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REVIEW ARTICLE

Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research?

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Abstract

Registry-based randomized controlled trials are defined as pragmatic trials that use registries as a platform for case records, data collection, randomization, and follow-up. Recently, the application of registry-based randomized controlled trials has attracted increasing attention in health research to address comparative effectiveness research questions in real-world settings, mainly due to their low cost, enhanced generalizability of findings, rapid consecutive enrollment, and the potential completeness of follow-up for the reference population, when compared with conventional randomized effectiveness trials. However several challenges of registry-based randomized controlled trials have to be taken into consideration, including registry data quality, ethical issues, and methodological challenges. In this article, we summarize the advantages, challenges, and areas for future research related to registry-based randomized controlled trials.

Keywords: Registry-based randomized controlled trial; Registry; Effectiveness; Pragmatic trial; Clinical trial; Real-world setting

1. Introduction

A health registry can be defined as a health resource that allows authorized parties to collect and accurately access patients' health information for clinical, administrative, scientific, and/or policy-related purposes to improve clinical decision making among other roles [1,2]. In general, the data sources of registries include patient-reported data, physician-reported data, medical chart abstraction, electronic health records, administrative databases, institutional or organizational databases, and others [3]. Because of the advancement of electronic data collection systems, increasing number of registries are being developed and used for research, policy, and administrative purposes.

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What is new?

- The application of registry-based randomized controlled trials has attracted increasing attention in health research to address comparative effectiveness research questions in real-world settings.
- When compared with conventional randomized effectiveness trials, the advantages of registry-based randomized controlled trials include low cost, enhanced generalizability of findings, rapid consecutive enrolment, and the potential completeness of follow-up for the reference population.
- Challenges of registry-based randomized controlled trials such as registry data quality, ethical issues and methodological challenges have to be taken into consideration before conducting such trials

According to Gliklich et al., registries can be classified according to how the populations on which data are collected are defined [4]. These can include health services registries, disease- or condition-specific registries, or product registries. For example, the Canadian Institute for Health Information is a type of health services registry, which was established to improve health system and the well-being of Canadians, and has developed multiple registries that regularly and accumulatively collect administrative data on primary health care, hospital care, community care, pharmaceutical care and utilization, and specialized services [5]. On the other hand, disease- or condition-specific registries are usually a cohort of patients with similar disease conditions. For example, the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry of cardiac patients who have undergone catheterization in the province of Alberta, Canada, is a type of disease registry. Similarly, product registries are the type of registries used for post-marketing surveillance in procedures, device, and pharmaceutical trials to demonstrate effectiveness and safety of products in real-world settings [6]. According to the US Food and Drug Administration, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources and evaluate the factors that affect the risk of adverse outcomes such as dose, timing of exposure, or patient characteristics through the creation of patient registries [7].

Registries are generally designed as prospective observational studies and are flexible to address several research questions. In recent years, there has been a move toward the implementation of randomized controlled trials using patient registries as platform for patient recruitment and trial operationalization. The type of trial, also called "registry-based randomized controlled trials," was first proposed in the protocol of the Thrombus Aspiration during ST-segment Elevation myocardial infarction (TASTE) trial, to mean trials in which registries as a platform for case records, data collection, randomization, and follow-up [8]. Recently, the application of registry-based randomized controlled trials has attracted increasing attention in health research, with its potential of being "the next disruptive technology in clinical research" [9]. Registry-based randomized controlled trials are particularly advantageous as they enable rapid consecutive enrollment, and potential completeness of follow-up for the reference population, and result in reduced per-patient cost of implementation. They are essentially pragmatic trials with the use of registries as a platform [10,11], hence the findings from registry-based randomized controlled trials can be generalized to the population. Despite these benefits, the design and implementation of registry-based randomized controlled trials may be laden with several methodological, ethical, and operational challenges many of which are inherent in the features and types of the registry. The purpose of this review is to present a description of registry-based randomized controlled trials, with a focus on challenges, advantages, and areas for future research of registry-based randomized controlled trials.

2. Examples of registry-based randomized controlled trials

Registry-based randomized controlled trials have been used across different settings and populations. Using clinical quality registries, a prospective registry-based randomized controlled trial can be used pragmatically to assess comparative effectiveness in real-world settings. The TASTE trial, an example of a large-scale registry-based randomized controlled trial, leveraged the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) for trial conduction [12]. The TASTE trial evaluated the effectiveness of intracoronary thrombus aspiration plus primary percutaneous coronary intervention (PCI) compared with PCI alone on 30-day mortality in 7,244 patients with ST-segment elevation myocardial infarction. The trial used the SCAAR implemented within 29 Swedish, one Icelandic, and one Danish PCI centers to randomly assign the intervention to eligible patients in the registry report form directly. Due to preexisting information already gathered in the registry, participant enrollment was rapidly completed to satisfy sample size required [9,13]. No patient was lost to follow-up for the outcome assessment, because of the automatic and personalized tracking in the registry using patients' unique identification number [13]. The cost of this registry-based randomized controlled trial was substantially low, with only US $50 per patient approximately [12]. No significant difference between thrombus aspiration plus PCI and PCI alone was observed for 30-day [9] and 1-year [14] mortality. Findings from the TASTE trial were in agreement with a subsequent conventional randomized

controlled trial comparing the effect of thrombus aspiration followed by PCI with PCI alone on 180-day cardiovascular death in 10,732 patients [15]. Table 1 summarizes the key characteristics of the TASTE trial.

Another example of a registry-based randomized controlled trial is the cluster trial of Cardiovascular Health Awareness Program (CHAP) conducted in 39 midsized communities in Ontario, Canada [16]. The CHAP trial aimed to evaluate the effectiveness of cardiovascular risk assessment and education sessions held in community-based pharmacies over a 10-week period vs. usual care on hospital admissions for acute myocardial infarction, stroke, and congestive heart failure in 15,889 community dwellers aged ≥65 years old. The trial used 10 administrative database sources for data collection, follow-up, and outcome measures, where the databases included the Census Data, the Client Agency Enrolment Program, the Corporate Provider Database, the Discharge Abstract Database, the National Ambulatory Care Reporting System, the Ontario Drug Benefit Program Database, the Ontario Health Insurance Plan Claims History Database, the Ontario Physician Human Resources Database, the Registered Person's Database, and the Statistics Canada's Postal Code Conversion File [11,16]. The trial showed that the intervention was significantly related to decreased risk of the composite of hospital admissions, compared with usual care [16]. A third registry-based randomized controlled trial example is the Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate methicillin-resistant *Staphylococcus aureus* (REDUCE MRSA) trial conducted in patients admitted to intensive care units (ICUs) who were at high risk of health care−associated infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [17]. The trial compared targeted or universal decolonization for MRSA with MRSA screening and isolation in 74,256 patients in 43 hospitals (74 ICUs). The corporate data warehouses were used to collect data and assess outcomes, with a remarkably low cost of US $40 per patient [10,17]. The study found that universal decolonization was more effective than targeted decolonization or MRSA screening and isolation in prevention of MRSA infections in patients admitted to ICUs [17]. More description for the key elements of the CHAP trial and the REDUCE MRSA trial is presented in Table 1.

3. Advantages of registry-based randomized controlled trials

Generally, registry-based randomized controlled trials have several advantages compared with conventional randomized trials, including their low cost, enhanced generalizability of findings, rapid consecutive enrollment, and the potential completeness of follow-up for the reference population (Table 2).

3.1. Low cost

One of the most significant advantages of registry-based randomized controlled trials is their relative low cost. For instance, the TASTE trial involving over 7,200 patients only spent US $300,000 or US $50 per patient, which was estimated at 2% of a conventional randomized trial [10,12,13]. For the CHAP trial, it was reported that the trial spent CAN $20 (or US $16) per resident [16,18]. This is substantially less expensive than most explanatory trials of cardiovascular disease that cost at least CAN $5,500 (or US $4,280) per patient [11,19]. Likewise, the total cost of the REDUCE MRSA trial was less than US $3 million, or US $ 40 per patient [10,17]. The cost-saving advantage of registry-based randomized controlled trials relies on the fact that they can use existing registries to identify participants, collect baseline and study data, and detect outcomes of interest, rather than rebuilding and establishing electronic records, other platforms, and infrastructures [10,13]; therefore, costs that would normally be incurred in a more traditional randomized controlled trial are indirectly transferred onto the health system where electronic registries are maintained. Other reasons include the reducing cost of additional study visits, the minimization of extra administrative costs, and the potential cost saving in training site staff and research coordinators [13,20]. For example, virtually, the only extra work in the TASTE trial was for setting up the randomization process. The trial did not create any additional case report forms for data collection, or require any additional patient visits, or organize training sessions for trialists and staff [10,12].

3.2. Enhanced generalizability of findings

Registry-based randomized controlled trials are pragmatic trials using registries as a platform for one or more of the trial activities including patient identification, randomization, intervention delivery, follow-up, and outcome assessment [10,11]. Generally, these trials have less stringent inclusion and/or exclusion criteria, and patient monitoring and follow-up are more akin to real world than the more intensive monitoring in explanatory trials, which enhances the generalizability of their findings. The cost and recruitment efficiencies of registry-based randomized controlled trials are most times fully realized with trial designs that allow recruitment of less-selected populations in real-world settings, where blinding or crossover prohibitions are not required, and where follow-up end points can be abstracted from other registries or health care administrative data [11,21]. Consequently, findings from well-designed registry-based randomized controlled trials may be broadly generalizable while answering a comparative effectiveness research question [9].

3.3. Rapid consecutive enrollment

Rapid consecutive enrollment in a randomized trial is appealing, especially in trials requiring a large-scale sample size to detect appropriate outcome events [9]. In registry-based randomized controlled trials, investigators use

Table 1. Key elements of examples of registry-based randomized controlled trials

Study [Ref no.]	Population	Intervention	Comparison
The TASTE trial [12]	Patients with ST-segment elevation myocardial infarction	Thrombus aspiration plus PCI	PCI alone
The CHAP trial [16]	Community residents aged ≥65 years old	Cardiovascular risk assessment and education sessions held in community-based pharmacies over a 10-week period	No intervention (usual care)
The REDUCE MRSA trial [17]	Patients admitted to ICUs at high risk of MRSA infections	Targeted decolonization for MRSA; universal decolonization for MRSA	MRSA screening and isolation

Abbreviations: Ref, reference; TASTE, Thrombus Aspiration during ST-segment Elevation myocardial infarction; PCI, percutaneous coronary intervention; CHAP, Cardiovascular Health Awareness Program; REDUCE MRSA, Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA; MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

registries with existing clinical information to rapidly identify eligible participants for consecutive enrollment. That is, they may no longer be required to fill out long case report forms for participant eligibility assessment because data are already available in the registry, thereby significantly facilitating patient enrollment [9]. For instance, in the TASTE trial, for all patients who presented with ST-segment elevation myocardial infarction and were referred for PCI, 76.9% were randomized within 2 years and 9 months [13,14].

3.4. Potential completeness of follow-up

Another advantage of registry-based randomized controlled trials is the potential completeness of participant follow-up. For example, unique patient identification numbers in registries are available in the Nordic countries [22], in Canada and will be available in India [23], and these allow for an almost complete tracking of patients across registries. Because of the linkage to registries such as interconnected health records, it is possible to retrieve extensive clinical information of participants using their unique identification number in the tracking system. Even for the eligible but nonrandomized participants, as well as those noneligible participants, registry-based randomized controlled trials have the potential to describe and follow up the complete reference population [13].

4. Challenges of registry-based randomized controlled trials

Nevertheless, several challenges of registry-based randomized controlled trials have to be taken into consideration. These are described in the following sections and in Table 2.

4.1. Registry data quality

A key limitation to the application of registry-based randomized controlled trials is the lack of high-quality registries [9]. Concerns exist about data quality related to baseline variables as well as outcome measures in registries [13]. The definition, the collection, and the accuracy of baseline data gathered in registries may vary across registries, depending on the initial purpose for which the registry was created. Similarly, because outcomes may not be usually adjudicated in registry-based randomized controlled trials, data on outcome events may be subject to uncertainty. It is therefore recommended that registry-based

Outcome	Trial duration	Registry used	Cost of trial	Main result
30-day all-cause mortality	Two years and 9 mo	The Swedish Coronary Angiography and Angioplasty Registry	US $50 per patient	No significant difference between thrombus aspiration plus PCI and PCI alone in 30-day mortality
Hospital admissions for acute myocardial infarction, stroke, and congestive heart failure	Over 12 mo	The Census Data; the Client Agency Enrolment Program; the Corporate Provider Database; the Discharge Abstract Database; the National Ambulatory Care Reporting System; the Ontario Drug Benefit Program Database; the Ontario Health Insurance Plan Claims History Database; the Ontario Physician Human Resources Database; the Registered Person's Database; and the Statistics Canada's Postal Code Conversion File	CAN $20 (or US $16) per resident	The CHAP was significantly related to decreased risk of the composite of hospital admissions, compared with no intervention
Rates of MRSA clinical isolates and bloodstream infections	30 mo	The corporate data warehouses	US $40 per patient	Universal decolonization was more effective than targeted decolonization or MRSA screening and isolation

randomized controlled trials choose hard clinical end points (e.g., death) that are less susceptible to ascertainment bias and diverse definitions [13]. Nevertheless, it is also possible to adjudicate outcome events or perform random audits in registry-based randomized controlled trials to ensure the accuracy of outcome measures [24]. For example, all the outcome events are centrally adjudicated in the ongoing VALIDATE-SWEDEHEART (bivalirudin vs. heparin in non-ST and ST-segment elevation myocardial infarction) trial [25] and the iFR-SWEDEHEART (instantaneous wave-free ratio vs. fractional flow reserve—guided intervention) trial [26]. Another issue related to registry quality is the completeness of relevant variables. Preexisting registries may have missing data or fail to capture important prognostic factors that then affect the study findings [9,24]. Trialists need to be aware of these limitations and address them appropriately.

4.2. Ethical challenges

Registry-based randomized controlled trials may face new ethical issues. These include the following: (1) screening registry participants for trial inclusion if they have not previously consented to records review, (2) the potential need for formal informed consent for a treatment that is already being used in routine practice, (3) protecting the data and participant privacy in the absence of platforms and infrastructures established in most registry-based randomized controlled trials to oversee and manage the trial, (4) how to handle participant withdrawal from the trial or registry, and (5) how to coordinate the overlapping role of Data and Safety Monitoring Board in the trial with the role of registry executives while collecting data on safety in registry-based randomized controlled trials. These ethical challenges have to be fully addressed before the implementation of a registry-based randomized controlled trial.

4.3. Methodological challenges

One of the methodological considerations about the registry-based randomized controlled trials rests on common confusion about the research question being addressed by the design. Typically, registry-based randomized controlled trials are conducted to answer questions about effectiveness of treatments or interventions in real-world practice using pragmatic strategies. Therefore, it is possible that registry-based randomized controlled trials might not have blinding, standardized implementation procedures, fixed follow-up,

Table 2. Advantages and challenges of registry-based randomized controlled trials

Advantages	Challenges
Remarkably low cost	Registry data quality including the following:
Enhanced generalizability of findings	Definition, collection, and accuracy of baseline data gathered in registries may be various and questionable;
Rapid consecutive enrollment	Outcome data documented in registries may be subject to uncertainty;
Potential completeness of participant follow-up	Registries may have many missing data or fail to capture important prognostic factors.
	Ethical issues including the following:
	Screening registry participants for trial inclusion if they have not previously consented to records review;
	The potential need for formal informed consent for a treatment that is already being used in routine practice;
	Protecting the data and participant privacy;
	How to handle participant withdrawal from the trial or registry;
	How to coordinate the overlapping role of Data and Safety Monitoring Board in the trial with the role of registry executives.
	Methodological challenges including the following:
	Common confusion and controversies about the research question being addressed by the design;
	Ensuring the representativeness of study participants in recruitment;
	Research questions, study designs, and types of outcomes limited by quality and features of registry used.

and/or central adjudication for outcome measures. We refer readers to the tutorial by Thabane et al. for the common confusion and controversies around pragmatic trials and how to address them [11]. Another methodological challenge is related to recruitment of patients in registry-based randomized controlled trials. Patients may be diagnosed with some specific diseases of interest by different health providers from different participating centers with their own registries [27]. If their registries are not linked, even in a same referral center, failure to enroll the eligible patients in a registry-based randomized controlled trial will impair the representativeness of study participants and weaken the external validity of the findings.

Despite the various benefits of registry-based randomized controlled trials, this class of trials often depends on the size, quality, and feature of the registry on which the trials are based. Hence, the type of research question, study design, and type of study end points adopted for a registry-based randomized controlled trial may be limited by the quality and features of the registry used. For example, although conventional explanatory trials often rely on power analysis to determine the expected sample size for treatment effect estimates, the number of patients in a registry-based randomized controlled trial may be restricted by the size of the registry on which the trial is conducted. This implies that investigators may be limited to designing a registry-based randomized controlled trial to fit the features of the registry and not vice versa, especially in situations where investigators are not able to use multiply linked registries. Registry-based randomized controlled trials that are based on linked registries, on the other hand, may be advantageous because they may result in larger number of eligible participants and more robust outcome assessments. However, these linked registries may differ with respect to quality of data collection, number and type of baseline information collected, and data storage infrastructure (e.g., paper vs. electronic), which, in turn, can influence outcome assessments and size of treatment effect detected in such studies.

5. Considerations of designing a registry-based randomized controlled trial

5.1. When to conduct a registry-based randomized controlled trial

Registry-based randomized controlled trials are usually performed to address comparative effectiveness research questions in real-world settings when high-quality registries are available. Therefore, registry-based randomized controlled trials cannot be used to answer questions of treatment efficacy under ideal circumstances [28]. By contrast, registry-based randomized controlled trials are pragmatic trials and can address practical questions on whether a treatment does more good than harm compared with alternatives in routine health care practice. More specifically, in a registry-based randomized controlled trial, it is acceptable and not uncommon that (1) patients and/or health care providers may be partly or completely blinded; (2) patients may be nonadherent, take multiple medications, or withdraw; (3) health care providers make various decisions based on their preferences in practice, and so forth [11]. Nevertheless, for those trials requiring comprehensive safety monitoring, intense pharmacodynamic or pharmacokinetic modeling, strict inclusion criteria and well-defined end points, registry-based randomized controlled trials are not an adequate choice. Instead, a conventional explanatory trial that necessitates blinding, dedicated follow-up, formal management, and central adjudication would be needed to ensure data accuracy and patient safety. A registry-based

randomized controlled trial can be especially suited to phase IV studies to explore new signals and indications of approved interventions or devices such as open-label assessment of commonly used therapeutic alternatives as part of post-marketing surveillance or other studies mandated by regulatory authorities. Similarly, registry-based randomized controlled trials can be suitable for implementing knowledge translation type of interventions (e.g., CHAP trial). The application of registry-based randomized controlled trials can be a solution to the dilemma that exists between the costly conventional randomized trials and observational studies with questionable internal validity because registry-based randomized controlled trials are inexpensive and methodologically rigorous in the presence of randomization [9,10]. Registry-based randomized controlled trials with open-label randomization, data focused on key hard end points, and small budgets are receiving increasing recognition currently to appraise treatment alternatives and strategies, as long as patient safety is guaranteed and existing regulations are fully followed [13].

5.2. Key considerations for establishing the registry platform to conduct a registry-based randomized controlled trial

To make a registry-based randomized controlled trial realizable and successful, we propose some considerations in establishing the registry platform to conduct a registry-based randomized controlled trial: (1) capturing key demographic, historical, and disease condition-specific variables to allow patient selection and to assess for confounding in registries, with high completeness and accuracy; (2) capturing information on key hard clinical end points with completeness and accuracy; (3) making plans for verification of data accuracy (e.g., through random and periodic audit); (4) collecting unique patient identifiable information to allow linkage across patient episodes of care and between data sources; (5) linking multiple administrative data sources for complete follow-up; (6) protecting data and patient privacy appropriately; (7) gaining access to services for ethical and legal oversight of research activity; (8) identifying internal processes for liaising with clinical trialists to vet and implement registry-based randomized controlled trial proposals; and (9) seeking permission from registry participants to allow them to be contacted for future research studies.

6. Areas for future research

Currently, there is no guideline or recommendation for reporting a registry-based randomized controlled trial. Although the extension of the Consolidated Standards of Reporting Trials (CONSORT) to pragmatic trials [29] may be a useful resource, we propose that developing a CONSORT extension to registry-based trials to aid complete and transparent reporting for registry-based randomized controlled trials would be a worthwhile endeavor. Although the guideline or recommendation may be also restrictive because registry-based randomized controlled trials are a relatively new type of clinical trials at an early stage, a systematic and standardized tool would be helpful to broaden our understanding and assessment of registry-based randomized controlled trials and accelerate our adjudication on their feasibility and applicability. Moreover, no validated tool or guidance is available to help with critical appraisal of quality of a registry-based randomized controlled trial. Although the Cochrane Handbook for Systematic Reviews of Interventions [30] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [31] were developed to assess quality of evidence and grade strength of recommendations for explanatory trials and systematic reviews of explanatory trials, analogous criteria for registry-based randomized controlled trials are still lacking.

The synthesis of evidence from explanatory randomized controlled trials is an integral part of evidence-based clinical and policy decision making. Although the methodology and guidelines for reporting and synthesizing evidences from randomized controlled trials are well developed, there is currently no recommendation for synthesizing evidence from registry-based randomized controlled trials and explanatory trials. For example, there are no clear guidelines on whether we can, should, or must pool the evidence from registry-based randomized controlled trials and explanatory trials together. If so, when and how to synthesize the evidence, and what criteria should be applied, remain to be answered. Further research is needed to develop appropriate methodology and reporting guidelines for pooling results from registry-based randomized controlled trials and explanatory trials to aid in clinical and policy-based decisions.

It is not uncommon in registry-based randomized controlled trials to link data between multiple registries from different stakeholders including patients, physicians, institutions, organizations, or governments [10]. Registry-based randomized controlled trials may benefit from the use of multiply linked patient registries for recruitment or outcome assessment (e.g., CHAP trial). However, there has been limited research on the impact of the quality of these multiple registries and/or data sources on the accuracy of registry-based randomized controlled trial study findings. On the other hand, electronic health/medical records (EMRs) are increasingly being used for clinical and population health research. For example, the Canadian Primary Care Sentinel Surveillance Network routinely collects deidentified longitudinal data from primary care EMRs across the country [32]. As of December 2015, this included information on approximately 1.3 million Canadians [33]. These large EMR data sources can be potentially useful for assessing study end points in registry-based randomized controlled trial studies; however, the

methodological tools necessary to use these data for registry-based randomized controlled trial purposes are still in development [34]. Further research will be needed to investigate the methodological challenges in data linkage and the impact of quality of registries and/or data sources on the treatment effect estimations and study findings.

Besides, validating the data and improving the quality of registries in registry-based randomized controlled trials necessitate more research to enhance data accuracy. Last but not least, the ethics of these practices remain unexplored.

7. Conclusions

By using registries as a platform for case records, data collection, randomization, and follow-up, registry-based randomized controlled trials are becoming a highly cost-effective and increasingly popular methodology to answer comparative effectiveness clinical research questions. Despite the advantages of registry-based randomized controlled trials, trialists need to acknowledge the challenges inherent in registry-based randomized controlled trials before conducting such trials.

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