Registry-based randomized clinical trials' indications, methods, health outcomes and reporting: A scoping review protocol

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Introduction

Patient registries are an organized system that utilize observational study methods to collect uniform data for a specific population to evaluate specified outcomes, defined by a particular disease, condition, or exposure.¹ Clinical trials derived from patient, disease, and population health registries can address clinical research questions in real-world settings, and are known as registry-based randomized control trials (RRCT).¹ RRCTs embed a randomized controlled trial (RCT) in a patient, disease, or health population registry for the purposes of determining trial eligibility, recruitment, baseline data collection, and/or measurement of outcomes.² In the last decade, there has been a steady increase in interest in RRCT conduct, which may be due to their potential benefits such as ease of participant recruitment, increased generalizability of findings, ability to conduct long-term follow-up, and cost-effectiveness.² For example, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) Trial used 90% less funding than most similarly sized RCTs.^{3,4}

Conversely, there are also potential challenges associated with registry use in trials, such as poor data quality, non-standardized trial to registry implementation procedures, issues with the coordination of trial procedures with registry procedures, and insufficient methods for updating registry information.⁴ These challenges may undermine a registry's ability to adequately serve as an information source for an RRCT, i.e., its "trial readiness".⁵ The reported benefits and limitations of RRCTs however have yet to be systematically explored.

There is currently limited information available on the characteristics of existing and planned RRCTs in both adult and paediatric populations that could be used to inform the design, conduct, and reporting of future RRCTs, necessitating an examination of the various ways registries are used in trials. In a recent study conducted by McCord et al., it was found that the reporting of RRCTs published between 2010 and 2018 is inadequate.⁶ The ways in which registries influence the conduct of trials and vice versa are unclear, such as in defining trial eligibility criteria, selection of outcomes, and collection of outcome data at various timepoints. Additionally, little is known about the methods used to select, measure, analyze, and report RRCT outcomes. Core outcome sets (COS), defined as a minimum set of outcomes that should be measured and reported for a specific disease area have been implemented in non-registry-based trials.⁷ A recent systematic review of COS uptake in RCTs demonstrated that while uptake rates vary, in certain disease areas such as rheumatoid arthritis up to 82% of RCTs used a COS.⁸ However, their uptake in RRCTs remains unknown. Further, the extent to which RRCTs rely on existing registry outcome data or need to collect additional, trial-specific outcomes "outside" of the registry, is uncertain. Acknowledging the potential benefits of RRCTs and the lack of standardized guidance regarding their conduct, it is also important to understand author-reported strengths and weaknesses of the trial design to inform the creation of practical guidelines. Therefore, this review aims to identify and synthesize recent RRCTs and protocols to help inform the future design, conduct, and reporting of RRCTs. The specific research questions are:

Research Questions

1. What are the characteristics of RRCTs completed in the last 10 years, or are currently planned (i.e., registered with a published protocol in the last 3 years), for example, disease areas studied, intervention types, trial design, sample sizes, participant retention rates)

2. In what ways and how often do trials embedded in registries require additional data collection outside of what is in the registry (e.g., additional outcomes measured, changes in timing of data collection)?
3. What types of primary outcomes have been used to evaluate treatment effects in RRCTs, and how were these outcomes selected, measured, analyzed, and reported?
4. What common strengths and weaknesses associated with RRCT design and conduct are reported by trialists in published RRCTs?

Methods

The scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews.⁹ Drafting of this protocol has been guided by the JBI methodology for scoping reviews,⁹ as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols (PRISMA-P) reporting guideline (Supplemental Table 1).¹⁰ All named research team members have reviewed the protocol and provided feedback. This protocol has been made available on Open Science Framework (OSF) on 29 June 2021. Any revisions and amendments made to the protocol will be documented on OSF.

Eligibility Criteria

Population

This review will consider published RRCT manuscripts and protocols of any age group, disease status, or other classification so long as participants were part of a patient, disease/condition, and/or population health registry or registries. RRCTs that only use a registry for participant recruitment will be eligible if the registry is the primary source of recruitment. RRCTs assessing health outcomes and/or trial process outcomes will be included. Trials that only use population registries for recruitment and/or outcome ascertainment will not be included.

Concept

This review will consider published RRCT manuscripts and protocols that describe the use of registries to recruit patients and/or ascertain outcomes. Methodological reviews, commentaries, cost-effectiveness studies, or RCTs assessing non-health outcomes will be excluded.

Context

This review will consider eligible studies and protocols from any country. Only studies published in English will be included. Studies published in the last ten years (2011-2021, inclusive) and protocols published from 2018-2021 will be considered for inclusion, as RRCTs are a relatively recent form of clinical trial design, and our initial searches indicate that most have been published within this time-period.

Information sources and search strategy

McCord et al. searched for and included full-text RRCTs published between 2011 and 2018.⁶ This review will screen the 47 papers identified by the McCord et al. research team and exclude studies that only use population registries.⁶ All other studies identified by McCord et al. will be included in this review.⁶ Additionally, a search for RRCT protocols and full-text papers published from January 2018 to May 2021 will be conducted to expand the scope of the review. Databases Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE and EBM Reviews – Cochrane Methodology

Registry will be searched using the search strategy (Supplemental 1) developed by McCord et al.⁶ All included studies will be citation screened to identify any corresponding subgroup and/or primary publications. Protocols published between 2018 and 2021 will be searched on Google Scholar to locate any corresponding published full-text studies. Only protocols without an associated published full-text study will be included. The original McCord et al. search strategy used in this review was peer-reviewed using the Peer Review of the Electronic Search Strategy (PRESS)¹¹ tool and developed in consultation with an experienced research librarian and input from the McCord et al. project team,⁶ and has been reported here as per the PRISMA-Search extension (Supplemental Table 2).^{6,12}

Source selection

Following the search, duplicates will be removed using the Ovid Platform. References will be downloaded and imported into Mendeley reference management software and Covidence systematic review software, and any remaining duplicates will be removed. Screening will be conducted in duplicate by two independent reviewers (WD, AS) with previous systematic review experience and training. Prior to beginning screening, a training exercise for title/abstract and full-text screening will be conducted on a random sample of twenty records to ensure high inter-rater reliability between reviewers.¹³ If necessary, additional training and reliability testing on a larger sample will be performed. Resolution of discrepancies will occur through discussions between reviewers and, if needed, consultation with a third reviewer (KG, AB, NJB, or MO).

Following title/abstract screening, the full text of selected citations will be assessed in detail against the predefined inclusion criteria in duplicate by two independent reviewers (WD, AS). Reasons for exclusion of full-text papers will be recorded. If necessary, research team members will contact authors to clarify study eligibility criteria. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or by involving a third reviewer (KG, AB, NJB, or MO). The results of the search will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses for Scoping Reviews (PRISMA-ScR) flow diagram.¹⁴

Data extraction and charting

Data will be extracted from documents included in the scoping review by three independent reviewers (WD, AS, KG) using a standardized data extraction form developed using REDCap data management software.¹⁵ One reviewer will act as a verifier and confirm the accuracy of the extracted data for each study (WD, AS, KG). Any discrepancies that arise will be resolved through discussion between the reviewer and verifier and a senior team member will be consulted, if necessary (AB, NJB, or MO). The data extracted will include specific details about study characteristics, design elements, and quality of reporting. A draft data extraction form is provided (Supplemental 2). Prior to the commencement of data extraction, the data extraction forms will be piloted by team members and necessary revisions will be made to ensure all relevant information is captured (WD, AS, KG, NJB, MO).

Data analysis and presentation

Data analysis will consist of quantitative measures (counts, frequencies) to characterize included studies and protocols and a qualitative analysis to synthesize extracted text on author-reported strengths/advantages and weaknesses/limitations that resulted from using a RRCT design for their trials in order to gain a better understanding of the practical benefits and disadvantages of

RRCTs. Quantitative data will be summarized using simple descriptive statistics such as frequencies, medians, and interquartile ranges (IQRs). For the qualitative analysis, verbatim text of author reported RRCT strengths and weaknesses specific to their trial will be extracted from the papers. Text will be analyzed using Braun and Clarke's six-step framework for thematic analysis.¹⁶ To identify initial codes, one reviewer (WD) will read and code the text in full.¹⁷ One reviewer (AS), will act as a verifier and confirm that the codes are accurate. Any discrepancies will be resolved by a third reviewer (KG, AB, NJB or MO), who will also read and code a sample of the texts. An inductive approach will be taken in the generation of codes, which will be based on the research questions regarding strengths and weaknesses of RRCT conduct.¹⁷ Axial coding will be used to determine inter-relationships between codes, and broader, general themes will be generated.¹⁷ Lastly, a group discussion within the research team will take place to refine and name the generated themes surrounding RRCT author-reported strengths and weaknesses described in above papers. Qualitative data will be presented in lists of authorreported RRCT advantages and disadvantages and a description of the common themes identified across studies.

CreDIT authorship statement:

William A Douglas: Methodology, Investigation, Writing – original draft; **Adrian Sammy:** Methodology, Investigation, Writing – original draft; **Katherine Goren:** Methodology, Investigation, Writing - review & editing; **Ami Baba:** Methodology, Project administration, Writing - review & editing; **Brett D Thombs:** Methodology, Writing - review & editing; **Alison Howie:** Methodology, Writing - review & editing; **Beth K Potter:** Conceptualization, Methodology, Writing - review & editing; **Martin Offringa:** Conceptualization, Supervision, Methodology, Writing - review & editing; **Nancy J Butcher:** Conceptualization, Supervision, Methodology, Writing - review & editing

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Supplementary Material

Supplemental 1: Electronic search strategies

As reported previously,⁶ 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 conducted using Registry Data

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="2018 - 2021"
12. (registry or registries).ab,kf,ti.
13. (random* or RCT).ti,ab,kw.
14. 12 and 13
15. limit 14 to yr="2018 - 2021"
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

Supplemental 2

Data Extraction Forms attached

Supplemental Table 1: 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	Location(s) Reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	p. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	p. 3
Authors:			
Contact	3a	Provide name, institutional affiliation, 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. 1, 5
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	p. 3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	p. 5
Sponsor	5b	Provide name for the review funder and/or sponsor	p. 5
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	p. 5
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p. 2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p. 2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered,	p. 2, 3

RESEARCH PROTOCOL

		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	p. 3
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. 7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p. 3
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)	p. 3, 4
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	p. 4
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	p. 4, 7
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. 4, 7
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	N/A
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p. 4
	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)	p. 4
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p. 4
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	p. 4, 5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

Supplemental Table 2: PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	p. 3
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	p. 3, 7
Study registries	3	List any study registries searched.	N/A
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	p. 3
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	p. 3
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	p. 3
Other methods	7	Describe any additional information sources or search methods used.	p. 3
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	p. 7
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	p. 7
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	p. 7
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	p. 3

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Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	p. 3
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	p. 3
PEER REVIEW			
Peer review	14	Describe any search peer review process.	p. 3, 4
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	N/A
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	p. 4