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Use of tranexamic acid (TXA) to reduce preterm birth and other adverse obstetrical outcomes among pregnant individuals with placenta previa: a systematic review protocol

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ABSTRACT

Introduction Placenta previa is a placental implantation pathology where the placenta overlies the internal endocervical os. Placenta previa affects approximately 4 per 1000 pregnancies and increases the risk of antepartum bleeding, emergent preterm labour and emergency caesarean sections. Currently, placenta previa is managed through expectant management. Guidelines primarily revolve around the mode and timing of delivery, in-hospital admissions and surveillance. However, the methods to prolong pregnancy have not proven to be clinically effective. Tranexamic acid (TXA), an antifibrinolytic agent, is effectively used to prevent and treat postpartum haemorrhage as well as menorrhagia, with limited adverse effect, and may prove to be an effective treatment for placenta previa. The objective of this systematic review protocol is to review and synthesise the evidence of TXA use for antepartum haemorrhage in placenta previa.

Methods and analysis Preliminary searches were conducted on 12 July 2022. We will search MEDLINE, EMBASE, CINAHL, Scopus and the Cochrane Central Register of Controlled Trials. Grey literature resources such as clinical trials registries (ClinicalTrials.gov and the WHO's International Clinical Trials Registry) and preprint servers (Europe PMC and Open Science Framework) will also be searched. The search terms will comprise of index headings and keyword searches related to TXA and the placenta or antepartum bleeding. Cohort and randomised and non-randomised trials will be considered. The target population is pregnant people, of any age, with placenta previa. The intervention is TXA given in the antepartum period. The main outcome of interest is preterm birth before 37 weeks, however, all perinatal outcomes will be collected. Title and abstract will be screened by two reviewers and any conflict will be discussed and evaluated by a third reviewer. The literature will be summarised in narrative form.

Ethics and dissemination No ethics approval is required for this protocol. Findings will be disseminated through peer-review publication, lay summaries and conference presentations.

PROSPERO registration number CRD42022363009).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first systematic review to identify the use of tranexamic acid (TXA) for the treatment of placenta previa.
⇒ This systematic review will allow a group of experts in the field (obstetricians, haematologists, internists) to review the use of TXA for pregnant individuals with placenta previa, in an evidence-based manner, designed to guide a future clinical trial to evaluate the clinical effectiveness of TXA for the management of placenta previa.
⇒ The main limitation of our study protocol is that some studies may not be of high quality, due to the ethical issue raised when it comes to doing a randomised controlled trial for a pharmacological intervention during pregnancy.
⇒ Heterogeneity in study design may guide us towards a more narrative analysis compared with a data-based analysis, which may create a more subjective conclusion.

INTRODUCTION

Placenta previa is a placental implantation abnormality in pregnancy when the placenta completely or partially covers the endocervical os or cervix.[1] Placenta previa can result in severe bleeding during pregnancy or during labour and increases the risk of preterm birth before 37 weeks.[2] It is estimated that approximately 4 in 1000 pregnancies worldwide are affected by placenta previa.[3] Risk factors include advanced maternal age, multiple gestation, multiparity, previous placenta previa, previous caesarian section (C-section), diabetes mellitus, smoking and cocaine use during pregnancy and the use of assisted reproductive technology.[2 4]

A systematic review of 29 studies involving 4687 pregnant people with placenta previa, identified antepartum haemorrhage as a

major contributor to maternal and neonatal morbidity. The prevalence of antepartum haemorrhage was estimated at 51.9% among patients with placenta previa ranging from 20% to 78%, depending on the study.[5] A systematic review of 13 comparative and 26 descriptive studies on placenta previa, showed the significant association between placenta previa and preterm delivery, as well as low 1-min and 5-min Apgar scores, neonatal intensive care unit admissions and neonatal and perinatal death.[6]

There is an established association between placenta previa, antepartum haemorrhage and preterm birth. The mechanism in which antepartum haemorrhage causes preterm delivery is explained by a cycle of cervical effacement causing separation of the placenta and the underlying uterine segment causing myometrial tearing resulting in haemorrhage. The haemorrhage continues the positive feedback loop by stimulating contractions. Among those who experience antepartum haemorrhage, the incidence of emergency C-section is significantly higher in pregnant individuals with placenta previa compared with those without placenta previa.[2 7 8] Having three or more episodes of antepartum bleeding and having the first episode of bleeding before 29 weeks gestation are two factors associated with emergency C-section in patients with placenta previa.[8] Minimising bleeding episodes is one of the most important complications to target in placenta previa to improve maternal and neonatal outcomes.

The current management of placenta previa relies on expectant management.[2 9] Interventions used to prevent preterm delivery and delay labour in obstetrics include cervical cerclage and use of tocolytics. Cervical cerclage is a procedure performed to keep the cervix closed and tocolytics are drugs given to delay labour for a short period of time. In the context of placenta previa, such interventions have not shown significant clinical improvements in adverse outcomes and are not recommended in clinical guidelines.[9] Historically, bed rest has been a recommended intervention, but it is only currently recommended in more severe cases of placenta previa. For this reason, there is interest to explore pharmacological methods to control bleeding.

Tranexamic acid (TXA) is a synthetic lysine-analogue antifibrinolytic. It is most commonly used in surgeries, trauma and acute haemorrhage to control bleeding and minimise the need for blood transfusions.[10] In obstetrics and gynaecology, TXA has been successfully used for postpartum haemorrhage, blood loss at delivery and menorrhagia.[10] The WOMAN international randomised, double-blind placebo, controlled-trial showed that administration of TXA in postpartum haemorrhage, especially within 3 hours of onset of bleeding, reduced death due to bleeding and also showed no significant difference in adverse events between the treatment and the placebo group.[11]

TXA is considered to be class B in pregnancy, which means that preliminary animal studies have not detected a risk to the fetus, however, no well-controlled human studies have been conducted.[12] TXA crosses the placental barrier and appears in cord blood with a concentration as high as maternal blood. Careful evaluation of the risks and benefits of using TXA for placenta previa is needed. It is hypothesised that the thrombogenic effect of TXA is low but adverse maternal or neonatal thrombogenic events have not yet been clearly identified.[13] To date, there are no human trials of TXA use in pregnancy, however, TXA has been shown to reduce the duration of antepartum haemorrhage in cases of threatened abortion[14] and has been used in the treatment of antepartum haemorrhage in the context of placenta abruption.[12]

Objectives

Placenta previa is an important obstetrical condition with limited effective interventions. The objective of this systematic review protocol is to review and synthesise the evidence of TXA use for antepartum haemorrhage in placenta previa. This protocol and future systematic review are being conducted to inform the development of a clinical trial on TXA use during pregnancy to reduce bleeding and other adverse obstetrical outcomes in the patients with placenta previa.

METHODS

This protocol is developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) checklist (online supplemental appendix 1).[15] The systematic review will be conducted using PRISMA 2020 for systematic review which include searchers of databases, registers and others sources (online supplemental appendix 2).[16] This study protocol was registered in PROSPERO International Prospective Register of Systematic Reviews on the 30 October 2022. The primary search was conducted on 12 July 2022.

Eligibility criteria

Studies will be selected based on the following criteria:

Study design

Randomised and non-randomised clinical trials and cohort studies will be included. Case reports and case series will be excluded.

Participants

Pregnant obstetrical patients (regardless of age) with a diagnosis of placenta previa will be included in the review. Participants will not be restricted by other comorbidities including blood disorders or placental pathologies.

Intervention

The use of TXA among pregnant individuals with placenta previa with the intention to reduce, prevent or control antepartum bleeding and complications. We will include any route of administration (eg, intravenous, topical).

We will collect information on the dose, gestational age at administration, the duration and the posology. Search terms will also include brand names such as Cyklokapron, Lysteda, Cyklo-F and Menstralite.

Comparators

Comparisons can include (but are not restricted to) expectant management, bed rest or no intervention.

Outcomes

Primary outcome is preterm birth defined as delivery before 37 weeks gestations. Secondary outcomes include, but are not limited to, reductions in bleeding, antepartum haemorrhage, adverse effects and emergency C-section. Safety-related secondary outcomes include deep vein thrombosis, pulmonary embolism and any other thromboembolic events. All neonatal and maternal adverse outcome will be included.

Timing

Studies will be considered for inclusion if TXA is given in the antepartum period. Any treatment initiated in the postpartum period in the context of postpartum haemorrhage or just prior to C-section as prophylaxis for postpartum haemorrhage will be excluded.

Setting

There will be no restriction by type of setting.

Language

We will not restrict by language for this study as we anticipate a small number of studies. We will use a translation service, colleagues with proficiency with the language or software for studies in languages other than French or English.

Information sources

A literature search strategy (see table 1) was developed by a health sciences librarian (SV) and will use Medical Subject Headings and text words related to the placenta or antepartum bleeding and TXA. Published studies will be identified through MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL (via EBSO), Scopus (www.scopus.com) and the Cochrane Central Register of Controlled Trials (via Ovid). Each database will be searched from their inception. A hand search of references from identified studies will also be conducted.

In addition to the searches for primary studies, a broader search for existing systematic reviews on TXA use for bleeding complications in pregnancy will also conducted. The included study lists of relevant reviews will be screened, and relevant primary studies will be added to Covidence for screening in duplicate.

Grey literature resources such as clinical trials registries (ClinicalTrials.gov and the WHO's International Clinical Trials Registry) and preprint servers (Europe PMC and Open Science Framework) will also be searched. PROSPERO will be searched for ongoing systematic reviews.

Table 1 Sample search strategy

Database: Ovid MEDLINE(R) ALL Platform: Ovid	
#	Searches
1	Tranexamic Acid/
2	(achma or amca or AMCHA or amchafibrin* or amikapron* or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbo* acid or Aminomethylcyclohexan#carbo* acid or aminomethylcyclohexanoic acid or amstat or anexan* or antivoff* or anvitoff* or caprilon* or carxamin* or cl65336 or cyclocapron* or cyclo-F or cyclokapron* or cyklocapron* or cyklokapron* or emorhalt* or espercil* or exacyl* or Femstrual* or fibrinon* or frenolyse* or hemostan* or hexacapron* or hexakapron* or hexapromin* or hexatron* or kalnex* or kapron* or lysteda* or mastop* or Menstralite* or micranex* or nicolda* or retavase* or rikaparin* or rikavarin* or rizaben* or ronex* or spiramin* or spotof* or tamcha* or theranex* or tracid* or tramic* or tranex* or tranexam* or tranhexam* or tranesamic* or tranexic* or transamin* or transaminomethylcyclohexane carboxylic acid or transcam* or transexamic* or trasamlon* or traxamic* or traxyl* or trenaxin* or ugurol*).ti,ab,kf.
3	(1197-18-8 or 6T84R30KC1).rn.
4	or/1–3
5	exp Placenta/ or exp Placenta Diseases/
6	placenta*.ti,ab,kf.
7	((pregnan* or natal* or prenatal* or pre-natal* or antepartum* or ante-partum*) adj3 (bleed* or blood* or h?emorrhag*)).ti,ab,kf.
8	or/5–7
9	4 and 8

A hand search of reference lists will also be conducted. Where appropriate we will contact corresponding authors. See table 1 for the detailed MEDLINE search strategy draft.

Study records

Data management

Literature search results will be uploaded to Covidence,[17] an internet-based software designed for systematic review management and collaborative selection process.

Selection process

Title and abstracts will be first reviewed by two reviewers (NS and KAM) based on the inclusion criteria. Any conflicting opinion on inclusion in the title and abstract will be included for full-text review. The full-text review will be completed by the same reviewers and any disagreement on inclusion will be discussed. The reason for exclusion will be recorded. Information regarding the journal, authors or institution will not be hidden from the reviewers.

Data collection process

We will use an Excel spreadsheet for data collection. We have found that Covidence is excellent for data management and extraction for randomised controlled trials (RCTs), however, as we anticipate different study designs we will use Excel as it provides more flexibility. The data will be collected independently and will then be compared and reviewed. Conflicts will be resolved through discussion. Any unresolved conflict will be evaluated by a third reviewer.

Data items

The following items will be extracted from each study: study design, participants, baseline characteristics (eg, age, gestational age), country, location and setting, sample size, interventions, all outcomes, findings and study dates. We will extract information on TXA including brand name, dosage, timing of administration and duration of administration. The patient characteristics will also be noted, such as qualification, quantification and duration of symptoms (antepartum bleeding), gestational age at consultation, prenatal care, age, obstetrical comorbidities and personal medical relevant comorbidities.

Risk of bias in individual studies

We will search the Cochrane Risk of Bias Tool for RCTs, the Cochrane Risk of Bias in Non-Randomised Studies of Interventions for non-randomised interventions, Critical Appraisal Skills Programme (CASP) cohort study checklist for cohort studies and CASP case–control study checklist for case–control studies. Two authors (NS and KAM) will assess each study separately and any conflict will be resolved by a third reviewer.

Data synthesis

As this review includes cohort and randomised study design, we anticipate heterogeneity in statistical analyses and methodology (eg, outcomes, populations and treatment), results will summarised narratively using the Synthesis Without Meta-analysis guidelines, a nine-item checklist to promote transparency in reporting in diverse study designs. Tables of descriptive characteristics of the included studies will be generated. The narrative synthesis will allow us to explore the elements of safety, effectiveness and feasibility of using TXA for the treatment of placenta previa during pregnancy. We will report on the limitations and strengths of each study.

If feasible, we will carry out a meta-analysis. Study estimates will be presented in tables and forest plots reporting weighted summary statistics. We will report a summary measure of individual studies and a pooled estimate where possible. For the primary outcome of preterm birth, the pooled relative risk (RR) and 95% CIs in pregnant individuals with placenta previa receiving TXA will be compared with the RR in comparison groups with expectant management. Heterogeneity will be assessed by χ^2 test and the inconsistency index (I^2).[18] A random-effects model of DerSimonian and Laird will be used if substantial heterogeneity is identified, otherwise, a fixed-effect model will be applied.[19] If possible, we will conduct subgroup analyses by maternal age, parity and body mass index. Publication and reporting bias will be evaluated by funnel plot and Egger test.[20]

Confidence in cumulative evidence

The quality of the outcomes for all the selected studies will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. The quality will be judged by evaluating multiple factors including the study design, risk of bias, directness, consistency, preciseness, publication bias, and upgrading for dose effect, large estimates of accuracy and residual plausible confounding. Using this standardised method, the quality of studies will be graded as the following: high (very confident that the true effect and the estimate of the effect are similar), moderate (moderately confident in the estimate effect with a possibility of difference with the true effect), low (limited confidence in estimate effect with a true effect that may be different from the estimate effect) or very low (very little confidence in estimate effect with a true effect likely to be different from the estimate effect).

Patient and public involvement

No patients, partners or public stakeholders have been involved in the development of the protocol.

CONCLUSION

This systematic review aims to examine the existing evidence on the use of TXA for the treatment of placenta previa and explore if this treatment can be used as a safe, and potentially more effective, alternative to expectant management. This systematic review is designed to inform the development of a clinical trial to evaluate this novel treatment for a much-needed condition with limited successful interventions.

Ethics and dissemination

No ethics approval is required for this protocol. Findings will be disseminated through peer-review publication, lay summaries and conference presentations.

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Contributors NS, KAM and MW conceived the idea for the systematic review. All authors collaboratively designed the study. SV led the development of the search strategy. NS and KAM led the writing of the protocol. MW and SV critically reviewed the protocol. All authors approved the final version of this article. MW is the guarantor of the review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1: PRISMA-P for Systematic Review Protocols Checklist

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

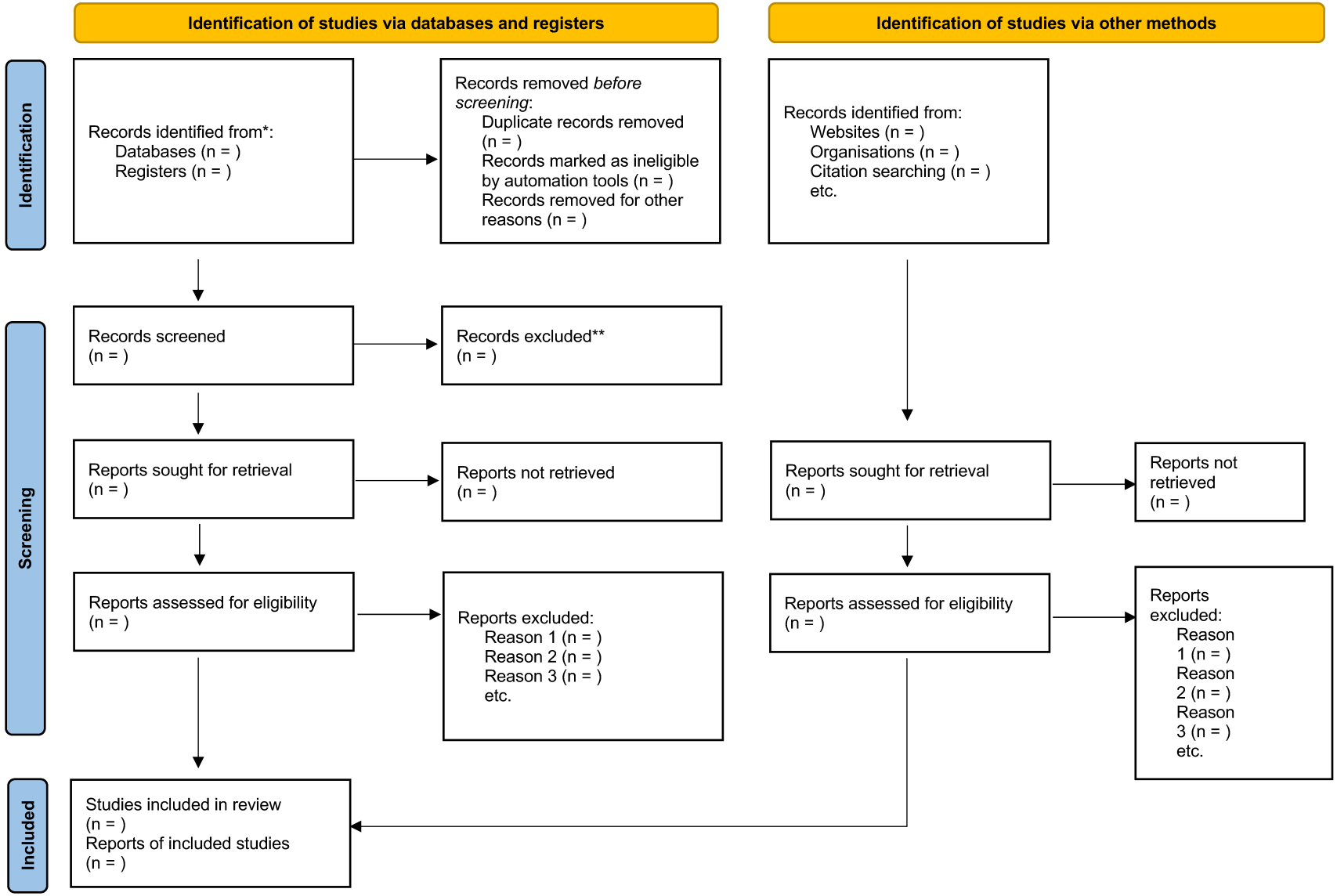
Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
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
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
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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)
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
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	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 I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2: PRISMA Flow Diagram which include searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/