR (re*anastomo*) OR (reanastomo*) OR (reconstruction))*

References

1. Mottet, N., et al., *EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent.* Eur Urol, 2017. **71**(4): p. 618-629.
2. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. **136**(5): p. E359-86.
3. Bott, S.R., et al., *Prostate cancer management: (1) an update on localised disease.* Postgrad Med J, 2003. **79**(936): p. 575-80.
4. Schröder, F.H., et al., *Prostate-cancer mortality at 11 years of follow-up.* New England Journal of Medicine, 2012. **366**(11): p. 981-990.
5. Cooperberg, M.R., J.M. Broering, and P.R. Carroll, *Time trends and local variation in primary treatment of localized prostate cancer.* Journal of Clinical Oncology, 2010. **28**(7): p. 1117-1123.
6. Ahlering, T.E., et al., *Robot-assisted versus open radical prostatectomy: a comparison of one surgeon's outcomes.* Urology, 2004. **63**(5): p. 819-822.
7. Tewari, A., et al., *Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy.* Eur Urol, 2012. **62**(1): p. 1-15.
8. Yaxley, J.W., et al., *Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study.* Lancet, 2016. **388**(10049): p. 1057-1066.
9. Hoznek, A., et al., *Vesicourethral anastomosis during laparoscopic radical prostatectomy: the running suture method.* J Endourol, 2000. **14**(9): p. 749-53.
10. Menon, M., et al., *The technique of apical dissection of the prostate and urethrovesical anastomosis in robotic radical prostatectomy.* BJU Int, 2004. **93**(6): p. 715-9.
11. Liss, M.A., et al., *Continence definition after radical prostatectomy using urinary quality of life: evaluation of patient reported validated questionnaires.* The Journal of urology, 2010. **183**(4): p. 1464-1468.
12. Eastham, J.A., et al., *Risk factors for urinary incontinence after radical prostatectomy.* The Journal of urology, 1996. **156**(5): p. 1707-1713.
13. Wang, R., et al., *Risk factors and quality of life for post-prostatectomy vesicourethral anastomotic stenoses.* Urology, 2012. **79**(2): p. 449-457.
14. Surya, B.V., et al., *Anastomotic strictures following radical prostatectomy: risk factors and management.* J Urol, 1990. **143**(4): p. 755-8.
15. Hisasue, S., et al., *Early and late complications of radical retropubic prostatectomy: experience in a single institution.* Jpn J Clin Oncol, 2004. **34**(5): p. 274-9.

16. Ramalingam, M., et al., *A comparison of continuous and interrupted suturing in laparoscopic pyeloplasty.* Jsls, 2014. **18**(2): p. 294-300.
17. Lee, S.W., et al., *Effect of Continuous Urethro-Vesical Anastomosis Technique in Incontinence After Radical Retropubic Prostatectomy, 1:1 Matching Study.* Int Neurourol J, 2015. **19**(2): p. 113-9.
18. Aitken, E., et al., *A randomized controlled trial of interrupted versus continuous suturing techniques for radiocephalic fistulas.* J Vasc Surg, 2015. **62**(6): p. 1575-82.
19. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic reviews, 2015. **4**(1): p. 1.
20. Booth, A., et al., *The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.* Systematic Reviews, 2012. **1**(1): p. 2.
21. Santos, C.M.d.C., C.A.d.M. Pimenta, and M.R.C. Nobre, *The PICO strategy for the research question construction and evidence search.* Revista latino-americana de enfermagem, 2007. **15**(3): p. 508-511.
22. Babineau, J., *Product review: Covidence (systematic review software).* Journal of the Canadian Health Libraries Association/Journal de l'Association des bibliothèques de la santé du Canada, 2014. **35**(2): p. 68-71.
23. Grasso, A.A., et al., *Posterior musculofascial reconstruction after radical prostatectomy: an updated systematic review and a meta-analysis.* BJU Int, 2016. **118**(1): p. 20-34.
24. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.
25. Wells, G., et al., *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Ottawa, Ontario: The Ottawa Health Research Institute*. 2011.
26. Guyatt, G.H., et al., *Rating quality of evidence and strength of recommendations: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ: British Medical Journal, 2008. **336**(7650): p. 924.
27. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* BMJ, 2003. **327**(7414): p. 557-60.
28. Hozo, S.P., B. Djulbegovic, and I. Hozo, *Estimating the mean and variance from the median, range, and the size of a sample.* BMC medical research methodology, 2005. **5**(1): p. 13.
29. Higgins, J.P. and S. Green, *Cochrane handbook for systematic reviews of interventions*. Vol. 4. 2011: John Wiley & Sons.
30. Lowrance, W.T., et al., *Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States.* J Urol, 2012. **187**(6): p. 2087-92.
31. Stolzenburg, J.U., et al., *National trends and differences in morbidity among surgical approaches for radical prostatectomy in Germany.* World J Urol, 2016. **34**(11): p. 1515-1520.
32. Koch, M.O., et al., *Early catheter removal after radical retropubic prostatectomy: long-term followup.* The Journal of urology, 2003. **169**(6): p. 2170-2172.
33. Avery, K., et al., *Questionnaires to assess urinary and anal incontinence: review and recommendations.* The Journal of urology, 2007. **177**(1): p. 39-49.
34. Klovning, A., et al., *Comparison of two questionnaires for assessing the severity of urinary incontinence: The ICIQ-UI SF versus the incontinence severity index.* Neurourology and urodynamics, 2009. **28**(5): p. 411-415.
35. Castillo, R.C., D.O. Scharfstein, and E.J. MacKenzie, *Observational studies in the era of randomized trials: finding the balance.* J Bone Joint Surg Am, 2012. **94 Suppl 1**: p. 112-7.
36. Grootendorst, D.C., et al., *Observational studies are complementary to randomized controlled trials.* Nephron Clin Pract, 2010. **114**(3): p. c173-7.
37. Black, N., *Why we need observational studies to evaluate the effectiveness of health care.* Bmj, 1996. **312**(7040): p. 1215-8.
38. Faber, T., et al., *Meta-analyses including non-randomized studies of therapeutic interventions: a methodological review.* BMC Med Res Methodol, 2016. **16**.

39. Hopewell, S., et al., *Grey literature in meta-analyses of randomized trials of health care interventions.* Cochrane Database Syst Rev, 2007(2): p. Mr000010.
40. Adams, R.J., P. Smart, and A.S. Huff, *Shades of Grey: Guidelines for Working with the Grey Literature in Systematic Reviews for Management and Organizational Studies.* International Journal of Management Reviews, 2016: p. n/a-n/a.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	p. 1, ll. 2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	p. 2, l. 27
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	p. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	p. 9 ll. 15-19
Amendments	4	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	☐	☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	p. 9, ll. 20-25
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	p. 9, ll. 20-25
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	p. 9, ll. 20-25
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	p. 4, p. ll. 1-20
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	p.4, ll. 21-23 p. 6, ll. 7-19
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	p. 5, ll. 25-28
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	p.5, ll. 13-19
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	☒	☐	p. 9, ll. 26ff
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	p. 5, ll. 16-17 p. 6, ll. 4-7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	p. 5, ll. 20-24
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	p. 5, ll. 20-24
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	p. 6, ll. 7-19
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	p. 6, ll. 22-25
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	☒	☐	p. 7, ll. 3-18
DATA					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	p. 7, 20-23
	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 (e.g., I^2, Kendall's tau)	☒	☐	p. 7f, ll. 24ff
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	p. 7f, ll. 24ff
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	p. 7f, ll. 24ff
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	p. 7, ll. 24-33
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	p-7, ll. 15-18

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Interrupted versus continuous suturing for vesicourethral anastomosis during radical prostatectomy: protocol for a systematic review and meta-analysis.

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Abstract

Introduction

Radical prostatectomy is the mainstay of treatment for prostate cancer. The vesicourethral anastomosis is a critical step, which most likely impacts urinary continence and urethral stenosis. To date, it still remains unclear whether interrupted and continuous suturing for the anastomosis have different outcomes. Therefore, the aim of this systematic review and meta-analysis is to compare different suture techniques for vesicourethral anastomosis in terms of surgical and functional parameters.

Methods and Analysis

A comprehensive literature search will be conducted covering MEDLINE, Embase, Web of Science, the Cochrane Central Register of Controlled Trails (CENTRAL) and ClinicalTrials.gov. Studies comparing interrupted versus continuous suturing will be included in the analyses. No language restrictions will be applied. Screening, data extraction, statistical analysis and reporting will be done in line with the PRISMA guidelines. Quality assessment will be performed with the help of the Cochrane Collaboration's tool for assessing risk of bias and the Newcastle-Ottawa Scale for assessing quality of nonrandomized studies. The quality of evidence will be evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The primary outcome will be the time until removal of the urinary catheter. Secondary outcomes include rate of extravasation, length of hospital stay, time needed to perform the anastomosis, continence level at defined postoperative intervals and development of urethral strictures. Quantitative analysis will be calculated if meaningful.

Ethics and dissemination

In order to meet the highest ethical and methodological standards we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)-2015 Checklist. Each item was answered appropriately. For systematic reviews the ethical issues are strictly methodological as only data which was published earlier will be used. The full manuscript will be submitted to a peer-reviewed journal. Furthermore, the results will be presented on national and international congresses.

PROSPERO registration number: CRD42017076126

Strengths and limitations of this study:

- Radical prostatectomy is one of the most commonly performed procedures in urological oncology thus affecting a tremendous amount of patients.
- To our best knowledge, this will be the first systematic review and meta-analysis comparing interrupted versus continuous suturing for vesicourethral anastomosis during radical prostatectomy.
- Subgroup analysis will differentiate between different surgical approaches in order to address a holistic but detailed overview for the individual patient.
- The reporting of outcome parameters might be variable among studies. Therefore, it remains to be determined what outcomes are feasible for pooling of the data.
- Quality assessment of included studies will provide an overview of the strength of evidence for each outcome.

Background

Prostate cancer (PCa) is the most frequently-occurring cancer among men worldwide [1, 2], with a cancer-specific mortality of about two to three percent in the western world [3, 4]. The mainstay of curative treatment, besides radiotherapy, is radical prostatectomy (RP). RP is chosen as primary treatment in about 50 percent of patients, compared to 25 percent who choose some kind of radiotherapy [5].

During the last two decades different surgical approaches to RP including open, laparoscopic (LRP) and robotic-assisted prostatectomy (RARP) were established. These have been shown to be comparable with regards to oncological outcome, postoperative complications and continence [6-8]. Despite its effectiveness, RP remains a challenging procedure with a high impact on the patient's life including continence, erectile function and quality of life.

The vesicourethral anastomosis (VUA) is a crucial and challenging step of RP even in the hands of experienced surgeons [9, 10]. Although the quality of the VUA is unlikely to have an impact on oncological outcome, it strongly affects functional outcome and thus quality of life [11]. Notably, VUA leakage was found to be the predominant risk factor for postoperative incontinence [12]. Furthermore, VUA quality possibly influences the development of postoperative vesicourethral anastomotic stenosis (VUAS), which occurs in around 2.1-7.5 percent of patients [13-15].

The suture technique, specifically interrupted (IS) versus continuous suturing (CS), might influence the outcome of the VUA. In general, CS is usually faster and associated with a lower leakage rate [16, 17]. On the other side, CS raises concerns for a higher incidence of strictures [18].

Currently, there is a lack of clear evidence concerning a conceivable superiority of IS or CS for VUA. Therefore, the aim of this systematic review and potential meta-analysis will be to compare different suture techniques for VUA in patients undergoing RP.

Methods/design

The protocol of the planned systematic review and potential meta-analysis is written in line with the PRISMA-P 2015 checklist [19]. Additionally, the systematic review and meta-analysis was registered with the international prospective register of systematic reviews PROSPERO (CRD42017076126)[20].

Search methodology

A systematic literature search will be conducted according to the PICO criteria [21]. In order to retrieve as much evidence as possible, the search will include MESH terms and free text combined with Boolean operators. The search will include synonyms of the following terms: single suture / continuous suture / vesicourethral / anastomosis / prostatectomy / barbed. A previous screening of relevant articles will help to identify synonyms for suture techniques and further relevant key words (e.g. vesicourethral vs. urethrovesical or single suture vs. interrupted suture).

The combined search term will be modified for each database and applied to MEDLINE (via PubMed), Embase, Web of Science and the Cochrane Central Register of Controlled Trails (CENTRAL) and ClinicalTrials.gov. By this approach, published, unpublished, and ongoing trails will be detected. After removing all duplicates, the remaining articles will be uploaded to convidence.org [22]. Furthermore, the reference section of all included articles and previous reviews will be searched manually, and experts will be consulted to identify additional literature. In case of missing data, the corresponding authors will be contacted directly.

Study selection and data extraction

Two researchers will independently screen title and abstract of each article. If considered eligible, the full text will be retrieved and reviewed for eligibility again. Potential disagreement in one of those steps will be solved by consensus and, if necessary, with the help of a third reviewer. This process will be documented in detail in order to create a PRISMA flow diagram.

Eligibility criteria

Studies are considered eligible if they compare IS versus CS. All types of studies will be included (RCT, non-RCT, observational studies). No language restrictions will be applied. If needed, studies will be translated by professional translators.

Exclusion criteria

Studies which focus on experiments and operations on animals, models or cadavers will be excluded. Additionally, if a posterior reconstruction was done previously to the VUA in one study group only, these studies or groups will be excluded from analysis. Posterior reconstruction has a potential impact on the operative outcome which was investigated elsewhere [23]. Furthermore, studies with no

comparison group or none of the defined outcome measures analyzed will be excluded. Studies reporting a perineal approach for RP, an indication for RP other than PCa, or salvage RP will be excluded.

Data extraction

All extracted data will be filled in a dedicated data sheet (Microsoft Excel™, Redmond, Washington, USA). The data sheet will then be tested on five studies to prove its suitability. Two reviewers will extract the data independently from each other. The following information will be retrieved:

1) Methods: authors, year of publication, journal, type of study, country, registration of trial
2) Patients: mean age, cancer stage, PSA level, Gleason score, body mass index,
3) Interventions: intervention technique (open / laparoscopic / robotic prostatectomy), suture technique (continuous / interrupted), suture material (Vicryl / monofilament)
4) Outcome: primary and secondary outcome of each study including but not limited to
    a. catheterization time
    b. anastomotic time
    c. urinary incontinence at reported intervals
    d. leakage / extravasation
    e. VUAS
    f. hospital stay
    g. prostate size / specimen weight

Endpoints

The primary endpoint will be catheterization time. Secondary endpoints will include rate of extravasation, urinary incontinence at 3, 6 and 12 months postoperatively, development of VUAS, length of hospital stay and time to perform the VUA intraoperatively.

Subgroup analysis

In order to evaluate the best surgical option for VUA, various comparisons of suture techniques and surgical approach will be performed. The following subgroup analysis will be done if the extracted data appears suitable:

1) interrupted suture vs. continuous suture
    a. in minimally invasive approaches
    b. in LRP
    c. in RARP
    d. in open surgery

e. in open surgery vs. minimally invasive approaches

f. in LRP vs. RARP

Quality assessment

Quality assessment of RCTs will be done with the help of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [24]. This tool incorporates the following seven domains: a) Random sequence generation, b) Allocation concealment, c) Blinding of participants and personnel, d) Blinding of outcome assessment, e) Selective reporting and f) Anything else, ideally prespecified (e.g. funding). All these domains can be rated as either high, low or unclear.

Quality assessment of all non-RCTs will be done with the Newcastle-Ottawa Scale for assessing quality of nonrandomized studies in meta-analyses [25]. Three domains a) selection, b) comparability and c) exposure will be rated with a maximum total score of nine stars.

Congress abstracts and further material which can be considered as 'grey literature', will be rated with the lowest possible quality. This literature will be reported separately and not included in statistical testing.

Quality of evidence

The strength of the body of evidence for relevant endpoints will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[26]. According to GRADE the quality of evidence can be rated as high, moderate, low and very low.

Statistical analysis

In case the extracted data is appropriate for pooled analyses (e.g. similar techniques and patients) a meta-analysis will be performed. Dichotomous data will be analyzed using the Mantel-Haenszel model and reported as odds ratio. In case of continuous data, inverse variance models will be used and reported as mean difference. Forest plots will be used for visualization of the results.

The heterogeneity of studies will be calculated using the I^2 index. An I^2 value of 0 - 25 % represents insignificant heterogeneity; > 25 % - 50 % low heterogeneity; > 50 % - 75 % moderate heterogeneity; and > 75 % high heterogeneity [27]. Insignificant heterogeneity will be calculated using a fixed-effects model and with a low or moderate heterogeneity using a random-effects model. If concerns for high heterogeneity exist, a sensitivity analysis will be performed. In case of a different reporting pattern, mean and standard deviation values (e.g. trials reporting median and range/interquartile range) will be transformed according to Hozo et al. and Higgins et al. [28, 29]. Funnel plots will be used to visualize publication bias. For other bias, a risk of bias assessment figure will be used. For all calculations, the Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) will be used.

A p-value of less than 0.05 will be considered as statistically significant.

Discussion

Over 90,000 RPs are performed per year in the U.S. [30] and about 25,500 in Germany [31]. Due to this high volume, even small differences in surgical outcomes can possibly affect a great number of patients. Therefore, we aim to increase the level of evidence concerning the optimal suture techniques for VUA. Our results might help to further standardize the procedure and to optimize functional outcome of patients undergoing RP for PCa.

In our analyses, the time until removal of the urinary catheter will be used as the primary outcome, as it is also a direct indicator for length of hospital stay and might has a positive influence in continence [32]. Furthermore, it is likely to be stated in the majority of studies, as its assessment is simple and thus little differences between the included studies are expected. In contrast, continence level or quality of life are commonly measured by different scores making comparison more difficult [33, 34].

Whereas the prevailing aim of the study is to assess differences between IS and CS for VUA in general, subgroup analysis might help to identify the optimal combinations of technique and surgical approach (open vs. LRP/RARP). In case of low sample sizes, the studies will be cumulated and subgroup analysis will only be performed if meaningful.

Following the “best evidence approach” and in order to gather all existing literature, we chose to include not only RCTs but also non-RCTs and observational studies. Whether non-RCTs should be included in systematic reviews and meta-analyses is controversial. Some argue that only RCTs provide the highest scientific quality [35]. Without appropriate randomization, studies are prone to confounding bias and to over- or underestimate the effect of interest [29]. In contrast, randomization is not feasible for some research questions [36, 37]. Besides, observational studies might reflect daily clinical work in a more realistic way [38]. Moreover, grey literature (e.g. congress presentations, registered trials) is generally considered as poor quality because detailed information on methodology and randomization are often impossible to reconstruct. Nonetheless, grey literature can be important because it often contains results which were not published since they did not show significant findings and could therefore address publication bias [39, 40]. In order to provide a holistic overview, grey literature will be included but marked as such. In addition, it will not be part of the meta-analysis, and conclusions will be drawn extremely carefully. Finally, the comprehensive literature search will also help to detect alternative surgical strategies which are not commonly used and could be of interest for future research.

In summary, the systematic review and meta-analysis will help to determine if there is any difference in CS or IS for VUA and if one technique is superior to the other. Furthermore, quality assessment of the included studies will yield if further well-designed studies are necessary.

Trial status:

Preliminary searches: started

Piloting of the study selection process: started

Formal screening: not started

Date extraction: not started

Risk of bias assessment: not started

Data analysis: not started

Abbreviations:

CS: continuous suturing; IS: interrupted suturing; LRP: laparoscopic radical prostatectomy; PCa: prostate cancer; RARP: robotic-assisted radical prostatectomy; RCT: randomized controlled trial; RP: radical prostatectomy; VUA: vesicourethral anastomosis; VUAS: vesicourethral anastomotic stenosis

Competing interests:

The authors have no competing interests to declare.

Authors' contributions:

KFK and CT drafted the manuscript and created the study concept. FN and PM gave methodological advice. SH provided statistical advice and will perform statistical analysis. MR provided supervision and guidance during the study. MK helped to concept the study and is the guarantor of the review. All authors reviewed and approved the manuscript in its current form.

Acknowledgements

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Draft of search strategy for MEDLINE

("Prostatectomy"[Mesh]) OR (vesicourethral) OR (vesico AND urethral) OR (urethrovesical) OR (urethro* AND vesical) OR (VUA) OR (prostatectomy))*

AND

((running) OR (running AND sutur*) OR (running* AND knot*) OR (interrupted) OR (interrupted* AND sutur*)*

OR (interrupted AND knot*) OR (single) OR (single* AND sutur*) OR (single* AND knot*) OR (velthoven)*

OR (barbed AND sutur*) OR (barbed) OR (sutur*) OR (knot*))*

AND

(("Anastomosis, Surgical"[Mesh]) OR (anastomo) OR (re*anastomo*) OR (reanastomo*) OR (reconstruction))*

References

1. Mottet, N., et al., *EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent.* Eur Urol, 2017. **71**(4): p. 618-629.
2. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. **136**(5): p. E359-86.
3. Bott, S.R., et al., *Prostate cancer management: (1) an update on localised disease.* Postgrad Med J, 2003. **79**(936): p. 575-80.
4. Schröder, F.H., et al., *Prostate-cancer mortality at 11 years of follow-up.* New England Journal of Medicine, 2012. **366**(11): p. 981-990.
5. Cooperberg, M.R., J.M. Broering, and P.R. Carroll, *Time trends and local variation in primary treatment of localized prostate cancer.* Journal of Clinical Oncology, 2010. **28**(7): p. 1117-1123.
6. Ahlering, T.E., et al., *Robot-assisted versus open radical prostatectomy: a comparison of one surgeon's outcomes.* Urology, 2004. **63**(5): p. 819-822.
7. Tewari, A., et al., *Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy.* Eur Urol, 2012. **62**(1): p. 1-15.
8. Yaxley, J.W., et al., *Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study.* Lancet, 2016. **388**(10049): p. 1057-1066.
9. Hoznek, A., et al., *Vesicourethral anastomosis during laparoscopic radical prostatectomy: the running suture method.* J Endourol, 2000. **14**(9): p. 749-53.
10. Menon, M., et al., *The technique of apical dissection of the prostate and urethrovesical anastomosis in robotic radical prostatectomy.* BJU Int, 2004. **93**(6): p. 715-9.
11. Liss, M.A., et al., *Continence definition after radical prostatectomy using urinary quality of life: evaluation of patient reported validated questionnaires.* The Journal of urology, 2010. **183**(4): p. 1464-1468.
12. Eastham, J.A., et al., *Risk factors for urinary incontinence after radical prostatectomy.* The Journal of urology, 1996. **156**(5): p. 1707-1713.
13. Wang, R., et al., *Risk factors and quality of life for post-prostatectomy vesicourethral anastomotic stenoses.* Urology, 2012. **79**(2): p. 449-457.
14. Surya, B.V., et al., *Anastomotic strictures following radical prostatectomy: risk factors and management.* J Urol, 1990. **143**(4): p. 755-8.
15. Hisasue, S., et al., *Early and late complications of radical retropubic prostatectomy: experience in a single institution.* Jpn J Clin Oncol, 2004. **34**(5): p. 274-9.

16. Ramalingam, M., et al., *A comparison of continuous and interrupted suturing in laparoscopic pyeloplasty.* Jsls, 2014. **18**(2): p. 294-300.
17. Lee, S.W., et al., *Effect of Continuous Urethro-Vesical Anastomosis Technique in Incontinence After Radical Retropubic Prostatectomy, 1:1 Matching Study.* Int Neurourol J, 2015. **19**(2): p. 113-9.
18. Aitken, E., et al., *A randomized controlled trial of interrupted versus continuous suturing techniques for radiocephalic fistulas.* J Vasc Surg, 2015. **62**(6): p. 1575-82.
19. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic reviews, 2015. **4**(1): p. 1.
20. Booth, A., et al., *The nuts and bolts of PROSPERO: an international prospective register of systematic reviews.* Systematic Reviews, 2012. **1**(1): p. 2.
21. Santos, C.M.d.C., C.A.d.M. Pimenta, and M.R.C. Nobre, *The PICO strategy for the research question construction and evidence search.* Revista latino-americana de enfermagem, 2007. **15**(3): p. 508-511.
22. Babineau, J., *Product review: Covidence (systematic review software).* Journal of the Canadian Health Libraries Association/Journal de l'Association des bibliothèques de la santé du Canada, 2014. **35**(2): p. 68-71.
23. Grasso, A.A., et al., *Posterior musculofascial reconstruction after radical prostatectomy: an updated systematic review and a meta-analysis.* BJU Int, 2016. **118**(1): p. 20-34.
24. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.
25. Wells, G., et al., *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Ottawa, Ontario: The Ottawa Health Research Institute*. 2011.
26. Guyatt, G.H., et al., *Rating quality of evidence and strength of recommendations: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ: British Medical Journal, 2008. **336**(7650): p. 924.
27. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* BMJ, 2003. **327**(7414): p. 557-60.
28. Hozo, S.P., B. Djulbegovic, and I. Hozo, *Estimating the mean and variance from the median, range, and the size of a sample.* BMC medical research methodology, 2005. **5**(1): p. 13.
29. Higgins, J.P. and S. Green, *Cochrane handbook for systematic reviews of interventions*. Vol. 4. 2011: John Wiley & Sons.
30. Lowrance, W.T., et al., *Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States.* J Urol, 2012. **187**(6): p. 2087-92.
31. Stolzenburg, J.U., et al., *National trends and differences in morbidity among surgical approaches for radical prostatectomy in Germany.* World J Urol, 2016. **34**(11): p. 1515-1520.
32. Koch, M.O., et al., *Early catheter removal after radical retropubic prostatectomy: long-term followup.* The Journal of urology, 2003. **169**(6): p. 2170-2172.
33. Avery, K., et al., *Questionnaires to assess urinary and anal incontinence: review and recommendations.* The Journal of urology, 2007. **177**(1): p. 39-49.
34. Klovning, A., et al., *Comparison of two questionnaires for assessing the severity of urinary incontinence: The ICIQ-UI SF versus the incontinence severity index.* Neurourology and urodynamics, 2009. **28**(5): p. 411-415.
35. Castillo, R.C., D.O. Scharfstein, and E.J. MacKenzie, *Observational studies in the era of randomized trials: finding the balance.* J Bone Joint Surg Am, 2012. **94 Suppl 1**: p. 112-7.
36. Grootendorst, D.C., et al., *Observational studies are complementary to randomized controlled trials.* Nephron Clin Pract, 2010. **114**(3): p. c173-7.
37. Black, N., *Why we need observational studies to evaluate the effectiveness of health care.* Bmj, 1996. **312**(7040): p. 1215-8.
38. Faber, T., et al., *Meta-analyses including non-randomized studies of therapeutic interventions: a methodological review.* BMC Med Res Methodol, 2016. **16**.

39. Hopewell, S., et al., *Grey literature in meta-analyses of randomized trials of health care interventions.* Cochrane Database Syst Rev, 2007(2): p. Mr000010.
40. Adams, R.J., P. Smart, and A.S. Huff, *Shades of Grey: Guidelines for Working with the Grey Literature in Systematic Reviews for Management and Organizational Studies.* International Journal of Management Reviews, 2016: p. n/a-n/a.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	p. 1, ll. 2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	p. 2, l. 27
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	p. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	p. 9 ll. 15-19
Amendments	4	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	☐	☐	not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	p. 9, ll. 20-25
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	p. 9, ll. 20-25
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	p. 9, ll. 20-25
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	p. 4, p. ll. 1-20
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	p.4, ll. 21-23 p. 6, ll. 7-19
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	p. 5, ll. 25-28
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	p.5, ll. 13-19
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	☒	☐	p. 9, ll. 26ff
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	p. 5, ll. 16-17 p. 6, ll. 4-7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	p. 5, ll. 20-24
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	p. 5, ll. 20-24
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	p. 6, ll. 7-19
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	p. 6, ll. 22-25
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	☒	☐	p. 7, ll. 3-18
DATA					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	p. 7, 20-23
	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 (e.g., I^2, Kendall's tau)	☒	☐	p. 7f, ll. 24ff
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	p. 7f, ll. 24ff
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	p. 7f, ll. 24ff
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	p. 7, ll. 24-33
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	p-7, ll. 15-18