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Protocol for a Scoping Review to Support Development of a CONSORT Extension for Randomized Controlled Trials Using Cohorts and Routinely Collected Health Data

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ABSTRACT

Introduction: Randomized controlled trials (RCTs) conducted using cohorts and routinely collected health data, including registries, electronic health records, and administrative databases, are increasingly used in health care intervention research. The development of an extension of the CONsolidated Standards of Reporting Trials (CONSORT) statement for RCTs using cohorts and routinely collected health data is being undertaken with the goal of improving reporting quality by setting standards early in the process of uptake of these designs. To develop this extension to the CONSORT statement, a scoping review will be conducted to identify potential modifications or clarifications of existing reporting guideline items, as well as additional items needed for reporting RCTs using cohorts and routinely collected health data.

Methods and analysis: In separate searches, we will seek publications on methods or reporting or that describe protocols or results from RCTs using cohorts, registries, electronic health records and administrative databases. Data sources will include Medline and the Cochrane Methodology Register. For each of the four main types of RCTs using cohorts and routinely collected health data, separately, two investigators will independently review included publications to extract potential checklist items. A potential item will either modify an existing CONSORT 2010, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) or REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) item or will be proposed as a new item. Additionally, we will identify examples of good reporting in RCTs using cohorts and routinely collected health data.

Ethics and dissemination: The proposed scoping review will help guide the development of the CONSORT extension statement for RCTs conducted using cohorts and routinely collected health data.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Our scoping review will be conducted using rigorous methods, with peer-reviewed searches developed by a research librarian that will comply with Institute of Medicine standards and are not limited by language.
- Due to the novelty of RCTs using cohorts and routinely collected health data, we anticipate identifying only a limited number of methods and reporting articles in our scoping review.
- To supplement articles on methods and reporting, we will review primary trial protocols and reports to identify elements that need reporting and to identify examples of good reporting.

INTRODUCTION

Randomized controlled trials (RCTs), when well-designed and conducted, are widely acknowledged to be the gold standard for evaluating the effectiveness and harms of medical interventions.[1-3] Important concerns exist, however, about many RCTs, including limitations related to difficulty recruiting sufficiently large and representative samples, limited real-world generalizability, and prohibitive costs.[4-12] To attempt to address these and other challenges, trial designs have been developed in which RCTs are conducted within the frameworks cohorts[4] and routinely collected health data. Routinely collected health data are defined as data collected for administrative and clinical purposes, without specific *a priori* research questions[13], and include registries[14], electronic health records[15], and health administrative databases.[16]

Biomedical research reporting guidelines have been developed to assist authors to report research studies as accurately, transparently, and completely as possible. Reporting guidelines typically describe a minimum set of information that should be clearly reported, provide examples of guideline-consistent reporting, and include a checklist to facilitate compliance.[17,18] Multiple existing reporting guidelines include items that are potentially applicable to RCTs conducted using cohorts and routinely collected health data. In addition to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting of parallel group RCTs,[19] reporting guidelines with the most direct overlap include the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for the reporting of observational studies, generally,[20] and the REporting of studies Conducted using Observational Routinely

collected Data (RECORD) guideline,[21] which addresses reporting specific to observational studies conducted using routinely collected health data.

The development of an extension of the CONSORT statement for RCTs conducted using cohorts and routinely collected health data is being undertaken with the goal of improving long-term reporting quality by setting standards early in the process of uptake of these trial designs.[22] To develop this CONSORT extension, information is needed to understand which items from CONSORT, STROBE, and RECORD can be utilized without modification and which should be included with adaptations, as well as aspects of reporting of RCTs conducted using cohorts and routinely collected health data that are not covered adequately in these reporting guidelines and that require new reporting items. In addition, examples of complete and transparent reporting of different aspects of these RCTs are needed.

Relatively little guidance has been published on the methods and reporting of RCTs conducted using cohorts and routinely collected health data. To account for this, the proposed scoping review will identify articles on the methods or reporting of RCTs conducted using cohorts, registries, electronic health records, and health administrative databases, as well as examples of protocols and reports of results from these types of RCTs. The objectives of the scoping review are to (1) determine which items from an initial long list of items based on CONSORT, STROBE, and RECORD that are being considered for possible inclusion in the CONSORT extension can be included without modification, identify items from the initial list that need adaptation, and identify additional reporting considerations to develop new items; and (2) identify examples of

complete and transparent reporting of different aspects of these types of RCTs that can be used to support the CONSORT extension.

METHODS

The scoping review will be conducted following the approach described by Arksey and O'Malley[23] and will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: extension for Scoping Reviews (PRISMA-ScR) guidelines.[24]

Database Searches

In separate searches, we will seek publications that describe aspects of methods or reporting or that describe protocols or results from RCTs (including cluster RCTs) using (1) cohorts; (2) registries; (3) electronic health records; and (4) health administrative databases. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE and EBM Reviews - Cochrane Methodology Registry (Final issue, 3rd Quarter 2012) will be searched by an experienced librarian familiar with knowledge synthesis for publications on methods or reporting of these types of RCTs and for examples of these types of RCTs. MEDLINE strategies for the searches were developed by a research librarian with input from the project team and were peer reviewed using the Peer Review of the Electronic Search Strategy (PRESS) standard.[25] The MEDLINE strategy was then adapted for the Cochrane Library Methodology Register, which includes methodological research available up to its last update in July 2012.

Search strategies comply with Institute of Medicine standards and are not limited by language.[26] We will search for articles on methods and reporting and examples of

RCTs published in the last 10 years (2008-2018), which will allow us to identify relatively recent reporting practices and focus on challenging aspects of reporting. See Supplementary File 1 for detailed search strategies. In addition to the database searches, references of included studies will be reviewed for additional eligible studies, a web search will be conducted, and members of the project team with experience in each type of trial will be consulted to provide additional studies that were not identified in our search.

Study Selection

For each search, separately, results will be downloaded into the citation management database RefWorks, and duplicate references will be removed. Following this, references will be transferred into the systematic review software DistillerSR® (Evidence Partners, Ottawa, Canada). A coding manual based on eligibility criteria has been developed, and a pilot test of the coding manual will be performed prior to the study's inception. The initial coding manuals for inclusion and exclusion for all four types of trial designs are shown in Supplementary File 2. Because the trial designs that will be included in the CONSORT extension reflect relatively recent developments, we anticipate that we will identify only a small number of articles on their methodology and reporting. Thus, we will also include publications of trial protocols and results.

We will assess the eligibility of each publication through a two-stage process. In the first stage, two reviewers will independently screen titles and abstracts to identify potentially relevant studies. We will use a liberal accelerated method[27] to screen titles and abstracts, meaning that articles deemed eligible by one of the reviewers will be included in full-text review, and only excluded articles will be screened by a second reviewer.

Since title and abstract screening is done randomly and concurrently, reviewers will not know if the other reviewer has excluded the reference or not. In the second stage, two investigators will independently conduct a full-text review. Disagreements after full-text review will be resolved by consensus, with a third investigator consulted as necessary. Translators will be consulted to evaluate titles and abstracts and full-text articles for languages other than those for which team members are fluent, if any. See Supplementary File 3 for the preliminary PRISMA flow of studies figures for the four types of trial designs.

Data Extraction and Verification

To develop a preliminary 'long list' of items to consider for the CONSORT extension checklist, as an initial step, items from the CONSORT 2010 will be examined to identify items where modifications will be needed for RCTs conducted using cohorts and routinely collected health data, and items from the STROBE and RECORD reporting guidelines will be examined to identify additional items to complement CONSORT items. Two investigators will independently review these reporting guidelines, and any item deemed possibly relevant to RCTs using cohorts and routinely collected health data by either or both investigator, will be included in the 'long list'. Additional preliminary 'long list' items will be provided by other members of the project team.

For each of the four types of RCTs conducted using cohorts and routinely collected health data, separately, two investigators will independently review included publications to extract additional potential items for the 'long list'. A potential item will either modify an existing CONSORT 2010, STROBE or RECORD item that has been included in the 'long list' or will be proposed as a new item. Potential items will be

identified from publications that report information relevant to conducting RCTs using cohorts and routinely collected health data, but that were not included in our initial 'long list'. In addition, potential items will be suggested based on gaps in reporting identified from primary trial protocols or reports. Data will be extracted and collected in DistillerSR® using a standardized data extraction form. The long-list of items will evolve dynamically as potential modifications and new items are added based on the review of publications identified from our literature search using the DistillerSR® Dynamic Question function. Thus, reviewers will add a potential item only once to the long-list, after which it becomes visible for all reviewers. Reviewers will not duplicate items already provided by other reviewers. This will be done to avoid redundancy, as we expect potential gaps in reporting to occur in multiple publications that will be reviewed. In addition to each proposed item modification or new item, reviewers will add a brief explanation of why the suggested modification or new item is deemed important.

In addition to identifying gaps in reporting, for each item on our long list, we will attempt to identify examples of complete and transparent reporting in RCTs using cohorts, registries, electronic health record, and health administrative databases. When examples of complete and transparent reporting for a particular item on the long list are identified, text corresponding to reporting of that item will be inserted in the data extraction form in DistillerSR®.

Prior to data extraction from included studies, all reviewers will assess a sample of trial reports. The results will be compared and discussed among the reviewers in order to ensure consistent application of the data extraction process.

CONCLUSION

This scoping review will gather previously published methods and recommendations for the reporting of RCTs using cohorts and routinely collected health data, as well as identify gaps in reporting of these studies. We will identify potential modifications or clarifications of CONSORT 2010, STROBE and RECORD items as well as potential additional items to develop an extension to the CONSORT statement for reporting RCTs using cohorts and routinely collected health data. Following the scoping review, identified items will be vetted using a 3-stage Delphi approach[28] and a face-to-face meeting, after which the reporting checklist and explanation and elaboration documents for the CONSORT extension will be finalized. The resulting CONSORT extension will promote transparency, clarity, reduce research waste and provide guidance to researchers on appropriate and consistent reporting of RCTs using cohorts and routinely collected health data.

ETHICS AND DISSEMINATION

This study does not require ethics approval, as required data will be collected through the review of published literature. The proposed scoping review will help guide the development of the CONSORT extension statement for RCTs conducted using cohorts and routinely collected health data. The findings will be disseminated through peer-reviewed publications and conference presentations.

AUTHORS' CONTRIBUTIONS

LK, MI, EJ, LGH, OF, CR, CG, MZ, SML, DM, and BDT held regular meetings to develop the conceptual framework, and project process and all other team members provided feedback. LK, MI and BDT were responsible for the first draft of the manuscript. All authors made contributions to previous drafts of the manuscript and approved the final version.

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COMPETING INTERESTS STATEMENT

The authors have read and understood the BMJ policy on declaration of interests and declare that they have no competing interests.

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Supplementary File 1 – Electronic Search Strategies

Searches were run in both MEDLINE and Cochrane Methodology Register simultaneously. As an example, in the registries search, lines 1-11 are the MEDLINE search and lines 12-15 are tailored for the Cochrane Methodology Register. The final lines of each search isolate the records from each database, combine them so duplicate records can be removed, then isolate the remaining records so they can be downloaded and imported into Reference Manager using customized import filters.

Searches for RCTs embedded in Registries

1. ((registry or registries) adj5 randomi#ed).ab,kf,ti.
2. ((registry or registries) adj5 RCT*).ab,kf,ti.)
3. ((registry or registries) adj5 controlled trial*).ab,kf,ti.
4. ((registry or registries) adj5 (RRCT* or R RCT*)).ab,kf,ti.
5. or/1-4
6. (meta analy* or metaanaly* or metanaly* or systematic review*).af.
7. 5 not 6
8. Registries/
9. limit 8 to randomized controlled trial
10. 7 or 9
11. limit 10 to yr="2007 - 2018"
12. (registry or registries).ab,kf,ti.
13. (random* or RCT).ti,ab,kw.
14. 12 and 13
15. limit 14 to yr="2007 - 2018"
16. 11 use medall
17. 15 use clcmr
18. 16 or 17 (1240)
19. remove duplicates from 18
20. 19 use medall
21. 19 use clcmr

Searches for RCTs embedded in Cohorts

1. (cohort adj5 (randomi#ed adj5 trial*)).ab,kf,ti.
2. (cohort adj5 RCT*).ab,kf,ti.
3. (cohort adj5 controlled trial*).ab,kf,ti.
4. (cmRCT or Cohort Multiple Randomised Controlled Trial*).ab,kf,ti.
5. or/1-4
6. cohort.af.
7. (embed* adj8 randomi#ed).ab,kf,ti.
8. (embed* adj8 RCT*).ab,kf,ti.
9. (embed* adj8 controlled trial*).ab,kf,ti.
10. or/7-9
11. 6 and 10
12. (pragmatic adj5 RCT*).ab,kf,ti.
13. (pragmatic adj5 randomi#ed).ab,kf,ti.

14. (pragmatic adj5 controlled trial*).ab,kf,ti.
15. or/12-14
16. 6 and 15
17. 5 or 11 or 16
18. (meta analy* or metaanaly* or metanaly* or systematic review*).af.
19. 17 not 18
20. limit 19 to yr="2007 - 2018"
21. ((Cohort* and (random* or RCT)) or cmRCT).ti,ab,kw.
22. limit 21 to yr="2007 - 2018"
23. 20 use medall
24. 22 use clcmr
25. 23 or 24
26. remove duplicates from 25
27. 26 use medall
28. 26 use clcmr

Searches for RCTs embedded in Electronic Health Records

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi?ed.ab.
4. placebo.ab.
5. randomly.ab.
6. clinical trials as topic.sh.
7. trial.ti.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Electronic Health Records/
12. (EHR or electronic health record*).ab,kf,ti.
13. (EMR or electronic medical record*).ab,kf,ti.
14. (PHR or personal health record*).ab,kf,ti.
15. (EPR or electronic patient record*).ab,kf,ti.
16. exp Health Records, Personal/
17. or/11-16
18. 10 and 17
19. limit 18 to yr="2007 - 2018"
20. (Electronic health record or electronic health records or EHR).ti,ab,kw.
21. (Electronic medical record or electronic medical records or EMR).ti,ab,kw.
22. (Electronic patient record or electronic patient records or EPR).ti,ab,kw.
23. or/20-22
24. limit 23 to yr="2007 - 2018"
25. 19 use medall
26. 24 use clcmr
27. 25 or 26
28. remove duplicates from 27
29. 28 use medall
30. 28 use clcmr

Searches for RCTs embedded in Administrative Databases

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi?ed.ab.
4. placebo.ab.
5. randomly.ab.
6. clinical trials as topic.sh.
7. trial.ti.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. administrative data*.ab,kf,ti.
12. healthcare data*.ab,kf,ti.
13. health care data*.ab,kf,ti.
14. or/11-13
15. 10 and 14
16. (administrative adj5 data*).ti,ab,kw.
17. health care data*.ti,ab,kw.
18. healthcare data*.ti,ab,kw.
19. or/16-18
20. (random* or RCT).ti,ab,kw.
21. 19 and 20
22. limit 15 to yr="2007 - 2018"
23. 22 use medall
24. limit 21 to yr="2007 - 2018"
25. 22 use clcmr

Supplementary File 2 – Coding Manual

Title/Abstract Screening

Does this study meet the title and abstract inclusion criteria for Cohort-based Randomized Controlled Trials (RCTs)?

No: not an RCT using a cohort. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of cohort-based RCTs, (2) a cohort intended to be used to conduct RCTs, or (3) a protocol or results from a RCT that will select or selected individuals from a cohort, it is excluded. For the purpose of this review, a cohort is defined as a group of individuals who are gathered for the purpose of conducting research and for whom there are multiple assessments over time. If it is clear from the title and abstract that the publication describes a study that enrolls patients only in a cohort or only in an RCT (e.g., comparative cohort trials, parallel cohorts) – but not both, it is excluded. If (observational) analyses are done on all participants or a subgroup of participants who were enrolled in an RCT, even if described by the authors as a 'cohort', it would be excluded. If the RCT involves non-human subjects, it is excluded.

No: the cohort is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which a cohort was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the cohort is only used for collecting trial outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to a cohort to ascertain health outcomes as trial endpoints, but does not otherwise use the cohort in the trial, it is excluded.

Yes: study eligible to be included in full-text review.

Does this study meet the title and abstract inclusion criteria for <u>Registry-based Randomized Controlled Trials (RCTs)</u>

No: not an RCT using a registry. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of registry-based RCTs, (2) a registry used to conduct RCTs, or (3) a protocol or results from a RCT conducted using a registry, it is excluded. A registry has been defined by the European Medicines Agency as "an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure, and that is followed over time." Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry). If the RCT involves non-human subjects, it is excluded.

No: the registry is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which the registry was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the registry is only used for collecting trial outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to a registry to ascertain health outcomes as trial endpoints, but does not otherwise use the registry in the trial, it is excluded.

Yes: study eligible to be included in full-text review.

Does this study meet the title and abstract inclusion criteria for Administrative Database-based Randomized Controlled Trials (RCTs)

No: not an RCT using administrative data. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of administrative database-based RCTs, (2) an administrative dataset used to conduct RCTs, or (3) a protocol or results from a RCT conducted using an administrative database, it is excluded. Administrative data refers to information collected primarily for administrative purposes (e.g., all users of healthcare in a province, all persons enrolled in a health insurance plan). If the RCT involves non-human subjects, it is excluded.

No: the administrative database is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which the administrative database was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the administrative database is only used for collecting trial outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to an administrative database to ascertain health outcomes, as trial endpoints, but does not otherwise use the administrative database in the trial, it is excluded.

Yes: study eligible to be included in full-text review.

Does this study meet the title and abstract inclusion criteria for Electronic Health Record (EHR)-based Randomized Controlled Trials (RCTs)

No: not an RCT using EHRs. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of electronic health records (EHR)-based RCTs, (2) EHRs that will be used to conduct RCTs, or (3) a protocol or results from a RCT conducted using EHRs, it is excluded. EHRs are electronic versions of a patient's medical history, and can include information that includes diagnoses, medications, and treatment plans, for instance. If the RCT involves non-human subjects, it is excluded.

No: the EHR is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which the EHR was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the EHRs is only used to ascertain health outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to EHRs to ascertain health outcomes, as trial endpoints, but does not otherwise use EHRs in the trial, it will be excluded.

Yes: study eligible to be included in full-text review.

Full-text review

Does this study meet the inclusion criteria for Cohort-based Randomized Controlled Trials (RCTs)?

No: not an RCT using a cohort. If the publication does not describe (1) issues related to methods or reporting of cohort-based RCTs, (2) a cohort intended to be used to conduct RCTs, or (3) a protocol or results from a RCT that will select or selected individuals from a cohort, it is excluded. For the purpose of this review, a cohort is defined as a group of individuals who are gathered for the purpose of conducting research and for whom there are multiple assessments over time. If it is clear from the title and abstract that the publication describes a study that enrolls patients only in a cohort or only in an RCT (e.g., comparative cohort trials, parallel cohorts) – but not both, it is excluded. If (observational) analyses are done on all participants or a subgroup of participants who were enrolled in an RCT, even if described by the authors as a 'cohort', it would be excluded. If the RCT involves non-human subjects, it is excluded.

No: the cohort is only used for identifying eligible participants. If the publication describes a trial in which a cohort was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the cohort is only used for collecting trial outcomes. If the publication describes a trial that only links to a cohort to ascertain health outcomes as trial endpoints, but does not otherwise use the cohort in the trial, it is excluded.

Yes: study eligible to be included in scoping review.

Does this study meet the inclusion criteria for Registry-based Randomized Controlled Trials (RCTs)

No: not an RCT using a registry. If the publication does not describe (1) issues related to methods or reporting of registry-based RCTs, (2) a registry used to conduct RCTs, or (3) a protocol or results from a RCT conducted using a registry, it is excluded. A registry has been defined by the European Medicines Agency as "an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure, and that is followed over time." Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry). If the RCT involves non-human subjects, it is excluded.

No: the registry is only used for identifying eligible participants. If the publication describes a trial in which the registry was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the registry is only used for collecting trial outcomes. If the publication describes a trial that only links to a registry to ascertain health outcomes as trial endpoints, but does not otherwise use the registry in the trial, it is excluded.

Yes: study eligible to be included in scoping review.

Does this study meet the inclusion criteria for Administrative Database-based Randomized Controlled Trials (RCTs)

No: not an RCT using administrative data. If it the publication does not describe (1) issues related to methods or reporting of administrative database-based RCTs, (2) an administrative dataset used to conduct RCTs, or (3) a protocol or results from a RCT conducted using an administrative database, it is excluded. Administrative data refers to information collected primarily for administrative purposes (e.g., all users of healthcare in a province, all persons enrolled in a health insurance plan). If the RCT involves non-human subjects, it is excluded.

No: the administrative database is only used for identifying eligible participants. If the publication describes a trial in which the administrative database was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the administrative database is only used for collecting trial outcomes. If the publication describes a trial that only links to an administrative database to ascertain health outcomes, as trial endpoints, but does not otherwise use the administrative database in the trial, it is excluded.

Yes: study eligible to be included in scoping review.

Does this study meet the inclusion criteria for Electronic Health Record (EHR)-based Randomized Controlled Trials (RCTs)

No: not an RCT using EHRs. If the publication does not describe (1) issues related to methods or reporting of electronic health records (EHR)-based RCTs, (2) EHRs that will be used to conduct RCTs, or (3) a protocol or results from a RCT conducted using EHRs, it is excluded. EHRs are electronic versions of a patient's medical history, and can include information that includes diagnoses, medications, and treatment plans, for instance. If the RCT involves non-human subjects, it is excluded.

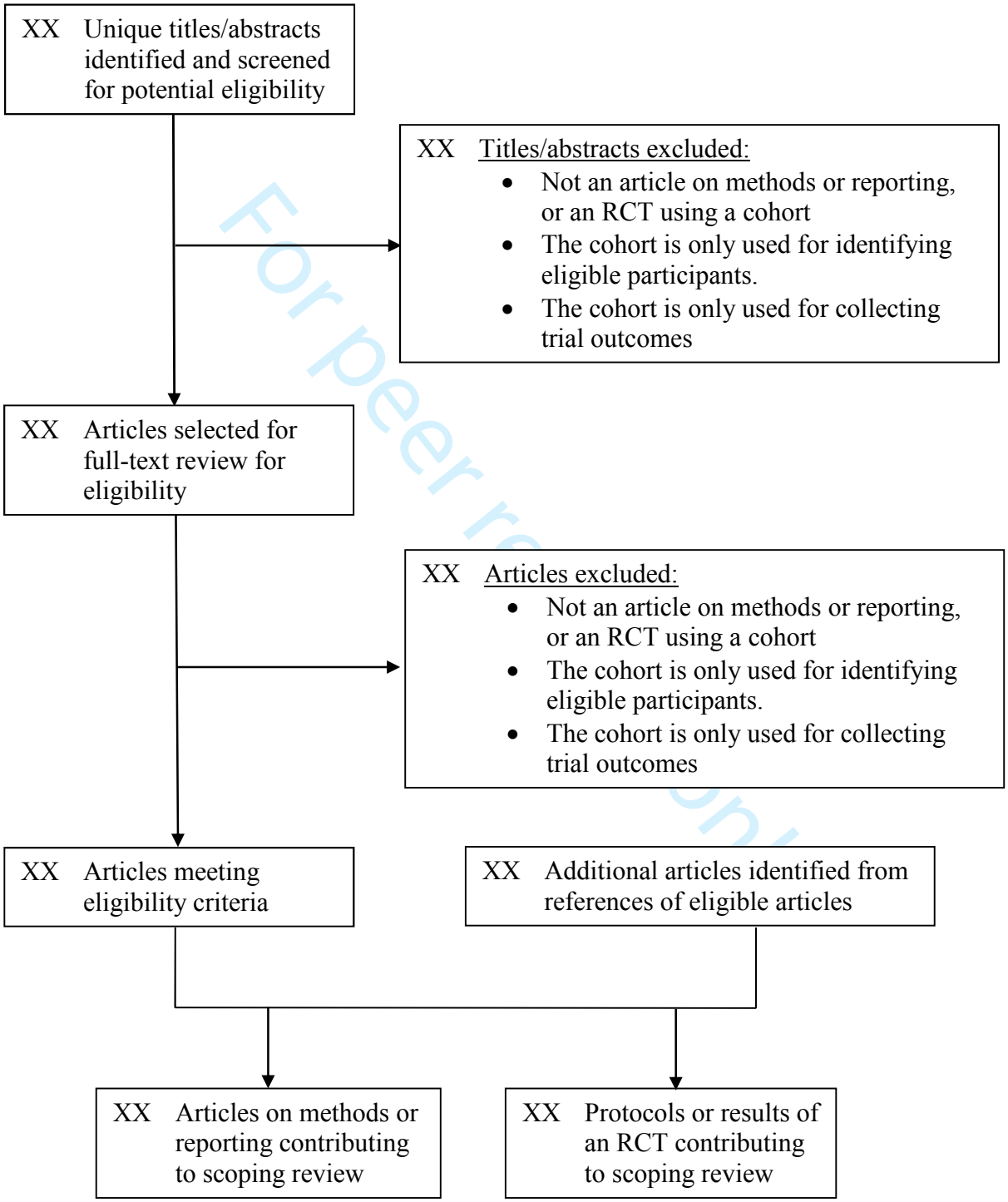
No: the EHR is only used for identifying eligible participants. If the publication describes a trial in which the EHR was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the EHRs is only used to ascertain health outcomes. If the publication describes a trial that only links to EHRs to ascertain health outcomes, as trial endpoints, but does not otherwise use EHRs in the trial, it will be excluded.

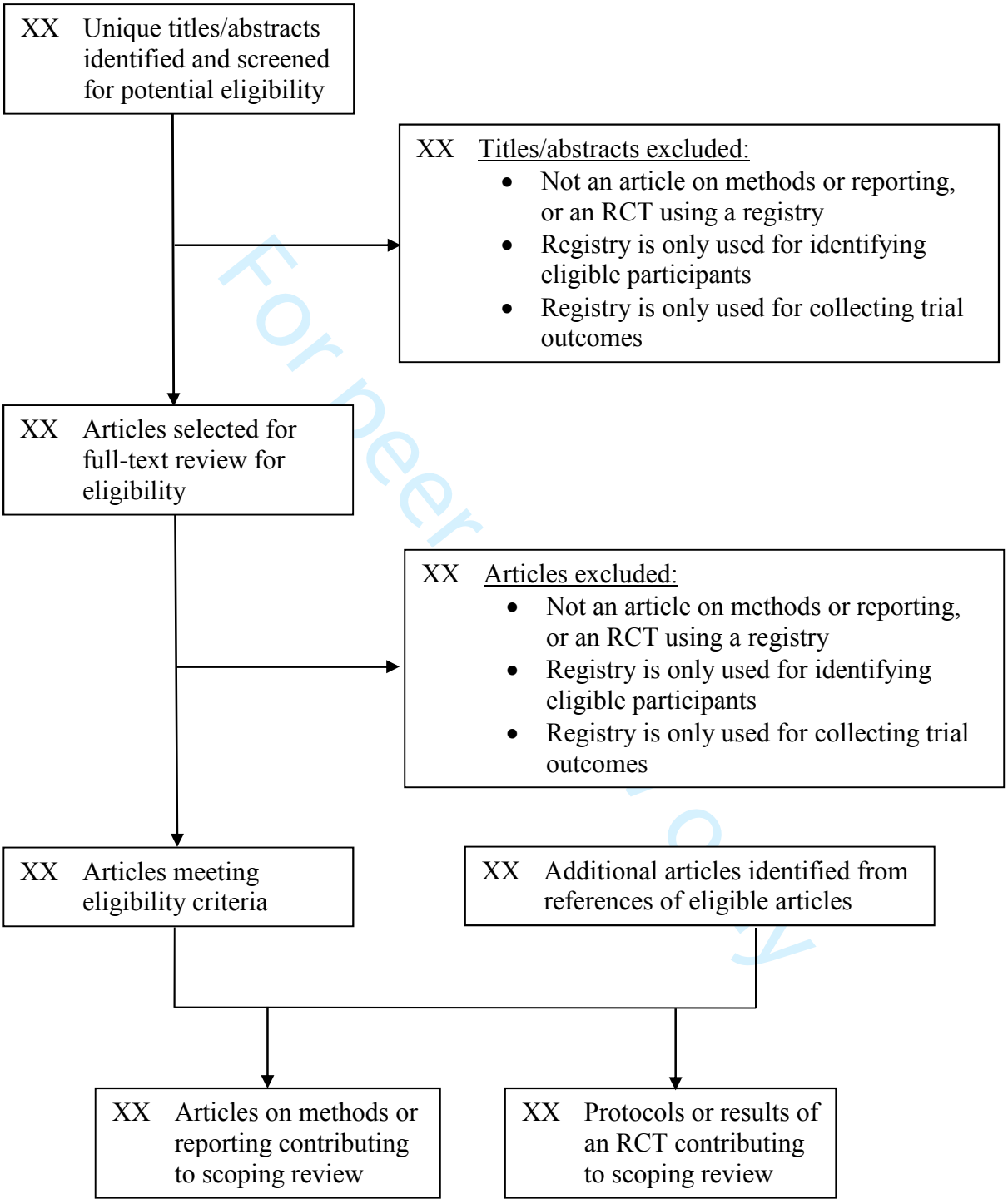
Yes: study eligible to be included in scoping review.

Supplementary File 3

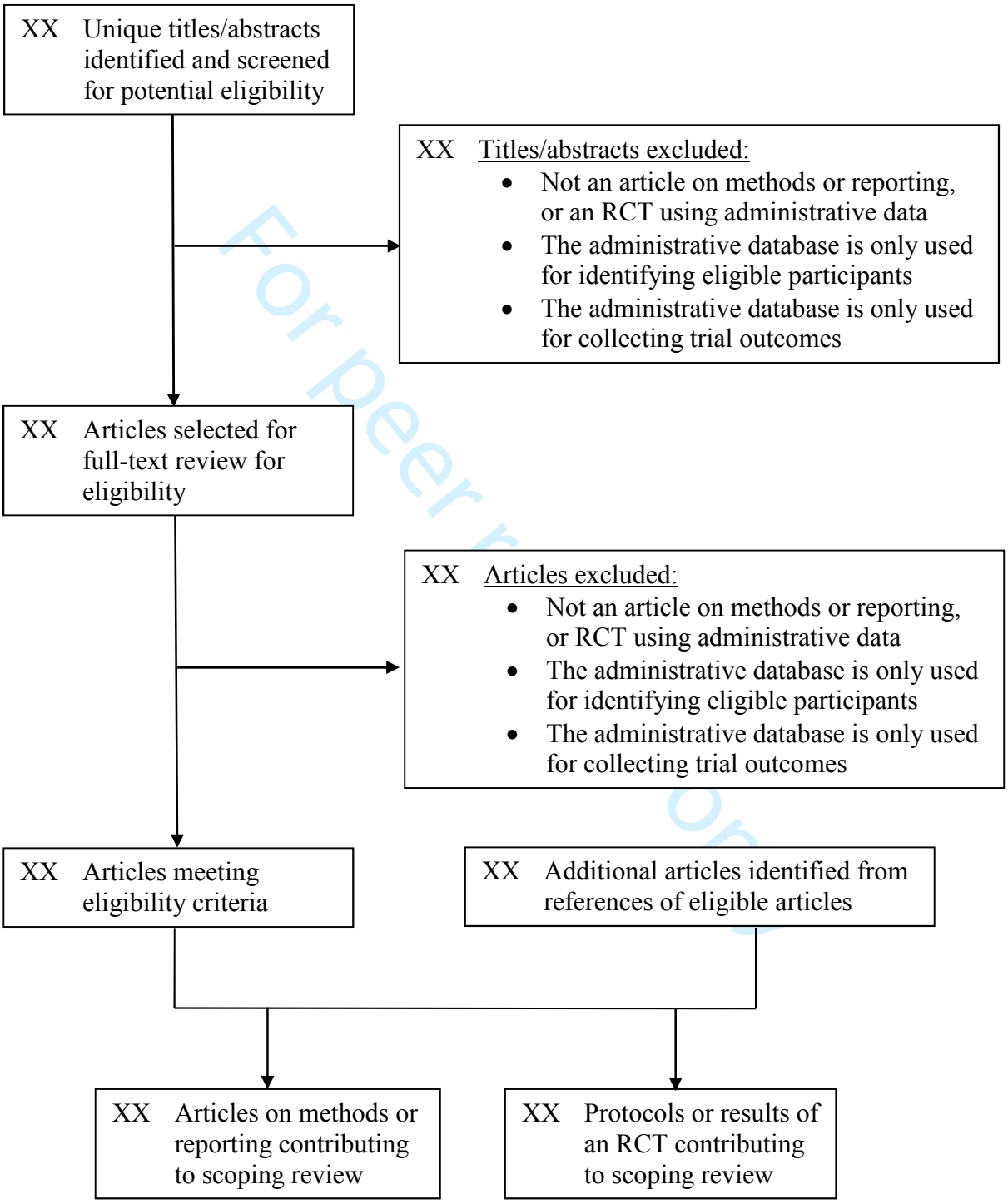
Draft Flow Diagram of Study Selection Process - Cohorts



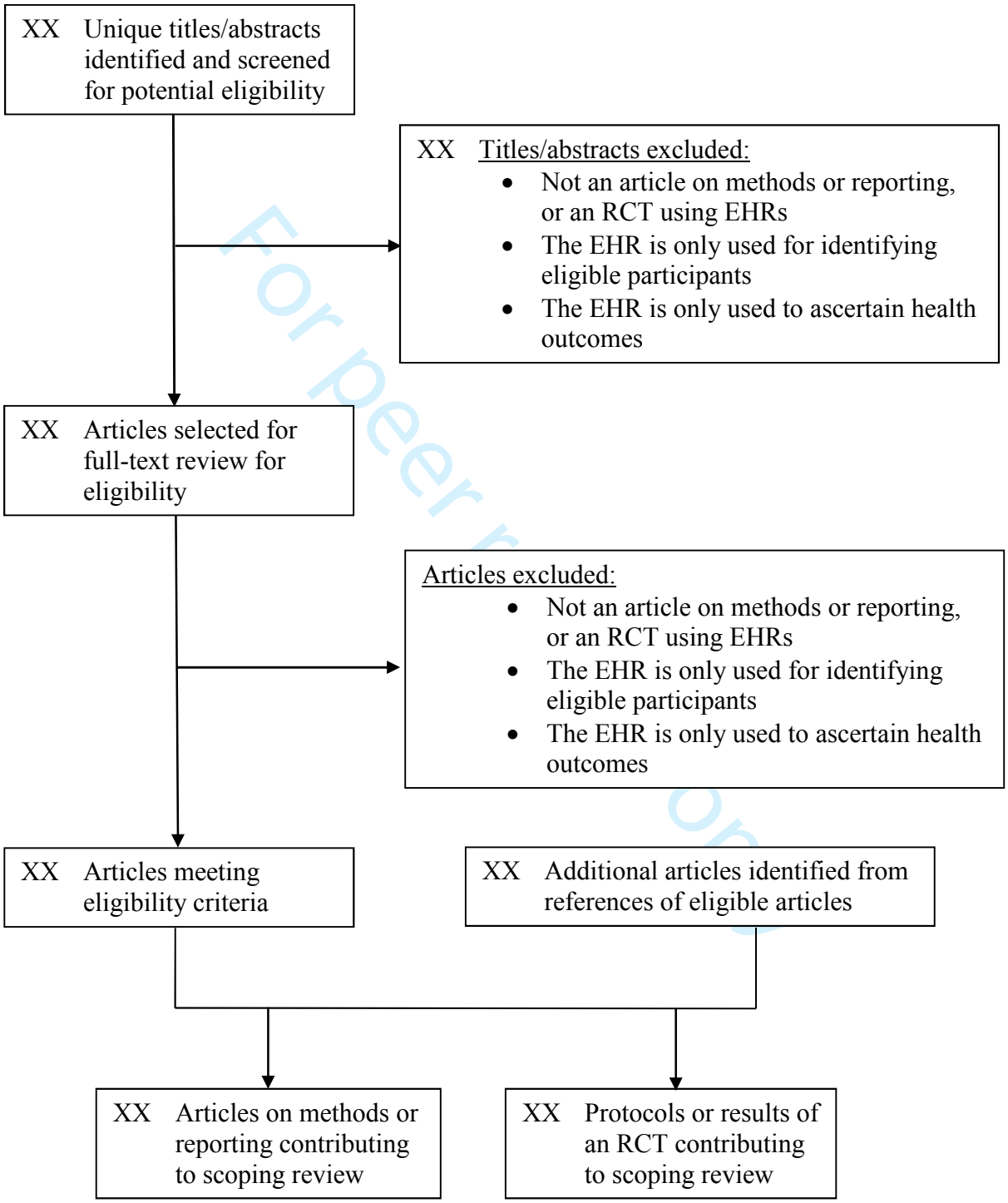
Draft Flow Diagram of Study Selection Process - Registries



Draft Flow Diagram of Study Selection Process – Administrative data



Draft Flow Diagram of Study Selection Process – Electronic Health Records (EHRs)



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Protocol for a Scoping Review to Support Development of a CONSORT Extension for Randomized Controlled Trials Using Cohorts and Routinely Collected Health Data

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Secondary Subject Heading:	Epidemiology
Keywords:	cohort, CONSORT, randomized controlled trials, reporting guideline, routinely collected health data, RCTs

Protocol for a Scoping Review to Support Development of a CONSORT Extension for Randomized Controlled Trials Using Cohorts and Routinely Collected Health Data

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ABSTRACT

Introduction: Randomized controlled trials (RCTs) conducted using cohorts and routinely collected health data, including registries, electronic health records, and administrative databases, are increasingly used in health care intervention research. The development of an extension of the CONsolidated Standards of Reporting Trials (CONSORT) statement for RCTs using cohorts and routinely collected health data is being undertaken with the goal of improving reporting quality by setting standards early in the process of uptake of these designs. To develop this extension to the CONSORT statement, a scoping review will be conducted to identify potential modifications or clarifications of existing reporting guideline items, as well as additional items needed for reporting RCTs using cohorts and routinely collected health data.

Methods and analysis: In separate searches, we will seek publications on methods or reporting or that describe protocols or results from RCTs using cohorts, registries, electronic health records and administrative databases. Data sources will include Medline and the Cochrane Methodology Register. For each of the four main types of RCTs using cohorts and routinely collected health data, separately, two investigators will independently review included publications to extract potential checklist items. A potential item will either modify an existing CONSORT 2010, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) or REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) item or will be proposed as a new item. Additionally, we will identify examples of good reporting in RCTs using cohorts and routinely collected health data.

Ethics and dissemination: The proposed scoping review will help guide the development of the CONSORT extension statement for RCTs conducted using cohorts and routinely collected health data.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Our scoping review will be conducted using rigorous methods, with peer-reviewed searches developed by a research librarian that will comply with Institute of Medicine standards and are not limited by language.
- Due to the novelty of RCTs using cohorts and routinely collected health data, we anticipate identifying only a limited number of methods and reporting articles in our scoping review.
- To supplement articles on methods and reporting, we will review primary trial protocols and reports to identify elements that need reporting and to identify examples of good reporting.

INTRODUCTION

Randomized controlled trials (RCTs), when well-designed and conducted, are widely acknowledged to be the gold standard for evaluating the effectiveness and harms of medical interventions.[1-3] Important concerns exist, however, about many RCTs, including limitations related to difficulty recruiting sufficiently large and representative samples, limited real-world generalizability, and prohibitive costs.[4-12] To attempt to address these and other challenges, trial designs have been developed in which RCTs are conducted within the frameworks cohorts[4] and routinely collected health data. Routinely collected health data are defined as data collected for administrative and clinical purposes, without specific *a priori* research questions[13], and include registries[14], electronic health records[15], and health administrative databases.[16]

Biomedical research reporting guidelines have been developed to assist authors to report research studies as accurately, transparently, and completely as possible. Reporting guidelines typically describe a minimum set of information that should be clearly reported, provide examples of guideline-consistent reporting, and include a checklist to facilitate compliance.[17,18] Multiple existing reporting guidelines include items that are potentially applicable to RCTs conducted using cohorts and routinely collected health data. In addition to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting of parallel group RCTs,[19] reporting guidelines with the most direct overlap include the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for the reporting of observational studies, generally,[20] and the REporting of studies Conducted using Observational Routinely

collected Data (RECORD) guideline,[21] which addresses reporting specific to observational studies conducted using routinely collected health data.

The development of an extension of the CONSORT statement for RCTs conducted using cohorts and routinely collected health data is being undertaken with the goal of improving long-term reporting quality by setting standards early in the process of uptake of these trial designs.[22] To develop this CONSORT extension, information is needed to understand which items from CONSORT, STROBE, and RECORD can be utilized without modification and which should be included with adaptations, as well as aspects of reporting of RCTs conducted using cohorts and routinely collected health data that are not covered adequately in these reporting guidelines and that require new reporting items. In addition, examples of complete and transparent reporting of different aspects of these RCTs are needed.

Relatively little guidance has been published on the methods and reporting of RCTs conducted using cohorts and routinely collected health data. To account for this, the proposed scoping review will identify articles on the methods or reporting of RCTs conducted using cohorts, registries, electronic health records, and health administrative databases, as well as examples of protocols and reports of results from these types of RCTs. The objectives of the scoping review are to (1) determine which items from an initial long list of items based on CONSORT, STROBE, and RECORD that are being considered for possible inclusion in the CONSORT extension can be included without modification, identify items from the initial list that need adaptation, and identify additional reporting considerations to develop new items; and (2) identify examples of

complete and transparent reporting of different aspects of these types of RCTs that can be used to support the CONSORT extension.

METHODS

The scoping review will be conducted following the approach described by Arksey and O'Malley[23] and will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: extension for Scoping Reviews (PRISMA-ScR) guidelines.[24]

Database Searches

In separate searches, we will seek publications that describe aspects of methods or reporting or that describe protocols or results from RCTs (including cluster RCTs) using (1) cohorts; (2) registries; (3) electronic health records; and (4) health administrative databases. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE and EBM Reviews - Cochrane Methodology Registry (Final issue, 3rd Quarter 2012) will be searched by an experienced librarian familiar with knowledge synthesis for publications on methods or reporting of these types of RCTs and for examples of these types of RCTs. MEDLINE strategies for the searches were developed by a research librarian with input from the project team and were peer reviewed using the Peer Review of the Electronic Search Strategy (PRESS) standard.[25] The MEDLINE strategy was then adapted for the Cochrane Library Methodology Register, which includes methodological research available up to its last update in July 2012.

Search strategies comply with Institute of Medicine standards and are not limited by language.[26] We will search for articles on methods and reporting and examples of

RCTs published in the last 10 years (2008-2018), which will allow us to identify relatively recent reporting practices and focus on challenging aspects of reporting. See Supplementary File 1 for detailed search strategies. In addition to the database searches, references of included studies will be reviewed for additional eligible studies, a web search will be conducted, and members of the project team with experience in each type of trial will be consulted to provide additional studies that were not identified in our search.

Study Selection

For each search, separately, results will be downloaded into the citation management database RefWorks, and duplicate references will be removed. Following this, references will be transferred into the systematic review software DistillerSR® (Evidence Partners, Ottawa, Canada). A coding manual based on eligibility criteria has been developed, and a pilot test of the coding manual will be performed prior to the study's inception. The initial coding manuals for inclusion and exclusion for all four types of trial designs are shown in Supplementary File 2. Because the trial designs that will be included in the CONSORT extension reflect relatively recent developments, we anticipate that we will identify only a small number of articles on their methodology and reporting. Thus, we will also include publications of trial protocols and results.

We will assess the eligibility of each publication through a two-stage process. In the first stage, two reviewers will independently screen titles and abstracts to identify potentially relevant studies. We will use a liberal accelerated method[27] to screen titles and abstracts, meaning that articles deemed eligible by one of the reviewers will be included in full-text review, and only excluded articles will be screened by a second reviewer.

Since title and abstract screening is done randomly and concurrently, reviewers will not know if the other reviewer has excluded the reference or not. In the second stage, two investigators will independently conduct a full-text review. Disagreements after full-text review will be resolved by consensus, with a third investigator consulted as necessary. Translators will be consulted to evaluate titles and abstracts and full-text articles for languages other than those for which team members are fluent, if any. See Supplementary File 3 for the preliminary PRISMA flow of studies figures for the four types of trial designs.

Data Extraction and Verification

To develop a preliminary 'long list' of items to consider for the CONSORT extension checklist, as an initial step, items from the CONSORT 2010 will be examined to identify items where modifications will be needed for RCTs conducted using cohorts and routinely collected health data, and items from the STROBE and RECORD reporting guidelines will be examined to identify additional items to complement CONSORT items. Two investigators will independently review these reporting guidelines, and any item deemed possibly relevant to RCTs using cohorts and routinely collected health data by either or both investigator, will be included in the 'long list'. Additional preliminary 'long list' items will be provided by other members of the project team.

For each of the four types of RCTs conducted using cohorts and routinely collected health data, separately, two investigators will independently review included publications to extract additional potential items for the 'long list'. A potential item will either modify an existing CONSORT 2010, STROBE or RECORD item that has been included in the 'long list' or will be proposed as a new item. Potential items will be

identified from publications that report information relevant to conducting RCTs using cohorts and routinely collected health data, but that were not included in our initial 'long list'. In addition, potential items will be suggested based on gaps in reporting identified from primary trial protocols or reports. Data will be extracted and collected in DistillerSR® using a standardized data extraction form. The long-list of items will evolve dynamically as potential modifications and new items are added based on the review of publications identified from our literature search using the DistillerSR® Dynamic Question function. Thus, reviewers will add a potential item only once to the long-list, after which it becomes visible for all reviewers. Reviewers will not duplicate items already provided by other reviewers. This will be done to avoid redundancy, as we expect potential gaps in reporting to occur in multiple publications that will be reviewed. In addition to each proposed item modification or new item, reviewers will add a brief explanation of why the suggested modification or new item is deemed important.

In addition to identifying gaps in reporting, for each item on our long list, we will attempt to identify examples of complete and transparent reporting in RCTs using cohorts, registries, electronic health record, and health administrative databases. When examples of complete and transparent reporting for a particular item on the long list are identified, text corresponding to reporting of that item will be inserted in the data extraction form in DistillerSR®.

Prior to data extraction from included studies, all reviewers will assess a sample of trial reports. The results will be compared and discussed among the reviewers in order to ensure consistent application of the data extraction process.

Patient and Public Involvement

One of the members of our extension to the CONSORT statement, Maureen Sauvé, is a patient organization leader. She has been involved in working with researchers to establish a cohort of patients living with the rare disease scleroderma, which supports RCTs of trials of online rehabilitation, self-management and psychological intervention programs[28].

CONCLUSION

This scoping review will gather previously published methods and recommendations for the reporting of RCTs using cohorts and routinely collected health data, as well as identify gaps in reporting of these studies. We will identify potential modifications or clarifications of CONSORT 2010, STROBE and RECORD items as well as potential additional items to develop an extension to the CONSORT statement for reporting RCTs using cohorts and routinely collected health data. Following the scoping review, identified items will be vetted using a 3-stage Delphi approach[29] and a face-to-face meeting, after which the reporting checklist and explanation and elaboration documents for the CONSORT extension will be finalized. The resulting CONSORT extension will promote transparency, clarity, reduce research waste and provide guidance to researchers on appropriate and consistent reporting of RCTs using cohorts and routinely collected health data.

ETHICS AND DISSEMINATION

This study does not require ethics approval, as required data will be collected through the review of published literature. The proposed scoping review will help guide the development of the CONSORT extension statement for RCTs conducted using cohorts

and routinely collected health data. The findings will be disseminated through peer-reviewed publications and conference presentations.

AUTHORS' CONTRIBUTIONS

LK, MI, EJ, LGH, OF, CR, CG, MZ, SML, DM, MS and BDT were involved in initial phases of study conception, design of the search strategy, and development of conceptual frameworks. KAM, EIB, IB, MKC, DE, SJ, PR, DR, MS, TPS, LT, RU and HMV provided regular feedback on each of these steps. LK, MI and BDT were responsible for the first draft of the manuscript. All authors made substantive intellectual contributions to the development of this protocol and approved the final version.

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COMPETING INTERESTS STATEMENT

The authors have read and understood the BMJ policy on declaration of interests and declare that they have no competing interests.

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Supplementary File 1 – Electronic Search Strategies

Searches were run in both MEDLINE and Cochrane Methodology Register simultaneously. As an example, in the registries search, lines 1-11 are the MEDLINE search and lines 12-15 are tailored for the Cochrane Methodology Register. The final lines of each search isolate the records from each database, combine them so duplicate records can be removed, then isolate the remaining records so they can be downloaded and imported into Reference Manager using customized import filters.

Searches for RCTs embedded in Registries

1. ((registry or registries) adj5 randomi#ed).ab,kf,ti.
2. ((registry or registries) adj5 RCT*).ab,kf,ti.)
3. ((registry or registries) adj5 controlled trial*).ab,kf,ti.
4. ((registry or registries) adj5 (RRCT* or R RCT*)).ab,kf,ti.
5. or/1-4
6. (meta analy* or metaanaly* or metanaly* or systematic review*).af.
7. 5 not 6
8. Registries/
9. limit 8 to randomized controlled trial
10. 7 or 9
11. limit 10 to yr="2007 - 2018"
12. (registry or registries).ab,kf,ti.
13. (random* or RCT).ti,ab,kw.
14. 12 and 13
15. limit 14 to yr="2007 - 2018"
16. 11 use medall
17. 15 use clcmr
18. 16 or 17 (1240)
19. remove duplicates from 18
20. 19 use medall
21. 19 use clcmr

Searches for RCTs embedded in Cohorts

1. (cohort adj5 (randomi#ed adj5 trial*)).ab,kf,ti.
2. (cohort adj5 RCT*).ab,kf,ti.
3. (cohort adj5 controlled trial*).ab,kf,ti.
4. (cmRCT or Cohort Multiple Randomised Controlled Trial*).ab,kf,ti.
5. or/1-4
6. cohort.af.
7. (embed* adj8 randomi#ed).ab,kf,ti.
8. (embed* adj8 RCT*).ab,kf,ti.
9. (embed* adj8 controlled trial*).ab,kf,ti.
10. or/7-9
11. 6 and 10
12. (pragmatic adj5 RCT*).ab,kf,ti.
13. (pragmatic adj5 randomi#ed).ab,kf,ti.

14. (pragmatic adj5 controlled trial*).ab,kf,ti.
15. or/12-14
16. 6 and 15
17. 5 or 11 or 16
18. (meta analy* or metaanaly* or metanaly* or systematic review*).af.
19. 17 not 18
20. limit 19 to yr="2007 - 2018"
21. ((Cohort* and (random* or RCT)) or cmRCT).ti,ab,kw.
22. limit 21 to yr="2007 - 2018"
23. 20 use medall
24. 22 use clcmr
25. 23 or 24
26. remove duplicates from 25
27. 26 use medall
28. 26 use clcmr

Searches for RCTs embedded in Electronic Health Records

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi?ed.ab.
4. placebo.ab.
5. randomly.ab.
6. clinical trials as topic.sh.
7. trial.ti.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp Electronic Health Records/
12. (EHR or electronic health record*).ab,kf,ti.
13. (EMR or electronic medical record*).ab,kf,ti.
14. (PHR or personal health record*).ab,kf,ti.
15. (EPR or electronic patient record*).ab,kf,ti.
16. exp Health Records, Personal/
17. or/11-16
18. 10 and 17
19. limit 18 to yr="2007 - 2018"
20. (Electronic health record or electronic health records or EHR).ti,ab,kw.
21. (Electronic medical record or electronic medical records or EMR).ti,ab,kw.
22. (Electronic patient record or electronic patient records or EPR).ti,ab,kw.
23. or/20-22
24. limit 23 to yr="2007 - 2018"
25. 19 use medall
26. 24 use clcmr
27. 25 or 26
28. remove duplicates from 27
29. 28 use medall
30. 28 use clcmr

Searches for RCTs embedded in Administrative Databases

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomi?ed.ab.
4. placebo.ab.
5. randomly.ab.
6. clinical trials as topic.sh.
7. trial.ti.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. administrative data*.ab,kf,ti.
12. healthcare data*.ab,kf,ti.
13. health care data*.ab,kf,ti.
14. or/11-13
15. 10 and 14
16. (administrative adj5 data*).ti,ab,kw.
17. health care data*.ti,ab,kw.
18. healthcare data*.ti,ab,kw.
19. or/16-18
20. (random* or RCT).ti,ab,kw.
21. 19 and 20
22. limit 15 to yr="2007 - 2018"
23. 22 use medall
24. limit 21 to yr="2007 - 2018"
25. 22 use clcmr

Supplementary File 2 – Coding Manual

Title/Abstract Screening

Does this study meet the title and abstract inclusion criteria for Cohort-based Randomized Controlled Trials (RCTs)?

No: not an RCT using a cohort. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of cohort-based RCTs, (2) a cohort intended to be used to conduct RCTs, or (3) a protocol or results from a RCT that will select or selected individuals from a cohort, it is excluded. For the purpose of this review, a cohort is defined as a group of individuals who are gathered for the purpose of conducting research and for whom there are multiple assessments over time. If it is clear from the title and abstract that the publication describes a study that enrolls patients only in a cohort or only in an RCT (e.g., comparative cohort trials, parallel cohorts) – but not both, it is excluded. If (observational) analyses are done on all participants or a subgroup of participants who were enrolled in an RCT, even if described by the authors as a 'cohort', it would be excluded. If the RCT involves non-human subjects, it is excluded.

No: the cohort is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which a cohort was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the cohort is only used for collecting trial outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to a cohort to ascertain health outcomes as trial endpoints, but does not otherwise use the cohort in the trial, it is excluded.

Yes: study eligible to be included in full-text review.

Does this study meet the title and abstract inclusion criteria for <u>Registry-based Randomized Controlled Trials (RCTs)</u>

No: not an RCT using a registry. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of registry-based RCTs, (2) a registry used to conduct RCTs, or (3) a protocol or results from a RCT conducted using a registry, it is excluded. A registry has been defined by the European Medicines Agency as "an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure, and that is followed over time." Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry). If the RCT involves non-human subjects, it is excluded.

No: the registry is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which the registry was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the registry is only used for collecting trial outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to a registry to ascertain health outcomes as trial endpoints, but does not otherwise use the registry in the trial, it is excluded.

Yes: study eligible to be included in full-text review.

Does this study meet the title and abstract inclusion criteria for Administrative Database-based Randomized Controlled Trials (RCTs)

No: not an RCT using administrative data. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of administrative database-based RCTs, (2) an administrative dataset used to conduct RCTs, or (3) a protocol or results from a RCT conducted using an administrative database, it is excluded. Administrative data refers to information collected primarily for administrative purposes (e.g., all users of healthcare in a province, all persons enrolled in a health insurance plan). If the RCT involves non-human subjects, it is excluded.

No: the administrative database is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which the administrative database was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the administrative database is only used for collecting trial outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to an administrative database to ascertain health outcomes, as trial endpoints, but does not otherwise use the administrative database in the trial, it is excluded.

Yes: study eligible to be included in full-text review.

Does this study meet the title and abstract inclusion criteria for Electronic Health Record (EHR)-based Randomized Controlled Trials (RCTs)

No: not an RCT using EHRs. If it is clear from the title and abstract that the publication does not describe (1) issues related to methods or reporting of electronic health records (EHR)-based RCTs, (2) EHRs that will be used to conduct RCTs, or (3) a protocol or results from a RCT conducted using EHRs, it is excluded. EHRs are electronic versions of a patient's medical history, and can include information that includes diagnoses, medications, and treatment plans, for instance. If the RCT involves non-human subjects, it is excluded.

No: the EHR is only used for identifying eligible participants. If it is clear from the title and abstract that the publication describes a trial in which the EHR was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the EHRs is only used to ascertain health outcomes. If it is clear from the title and abstract that the publication describes a trial that only links to EHRs to ascertain health outcomes, as trial endpoints, but does not otherwise use EHRs in the trial, it will be excluded.

Yes: study eligible to be included in full-text review.

Full-text review

Does this study meet the inclusion criteria for Cohort-based Randomized Controlled Trials (RCTs)?

No: not an RCT using a cohort. If the publication does not describe (1) issues related to methods or reporting of cohort-based RCTs, (2) a cohort intended to be used to conduct RCTs, or (3) a protocol or results from a RCT that will select or selected individuals from a cohort, it is excluded. For the purpose of this review, a cohort is defined as a group of individuals who are gathered for the purpose of conducting research and for whom there are multiple assessments over time. If it is clear from the title and abstract that the publication describes a study that enrolls patients only in a cohort or only in an RCT (e.g., comparative cohort trials, parallel cohorts) – but not both, it is excluded. If (observational) analyses are done on all participants or a subgroup of participants who were enrolled in an RCT, even if described by the authors as a 'cohort', it would be excluded. If the RCT involves non-human subjects, it is excluded.

No: the cohort is only used for identifying eligible participants. If the publication describes a trial in which a cohort was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the cohort is only used for collecting trial outcomes. If the publication describes a trial that only links to a cohort to ascertain health outcomes as trial endpoints, but does not otherwise use the cohort in the trial, it is excluded.

Yes: study eligible to be included in scoping review.

Does this study meet the inclusion criteria for Registry-based Randomized Controlled Trials (RCTs)

No: not an RCT using a registry. If the publication does not describe (1) issues related to methods or reporting of registry-based RCTs, (2) a registry used to conduct RCTs, or (3) a protocol or results from a RCT conducted using a registry, it is excluded. A registry has been defined by the European Medicines Agency as "an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure, and that is followed over time." Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry). If the RCT involves non-human subjects, it is excluded.

No: the registry is only used for identifying eligible participants. If the publication describes a trial in which the registry was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the registry is only used for collecting trial outcomes. If the publication describes a trial that only links to a registry to ascertain health outcomes as trial endpoints, but does not otherwise use the registry in the trial, it is excluded.

Yes: study eligible to be included in scoping review.

Does this study meet the inclusion criteria for Administrative Database-based Randomized Controlled Trials (RCTs)

No: not an RCT using administrative data. If it the publication does not describe (1) issues related to methods or reporting of administrative database-based RCTs, (2) an administrative dataset used to conduct RCTs, or (3) a protocol or results from a RCT conducted using an administrative database, it is excluded. Administrative data refers to information collected primarily for administrative purposes (e.g., all users of healthcare in a province, all persons enrolled in a health insurance plan). If the RCT involves non-human subjects, it is excluded.

No: the administrative database is only used for identifying eligible participants. If the publication describes a trial in which the administrative database was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the administrative database is only used for collecting trial outcomes. If the publication describes a trial that only links to an administrative database to ascertain health outcomes, as trial endpoints, but does not otherwise use the administrative database in the trial, it is excluded.

Yes: study eligible to be included in scoping review.

Does this study meet the inclusion criteria for Electronic Health Record (EHR)-based Randomized Controlled Trials (RCTs)

No: not an RCT using EHRs. If the publication does not describe (1) issues related to methods or reporting of electronic health records (EHR)-based RCTs, (2) EHRs that will be used to conduct RCTs, or (3) a protocol or results from a RCT conducted using EHRs, it is excluded. EHRs are electronic versions of a patient's medical history, and can include information that includes diagnoses, medications, and treatment plans, for instance. If the RCT involves non-human subjects, it is excluded.

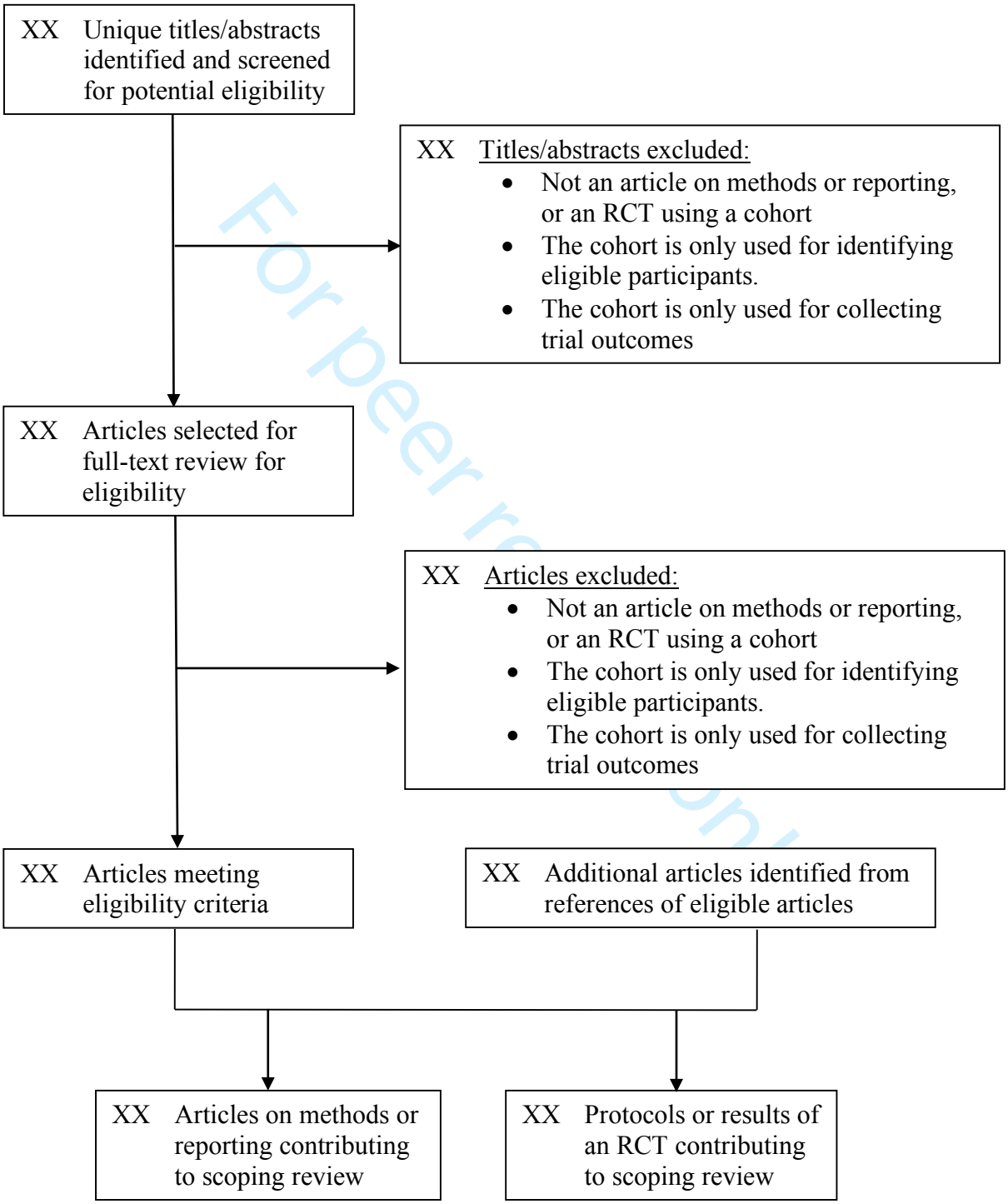
No: the EHR is only used for identifying eligible participants. If the publication describes a trial in which the EHR was solely used to identify eligible trial participants, but for no other purposes related to the trial, it is excluded.

No: the EHRs is only used to ascertain health outcomes. If the publication describes a trial that only links to EHRs to ascertain health outcomes, as trial endpoints, but does not otherwise use EHRs in the trial, it will be excluded.

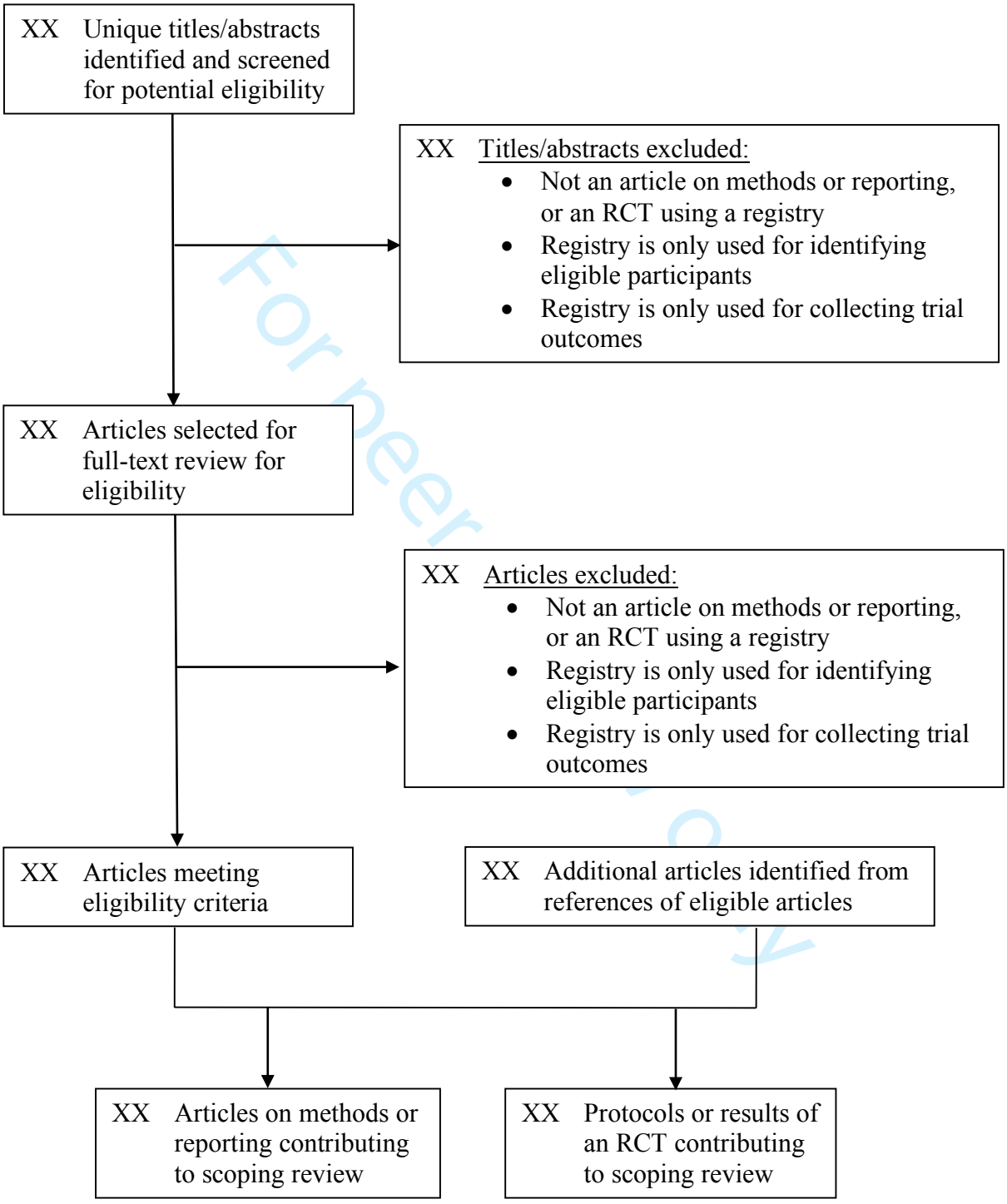
Yes: study eligible to be included in scoping review.

Supplementary File 3

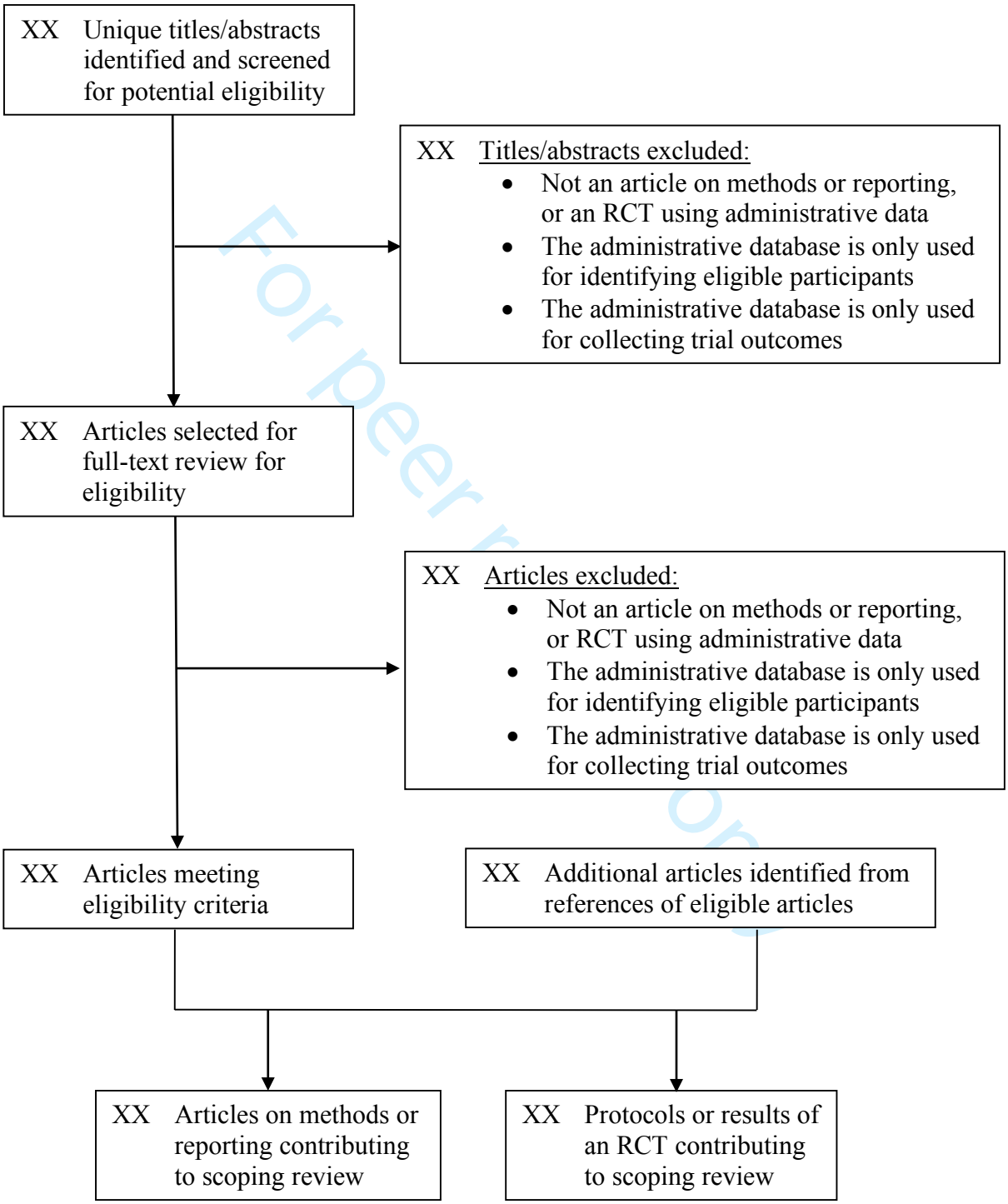
Draft Flow Diagram of Study Selection Process - Cohorts



Draft Flow Diagram of Study Selection Process - Registries



Draft Flow Diagram of Study Selection Process – Administrative data



Draft Flow Diagram of Study Selection Process – Electronic Health Records (EHRs)