The Use of Routinely Collected Data in Clinical Trial Research

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Kimberly Alba Mc Cord – De Iaco
from Lugano, Ticino

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Approved by the Faculty of Medicine

On application of:

PD Dr. med. Lars G. Hemkens MPH (first supervisor)

Prof. Dr. med. Heiner C. Bucher MPH (second supervisor)

Prof. Dr. med. Jörg Meerpohl (external expert)

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I. Table of Contents

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2 Plain Summary

RCTs are the gold standard for assessing the effects of medical interventions, but they also pose many challenges, including the often-high costs in conducting them and a potential lack of generalizability of their findings. The recent increase in the availability of so called routinely collected data (RCD) sources has led to great interest in their application to support RCTs in an effort to increase the efficiency of conducting clinical trials. We define all RCTs augmented by RCD in any form as RCD-RCTs. A major subset of RCD-RCTs are performed at the point of care using electronic health records (EHRs) and are referred to as point-of-care research (POC-R). RCD-RCTs offer several advantages over traditional trials regarding patient recruitment and data collection, and beyond. Using highly standardized EHR and registry data allows to assess patient characteristics for trial eligibility and to examine treatment effects through routinely collected endpoints or by linkage to other data sources like mortality registries. Thus, RCD can be used to augment traditional RCTs by providing a sampling framework for patient recruitment and by directly measuring patient relevant outcomes. The result of these efforts is the generation of real-world evidence (RWE).

Nevertheless, the utilization of RCD in clinical research brings novel methodological challenges, and issues related to data quality are frequently discussed, which need to be considered for RCD-RCTs. Some of the limitations surrounding RCD use in RCTs relate to data quality, data availability, ethical and informed consent challenges, and lack of endpoint adjudication which may all lead to uncertainties in the validity of their results.

The purpose of this thesis is to help fill the aforementioned research gaps in RCD-RCTs, encompassing tasks such as assessing their current application in clinical research and evaluating the methodological and technical challenges in performing them. Furthermore, it aims to assess the reporting quality of published reports on RCD-RCTs.

In this thesis, I strengthen the knowledge foundation of RCD-RCTs in clinical trial research by describing a framework of the application of RCD-RCTs in clinical research through an analysis collating the opinion and experience of several experts in the field of trials, ethics and RWE. Next, I performed a literature review including over 4000 publications, focusing on EHRs and their costs. It included 189 RCTs, most of which were performed in North America (81%). In 17 of the trials the EHR was not part of the intervention. For this subset we contacted the authors requesting cost information through a standardized email and extracted any cost

information reported in the publications. The per-patient costs varied from 44 to 2000 United States Dollars (USD), and total RCT costs from 67’750 to 5’026’000 USD.

Furthermore, in a meta-epidemiological study, I assessed the agreement of treatment effects estimates of RCD-RCTs compared to that of traditional RCTs addressing the same clinical question, supporting the understanding of the similarities between these two trials designs. It found that relative treatment effect estimates between RCD-RCTs and traditional RCTs deviated on average of a magnitude of 13%. The recommendations emerging from these projects are that further research will be necessary to distinguish if the treatment effect deviation in RCD-RCTs is due only to the difference in data used (and its quality) or if other design characteristics, such as trial pragmatism, may be responsible for this disagreement.

Additionally, through the collaboration in an international cooperation (the Consolidated Standards of Reporting Trials (CONSORT) Cohorts and Routinely Collected Data extension working group) aiming to develop a reporting guideline specifically for RCD-RCTs, I performed a reporting completeness and transparency assessment of RCD-RCTs using registries as their data source. The assessment included reports of 47 registry RCTs and supported the development of the upcoming reporting guideline. Of the 13 novel CONSORT extension items, only 6 items were adequately reported in at least half of the 47 trial reports (3 in at least 80%). The 7 other items were not adequately reported and were related to data linkage, validation and completeness of registry data for outcome assessment, validation and completeness of registry data for participant recruitment and interpretation of results in consideration of the RCD source.

In the future, the RCD-RCT research agenda will likely focus on understanding why they may provide different treatment effect estimates than traditional RCTs (especially considering trial pragmatism), as well as in determining the magnitude of costs reduction when incorporating RCD in trials. The impact of this research and whether it will eventually increase value in the RCD-RCT landscape will depend on further evaluation of these open questions. While a foreseeable uptake of RCD-RCT research design will transpire in the future, maintaining rigorous methodological standards, improving reporting and systematically evaluating the performance of the conducted RCD-RCTs by all stakeholders will be important to advance the generation of more affordable and valid evidence.

3 Introduction and Rationale

3.1 Introducing Randomized Controlled Trials using Routinely Collected Data

3.1.1 Randomized Controlled Trials (RCTs) as Gold Standard to Guide Healthcare Decisions

Whenever we must assess causality between interventions and measured effects, the gold standard approach is randomized controlled trials (RCTs) – in medicine and computer sciences, and increasingly proposed as such in other fields such as economics or policy making[1,2]. Randomization addresses bias resulting from confounding and allows us to draw causal conclusions on the measured intervention effect by balancing the prognosis of patients among the different treatment arms, thus bypassing major methodological challenges of non-randomized study designs[3,4]. The trade-off of RCTs is that they are sometimes difficult to conduct, they can be complex and resource intensive to plan and perform, and they are often expensive[5]. This is a major barrier in performing RCTs in underserved research areas; as well as in replicating RCT's finding in general. The majority of the RCTs' costs depend on the burdensome task of developing and maintaining a specifically designated research infrastructure[5]. This includes setting up research and clinical sites, with trained staff, in order to collect and record all data (or endpoints) that are necessary. Even when these steps are successfully implemented, recruiting trial participants is another major obstacle in successfully completing RCTs, and a major cause for discontinuing trials[6]. Finally, while randomization may be technically always feasible, there are scenarios where institutional review boards (IRBs) or ethical committees may be hesitant to allow randomized comparisons (usually when specific vulnerable populations such as pregnant women or children are involved, or in comparisons where providing a placebo might be unethical; such as in postoperative pain management[7]). In other fields, such as the technology industry, A/B testing are performed ubiquitously leading to rapid identification of features that are superior to others; such a system would be desirable in the clinical landscape but an expansive change in perspective from all major stakeholders would be needed[2].

3.1.2 Routinely Collected Data (RCD)

The digitalization of the healthcare field in the last 20 years has led to massive amounts of health data[8]. RCD can be differentiated from actively collected as to whether the data was collected outside of a specific research intent (such as from a traditional RCT)[9,10]. Any data that is created through everyday life or established data collection machineries, rather than to assess a specific research hypothesis, is considered routinely collected data. The major forms of RCD are electronic health records (EHRs), registries and administrative and billing databases. Whether this data is generated at the clinical encounter or is collected from efforts of governmental and private agencies, it may contain valuable information on outcomes, and could serve as the basis of comparative effectiveness research (the generation of comparative evidence through observational or experimental studies as well as evidence synthesis through meta-analysis[11]).

Healthcare stakeholders gravitate more and more towards value-based systems both in high income and low and middle income countries[12,13], and it becomes increasingly important to retrieve and elaborate on care and disease outcomes routinely. Value based health systems shift the focus from simply reimbursing procedures to assessing the efficacy and quality of the care provided;, measuring outcomes in addition to procedural costs and aligning reimbursements to this metric[14]. Thus, in addition to measuring performance codes, facilities would need to link the patients' outcomes for reimbursement. In this scenario the amount of RCD generated as well as its granularity would likely increase, expanding the potential for their utilizations in clinical research.

The possibilities of using RCD in clinical trials (hereafter referred to as RCD-RCTs) span from improving the identification and recruitment of patients, to serving as a clinically integrated research framework, to collecting valuable endpoints and clinical features.

3.1.2.1 Registries

Registries are repositories of data with a common feature[15], such as a disease, an exposure to a device or a geographic location. Common types of registries are population registries (such as civil registrations which can include a government-issued individual identification number and may track activities and movements of citizens throughout life) and health registries (which group individuals with common disease or exposures, for example a breast cancer registry[16] or a public health registry keeping track of lead exposure in children[17]).

Yet not one unique definition of registries exists, and different institutions often define registries differently. The U.S. Agency for Healthcare Research and Quality (AHRQ) defines registries used to measure patient outcomes as: "*A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes*"[15].

Unlike a general database, which is an organized collection of data usually stored and accessed electronically from a computer system, registries differ through their scope or purpose. The objective of a registry is clear, and data collection efforts are often geared to meet such objective a priori.

For a more thorough denotation which also places a distinction between registries and databases, we can draw from Drolet's and Johnson's definition of a medical registry "*We define a medical data registry as a system functioning in patient management or research, in which a standardized and complete dataset including associated follow-up is prospectively and systematically collected for a group of patients with a common disease or therapeutic intervention. This definition makes the important distinction that registries are a functional subset of databases (i.e., all registries are databases, but not all databases are registries)*"[18].

3.1.2.2 Electronic Health Records

Electronic health records (EHRs) are electronic versions of medical charts[19]. Whether they originate from distinct practice medical records, by pharmacies, or by specific medical departments (e.g. radiology) of a hospital, EHRs have a wealth of exposure and outcome data[19]. This source has been increasing the most in recent years, as many healthcare systems have invested in their development and adoption, particularly in the USA[20]. While EHRs contain large amounts of clinical information, it may be less accessible (low interoperability between systems[21], free-text format[22]) and understandable (classification and phenotyping issues[23]) than other data sources.

Additionally, EHRs can serve as a research intervention framework, as it can interact with clinicians and/or patients during the clinical exchange and thus has the potential to modify behaviors[24]. Special software can be added to EHRs which allow to interact with the clinicians. An example is computerized decision support systems (CDSS), that can alert caregivers of drug interactions or clinical guidelines directly during the patient exchange[24].

EHRs have been increasingly utilized for phenotyping and as such the "quality" of their data has become more apparent. EHR data phenotyping can be explained as follows "*In the context of EHRs, a computable phenotype or simply phenotype refers to a clinical condition or characteristic that can be ascertained via a computerized query to an EHR system or clinical data repository using a defined set of data elements and logical expressions. These queries can identify patients with a particular condition, such as diabetes mellitus, obesity, or heart failure, and can be used to support a variety of purposes and data needs for observational and interventional research. Standardized computable phenotypes can enable large-scale pragmatic clinical trials across multiple health systems while ensuring reliability and reproducibility*"[25]. Hospitals in the US have begun creating in-house "data core facilities", which similarly to traditional laboratory core facilities, support investigators for EHR-driven research (from basic consultation of project feasibility and data acquisition steps, to advanced algorithms for specific EHR phenotyping tasks). As natural language processing (NLP) and other AI technologies continue to improve the quality and usability of RWD, the amount of regulatory-grade RWD at research disposal will likely increase

3.1.2.3 Administrative Claims Databases

Administrative databases are repositories of clinical, demographic and diagnostic information routinely generated at the health service exchange[26,27]. In other words, most interactions between a patient and the health system generate billing and reimbursement information which is recorded by providers and insurance companies. Reimbursement of procedures may require medical codes to support and justify the necessity of the course of action taken, so that providers can be refunded. Thus, administrative databases have large records of healthcare and service utilization as well as clinical information. But unlike EHRs, which contain the entire medical record of the patient, administrative data contain medical codes such as the International Statistical Classification of Diseases and Related Health Problems[28] (ICD). ICD codes cover diseases, symptoms, clinical findings and procedures, and are standardized by the World Health Organization (WHO) to be identical in all countries. For this reason, administrative data is often the most indirect RCD source in terms of clinical information because the ICD codes only provide a glimpse of the health exchange but will lack the entire clinical context. Nonetheless they can be very informative when assessing cost and resource utilization, and often cover extensive population sizes[29].

3.1.2.4 Additional sources

There are several other sources of RCD. Telehealth apparatuses such as blood pressure monitoring cuffs or glucometers can transmit the measurements wirelessly to the EHR for remote healthcare services[30]. Mobile applications installed in smartphones can be used to directly collect health data, such as disease progression[31], or medication adehrence[32], by prompting the user. There were approximately 325,000 of these mobile health (mHealth) apps available in 2017[33]. Furthermore, smartphones can be leveraged to indirectly collect user data through their sensors. The variety of data collected from sensors is vast: "*Modern day smartphones come with a number of embedded sensors such as a high-resolution complementary metal-oxide semiconductor (CMOS) image sensor, global positioning system (GPS) sensor, accelerometer, gyroscope, magnetometer, ambient light sensor and microphone. These sensors can be used to measure several health parameters such as heart rate (HR), HR variability (HRV), respiratory rate (RR), and health conditions such as skin diseases and eye diseases, thus turning the communication device into a continuous and long-term health monitoring system.*"[31].

The FDA has recently developed MyStudies, an open source and customizable app that researchers can use to target specific research hypotheses while collecting and storing the data safely[34]. The safety functionality of MyStudies merits closer inspection "*The data storage environment is secure and supports auditing necessary for compliance with 21 CFR Part 11 and the Federal Information Security Management Act, so it can be used for trials under Investigational New Drug oversight*"[34].

3.1.3 RCD-RCTs

3.1.3.1 RCD-RCTs, the perfect blend

What emerges from the limitations of RCTs and the ubiquity of RCD is the potential for a combined design – merging the methods of RCTs with RCD: the RCD-RCT[9,35]. Using RCD to assess treatment outcomes within a randomized study allows to maintain the methodological validity of RCTs while including so called "real-world data"[10] (RWD) which may be available freely or at a fraction of the cost of actively collected data from a traditional RCT.

Real-world evidence (RWE), or evidence obtained from RCD, has become increasingly pertinent in the digitalized medical landscape; and the FDA explains this emerging trend as

follows "*The use of computers, mobile devices, wearables and other biosensors to gather and store huge amounts of health-related data has been rapidly accelerating. This data holds potential to allow us to better design and conduct clinical trials and studies in the health care setting to answer questions previously though infeasible*."[36].

RCD repositories can be queried to identify the trial participants, boosting recruitment and possibly reducing the amount of discontinued RCTs. Perhaps the most novel approach of RCD-RCTs are point-of-care trials[37–39], which are possible through the EHR. During the routine encounter a patient's chart can be screened and flagged for RCT eligibility, and upon signing of the informed consent, the participant can be automatically randomized to a given intervention while his/her outcomes are automatically collected from the EHR. These dynamic point-of-care trials are the core element of the so called "learning healthcare system"[40] where clinical questions are investigated continuously and consecutively, and its results are integrated in the healthcare system as quality improvement[41]. The US department of Veterans Affairs, which has a long-established EHR infrastructure, describes these trials as follows: "*Point of Care Research (POC-R) is a new approach to clinical study design that embeds trials into regular medical care. It is uniquely positioned to compare two or more approved treatments or diagnostic techniques that are considered to be equivalent. These trials take advantage of the electronic medical record (EMR) to facilitate participant recruitment and data collection, minimizing study overhead and streamlining the experience for patients*"[42].

But POC-R raises questions relating to trial participation and informed consent practices. Prompted Optional Randomization Trial (PORT)[1], or trials that prompt clinicians to randomize to equivalent treatments through the EHR as means to perform comparative-effectiveness research, are considered consent-free study designs which rely on the presence of a computerized decision support system to manage clinician orders and routinely collected outcomes to perform statistical analyses[43]. In such a case, informed consent may not be warranted, as the clinician could override the PORT randomized treatment arm and favor personal or patient preference instead; bypassing the need to obtain informed consent and contributing to the learning health system. Considerations of waived-consent RCTs embedded into the clinical exchange will become more relevant as POC-R becomes more utilized, and it is plausible to foresee a disruption in the clinical research environment.

Thus, RCTs can be augmented by RCD to recruit patients or to measure outcomes, or they can take a completely dynamic approach and serve as the intervention itself (mostly through

EHRs). RCD-RCTs may also allow to collect data on concomitant treatments or variables collected after randomization to provide further understanding of the treatment effects (e.g. allowing for time updated analyses). The embedding of clinical trial operations into the clinical care ecosystem ideally minimizes frictions for time intense data collection and may allow to generate more generalizable results with the possibility of rapid implementation of trial findings.

3.1.3.2 RCD-RCT examples

The Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (TASTE) trial[44] was a pioneering registry-RCT that used the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) cardiac registry to evaluate whether thrombus aspiration of culprit lesion compared to routine balloon angioplasty and stenting reduced 30 day mortality and tracked outcomes of patient undergoing stenting while suffering from myocardial infarction[44]. The extensiveness of the registry, which additionally included different national registry sources linked with the participant's Personal Identity Number, had no losses to follow-up and found that thrombus aspiration during stenting was not beneficial to reducing 30-day mortality[44].

The largest nationwide trial in Switzerland using RCD thus far[45], was a pragmatic RCT leveraging administrative prescription data from all statutory health insurers in Switzerland. It used the RCD to monitor the effect of mailing antibiotic prescription guidelines and feedback on prescribing to primary care physicians; and found that such a nationwide antibiotic stewardship program was not associated with an overall change in antibiotic use.

The Salford lung study[46] was the first RCD-RCT used to endorse the approval of a drug (once-daily inhaled fluticasone furoate combined with vilanterol), in patients with COPD or asthma. It was a phase 3, community-based trial supported by the clinical information from the EHR network of Salford, Scotland. However, while the data was collected routinely from the Salford EHR network system, the data collection was specifically optimized for the purpose of this trial (with blinded adjudication of all adverse events[47]), leading to costs approaching those of traditional approval RCT costs. This illustrates that even using RCD may not clearly reflect usual care settings and it has been argued that this study has not a pragmatic design for various reasons[48]. Nevertheless, its results, a benefit of the drug regimen for maintenance therapy in

patients with COPD, confirmed the previous findings from more traditional RCTs by generating real-world evidence.

3.2 Methodological Considerations

The methodological benefits and challenges of using RCD to support RCTs are numerous. These can be seen as pertaining to the internal or external validity of the trial[49]. A trial's validity refers to how appropriately its results apply to populations outside of that of the trial[1,2], whether that may be related to the establishment of cause-and-effect relationship (internal validity) or to the generalizability and applicability of the findings (external validity)[50]. Any threats to the validity of the trial's results, or introduction of systematic errors that favor one of the tested interventions (or controls) over the other, are called biases[51].

Using RCD in trials can have beneficial effects on internal validity but may likewise introduce other biases; consideration of this trade-off is essential when designing an RCD-RCT. For example, since RCD are often collected by individuals who are not directly related to the tested intervention or research agenda, the outcomes may be less likely to be altered due to detection bias (i.e. biases that occur due to differences in outcome ascertainment between groups[52]). In addition, performance bias (i.e. bias that results from systematically treating patients differently between groups[53]) may also be reduced because the care is not provided in artificial settings, but from unaffiliated healthcare staff. Nonetheless, when using EHRs to examine participant's health outcomes, informed presence bias (i.e. the presence of an EHR chart depends on the health status of the participant, which also affects the outcome[54]) must be taken into account to avoid making spurious associations.

Furthermore, allocation bias (i.e. the presence of systematic differences in how participants are assigned to treatment arms[55]) could be minimized as the randomization sequence and the allocation of participants in the groups can be fully embedded within the RCD-RCT and thus masked. This can easily be implemented in traditional RCTs as well, but history shows that this is often not the case[56,57]. By leveraging the EHR, such process is more likely to occur naturally, through central randomization.

On the other hand, the use of RCD in RCTs can introduce information bias (i.e. a systematic variation in the collection and records of outcomes in a study[58]). If only certain participants have misclassification errors due to data quality issues[59], this could bias the effect estimates. A practical example of this would be a scenario where immunization records are monitored after

a phone reminder intervention is carried out in a health management organization's population. When one of the clinics has a variability in updating the immunization records, we might conclude that the reminder was not effective in improving immunization receipt overall, when it possibly did (depending on whether the "missed" immunizations were more prevalent in the intervention or control arm). In such a case of differential misclassification, the true effect could deviate in either direction of the null[60]. While proper randomization should balance these errors among the groups, the effect estimates could be generally over- or underestimated; as it is discussed for other trial characteristics (such as trials size[61], blinding status[56,62] and publication era[63]).

In terms of external validity, RCD-RCTs are based on RWD, and while this data could have lower quality standards than actively collected data due to less standardization and validation, EHR phenotyping studies are showing promising accuracies[23,64,65]. The term "regulatory-grade RWD"[66] has been emerging as researcher attempt to define standard quality definition and measures in term of RWD, with the intent of using said data to generate RWE that could satisfy regulatory approvals[66,67].

The distinction between explanatory trials, or trials that aim to understand the mechanism of action of an intervention[68,69], and more pragmatic ones becomes important as stakeholders such as patients or investigators reach for more suitable ways to guide health decision making. Pragmatic trials, that aim to guide decisions and typically study an intervention with the least possible disruption to the pre-existing clinical environment[48,69,70], often align well with RCD-RCTs. Nonetheless, the double selection associated with RCD-RCTs could increase selection bias and limit the generalizability of the findings. If, for example, a registry already has inclusion criteria, those might add to the RCT ones, and reduce the representativeness of the trial population. Because RCD-RCTs include only patients with an RCD, a further selection criterion is introduced ("double selection"). This can impact the applicability of findings when patients with available RCD are systematically different to the others of the treatment target population with regards to a characteristic impacting the treatment effect. In practice this could be a scenario where only patients with higher income can afford the insurance that provides the RCD. If the experimental intervention works better in patients who have more resources to be adherent (for example a diet or physical therapy), then a trial filtering patients by RCD-availability may have less generalizable findings than a traditional trial without this additional filter. Finally, many RCD sources depend on the contact of populations with the healthcare

system, potentially resulting in underrepresentation of these populations within such system (rural populations, as well as groups that do not seek medical care).

3.3 Practical Considerations

As discussed in section 3.2, RCD-RCTs have immense potential for augmenting the conduct of randomized experiments and as many limitations. In practice, data availability and formatting issues may lead to barriers in using RCD.

Not all desired outcomes for the trial will be available within the RCD source. Many outcomes relevant to patients and clinicians are collected routinely (i.e. mortality or hospitalizations) and thus researchers could adjust their design by varying the outcome; but this may also be a major limitation of using RCD in more explanatory designs. Furthermore, RCD may lack patient reported outcomes, such as quality of life, which are gaining importance in the clinical research world[71].

Even once the desired endpoints are selected and the data is obtained, the efforts necessary to clean and prepare the data might be extensive. Data cleaning and preparation will be required, and each data source will have its strengths and weaknesses. Administrative databases might have larger amounts of missing data, while EHR data is often chockful of free-text notes that hinder the extraction of valuable information (without natural language processing – NLP). Regardless of the data preparation costs, these are unlikely to be as extensive as actively collecting the data. Nonetheless, there is a lack of cost comparison between the direct costs of collecting outcomes or securing routinely collected ones and including data preparation. While standardization efforts across healthcare stakeholders are essential to improving the quality and interoperability of RCD sources[72] and would reduce the data cleaning and transformation efforts; the current tendency is still the development of siloed health IT systems, effectively creating a barrier in data sharing and repurposing of this data for research[73].

Time-variations in the endpoint retrieval can pose challenges in collecting shorter-term endpoints. For example, if a trial is aiming to assess the effect of an intervention after three weeks, but regular clinical encounters occur at increments of months, this could prove problematic; and even more so when they are irregular[74]. Conversely, RCD can be very useful in collecting longer term endpoints than traditional trials as a designated research infrastructure is not necessary to do so[75]. The choice of follow-up time will have to be weighted in when designing an RCD-RCT based on time lags of the endpoint and clinical significance of the

follow up time. Information in the EHR are updated frequently, sometimes even with changing coding practices (i.e. ICD 9 to ICD 10[28]); thus, an investigator might find certain outcomes one day and different outcomes a short time after[76].

A final consideration in the practical use of RWD for clinical research is the issue of data governance and ethical access to data. Collecting and storing large amounts of sensitive medical data can lead to data breaches or unlawful sharing practices. This leads to many barriers in acquiring and sharing data for research purposes. Balancing patient protection and scientific innovation is a difficult act; but placing health data in the wrong hand can have catastrophic consequences[77]. There are ethical aspects to collecting RCD, and unintended consequences to the patient could occur. If a stakeholder that has a conflict of interest in reviewing patient data, such as a health insurance company which could adapt their premiums based on billing and clinical data, may have indiscriminate access to RCD with potentially unethical implications[77]. As the application of RCD in research will continue to progress, ethical frameworks will likely be developed factoring in patient safety and research innovation.

Overall, the important practical barriers in using RCD at the current time are a lack of interoperability of RCD sources (there are many data silos)[73], the difficulty in extracting the data in a meaningful format[21], and the lack of access to the data in the first place due to ethical or regulatory restrains.

3.4 Reporting

The difficult task of critically appraising medical research is exacerbated by poor reporting. This has been well studied[78,79], and there is no shortage of reporting guidelines for many diverse study types. In the field of clinical trials, the Consolidated Standards of Reporting Trials (CONSORT)[80] statement and checklists are the foundation of reporting standards, and several extensions have been published to better address domain-specific reporting needs (for example cluster trials[81] or multi-arm parallel-group trials[82]).

The RCD domain also carries features that must be reported to interpret the plausibility of the results of RCD-RCTs. This trial design leverages data that can completely impact the relevance of the estimates. Those assessing the evidence generated by an RCD-RCT might wish to know what the source of the data were, how they were collected, by whom, for how long, and whether this was done in a specific population only.

Accurately reporting the inclusion criteria for the RCT participants only, without explaining the additional selection of the RCD source population, for instance, would not permit to replicate the trial results, or an appropriate appreciation of the external validity of said evidence. As an example, if an administrative claims database is used as the source of data in an RCD-RCT that explores an intervention which has shown to work better in persons with higher education and the insured population is prevalently wealthy and/or highly educated, then it might be not appropriate to generalize its findings to low-income or lowly educated populations; here reporting the RCT inclusion criteria alone could have been misleading.

This is true for all of the aforementioned validity elements (section 3.2, including the establishment of cause-and-effect relationship and the generalizability of findings), which cannot be established if a certain level of reporting transparency is not present. While an RCD-specific reporting guideline does not yet exist, an international collaboration (the Consolidated Standards of Reporting Trials (CONSORT) Cohorts and Routinely Collected Data extension working group) in which I am a supporter and member, is currently developing it[83], highlighting its need.

3.5 PhD Aims

The aims of the PhD thesis are:

1. To systematically describe characteristics of RCD-RCTs, and explore the potential and limitations associated with using RCD in clinical trials
2. To assess the current use and costs of RCD-RCTs based on electronic health records
3. To assess the agreement of treatment effect estimates arising from RCT-RCTs and traditional RCTs investigating the same research question
4. To support the development of a reporting guideline (CONSORT-extension) by assessing the current reporting quality and transparency of RCD-RCTs using registries

3.6 Contribution by PhD student

After having collaborated with PD Dr Hemkens and the Basel Institute for Clinical Epidemiology and Biostatistics (CEB) in my master thesis, I was fortunate to have considerable flexibility in designing the PhD topics that we both wanted to explore and that were feasible with the resources and time at our disposal. Throughout my PhD, I was able to perform many of the activities independently, while learning the fundamentals of evidence synthesis, comparative-effectiveness research and clinical trial setup.

To begin with assessing the current use and quality of RCD-RCTs, we first benchmarked the definitions, expected potential and possible limitations associated with using RCD in randomized trials. I developed, based on the knowledge which emerged from my master thesis work (which included a literature review of clinical trials using RCD), an overview of how RCD can be used to inform clinical trials and as a tool for novel research designs. During this phase, I was involved with a clinical trial[84] which used individual patient-based insurance claims data from major Swiss health insurers to supply information on antibiotic prescriptions by physicians. I experienced firsthand the difficulty in coordinating with data managers, statisticians and investigators in obtaining the data we needed, in the correct format, in a timely fashion. But I also learnt the ins and outs of an RCD-RCT and saw first handedly the immense potential that coexist with the barriers. This resulted in my first PhD publication in Trials[35] (section 4.1), and an accompanying blog [85].

The next step in my PhD journey was to assess the current application of RCD in randomized trials by performing a systematic literature review, which we subdivided in two projects. In

addition to performing the title and abstract and full-text assessment, I was responsible for the data extraction, and for adapting the needs of the extractions based on what I was learning form the manuscripts. This flexible approach was necessary due to the novelty of the topic, and I have assessed the full-text of over 600 RCD-related manuscripts during my PhD work. The output of this project was a split publication in CMAJ (section 4.3) and CMAJ Open (section 4.2), the first exploring the implications of these results including cost "perspectives", the latter reporting the results of the literature review.

In parallel we looked at RCD-RCTs in general. We wanted to compare the treatment effects of RCD-RCTs to those of traditional RCTs and performed a meta-epidemiologic analysis. I had to learn the programming language R where the meta-analyses were performed. I obtained additional funding (PPHS top-up fund) so that I could enlist the support of a biostatistician (Soheila Aghlmandi), and her assistance proved invaluable in learning and understanding the analysis codes developed by PD Dr. Hemkens with my support. This meta-epidemiological project led to the manuscript described in section 4.4.

Furthermore, I was part of a group of international researchers developing the Consolidated Standards of Reporting Trials (CONSORT) extension for Trials Using Cohorts and Routinely Collected Data[83]. This final step in my PhD journey was a whirlwind of meeting with researchers from all over the world, Delphi process, and learning key steps behind developing a reporting guideline. In addition to contributing to the entire process, from the literature review, to the stakeholders meeting, to the development of the guideline manuscript, I screened and assessed the publications on trials using RCD identified for the development of the CONSORT extension and was in charge to provide a baseline estimate of the reporting quality before the CONSORT extension is established. This project, ongoing in February 2020, led to several publications (co-author, section 5.1), as well as the manuscripts on reporting quality of RCTs using registry sources (section 4.5).

At CEB I was fortunate to be exposed to a collaborative environment and contributed to several projects unrelated to my PhD. In addition to teaching me how to work with different processes, I learned about different topics such as oncology, reporting quality in surgical trials and causal inference on observational studies. Several of these projects have led to publications that I co-authored (section 7).

In essence, I have contributed to all of the systematic literature reviews, data extraction, manuscript preparation; and was fully involved in the organization and management of my projects' progress and timeliness.

4 First Author Publications

4.1 Manuscript 1

Routinely Collected Data for Randomized Trials: Promises, Barriers, and Implications

Kimberly A. Mc Cord, PhD student[1], Rustam Al-Shahi Salman, Chair of Clinical Neurology[2], Shaun Treweek, Professor of Health Services Research[3], Heidi Gardner, PhD student[3], Daniel Strech, Professor[4], William Whiteley, Senior Research Fellow[2], John P.A. Ioannidis, Professor[5-9], Lars G. Hemkens, Senior Scientist[1]

[1]*Basel Institute for Clinical Epidemiology and Biostatistics (CEB), Department of Clinical Research, University Hospital Basel, University of Basel, 4031 Basel, Switzerland*

[2]*Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, EH16 4SB, UK*

[3]*Health Services Research Unit, University of Aberdeen, Aberdeen, AB25 2ZD, UK*

[4]*Institute for History, Ethics and Philosophy of Medicine, Hannover Medical School, 30625 Hannover, Germany*

[5]*Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA*

[6]*Meta-Research Innovation Center at Stanford (METRICS), Stanford School of Medicine, Palo Alto, CA 94304 USA*

[7]*Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA 94305, USA*

[8]*Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA 94305, USA*

[9]*Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, CA 94305, USA*

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Abstract

BACKGROUND: Routinely collected data (RCD) are increasingly used for randomized controlled trials (RCTs). This can provide three major benefits: increasing value through better feasibility (reducing costs, time and resources), expanding the research agenda (performing trials for research questions otherwise not amenable to trials), and offering novel design and data collection options (for example point of care trials and other designs directly embedded in routine care). However, numerous hurdles and barriers must be considered pertaining to regulatory, ethical and data aspects, and the costs of setting up the RCD infrastructure. Methodological considerations may be different to those in traditional RCTs: RCD are often collected by individuals not involved in the study and who are therefore blinded to the allocation of trial participants. Another consideration is that RCD trials may lead to greater misclassification biases or dilution effects, although these may be offset by randomization and larger sample sizes. Finally, valuable insights into external validity may be provided when using RCD as it allows for pragmatic trials to be performed.

METHODS: Here we collate an overview of the promises, challenges and potential barriers, methodological implications, and research needs.

RESULTS: RCD have substantial potential in improving the conduct and reducing the costs of RCTs but a multidisciplinary approach is essential to address emerging practical barriers and methodological implications.

CONCLUSION: Future research should be directed to such issues and specifically focus on data quality validation, alternate research designs and how they affect outcome assessment, and aspects of reporting and transparency.

KEYWORDS: Routinely collected data, electronic health records, registries, evidence-based medicine, trials, clinical epidemiology.

Background

Routinely collected health data (RCD), such as electronic health records (EHRs), registries or administrative claims data are useful for randomized trials (RCTs), especially those that aim to be pragmatic. Randomized trials embedded in routine data collections might be the next disruptive clinical research technology [1]. However, numerous fundamental questions have recently been raised[1-8]. Here, we will summarize the promise and potential barriers followed by methodological implications, and research needs for the better use of RCD for RCTs, thus collating an overview of the current applicability and promises of routine data in clinical trials.

Potential value of RCD for RCTs

RCTs are often very expensive. Some trials stop early because of failure to recruit, some fail to generate useful evidence for clinical practice, or they do not disseminate their results at all. Various limitations of RCTs are used as arguments to support observational "real world" RCD-studies[9,10]. We argue that some of the limitations of RCTs are better addressed with RCD within a randomized design, avoiding the problems of confounding when assessing treatment effects (Table 1). The use of RCD can replace or supplement some or all procedures of traditional trials, and sometimes a blend of routinely collected and actively collected data may be more feasible and useful. In Figure 1 we illustrate the roles of RCD during the subsequent phases of a trial based on a modified CONSORT (Consolidated Standards Of Reporting Trials)[11] trial flow diagram.

RCDs may make RCTs easier and more feasible, by reducing costs, time and other resources. This might mean larger RCTs for the same cost, or RCTs in research areas where high costs and insufficient funding previously precluded their conduct. Finally, even when cost and resource limitations don't exist, RCD may foster novel research activities, such as the use of registries for rapid, consecutive trial enrollment[3,4].

Value through better feasibility

Effective recruitment is necessary for a successful trial[12]. Targeted screening strategies to identify eligible patients with routine data may lead to more efficient recruitment. They may be used alone but also as a supplement to traditional methods. Researchers can screen electronic databases and contact eligible patients or their healthcare professionals, reducing costs associated with recruitment during the delivery of healthcare, sometimes for hefty fees[13]. Data

mining tools implemented in pre-existing EHR systems can scan patient charts to identify eligible patients automatically; electronic chart alerts can then prompt the physician to suggest participation during a routine clinical encounter, or through contact via a letter[14]. Registries of medical conditions, drug therapy, or devices are especially valuable, particularly when patients with rare diseases or other uncommon characteristics are sought[15]. Registers of individuals interested in research (see for example www.registerforshare.org) that can be linked to EHRs also support pre-trial identification of potentially eligible participants. Even more widely available than registries, health insurance databases provide an extensive sampling frame for patient recruitment, as well as a wealth of outcome data[5].

All or some outcome data could be taken from RCD, reducing the need for cumbersome follow-up visits, bespoke data collection, costly monitoring and audits. Building new infrastructures outside of standard healthcare, training research staff, or purchasing additional equipment are avoided. This may accelerate trial set-up and provide faster results and also reduce trial costs significantly: site-monitoring accounts for 9 to 14% of total trial costs[16]. In addition, administrative burden and staff cost account for 15 to 22% of the traditional total trial expenditures[16]. Most issues detected by monitoring are due to poor source documentation[17] (i.e. a data point is not inserted in the trial master file, or a consent form isn't properly filled).

Value through expanded research agenda

Research questions otherwise not amenable to trials (e.g. in rare diseases) might be answerable with RCD. For example, local and national registers of people with myotonic dystrophy played an important role in the successful recruitment strategy of the OPTIMISTIC trial[18].

Using RCD may help to address some traditional imbalances in the evidence landscape and reduce traditional research agenda biases. Treatments that are typically not championed by commercial interests, e.g. exercise or physical therapy, speech therapy, psychotherapy or surgeries, are less supported by randomized evidence than drugs or devices. Any cost reduction could facilitate trials for interventions that typically strongly depend on public funding structures and non-commercial research support. By saving resources elsewhere, RCD-based trial research may broaden therapeutic options or even reveal better treatments.

For drug therapies, use of RCD may allow independent realizations of notoriously lacking head-to-head comparisons and evaluations of "blockbuster drugs" in pragmatic mega trials[19]. Those drugs are used by millions of individuals, but RCT evidence to support them comes only

from several hundred or a few thousands of patients, often without patient-relevant outcomes and with strict eligibility criteria. The possibility of long-term outcome assessments makes RCD an excellent tool for post-marketing surveillance. Public funders may also have more chances to initiate independent research, increasing transparency and potentially directly addressing areas with suspected publication or reporting biases. The conducted RCTs may better reflect the true healthcare needs and avoid "cost and convenience" biases resulting from choosing a research question based on what one can afford.

While many outcomes that are traditionally of interest in clinical research – including biomarkers and patient-reported outcomes – are not included in most RCD sources, RCD typically include outcomes that are not included in many traditional RCTs (return to work, need for home nursing, sick-days, disability, and major events such as cancer diagnoses or accidents). Implementing RCTs at the "point of care", with randomization occurring directly in EHR platforms, might mean RCTs with more generalizable results that assess more patient and clinically relevant outcomes[6,20,21]. They could provide insight in situations where surrogate or combined outcomes are often used for convenience or safety reasons, yet considered subpar[22,23]. RCD-based RCTs often have more patient and clinician-relevant outcomes that can inform comparative effectiveness research and guide clinical decision-making, rather than provide information for mechanistic or proof-of-concept studies[21]. With increasing incorporation of patient reported outcomes and even mechanistic data (e.g. genomics) in EHR in routine care[24], this gap may eventually be removed. Indeed, increasing the research use of RCD may lead to changes to the outcomes collected in routine data, a process that needs to maintain a careful balance between workload and utility.

Value through improved design and data collection options

Instead of inviting a patient for a repeated measurement or calling his/her healthcare provider for their clinical information, the researcher can access the RCD database and extract it autonomously, which will avoid disrupting the usual care environment and without coming to the attention of the patient or care provider, or requiring additional work from either. By reducing the need to affect the flow of routine care and the need to contact patients and care providers, for example by artificial blinding and outcome assessment procedures, observer bias ("Hawthorne effects") is minimized. This may be especially true for behavioural interventions[25].

Administrative databases offer a wider array of variables of interest to use in a RCT, including social factors, unemployment or disability status or healthcare utilization. For example, an insurance claims database could be queried automatically at admission to identify individuals frequently visiting an emergency department to target them for a discharge planning intervention.

Retrospectively linking RCT databases with RCD supports data collection after regulatory approval is given for a drug or device. For example, data from large approval trials could be linked with cancer registries for evaluation of post-approval safety concerns, or very long-term trial outcomes can be collected from registries as was done in the West of Scotland Coronary Prevention Study (WOSCOPS)[26].

Practical barriers of using RCD for RCTs

Greater use of RCD in RCTs is challenging. When using RCD to overcome some of the limitations of traditional RCTs, several additional barriers may occur and can be classified into four principal domains: data, regulatory and ethical aspects, costs, and novelty (Table 2).

Data

Even when the RCD necessary to answer a research question are available, they may be difficult to locate and access. The data owner may not be easy to contact, may not be willing to provide or share the data, or may not be able to provide it in a form that one may need to conduct a RCT, for example, aggregated data may be offered when individual patient data are what is needed.

The datasets may be very large, requiring a substantial IT system, including human resources, hardware and software to sort through and organize the data in such a way that they can then be analyzed. To connect or link a research database with a system that is either continuously collecting the data (such as an EHR) or to another database (such as insurance claims database), requires significant planning and software development.

A few RCD variables and some RCD source types may be more accurate and better validated than others. Each variable for each source has a variability in its accuracy that makes it difficult to make a general accuracy judgement. Hence, different EHRs or registries may have different data quality (quantity of missing data, as well as actual correctness of the data), but the major obstacle remains the variability within the same source[2,7]. However, a validation of the RCD

source by manually checking a sample of the dataset before each trial would become cumbersome and may offset the advantages of RCD use in the first place. Even with randomization, the quality of the data may sometimes still depend on the assigned intervention and thus may be different between the comparison groups.

All in all, each research question or even outcome estimate should be carefully examined paired with the specific RCD source and variables used, to establish whether such elements were appropriate and what confidence can be placed in such outcome assessment. A population registry based on a unique identifier that every individual receives at birth and has been established for many years with considerable resources for quality assurance (as, for example, in Denmark[27]) is likely more accurate than EHRs of a small commercial practice.

Systematic validation standards clearly describing and comparing validity and accuracy of codes and algorithms used for identification of patients, conditions, treatment or outcomes are currently not universally established for RCD.

Regulatory and ethical aspects

Core ethical principles for clinical research include informed consent, independent ethics review, confidentiality, or risk management (e.g. audit, serious adverse events reporting). While the principles themselves remain the same, differences exist in the way in which they can and should be applied in research with RCD. Some ethical issues, such as confidentiality, can become more significant while others such as consent and audit might be simplified. In particular when variations of usual care are explored, privacy-related issues typically dominate ethical assessments. Recent guidelines[28] and reports[29] addressing research with collected and linked health data, highlight the opportunities and challenges of innovative and feasible concepts for consent and further oversight. While some argue that even a “no-consent” model where patients would be unaware of participating in a randomized clinical trial could be in line with ethical principles and current law[30], others advocate for the so-called integrated, verbal-consent models which incorporate a notification of randomization into the usual clinical discussion between physician and patient [8]. While in recent public surveys the majority of the community still preferred written consent prior to participating in pragmatic RCTs[31], most would also accept verbal consent or general notification if written consent would make the research too difficult to carry out [32].

Templates for broad consent texts have already been developed and implemented for research with human bio-specimens and might be applied in a modified and simplified version for research with RCD[33,34]. Consistent with international ethical guidelines, ethics review committees may also waive the requirement for informed consent when research participation involves no more than minimal risk, and requiring informed consent would make the study impracticable.

When using high-dimension datasets, effective anonymization is often quite difficult[35]. With larger sample size, anonymity may be easier to achieve, while more detailed data may allow easier breach. The most appropriate data protection model, therefore, needs to be tailored to the individual RCD project. In general, research staff with access to confidential records must be adequately trained and a liability protection considering patient privacy and potential data breech should be considered.

At a policy level, public and patient involvement builds another cornerstone for long-term public trust in research with RCD especially when such research includes consent waivers or broad consent[29,36]. Public interests, however, not only reflect the protection of privacy but also research with RCD that can improve public health.

Overall, the uses of RCD, in particular their collection, storage and dissemination raises novel ethical considerations which may require further development of regulations to ensure adequate protections but without unduly constraining the potential benefits of greater research use of RCD.

Costs

Setting up infrastructures to implement use of RCD for clinical research may be associated with enormous overhead costs. Specific investments may be needed before starting such research. While the costs related to maintaining the RCD source (e.g. insurance claims databases) may not rely on the researcher, this should be considered in institutions where both clinical practice and research take place, for example university hospitals. It may become common practice to charge for the release of RCD once those would become more widely used. Alternative models involving supported access to RCD are also possible; Scotland's electronic Data Research and Innovation Service (eDRIS) provides access and support and publishes charging structures[37]. Even if data are shared for free, costs are associated with finding the correct data, negotiating its acquisition or access, and transferring or linking such data to the

trial database. Specifically-trained personnel and specific resources may be required to manage and link the data, and to ensure privacy and data protection. Once a trial database is established and linked to the RCD source, maintenance costs may incur. Nonetheless, it may be argued that many of these investments will be offset by later cost savings when using RCD in trials (e.g. by making some monitoring activities obsolete). The real challenge here will arise when costs and savings are borne and won by different organizations.

Novelty

The novelty of using RCD for trials may itself be a barrier. Established structures, for example templates for ethical approval or grant proposals, are often not yet designed to apply to this kind of research.

Guidelines for use and handling of RCD often stem from non-experimental research with other foci. For example, the most widely used reporting guideline for this type of data was developed for observational RCD analyses [The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement][38], but there is no reporting guideline addressing the specific issues of RCD in the context of RCTs. On the other hand, there are initiatives to provide guidance, for example the recently drafted guidance for industry on approval of medical devices by the US FDA[39].

Furthermore, the novelty of the technology itself will require additional training and data science staff necessary to implement RCD-RCTs embedded in routine care. While RCD-RCTs may reduce the costs associated with training research staff for patient recruitment or outcome ascertainment, any savings may be offset by new expenses for training those who generate and collect the RCD so that the data can be used for research and for training researchers to prepare, manage and analyze this data within a clinical trial framework.

Methodological implications

In addition to general barriers of using RCD in clinical trial research, novel methodological problems and potential biases may be introduced. However, use of RCD may also reduce and preemptively avoid some internal validity biases and provide valuable insights into external validity by showing potential differences between included patients and/or non-included yet eligible individuals.

RCD research obviously requires reasonable data quality, but this holds for both randomized and observational research using RCD. Data quality issues, including misclassifications are, however, much less a problem with randomization, as this typically rules out that the explored intervention is related to data quality. This is in sharp contrast to observational studies, where determination of exposures may actually be strongly associated with data quality and increase risks of misclassification and detection biases. However, even in a trial, it may be problematic when the measurement of outcomes is associated with the allocated intervention. Bias might occur for example when one study intervention leads to more contact with health care professionals who collect the routine outcome data in a different way (e.g. by using more sensitive diagnostic procedures, by coding the data differently, or by using different time schedules for examinations). Possible solutions include standardized documentations of core outcomes (for example through a structured assessment of all patients at hospital discharge) and training of healthcare professionals to perform standardized data entering. Efforts of standardization may escalate cost, however, and diminish the advantages related to the ease and low cost of using the routinely collected data.

Not only quality but also timeliness deserves attention because timely assessment of safety issues may be challenging when a specific adverse event data collection mechanism is not in place as in traditional RCTs[7]. Since routine data are typically collected only at the times of clinical encounters, and then RCD need to be processed, registered in the database and accessible to the researcher, there may be substantial delay between occurrence of adverse events and recognition by the researchers. Combining routine data with active collection in a hybrid approach may help, for example by performing telephone checks to randomized patients in order to seek adverse event information[7]. Active collection, however, requires substantial resources.

However, outcome data collection in RCD-RCTs may have advantages as it is often formally blinded as in any traditional trial with blinded end-point assessment. Then, and when outcome data collection is standardized and unrelated to the intervention, any misclassification would be completely at random and only introducing noise and decreasing precision of outcome estimates.

Dilution of effects due to imprecision and misclassification may gain particular importance for non-inferiority questions or evaluation of some adverse events, which may be less adequately addressed with RCD of uncertain data quality. One potential solution is to increase sample size

to account for the increased noise that RCD bring. In principle at least, easy provision of larger sample sizes is one of the key advantages of RCD-RCTs, so making this a routine requirement ought not to be a substantive barrier.

Data completeness of RCD-RCTs is not necessarily a problem, sometimes quite the opposite, with levels of completeness that are rare in traditional trials. For example the TASTE trial[40], embedded within the Swedish Coronary Angiography and Angioplasty Registry, evaluated more 7244 participants with zero patients lost-to-follow up. Internal validity may be compromised when mechanisms leading to losses to follow-up and missing data are not completely at random. RCD may shed light on this because often there are still data collected for those patients even after dropping out. RCD may in fact provide excellent information on whether a treatment is well-tolerated, by whom it is not, as well as to the intervention's side effects or drawbacks. Furthermore, one can examine the outcomes of patients who deviated from the original treatment plan, e.g. patients who discontinued taking the allocated drug and had surgery instead. With an expanded RCD source such as a national EHR system, outcomes can be available even for those patients who were lost to follow-up. However, this is only possible when the RCD data sources are accurate and extensive enough (such as in Sweden[41], or Canada[42]) to track withdrawn patients.

Next steps and research needs

Careful evaluation of data accuracy, including validation and clarification of algorithms appears to be one of the most important issues. Other important questions may be asked. Are outcome estimates different when measured in RCD-RCTs compared to RCTs with traditional active data collection? And if so, are they source-specific or depend on the type of outcome? How can users of trial research determine if the data are sufficiently accurate? A central register listing routine datasets available for trial research, including information on the data quality and validity would be helpful. A general standardization of routine data collection to ensure that it is useful not only for patient care and administration but also for research would be desirable. Employment of electronic algorithms that could be used to automatically perform validation checks (either at the moment of data entry or as random, systematic and regular checks) might also be helpful[7].

Other questions that require exploring relate to patient recruitment and consent. Does pragmatism affect the estimates of treatment effects? Maybe different consent models are

needed? Are Zelen trials done without obtaining consent from each and all participants giving similar results to other trials that require consent from everyone? And how can randomization become a standard usual care procedure despite short appointments and constrained resources in clinical care?

Guidelines for review, conduct, and reporting of trials using RCD may be helpful to develop. Systematic reviewers, health technology assessors but also regulators and other users of this research may need novel tools and some training to assess the quality and risk of bias of such evidence.

Many of these issues will require multidisciplinary research efforts and a large international research initiative on RCD for RCTs. This will allow to exchange, collaborate and learn but would require support by some structured funding and resources. Overall, we need a better understanding of how to make best use of RCD for RCTs.

List of abbreviations

EHR; Electronic health records

IT; Information technology

RCD; Routinely collected data

RCT; Randomized controlled trials

US FDA; Unites States Food and Drug Administration

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Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf. LGH is member of the RECORD initiative which aims to improve reporting of observational studies using routinely collected health data. He has no other relationships or activities that could appear to have influenced the submitted work. All other authors declare no financial relationships with any organization that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work. The Health Services Research Unit, University of Aberdeen, receives core funding from the Chief Scientist Office of the Scottish Government Health Directorates. Rustam Al-Shahi Salman, Shaun Treweek and William Whiteley are Editors within the Trials Journal.

Contributors

KAM wrote the first draft, provided input on the study design and interpeted the underlying literature. RAS provided input on the study design, interpeted the underlying literature, and made revisions on the manuscript. ST provided input on the study design, interpeted the underlying literature, and made revisions on the manuscript. HG provided input on the study design, interpeted the underlying literature, and made revisions on the manuscript. DS provided input on the study design, interpeted the underlying literature, and made revisions on the manuscript. WW provided input on the study design, interpeted the underlying literature, and made revisions on the manuscript. JPAI provided input on the study design, interpeted the underlying literature, and made revisions on the manuscript. LGH conceived the study wrote

the first draft, provided input on the study design and interpeted the underlying literature. All authors read and approved the final version of the paper. LGH is the guarantor.

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Transparency declaration

The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Availability of data and material

No additional data available.

Ethics approval and consent to participate

Not required, this article does not contain any personal medical information about any identifiable living individuals.

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Tables and Figures

Table 1: Common limitations of RCTs and whether they can be amended by RCD

Limitations of RCTs [10]	What using RCD for RCTs can offer	Challenges	Potential of RCD to improve RCTs
Generalizability and real-world relevance	No specific data collection processes (follow-up visits, measurements) outside of routine care, avoiding artificial situations.	Random allocation of interventions may still require some deviation from routine care processes (e.g. obtaining informed consent)	Very high
Costs and resources	No costs to the trial for data collection processes and related activities (study site set-ups, study staff salary, monitoring and auditing activities, training costs)	Potential costs for obtaining the RCD (if the collecting entity doesn't provide it for free, e.g. data brokers) Additional costs for data management, processing, merging, cleaning, etc.	Very high
Specific conditions/ subgroup effects	Larger sample sizes that are less influenced by resource constraints and feasibility issues may provide sufficient power for evaluating subgroups	More opportunities for exploratory analyses with spurious findings	High

Late outcomes	RCD can provide long-term outcomes data without actively following up with patients and often reducing the number of patients lost to follow up	Patients moving away from RCD infrastructure will be lost and may still require active contacting , highly dependent on RCD infrastructure	High
Speed	No cumbersome outcomes ascertainment (follow-up contacts, data recording and collection) and no need for setting up the data collection infrastructure, results can be obtained faster	Management, processing, merging, and "cleaning" of large datasets may be time consuming Reporting of specific adverse events may be delayed	High to moderate
Conflicts of interest/ sponsorship bias	Collection of RCD more objective and less easily manipulated to obtain a desired result	Data may still be analyzed and reported non-objectively as to convey preferred conclusions	Moderate
Understudied health care questions	Providing information of routine care allows to address understudied healthcare questions since more resources are spared or different outcomes are collected	Not all desired endpoints might be available; funding may not be the sole barrier	Moderate
Regulations	Obtaining approval for intervention imposes several bureaucratic loopholes, RCD are already available and might require different ethical clearance	RCD still require approval in terms of data protection and confidentiality	Moderate

Rare or uncommon conditions	Recruiting an appropriate sample size may be hard with rare diseases; larger samples with RCD and easier EHR or registry recruitment can reduce these difficulties	Only possible if RCD resources are extensive, highly dependent on RCD infrastructure	Moderate

Table 2: Barriers in the use of RCD for RCTs and options to improve

General barriers or issues	Pressing questions	Possible solutions, actions and additional comments
Data		
▪ Availability ▪ Management ▪ Linkage ▪ Accuracy ▪ Validity	▪ Is the desired outcome variable or RCD source available? ▪ Will it be possible to achieve the same data quality and accuracy with RCD as in traditional trials? ▪ Is the data linkage and management feasible in institutions with limited IT infrastructures?	▪ A central register of databases available for clinical trial research would be helpful, ideally with details about data quality ▪ Establish core outcomes and structured outcome assessments in routine care ▪ Create RCD trial guidelines and RCD source validation guidelines, to help standardize their use and reduce sources of bias or uncertainty ▪ Increase IT presence (particularly data analysts) to health research teams ▪ The more RCD is sought out and used in research, the greater its availability and differentiation.

Regulatory and ethics		
▪ Collecting and obtaining the data ▪ Using and sharing the data	▪ What type of release must be given by the patients before their data can be collected or shared? ▪ Is it ethical to use routinely collected patient data without asking for their permission, even if their data is anonymized? ▪ Can this data be considered of value and morally be sold? ▪ How are concerns about privacy and informed consent approached (particularly in the context of population-wide trials or Zelen designs)? ▪ Are data safety standards applied to RCD just as strictly as they are to traditional actively collected data? ▪ Who is responsible for the safety of the data?	▪ Ethical guidelines specifically regarding the collection and dissemination of RCD should be developed ▪ Ethics and approval committees should deepen their knowledge of these novel ethical challenges ▪ While personal data is collected daily from many sources (e.g., phone use), collection, storage and dissemination of data related to health requires more definite ethical oversight and greater transparency to the general public ▪ After safety issues are defined, researchers and stakeholders must ensure that data is safely handled, with full transparency of access
Costs		

▪ Obtaining the data ▪ Managing the data	▪ Will data collectors (e.g. health insurers, etc.) share their data? Freely or at a cost? ▪ Is a constant increase in the generation of routine data really reducing the overall trial costs, if the same institution collected the data in the first place? ▪ When is the use of RCD cost-effective?	▪ Financial worth of health data is not defined or explored, empirical data is necessary to determine both the cost of producing and maintaining health data ▪ Health data is already legally sold to many industries and regulations/legislations must catch up to this aspect
Novelty		
▪ Bureaucratic obstacles ▪ Unawareness ▪ Training to generate, collect, prepare, manage and analyze RCD for trials	▪ Will approval committees understand the implications of using RCD sources for clinical trials? ▪ What are the challenges that can be expected bureaucratically since most submission templates do not assume the use of RCD and absence of patient contact? ▪ Are data anonymization techniques clear? ▪ What training is required to qualify individuals who generate, collect, prepare and manage RCD for clinical trial research?	▪ Develop, in collaboration with approval committees, RCD-specific templates and submission forms, especially in such studies where no patient contact is foreseen and therefore speedy approval is desired. ▪ Educate regarding data anonymization and confidentiality risks ▪ Include the concept of using RCD for RCT in clinical research education and teaching ▪ Create and use reporting guidance specifically for RCD-RCTs

4.2 Manuscript 2

Current use and cost of electronic health records for clinical trial research: a meta-epidemiological survey

Kimberly A. Mc Cord MSc[1], Hannah Ewald PhD MPH[1,2], Aviv Ladanie MSc[1,3], Matthias Briel MD MSc [1,4], Benjamin Speich PhD[1], Heiner C. Bucher MD MPH[1], Lars G. Hemkens MD MPH[1], a collaboration of the RCD for RCT-initiative and the MARTA-Group

[1]*Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Switzerland*

[2]*University Medical Library, University of Basel, Basel, Switzerland*

[3]*Swiss Tropical and Public Health Institute, University of Basel, Switzerland*

[4]*Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada*

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Abstract

BACKGROUND: Electronic Health Records (EHRs) may facilitate randomized clinical trials (RCTs), mainly by using pre-existing data infrastructures for recruitment and outcome assessment and potentially saving costs, time, and other resources. We aimed to evaluate the current use and costs of EHRs in RCTs with a focus on recruitment and outcome assessment facilitated by EHRs.

METHODS: We searched PubMed for RCTs published since 2000 that evaluated any medical intervention while utilizing EHRs. We described the use of EHRs and the characteristics of respective RCTs. We asked authors to provide information on costs of RCTs using EHR infrastructures for recruitment or outcome measurement but not exploring EHR technology itself.

RESULTS: We included 189 RCTs. Most were carried out in North America [153 of 189, (81%)] and published recently [median 2012; interquartile range (IQR) 2009 to 2014]. Seventeen RCTs (9%) including a median of 732 patients [IQR 73 to 2513] explored interventions not related to EHRs, but instead used EHRs for recruitment [14 of 17; (82%)] or outcome measurement [15 of 17; (88%)]. Overall, the majority of studies measured the outcome using EHRs [158 of 189; (84%)]. The per-patient costs varied from 44 to 2000 United States Dollars (USD), and total RCT costs from 67’750 to 5’026’000 USD. The other 172 of 189 RCTs evaluated EHR or EHR-modifications as modality of the intervention.

INTERPRETATION: RCTs are frequently and increasingly conducted using EHRs, but mainly as part of the intervention. Some RCTs successfully used EHRs to support recruitment and outcome assessment with possible cost savings once the data infrastructure is established.

Background

Randomized clinical trials (RCTs) are the standard for evaluating benefits and harms of medical treatments. However, they are often time consuming and expensive to conduct and some trials rely on strictly standardized research settings that may limit the generalizability of their results(1). Electronic health records (EHR), or electronic databases containing patient level variables that are gathered during routine medical care (Table 1), provide great potential for implementing large scale and pragmatic trials(2, 3). RCTs could be directly integrated in routine care offering almost perfect generalizability of their results(4). Recently, the Patient-Centered Outcomes Research Institute (PCORI) has awarded 332 million United States Dollars (USD) to 28 pragmatic clinical studies, many of them utilizing EHR infrastructures and many of them integrated in routine care(5).

Great debate of the potential barriers and limitations of EHR use in clinical research persists, and further details on these obstacles have been discussed elsewhere(3, 6). Briefly, the two largest advantages of using routinely collected data (RCD) for clinical trials may be the facilitation of patient recruitment and of outcome assessment. Randomization of treatment may occur directly from the EHR during the patient's visit, maximizing recruitment rates(7). Recruiting patients through the EHR would allow to pre-screen for eligibility before approaching the potential participant and thus allowing to tailor the efforts towards the appropriate sample; furthermore, rapid consecutive enrollment would favor recruitments through automatic screening and selection of participants through the EHR database(8). This could substantially boost trials requiring large sample sizes or slow recruiting trials. Yet, the ability to assess outcomes without having to measure or collect them could be the most appealing resource-sparing advantage of EHRs in RCTs. Even when funds are not at issue, just the decrease in logistical difficulties themselves, particularly in large RCTs, could be worth extracting routinely collected EHR data. Thus, EHR may have an important role in the potential of implementing large scale and pragmatic trials(2, 3). This offers entirely new perspectives on evaluating health care interventions that favor the development of learning healthcare systems(7).

Nonetheless, the cost associated with implementing the EHR/EMR infrastructure in the first place may be substantial(9). While one could argue that using EHRs for research purposes

might lead to more affordable trials, there is no systematic overview of empirical cost estimates per individual trial participant in EHR-supported RCTs.

We conducted a systematic meta-epidemiologic survey of the use of EHRs in RCTs to determine how EHRs are implemented in clinical research settings and to describe specifically how this technology is used to facilitate recruitment and outcome assessment. We aimed to determine their frequency of use and describe possible applications of the EHR technology in current practice, focusing on trials that were supported by the EHR rather than evaluating the EHR itself.

Methods

We included any RCT in humans, addressing any health-related topic, published in English since January 2000, that utilized EHR for any purpose, including the recruitment of participants, intervention delivery, or outcome assessment(10). Focusing on modern technology we did not include older trials. There were no other eligibility criteria.

Definitions for EHR and related data vary(10-12). Our working definitions are shown in Table 5. Briefly, we considered EHRs an archive of health-related data in digital form, collected during routine clinical care for each individual patient, stored and exchanged securely, and accessible by multiple authorized users in a network of care providers(11). The EHR infrastructure used in eligible RCTs must have already existed and data just been obtained through a query of the EHR-database (i.e. no data specifically fabricated for the experiment would be considered routinely collected, for example when the trial was about the novel implementation of an EHR vs. no such implementation). There is no protocol published for this meta-epidemiologic survey.

Literature search

We queried PubMed (last search on 13 September 2017) for English articles, published since 1 January 2000 using keywords such as “electronic health record”, “electronic medical record”, “health information exchange“, “patient health record”, ”e-health” using an established RCT filter(13) (Appendix 1). Our search integrated the search strategy for EHRs provided by the U.S. National Library of Medicine(14), and was developed with the support of an information specialist (HE). Two reviewers (KAM and HE or AL) screened titles and abstracts. We obtained any article deemed pertinent by at least one reviewer as full text. One reviewer (KAM)

evaluated full texts and determined eligibility, another reviewer confirmed all exclusions (LGH).

Data extraction

Eligible RCTs were classified based on the way in which the EHRs were utilized: (a) for patient recruitment in any form, (b) outcome assessment in any form, (c) for the trial intervention itself, or (d) other possible purposes. For patient recruitment, we considered any effort of identifying trial participants based on certain characteristics, which was done through an EHR query, as well as any randomization of consecutive patients done through the EHR. For outcome assessment, we considered any trial in which any of the outcomes was obtained by querying or manually checking the EHR document (thus, where the endpoint was routinely found within the EHR).

We then sub-classified included RCTs into, (1) EHR-supported trials, where the EHR was used as research tool for conducting the trial (e.g. when patients with certain conditions are identified as enhanced recruitment strategy or adverse event outcomes are queried through a hospital) and into, (2) EHR-evaluating trials, in which using an EHR or an EHR-modification was evaluated as part of the randomly allocated intervention (i.e. software alteration or addition, e.g. a randomized implementation of a drug interaction alert system in a hospital's EHR ordering system). Furthermore, we extracted the RCT's research question, other study characteristics (sample size, country of origin, and unit of randomization), and whether the trials included order entry systems (CPOE/CDS, see Table 1), telehealth or personal health records (PHRs).

For EHR-supported trials, we additionally determined the trial settings and more specific EHR utilizations (type of EHR and application in the trial, such as the type of alerts it would display in decision support systems). Furthermore, we extracted whether an advanced algorithm for patient identification/recruitment, or other purpose was developed. We also recorded if the recruitment was done prospectively (e.g. by advertisement and invitation, not through EHR), concurrently (i.e. in the point-of-care setting, through EHR), or retrospectively (i.e. screening a patient list, may be through EHR or not); and whether RCD were the only outcome source or if a hybrid approach was utilized. A hybrid approach could be that (1) some outcomes were based on RCD alone and other outcomes were entirely actively collected or (2) some outcomes were measured based on RCD and this measurement was supplemented by active data

collection (e.g. when reported by patients outside an EHR network), or if a relevant amount (more than 10% of the total RCD source) was manually checked for validation. We specifically recorded the primary outcome of the trial and if it was measured using routinely collected EHR data alone, when it was measured (duration of follow-up), and any information on missing data or loss to follow-up. Furthermore, we extracted, for each trial, whether blinding and allocation concealment measures were performed. We searched the full-texts for keywords, such as "placebo", "blind", "label" and "mask" to identify such statements, and then proceeded with extracting the statement when reported. One reviewer (KM) extracted all data. A second reviewer (LGH or BS) verified the extractions for the EHR-supported trials. Any disagreement was resolved by discussion.

Trial costs

We contacted the authors of included EHR-supported trials, requested cost information through a standardized email and extracted any cost information reported in the publications. We aimed to obtain a cost estimate which would allow comparison with traditional trials. Therefore, we were not interested in costs of EHR-evaluating trials.

We explained to the authors that the costs of the trial could have been divided in three major ways(15): (1) Cost of the project/trial development and preparation (e.g. for insurance, travelling, infrastructure, consulting, sample size calculation, database set up, etc.), (2) Cost of enrollment, treatment and follow up (e.g. per-patient costs, salary costs, patient reimbursement costs, materials and/or drugs costs; etc.) and (3) Cost after last patient out (data cleaning costs, analysis costs, publications costs; etc.).

We aimed for only a raw cost estimate and accepted any information we could. We converted cost values to USD where applicable, based on the exchange rate on 1 November 2017(16). We sent the data presented here to all trial authors for confirmation.

Statistical analysis

Results are reported descriptively using proportions and medians with interquartile ranges if not otherwise stated. Since our study was exploratory, we did not use any statistical tests.

Results

After screening 1680 titles and abstracts, 394 potentially relevant articles were obtained as full texts and 189 EHR-RCTs were eligible (Figure 1).

All RCTs

Of the 189 RCTs, 17 were facilitated by an EHR (EHR-supported trials; 9%) while the majority [172; (91%)] utilized EHRs as modality of intervention (EHR-evaluating).

The vast majority of both EHR-supported and EHR-evaluating trials originated from North America [13 of 17; (76%) and 140 of 172; (81%), respectively] and were published recently [median 2012; (IQR 2009 to 2014)]. EHR-supported trials were cluster-randomized in 3 of 17 of trials (18%), while the EHR-evaluating trials were cluster randomized in 61 of 172 of trials (35%). There were no placebo controlled trials in our sample, and the majority of trials did not report the level of blinding [101 of 189; (53%)]; blinded outcome assessment was the most frequent type of blinding reported (19%), followed by open label (14%), single-blinding (10%) and double-blinding (4%)(Table 3).

RCTs supported by EHRs

The interventions and settings varied among the 17 EHR-supported trials(17-33) (Table 4). Five trials (29%) utilized the EHR of a U.S. Veteran's Affairs or affiliated facility. Most trials evaluated quality improvement interventions which often involved clinician education and feedback initiatives [8 of 17; (47%)], screening programs [4 of 17; (24%)], and collaborative care and disease management interventions integrated in primary care settings [3 of 17; (18%)]. Almost half of the studies took place in primary care clinics [8 of 17; (47%)], in healthcare networks [5 of 17; (29%)] and in hospitals [3 of 17 (18%)]. One trial was performed entirely within a pharmacy EMR (6%).

<u>Facilitated outcome measurement</u>

Of the 17 EHR-supported trials, 15 measured outcomes using the EHR (88%) (Table 3). The EHR-assessed outcomes were typically screening uptake (e.g. women seeking a Pap-test after receiving an automated call from the EHR prompting cervical cancer screening) [6 of 15; (40%)], clinical outcomes [4 of 15; (27%)], drug adherence [2 of 15; (13%)], or guideline concordant care measures [2 of 15; (13%)]. In 7 out of 15 trials (47%) the RCD source was the only source of outcome data in the entire trial, while in the remaining 8 (53%) a hybrid

approach was applied with some outcome data being actively collected. In 4 of these 8 cases(18, 19, 27, 30), the primary outcome was fully extracted from an EHR but additional outcomes were actively collected while in 3 cases(20, 21, 32), the primary outcome was actively collected but additional outcomes were EHR-based. In one case, the primary outcome was collected through the EHR but verified with actively collected data(22). Overall, 12 of 15 of the trials (80%) relied on EHR for the primary outcome assessment. The trial duration was on median 10 months (IQR 5 to 12); 10 of 17 trials (59%) reported the number of missing data or patients lost to follow-up, but none reported on the quality of the data.

Facilitated recruitment

Of the 17 EHR-supported trials, 14 (82%) used the EHR as tool for patient recruitment (Table 3). One(29) of them reported a prospective approach, while the remaining 13 used the EHR retrospectively (i.e. they reported merely using a manual check or simple retrospective query of eligible patients via EHR); additionally, only one(17) reported using a complex querying system (another one(26) appeared to but did not report it specifically). The other 3 of the 17 trials used a (traditional) prospective recruitment approach without EHR (18%).

Costs

We contacted 13 of the 17 corresponding authors from the EHR-supported trials. Emails were undeliverable to 3 addresses, for which we were also unable to find an alternative contact online and we were never able to reach the authors. We obtained information of trial costs for 4 (17, 23, 26, 29) of the 17 trials and, additionally, intervention cost data from one trial(33) (24% response rate).

Cost information came from one Australian (17) and 4 U.S. trials(23, 26, 29, 33) (2 within the Veterans Affairs network(26, 33)). The costs varied from 67’750 USD to 5’026’000 USD for total trial costs (median 86’753 USD) and from 44 USD to 2000 USD for per-patient costs (median 315 USD) (Table 4). Overall trial costs were derived from funding budgets in three cases while one author stated that the overall costs were 2000 USD per patient. In the trial(17) which leveraged the EHR database through automated data extraction, the per-patient costs was 44 USD. In the 2 cases(23, 29) where the extraction of study data from the EHR source was still done manually, the per-patient costs varied from 560 to 2000 USD. We have no information in this regard for one trial(26). The trial which presented only the costs of the intervention (extracting data from EHR to give a feedback to health–care providers) reported

costs of 44 USD per patient when the data was extracted manually and a sensitivity analysis indicated that these costs could decrease to only 9 USD if the data were extracted automatically(33).

RCTs using EHR for intervention

Of the 172 EHR-evaluating trials (references in **Appendix 2**), 143 measured outcomes using the EHR (83%), and 91 (53%) used the EHR as tool for patient recruitment (Table 3). Computerized decision support systems such as CPOE or CDS (definitions in Table 5) were evaluated in 75% (128 of 172) of the trials. Personal health records were evaluated in 15% (26 of 172) of the trials. Telemonitoring tethered vital sign measuring devices connected to the EHR were evaluated in 8% (14 of 172) of the trials and very few [4 of 172; (2%] evaluated electronic patient reported outcomes (Table 2).

Interpretation

The majority of trials using EHR explored the EHR technology itself. However, we identified 17 trials that investigated an EHR-unrelated intervention and were supported by using EHR for patient recruitment or for outcome assessment. Most of them were published recently, indicating a rapid development in this field.

There is, to our knowledge, no similar study describing the current use of EHR in clinical trials. However, the potential of registry-based trials for comparative effectiveness research and the current state of using registries for RCTs, in particular for outcome ascertainment, has been reviewed recently(8, 34). Interestingly, while the settings and implementation were similar to those identified in our sample, registry trials are most frequently performed in Scandinavian countries(34), and EHR trials predominantly in North America. Registry trials also often collect their primary outcome data using routine data (82%), similarly to EHR trials (80%), indicating confidence in the reliability of this data(34). Information about data quality and validity was rarely reported for registry-based trials (11%)(34) as well as in our sample of EHR-supported RCTs (where it was not reported by any of the trials), indicating similar reporting problems as in observational RCD research(35). This may be expected given the current lack of a standardized reporting guideline for RCD-RCTs but also highlights a substantial transparency problem.

The overwhelming majority of trials in our sample were measuring an outcome with EHRs [158 of 189; (84%], including many of the most patient-relevant clinical endpoints, from unscheduled hospitalizations to mortality. But there were also less pragmatic and more exploratory, mechanistic(36, 37) outcomes which help to understand pathophysiological processes (for example one study even utilized EHR-extracted lipid levels during a lipid-lowering agent trial(38)). We also identified the, to our knowledge, first trial that used routinely collected data in a pre-licensing setting in the context of drug approval (the Salford lung study(32)).

The identified EHR-supported trials were quite heterogeneous concerning their targeted populations and outcomes measured, with a few exceptions. For example, over a third of this subsample was comprised of Veteran's Affairs trials, all of which utilized EHR for outcome and patient identification. This is likely due to the fact the VA has had a long established EHR

system, and its widespread network allows for ease in designing and implementing these types of trials.

Another interesting finding that relates to the EHR-evaluating trials in our sample is the high proportion, approximately one third, of trials using cluster-randomization. This indicates that EHR-based trials mostly evaluate interventions not on at the patient-level but more at a system-level, as when aiming to redirect physician behavior, etc. This introduces the risk of contamination between the randomized units (e.g. physicians) and thus requires a cluster design to be implemented.

Other than by its affordability, the great theoretical value of integrating EHR in clinical trials lies in its potential for patient recruitment. For example, D'Avolio et al (Implementation of the Department of Veterans Affairs' first point-of-care clinical trial.) reports on a VA pilot study(39) that in addition to those identified in our sample shows how convenient it can be to identify patients based on specific characteristics (the EHR database is "scanned" and a list of possibly eligible patients results), and even to recruit them, by sending an automatic electronic message to their clinician. Even with a smaller response rate, when the contacted patients are in the order of thousands, this could lead to greater recruitment capacity; which could be of substantial value particularly in those RCTs where difficult recruitment is already suspected during planning. We identified that almost half of the EHR-supported trials that used EHR for recruitment made use of more sophisticated techniques such as the proposed mechanisms of data-mining. While there are trials that recruited patients by screening the EHR without specifying the use of a particular algorithm addition, most EHRs will require some programming to identify specific traits in the system that go beyond the basic EHR abilities (i.e., typing a diabetes ICD-10-CM code in a search window and obtain a list of patients, which can be done manually). More advanced EHR add-ons, which can screen for multiple variables at multiple levels contemporary and continuously (i.e. screening the system every two hours or instantly during care for the whole time of the trial) do require planning and validation. An example of such EHR screening tool is one developed and used in the Bereznicki 2008 trial, where this "data-mining tool" scrutinized the pharmacy EMR based on a specified protocol (history of asthma medication being dispensed more frequently than guideline customs, such as patient refilling its rescue inhaler more often than expected) which flagged patients with poorly controlled asthma. These patients were then contacted, received educational material for self-management, and were prompted to contact their care providers. This example shows

how using an EHR for patient identification and recruitment can be efficiently done yet that it requires significant planning and software development. We provide a general framework with the various potential applications and challenges of using RCD in different trial conduct phases elsewhere(3, 6).

The author-reported costs could support the assumption that using RCD for RCT may promote cost reduction as long as the outcome data source is already established and not a financial responsibility of the research endeavor. In the three trials(17, 26, 33) in which the EHR infrastructure was well established and merely redirected for use in these trials, the costs per patient (median 44 USD) were much lower than often reported costs in traditional trials(40). The costs of the two trials(23, 29) in which the infrastructure was less integrated (such as actively screening the EHR for assessing the clinical endpoint), remained more similar to those of traditional RCTs (median 1280 USD per patient). The recently published overview of registry trials by Li et al. (8) found similar trial cost patterns (i.e. a reduction of costs when the outcome data did not require manual collection but leveraged the registry infrastructure instead).

Limitations

Some limitations of our study merit closer attention. Firstly, we did not aim for a complete sample of all published EHR-based trials and we searched PubMed only, but we aimed for a systematic, comprehensible and reproducible survey of the current literature. We used a highly sensitive search algorithm and implemented specific EHR search filters provided by the U.S. National Library of Medicine. Nonetheless, we assume that we overlooked several pertinent publications that did not indicate in their keywords, title or abstract the application of EHRs. This may have engendered an overrepresentation of EHRs used for interventions in our sample and especially the observed disproportion of EHR-evaluating and EHR-supported trials needs to be interpreted with caution.

Secondly, searching for English articles indexed in PubMed alone may have created regional bias, with a potential overrepresentation of Anglo-American studies. This could explain the high proportion of studies from the USA. Nonetheless, substantial legislative and financial efforts have been placed in North-America, encouraging the acquisition and employment of EHR technology, which may be more likely the reason for this critical imbalance.

Thirdly, the trials were highly diverse showing the various fields of EHR application, but we would need more data to further evaluate individual details and explore, for example, the ethical constraints associated with no-consent point-of-care trials(41, 42).

Fourthly, only one reviewer (KAM) assessed the full-text eligibility and completed the data extraction, which could have introduced some error in the selection of the trials. Nonetheless, we feel that the identified trials still provide an overview of the mode of utilization of EHR trials.

Fifthly, we did not test any hypothesis regarding the effect of using EHR in trials, nor did we assess their impact on endpoint ascertainment. While we extracted a few characteristics that can point to the methodological quality of the study, we did not perform any risk of bias assessments, as we did not evaluate the effect of the EHR trials; but merely offered an observation of their use.

Finally, we obtained only a few rough cost estimates without details, not allowing us to deduce any cost patterns; however, it provides first estimates to shed some light in this area.

Conclusions

We conclude that EHRs are a novel and valuable addition to clinical research. There are numerous examples of how EHR successfully implemented in clinical research settings facilitated recruitment and outcome measurement in randomized trials. They may be associated with lower research costs, overall allowing the conduct of more or larger RCTs. Altogether, these are very promising developments towards more randomized real-world evidence.

Acknowledgments

Data sharing

No additional data available.

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare no financial relationships with any organization that might have an interest in the submitted work in the previous three years.

KAM, MB, HCB and LGH support the RCD for RCT initiative, which aims to explore the use of routinely collected data for clinical trials. KAM, MB, BS and LGH are members of the MARTA-Group, which aims to explore how to Make Randomized Trials more Affordable.

They have no other relationships or activities that could appear to have influenced the submitted work. All other authors declare to have no relationships or activities that could appear to have influenced the submitted work

Contributors

LGH conceived the study. KAM, HE and AL screened titles, abstracts and full-text publications. KAM extracted the data. KAM and LGH analysed the data. All authors interpreted the results. KAM and LGH wrote the first draft and all authors made revisions on the manuscript. All authors read and approved the final version of the paper. KAM and LGH are the guarantors.

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Transparency declaration

The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

Not required, this article does not contain any personal medical information about any identifiable living individuals.

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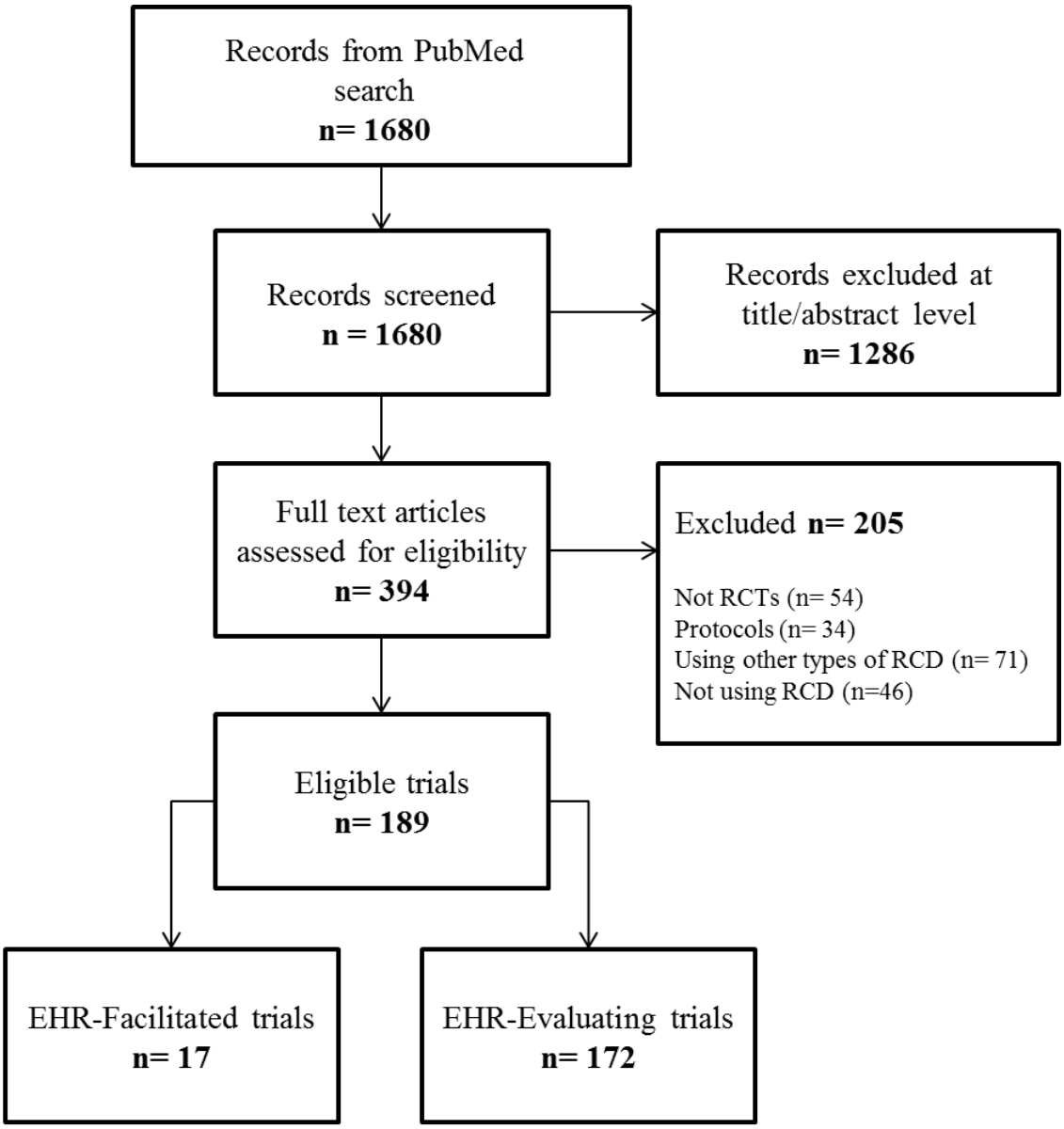
Figures

Figure 1: Flow-chart:



EHR: Electronic health records; RCD: Routinely collected data; RCT: Randomized controlled trial

Tables

Box 2: Definitions, types and applications of Electronic Health Records (EHRs)

EHR type	***Definition***
Electronic Health Record (EHR)	EHRs are electronic platforms that contain health-related data collected during medical care in practices, clinics and other medical settings from various sources, connected to form a network of patient clinical data. EHRs can also incorporate software that allow straightforward physician ordering practice (CPOEs), even including safety features; or that guide them through clinical decision making with up-to-date guidelines (CDS).
Electronic Medical Record (EMR)	EMR are routinely collected data sources that contain standard medical and clinical data gathered during medical care in an individual location of a practice, clinic or other medical setting. When the data is shared among different locations and units it becomes a network and it is considered an EHR (i.e. a primary care practice with electronic chart system that cannot be accessed by any other entity is an EMR, a hospital system where laboratory data, affiliated clinic charts, etc., are all accessed under one platform, is an EHR).
EHR applications	*Definition*
Personal Health Records (PHR)	PHRs are electronic platforms (often online interfaces such as web pages) that securely store patient's health information and allow patients to actively engage in their own health. Often, they can add information to a PHR, can exchange it with health providers, see test results, make appointments, or receive educational information. We consider PHR only those platforms that are tethered to an EHR, where information can be exchanged in both directions (otherwise if the patient is simply adding data but not viewing any of his/her data, we consider it ePRO).
Clinical Decision Support System (CDSS)	A CDSS is an application that supports health providers in performing health care by mining data of an EHR or EMR and providing guideline specific recommendations. CDSS systems can often identify errors or missing data and display alerts or messages through the EHR.
Computerized Physician Order	CPOE systems are electronic ordering technology where physician orders can be entered and processed in a computerized way, often mimicking the workflow found in clinical settings. CPOEs can be more advanced and identify ordering mistakes, display preferred

Entry (CPOE) system	treatments by individual patient EHR query, or even set up blocks with medication interaction orders.
Telehealth	Telehealth is the use of telecommunication technologies (telemonitoring) to improve the provision of care. This allows for care to be provided at a distance and therefore to maintain clinical contact with patients at home without requiring the same amount of resources to be dispensed. Examples of telehealth are blood glucose monitoring machines tethered to an EHR that integrate blood glucose levels taken by the patient at home into the EHR automatically (and can send an alert in the EHR interface to the clinician if the values are out of a predefined range and action must be taken); and increasingly mobile health data collected by wearable devices.
Electronic Patient Reported Outcomes (ePRO)	ePROs are health related information recorded by the patient themselves in electronic form, often through a web page or application. While ePROs have often been utilized in clinical trials, we also consider ePROs any data that have been collected by the patients themselves and tethered to an EHR or PHR. An example would be a patient pain diary, in which a pain score and information are inputted daily on a webpage or via a smartphone app and these data are added to an EHR; where the clinician can monitor it and consult it during a visit.
These definitions are our own working definitions used for this project and have been adapted from HealthIT.gov(10) and CMS.gov(12).	

Table 3: Characteristics of all RCTs using Electronic Health Records

	EHR trials, overall		**EHR-evaluating trials**		**EHR-supported trials**	
	N	%	N	%	N	%
Total	189	(100%)	172	(100%)	17	(100%)
EHR for intervention	172	(91%)	172	(100%)	-	-
▪ Computerized decision or physician order entering system (CPOE/CDS)	128	(68%)	128	(75%)	-	-
▪ Telehealth	14	(7%)	14	(8%)	-	-
▪ Personal health record (PHR)	26	(14%)	26	(15%)	-	-
▪ Electronic patient reported outcomes (ePRO)	4	(2%)	4	(2%)	-	-
EHR for outcome measurement	158	(84%)	143	(83%)	15	(88%)
EHR for patient recruitment	105	(55%)	91	(53%)	14	(82%)
Country						
▪ North America	153	(81%)	140	(81%)	13	(76%)
▪ UK	9	(5%)	7	(4%)	2	(12%)
▪ Continental Europe	15	(8%)	14	(8%)	1	(6%)
▪ Other*	12	(6%)	11	(7%)	1	(6%)
Cluster-RCT	64	(34%)	61	(35%)	3	(18%)
Unit of randomization:						
▪ Clinicians	49	(26%)	46	(27%)	3	(18%)
▪ Patients	76	(40%)	65	(38%)	11	(65%)
▪ Pharmacies	1	(<1%)	1	(<1%)	0	(0%)
▪ Practice/Clinic	54	(28%)	51	(29%)	3	(18%)
▪ Unit/Floor	9	(5%)	9	(5%)	0	(0%)
Publication year	2012 (2009 - 2014)		2012 (2009 - 2014)		2013 (2010 - 2013)	
Sample size:**						
▪ Total	89 (24 -732)		80 (22 - 513)		732 (73-2513)	
▪ Cluster-RCT excluded	239 (57 - 1187)		254 (60 – 1187)		900 (111 - 3075)	
▪ Cluster-RCTs only	24 (12 - 47)		24 (12 - 52)		18 (12-24)	
Blinding:						

▪ Open label	27	(14%)	23	(13%)	4	(24%)
▪ Single blinded	19	(10%)	18	(11%)	1	(6%)
▪ Double blinded	7	(4%)	6	(3%)	1	(6%)
▪ Outcome assessment blinded	35	(19%)	30	(17%)	5	(29%)
▪ Not reported	101	(53%)	95	(55%)	6	(35%)
Placebo use	0	(0%)	0	(0%)	0	(0%)

***Other: includes China, Japan, Taiwan, Iran, India, Pakistan, Lebanon, Australia and Kenya.**
****Data are medians and IQR if not stated otherwise.**
Abbreviations: EHR, Electronic health record; RCT, Randomized clinical trial.

Table 4: Characteristics of EHR-supported trials

Trial Year	Country Sample size	EHR use for Recruitment Type	EHR use for Outcome assessment Extent of RCD use*	Patient population/ Indication	Intervention and Control**	Primary Outcome Follow-up (FU) Missing data	Setting
Bereznicki, Peterson, et al.(17) 2008	Australia 1551 patients	Yes Retrospective	Yes EHR alone	Uncontrolled asthma	Intervention: Contact by community pharmacist, plus educational material and referral to GP for asthma management	Ratio of dispensed preventer and reliever medication FU: 6 months Missing data: NR	Community pharmacy network
Corson, Doak, et al(18) 2011 (SEACAP)	USA 42 care givers randomized (365 patients)	No Prospective	Yes Hybrid; Primary outcome EHR alone	Musculoskeletal pain	Intervention: Patient and clinician education, symptom monitoring and feedback to clinicians	Guideline–concordant care FU: 12 months Missing data: NR	Primary care clinics associated with VA medical center and a urban hospital
de Jong, Visser, et al(19) 2013	Netherlands 73 general practitioner trainees randomized (No. of patients not reported)	Yes Retrospective	Yes Hybrid; Primary outcome EHR alone	Skin and psychosocial conditions	Steering patient mix of general practitioner trainees	Trainees exposure to specific field (patient mix); knowledge and self-efficacy FU: 6 months Missing data: 5%-10%	Practice network with GP training program
Fu, van Ryn, et al.(20) 2014	USA 6400 patients	Yes Retrospective	Yes Hybrid; Primary outcome active data collection alone	Current smokers	Proactive outreach plus choice of smoking cessation services	6-month prolonged smoking, abstinence at 1 year FU: 12 months Missing data: 48.3% (but 0% for EHR outcome)	Veteran's Affair medical center

Galbreath, Krasuski, et al.(21) 2004	USA 1069 patients	Yes Retrospective	Yes Hybrid; Primary outcome active data collection alone	Symptomatic congestive heart failure	Congestive heart failure management program (plus at-home scale)	All-cause mortality and healthcare utilization FU: NR, time to event Missing data: NR	Various healthcare networks and Medicare/-aid participants
Gerber, Prasad, et al.(22) 2013	USA 18 practices, 170 caregivers randomized (185212 patients)	Yes Retrospective	Yes Hybrid; Primary outcome hybrid	Clinical practice groups with primary care pediatricians (Children with acute respiratory tract infections)	Antibiotic stewardship program	Change in broad spectrum antibiotics prescribed for bacterial infections or change in antibiotic prescribed for viral infections FU: 12 months Missing data: 5% of caregivers	Pediatric primary care network
Green, Wang, et al.(23) 2013	USA 4675 patients	Yes Retrospective	Yes EHR alone	Prevention of colorectal cancer	Automated Interventions, vs Assisted care vs Navigated care, vs Usual care	Receiving any colorectal cancer test and being current for colorectal cancer testing in years 1 and 2. FU: 24 months Missing data: 0.2%	Primary care practice network
Hoffman, Steel, et al.(24) 2010	USA 404 patients	Yes Retrospective	No Active data collection alone	Prevention of colorectal cancer	Fecal Immunochemical test (vs Guaiac-based occult blood test)	Screening adherence FU: 3 months Missing data: NR	VA network (primary care clinics and laboratory)
Israel, Farley, et al.(25) 2013	USA 732 patients	Yes Retrospective	No Active data collection alone	Inpatient adults with at least one of several cardiovascular disease diagnoses in EHR	Minimal intervention (medication reconciliation) or enhanced intervention (minimal intervention plus pharmacist) follow-up usual care	Rate of underutilization of cardiovascular drugs FU: 3 months Missing data: NR	University hospital (orthopedic, internal medicine, family medicine and cardiology wards)

McCarren, Furmaga, et al.(26) 2013	USA 12 practices randomized (220 patients)	Yes Retrospective	Yes EHR alone	Heart failure and guideline nonconcordant beta-blocker prescription	Information to pharmacy about prescription non-concordance	Guideline concordant prescriptions FU: 6 months Missing data: 0%	VHA facilities and pharmacies
Phillips, Rothstein, et al.(28) 2011	USA 3895 patients	Yes Retrospective	Yes EHR alone	Prevention of breast cancer	Quality improvement patient navigation	Adherence to biennial mammography FU: 9 months Missing data: NR	Hospital-based internal medicine practices
Piazza, Anderson, et al.(29) 2013	USA 2513 patients	Yes Retrospective	Yes EHR alone	Hospitalized medical service's patients at risk for venous thromboembolism and planned discharge within 48 hours	Alert for physician	Symptomatic deep vein thrombosis or pulmonary embolism FU: 3 months Missing data: <0.1%	Inpatient medical unit
Qureshi, Armstrong, et al.(30) 2012	UK 24 caregivers randomized (748 patients)	No Prospective	Yes Hybrid; Primary outcome EHR alone	Adult primary care patients no previously diagnosed cardiovascular risk	Family history questionnaire (in addition to Framingham risk score)	Proportion of identified participants with high cardiovascular risk scores FU: NA Missing data: 1.7%	Family practices in research network
Skinner, Halm, et al.(31) 2015	USA 1032 patients	Yes Retrospective	Yes EHR alone	Prevention of colorectal cancer	Tablet-based Cancer Risk Intake System (CRIS) assessment prior to an appointment (tailored and non-tailored) and control group	Received risk-appropriate colorectal cancer testing and any type of colorectal cancer testing FU: 12 months Missing data: 0%	Family practices affiliated with a university medical center
Stewart, Perkins, et al.(27) 2014	USA 235 patients	Yes Retrospective	Yes Hybrid; Primary outcome EHR alone	Dysthymia or major depressive disorder	Collaborative care program with psychotherapy and antidepressant drugs	Cardiovascular events FU: 96 months (8 years) Missing data: 0%	Academic group practice

Vestbo, et al.(32) 2016 (Salford Lung Study)	UK 2802 patients	No Prospective	Yes Hybrid; Primary outcome active data collection alone	COPD and regular maintenance inhaler therapy	Once a day inhaled fluticasone furoate 100 µg and vilanterol 25 µg	Moderate or severe COPD exacerbations FU: 12 months Missing data: 24.8%	Healthcare network in (and around) Salford, hospitals, GPs, pharmacies
Wolf, Fitzner, et al.(33) 2005	USA 113 health-care provider (randomized) 1290 patients	Yes Retrospective	Yes EHR alone	Prevention of colorectal cancer	Education session plus performance feedback	Completion of colorectal cancer screening FU: NA Missing data: NR	VA primary care clinics

*The extent of RCD use can be: EHR alone (all of the RCT's outcomes are routinely collected), Hybrid (either the primary outcome or other outcomes are entirely routinely collected and some outcome in the RCT is also entirely actively collected, or some outcomes are routinely collected and supplemented by active data collections) and Active data collection alone (all of the outcomes are actively collected, no RCD).

**All comparisons are "usual care" unless otherwise specified.

[1]University of Texas Health Science Center at San Antonio, in partnership with Wilford Hall Medical Center, Brooke Army Medical Center, South Texas Veterans Health Care System, TRICARE Region 6, and University Health System.

Abbreviations: COPD, chronic obstructive pulmonary disease; EHR, electronic health record; EMR, electronic medical record; GP, general practitioner; QOL, quality of life; RMDQ, Roland Morris Disability Questionnaire; VA, Veterans Affairs; VHA, Veterans Health Administration.

Table 4: Costs of EHR-supported trials

EHR trial Author, Year	EHR use for	EHR source pre-existing	Intervention integrated during routine care (no additional staff needed)	Total trial cost in US$	N patients	Per patient cost in US$
Automatic data extraction from EHR source						
Bereznicki, Peterson, et al. 2008	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	Yes	67750[1]	1551	44
Manual data extraction from EHR source						
Green, Wang, et al. 2013	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	No	2800000[2]	5000	560
Piazza, Anderson, et al. 2013	Recruitment (retrospective) Outcome assessment (all with EHR alone)	unclear	No	5026000[3]	2513	2‘000
Wolf, Fitzner, et al. 2005	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	Yes	86753[4]	1978	44
Unclear if data extraction from EHR source was automatic or manual						
McCarren, Furmaga, et al. 2013	Recruitment (retrospective) Outcome assessment (all with EHR alone)	Yes	Yes	69300[5]	220	315

[1]Total received funding; including USD 42157 for staff costs for the duration of the project, USD 6132 for a consultant programmer (for software development), USD 15330 for pharmacy payments and USD 6132 for non-salary costs such as printing, postage, travel, and others.
[2]Total received funding.
[3]The study costs were USD 2000 per patient and included costs of the trial startup and close out.
[4]Total cost of the colorectal cancer screening promotional effort (intervention only).
[5]Total received funding. “Most of the [working] time was donated”

Appendices

Appendix 1: Search strategy

Search	Query
#12	(#11 AND #10)
#11	((health information exchange [tw] OR hie [tw] OR rhio [tw] OR regional health information organization [tw] OR hl7 [tw] OR health level seven [tw] OR unified medical language system [majr] OR umls [tw] OR loinc [tw] OR rxnorm [tw] OR snomed [tw] OR icd9 cm [ti] OR icd 9 cm [ti] OR icd10 [ti] OR icd 10 [ti] OR metathesaurus [tw] OR patient card [tw] OR patient cards [tw] OR health card [tw] OR health cards [tw] OR electronic health data [tw] OR personal health data [tw] OR personal health record [tw] OR personal health records [tw] OR Health Records, Personal [Majr] OR Health Record, Personal [Majr] OR ehealth [tw] OR e-health [tw] OR medical informatics application [mh] OR medical informatics applications [mh] OR medical records system, computerized [mh] OR medical records systems, computerized [mh] OR computerized patient medical records [tw] OR automated medical record system [tw] OR automated medical record systems [tw] OR automated medical records system [tw] OR automated medical records systems [tw] OR computerized medical record [tw] OR computerized medical records [tw] OR computerized patient records [tw] OR computerized patient record [tw] OR computerized patient medical record [tw] OR electronic health record [tw] OR electronic health records [tw] OR Electronic Health Record [Majr] OR Electronic Health Records [Majr] OR electronic patient record [tw] OR electronic patient records [tw] OR electronic medical record [tw] OR electronic medical records [tw] OR electronic healthcare records [tw] OR electronic healthcare record [tw] OR electronic health care record [tw] OR electronic health care records [tw] OR archives [majr] OR ehr [tw] OR ehrs [tw] OR phr [tw] OR phrs [tw] OR emr [tw] OR emr[tw] OR Health Information Systems [Majr]) AND (medical record [ti] OR medical records [mh] OR medical records [ti] OR patient record [ti] OR patient records [ti] OR patient health record [ti] OR patient health records [ti] OR patient identification system [mh] OR patient identification systems [mh] OR Patient Outcome Assessment[Majr] OR Patient Discharge Summaries[Majr] OR healthcare record [ti] OR healthcare records [ti] OR health care record [ti] OR health care records [ti] OR health record [ti] OR health records [ti] OR hospital information system [tw] OR hospital information systems [tw] OR umae [ti] OR attitude to computers [mh] OR medical informatics [ti])) OR ((medical records systems, computerized [majr] OR medical records systems, computerized [mh] OR computerized patient medical record [tw] OR computerized patient medical records [tw] OR automated medical record system [tw] OR automated medical record systems [tw] OR automated medical records system [tw] OR automated medical records systems [tw] OR computerized medical record [tw] OR computerized medical records [tw] OR computerized patient records [tw] OR computerized patient record [tw] OR electronic health record [tw] OR electronic health records [tw] OR electronic patient record [tw] OR electronic patient records [tw] OR electronic medical record [tw] OR electronic medical records [tw] OR electronic healthcare records [tw] OR electronic healthcare record [tw] OR electronic health care record [tw] OR electronic health care records [tw] OR unified medical language system [majr] OR unified medical language system [tw] OR umls [tw] OR loinc [tw] OR rxnorm [tw] OR snomed [tw] OR icd9 cm [ti] OR icd 9 cm [ti] OR icd10 [ti] OR icd 10 [ti] OR Metathesaurus [tw] OR ehr [tw] OR ehrs [tw] OR phr [tw] OR phrs [tw] OR emr [tw] OR emrs [tw] OR meaningful use [tiab] OR meaningful use [tw]OR Meaningful Use [Majr]) AND (j ahima [ta] OR j am med inform assoc [ta] OR amia annu symp proc [ta] OR health data manag [ta] OR int j med inform [ta] OR yearb med inform [ta] OR telemed j e health [ta] OR stud health technol inform [ta]))
#10	(#8 NOT #9)
#9	(((animals [mh] NOT humans [mh])))
#8	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7))
#7	trial [ti]

#6	randomly [tiab]
#5	clinical trials as topic [mesh: noexp]
#4	placebo [tiab]
#3	randomized [tiab]
#2	controlled clinical trial [pt]
#1	randomized controlled trial [pt]

Interface: PubMed; Filters: English and date from 2000/01/01

Date of last search: 13 September 2017

Appendix 2: References of all included EHR-Evaluating RCTs

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4.3 Manuscript 3

Using Electronic Health Records for clinical trials: Where do we stand and where can we go?

Kimberly A. Mc Cord MSc[1], Lars G. Hemkens MD MPH[1]

[1]*Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Switzerland*

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Key points:

1) Randomized clinical trials using Electronic Health Records can be directly integrated in routine care and allow large scale and pragmatic trials with almost perfect generalizability
2) Currently, Electronic Health Records are mostly used in randomized trials as part of the intervention, for example, when decision support systems are evaluated as modifications or additions within the EHR infrastructure.
3) Increasingly, EHR infrastructure is leveraged for patient recruitment or outcome assessment to support trials that assess conventional interventions
4) RCTs within EHRs may address the limitations of traditional RCTs by increasing generalizability, reducing costs and time, expanding the research fields and allowing a democratization of research agendas
5) The challenges may not be underestimated and include infrastructure costs, interoperability, standardization and quality of data as well as ethical, privacy and data security considerations

Introduction

Increasing interest in use of routinely collected data for research has been paralleled by a rising interest in using Electronic Health Record (EHR) data for health research, as such records have become more widely used in clinical practice (1). In Canada, adoption of EHRs has been patchy, hampered by fragmentation of the healthcare system, , variable funding streams and different priorities of individual provinces and territories. (2) However, both government, by supporting the Canada Health Infoway, and non-governmental organizations, such as the Canadian Medical Association and Canadian Pharmacists Association, have identified national adoption and interoperability of EHRs as a priority (2).

A national EHR infrastructure could revolutionize health research in Canada if EHRs were used to facilitate large-scale randomized studies. Traditional randomized clinical trials (RCTs) are costly and their strict inclusion and exclusion criteria and standardized settings often mean that study findings are not generalizable to all populations (3). However, randomization within EHRs could allow large-scale pragmatic RCTs to be conducted within the routine care setting, offering almost perfect generalizability of their findings (1, 4-7). Such an approach would transform the evaluation of health care interventions, allowing continuous learning from series of systematic evaluations of aggregated and shared information continuously fed back into the original systems (the "learning healthcare system") and allowing agile improvements in clinical care, service delivery and the health system (8).

We outline the potential benefits and difficulties of conducting RCTs using EHRs, drawing on a systematic evaluation of existing trials (7).

How are EHRs currently used in clinical research?

We recently evaluated systematically the current use of EHRs for RCTs(7) (see box 1).

We distinguish two general types of EHR-based RCTs. Firstly, conventional trials, in which patients are recruited and/or outcomes are collected via EHRs (EHR-supported trials), or secondly, EHR-evaluating trials that depend on the EHRs to actually deliver the intervention. While most RCTs currently evaluate the EHR technology itself (for example by testing if adding an alert to a prescription software would reduce the rates of prescription mistakes), some RCTs have successfully used EHRs as supportive tool to facilitate recruitment and

assessment of outcomes while testing an intervention not related to the HER technology itself (for example by assessing rates of cardiovascular events(9)).

Most EHR-trials are currently performed in North America where the uptake of EHRs has been promoted heavily by many stakeholders, and large health management organizations (such as Kaiser Permanente in the USA) have been developing their EHR infrastructures for several years (10).

How can a RCT be conducted within the EHR?

EHR-evaluating trials frequently aim to improve care by directing physicians through clinical decision support (CDS) and computerized physician order entry (CPOE) systems interventions (definitions in Table 1). This is done by identifying at-risk patients and flagging them, by monitoring the ordering system and submitting alerts in case of discrepancies, by displaying guidelines and advices into the EHRs, or by health care performance auditing and feedback. Overall, these trials mostly evaluate system-level as opposed to patient-level interventions, for example by leveraging PHRs, telehealth or ePROs (Table 1). This may require additional software development and hardware that may in turn increase logistical difficulties and costs, particularly in telehealth trials.

EHR-supported trials, on the other hand, can be conducted in widespread EHRs networks, such as the Veteran's Affairs health system (11). Using EHRs for recruitment, typically with a retrospective procedure of simple backward querying of the EHR database, can help to obtain a list of possibly eligible patients(4). Some trials promote concurrent recruitment by sending an electronic message to the clinician or an automatically generated letter to the patient directly(12), while others(13) use a more sophisticated data-mining approach to scrutinize the pharmacy EMR to flag particular patients, e.g., those with poorly controlled asthma (Box 2).

How can RCTs conducted within EHRs help to address the limitations of traditional RCTs?

<u>Costs</u>

RCTs are often expensive to conduct, but this not actually due to their nature or study design. A recent evaluation of trial costs suggested that it is possible to conduct trials at low cost with high impact on patient care using smart designs and framing clear and simple research questions(14). The high burden of tasks involved in the development and maintenance of data

collection is a main cost driver of trial costs and setting up a specific data collection infrastructure can be difficult in many medical settings. Innovative use of EHRs can reduce the costs associated with data collection in trials. We found a trend of substantial cost conservation by using fully automated EHR-driven data (7). For example, the per-patient costs reported in a trial using fully automated EHR infrastructure was 44 USD(13), compared to 2'000 USD per participant in a less well automated one(15). We provide more information on costs, including more reasons for such cost-spreads, elsewhere(7).

Time

Even when funds are not at issue, just the decrease in logistical difficulties themselves, particularly in large RCTs, could be worth extracting routinely collected EHR data. Trials could be set-up earlier and results obtained much faster. Ideally, results could be collected in real-time, possibly even days after the implementation of changes first results could be obtained. For example, the impact of certain control measures in infectious disease outbreaks could be directly assessed by using information centrally collected by EHRs.

Recruitment

One of the largest advantages of using EHRs for clinical trials may be their facilitation of patient recruitment and of outcome assessment. Randomization can occur directly from the EHR during a patient's visit, minimizing any disruption of the flow of clinical care (16) (Figure 1). Recruiting patients through the EHR allows pre-screening for eligibility before approaching any potential participant, thus reducing effort required to enrrol an appropriate patient sample. Rapid consecutive enrollment could favor recruitment through automatic screening *and* selection of participants within the EHR database(4, 16) (Figure 1), which could boost and speed up recruitment in trials requiring large sample sizes. Poor recruitment is the most frequent reason for trials to be discontinued before reaching the required sample size and overestimating the prevalence of eligible patients is the most frequently reported reason for recruitment failure (17, 18); such trials waste many resources. Using EHRs to predict recruitment rates and as a recruiting framework is an innovation that may lead to enormous cost savings in research.

Outcomes

The ability to assess outcomes without having to measure or collect them in a dedicated data collection system is another appealing advantage of using EHR data for RCTs. A frequently

raised argument against clinical trials is that it would require too much time and too many patients to measure patient-relevant outcomes such as clinical events or death. However, outcomes such as stroke, myocardial infarction, hospitalizations or serious side effects are typically recorded in EHRs and therefore the data are readily available. Evaluation of outcomes that are most relevant to decision-making in clinical care may also be encouraged when EHRs are used for large pragmatic trials. Trials that are more mechanistic in design, i.e. those aiming to better understand biological pathways and treatment mechanisms, could also benefit from using EHRs that include real-time information from wireless devices and monitoring systems, such as body weight, temperature, blood pressure or other vital parameters.

Expanding the scope of research and democratizing research agendas

Another advantage of using EHRs for prospective clinical research is that they offer a wide palette of options to answer research questions. For example, patient involvement may be expanded, evaluated and optimized by using personal health records (PHRs) i.e., records that allow patients to receive important health information, to access their clinical data, and to monitor progression of their health (19). It is now possible to connect tele-medical apparatuses, such as blood glucose monitoring devices, via wireless data transmission to EHR systems, sending clinical parameters directly to the patient charts, and allowing for remote monitoring of the patient clinical status(20). This information could be used for novel care models, which can be directly evaluated and optimized, truly as system learning from innovation and evaluation. Furthermore, the ranges of interventions that can be assessed through EHRs are unprecedented. EHRs allow to add-on interventions or software directly in the workflow of the clinical team, enabling clinicians to become the research team. EHRs open the doors to point-of-care trials(16, 21), or trials embedded in the clinical care, where patients are automatically assessed for eligibility, included and randomized directly at the clinician's side. EHR-based trials also lend themselves to the evaluation of non-drug treatments and interventions for which there is little evidence. For example, in the areas of speech therapy or physical therapy, patients could be assigned to different therapy regimens vs. standard regimens and evaluation of effectiveness and even cost-effectiveness conducted using outcome data from the EHR.

What are the limitations of carrying out RCTs within the EHR?

Infrastructure costs

Initial investments associated with implementing an EHR infrastructure that can facilitate research may be substantial(22). While research stakeholders may save resources in the longer term, healthcare institutions may balk at the high cost of setting up and maintaining the infrastructure.

Interoperability

The technological potential of EHRs has developed more quickly than healthcare systems have been able to adapt and implement them, which has created an often fractured and unequal distribution of technologies across different jurisdictions, health care systems, or facilities. A frequent limitation is the lack of interoperability of the EHRs systems(23). While two hospitals may well be routinely collecting useful clinical data using an EHR, it may be difficult to link two different systems to facilitate data collection and analysis in multicenter and international trials. With increasing uptake of EHRs, greater efforts will be needed to increase and promote their interoperability. EHR-developers and researchers would also need to come together and converge their interest(23). Nonetheless, even with perfect interoperability, EHRs do not often contain the complete medical history and health picture of patients, and trials using EHRs might require either a combination of data sources or a supplementation with active data collection(24).

Standardization and data quality

Probably the largest limitation of using EHR data for research is that collection of data that is not primarily intended for research purposes naturally leads to problems of poor standardization both in the type of data collected and in the quality of data collection(25). When clinical staff enter information in electronic charts they often use free-text boxes; these data are typically not easily linked to electronic case report forms or trial databases. Text recognition, advanced algorithms and machine learning could help with data extraction and artificial intelligence may help to streamline information (26). However , the completeness and granularity of the data may be compromised(27). Sometimes, clinical notes and discharge letters include context-related and “between-the-lines” information which may be difficult to capture automatically. As data collection for EHRs will always be oriented towards the individual patient, its format and intervals might never match those expected by clinical trials protocol; this requires that triallists give careful thought to their research question and potential adaptation of the design of their study(24).

Different EHRs systems, different staff members and different settings will likely all influence the detail and accuracy of data available for study. It is important that this is carefully considered and evaluated during the trial setup. Ideally, the accuracy of each data item, possible biases and misclassification risks are well described and quantified. Healthcare providers may need to be educated to understand the importance of proper documentation for the patient's wellbeing, particularly for important patient-relevant clinical outcomes. As the clinical workforce becomes more accustomed to using EHRs, it is reasonable to anticipate that the quality of EHR data available to researchers may improve. A continuous exchange between researchers and information technology specialists will likely be required, to align the data format needs of researchers with the technical data processing options and possibilities. In any case, the need for accurate data in randomized trials using EHRs is lower than in non-randomized studies, which must measure much more information on potential confounders to ensure sufficient statistical adjustment.

Privacy, data security and ethical considerations

Finally, there is a need to consider the complex and multifaceted ethical and privacy issues related to using EHR data for research. Different consent systems may be necessary, for example consent that is given for the data use and sharing on one hand (e.g. as in a cancer registry), and for the implementation of interventions on the other hand. Obtaining informed consent for automated trials conducted within the EHR may be difficult(4). It remains to be discussed whether informed consent needs to be acquired when only variations of usual care are explored (7). A disconnect exists between modern trials using EHRs and structures created for traditional RCTs (for example requirements of institutional review boards); however, with more examples of such trials being performed it is likely that processes will alter and align. Further research and constructive dialogues among all stakeholders on this issue are urgently needed.

Data security remains paramount (30, 31). Healthcare organizations are often caught between the desire to share EHR data for research advancement and risk of data breaches in doing so. Introduction of innovative technologies in healthcare networks, such as big data analytics (with accompanying loss of anonymization(32)) or blockchain databases (with a potential increase in data safety as well as immutable audit trail(33)), will influence discussions on privacy and confidentiality of patient data.

Conclusion

EHRs have enormous potential to increase and to change the capacity of clinical health research by facilitating RCTs in the real world setting. Many RCTs have successfully evaluated within-EHR interventions, recruited patients, or assessed clinical endpoints with minimal patient contact. EHR uptake is likely to increase in all healthcare settings, which will increase the amount of data available research. Nonetheless, various stakeholders will need to be involved in ensuring that EHR implementation suit both the clinical workflow and clinical research requirements. We need EHR- systems that ensure interoperability, provide standardized and high-quality data and carefully address privacy and data security issues.

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Data sharing

No additional data available.

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare no financial relationships with any organization that might have an interest in the submitted work in the previous three years.

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Transparency declaration

The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

Not required, this article does not contain any personal medical information about any identifiable living individuals.

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Tables, boxes and figures

Box 1: The use of EHRs in randomized clinical trials published since 2000(7)

- 91% of randomized clinical trials using EHRs evaluated the merits of EHRs-based interventions such as alerts or other clinical decision support systems
- There are some examples of RCTs supported by using EHRs for patient recruitment and outcome assessment alone
- The vast majority originated from North America (USA and Canada)
- Most trials were published recently (median publication year 2012)
- Trials supported by EHRs costed between 44 USD to 2000 USD per patient.

Box 2: Examples of two EHRs-based RCTs

Salford lung study(34)	**Bereznicki 2008 (13)**
• GlaxoSmithKline pre-approval trial in 2802 patients conducted in UK between 2014 and 2016 • Patients with asthma or COPD were recruited in GP practices and asked if they would agree to be randomized to Relvar Ellipta (combination inhaler for asthma and COPD) or to usual care • Most outcome data was routinely collected from EHRs over 12 months • Overall, 80+ general practitioner sites, 130+ community pharmacies	• 1551 patients included between 2006 and 2007 to explore the impact of a data-mining application of medication records to improve asthma management • Pharmacy EHRs queried for patients non-compliant with asthma medication • Pharmacist collaborated with clinician to improve medication adherence • 35 pharmacies participated

Box 3: Examples of two EHR-evaluating RCTs from Canada

Tamblyn 2015(35)	**Price 2017(36)**
• Study performed in the Quebec region on 81 primary care physicians and 4447 patients • Physicians received access to an asthma decision support system, which identified patients with poorly controlled asthma and displayed evidence-based management advice • After 3-33 months, the patient's asthma medication use was monitored in the EHR	• Study performed in British Columbia on the EHR of 28 physicians and 23976 elderly patients • Development of 40 prescribing rules in EHR, aiming to reduce potentially inappropriate prescriptions (PIP) • After 16 weeks, the PIP rates were assessed, as well as a physician's experiences (mixed-methods approach)

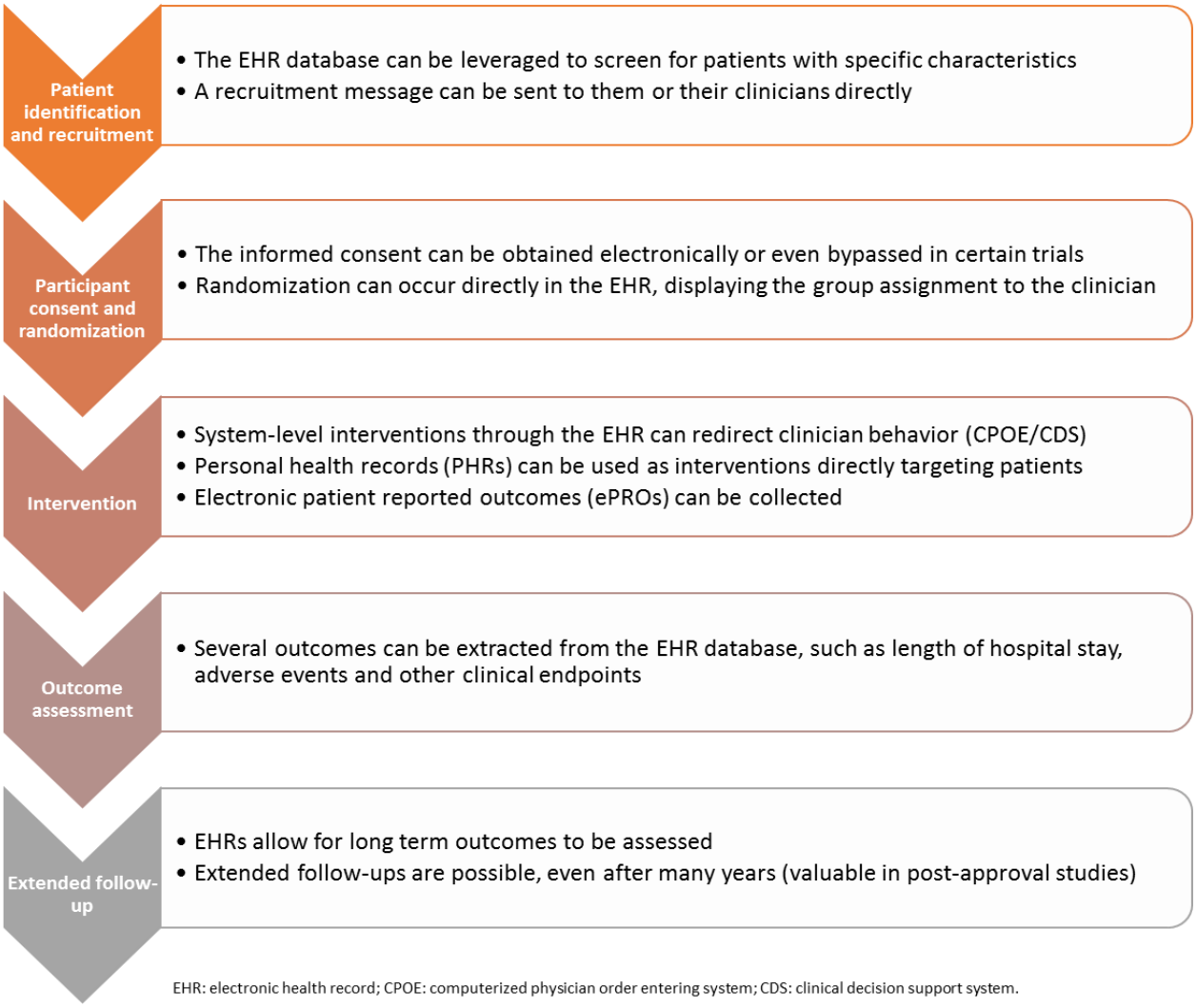
Table 5: Electronic Health Records (EHRs) and Electronic Medical Records (EMR)

EHRs type	**Definition**
Electronic Health Record (EHR)	EHRs are electronic platforms that contain health-related data collected during medical care in practices, clinics and other medical settings from various sources, connected to form a network of patient clinical data. EHRs can also incorporate software that allow straightforward physician ordering practice (CPOEs), even including safety features; or that guide them through clinical decision making with up-to-date guidelines (CDS).
Electronic Medical Record (EMR)	EMRs are routinely collected data sources that contain standard medical and clinical data gathered during medical care in an individual location of a practice, clinic or other medical setting. When the data is shared among different locations and units it becomes a network and it is considered an EHR (i.e. a primary care practice with electronic chart system that cannot be accessed by any other entity is an EMR, a hospital system where laboratory data, affiliated clinic charts, etc., are all accessed under one platform, is an EHR).
EHRs applications	**Definition**
Clinical Decision Support System (CDSS)	A CDSS is an application that supports health providers in performing health care by mining data of an EHR or EMR and providing guideline specific recommendations. CDSS systems can often identify errors or missing data and display alerts or messages through the EHRs.
Computerized Physician Order Entry (CPOE) system	CPOE systems are electronic ordering technology where physician orders can be entered and processed in a computerized way, often mimicking the workflow found in clinical settings. CPOEs can be more advanced and identify ordering mistakes, display preferred treatments by individual patient EHR query, or even set up blocks with medication interaction orders.
Personal Health Records (PHR)	PHRs are electronic platforms (often online interfaces such as web pages) that securely store patient's health information and allow patients to actively engage in their own health. Often, they can add information to a PHR, can exchange it with health providers, see test results, make appointments, or receive educational information. We consider PHR only those platforms that are tethered to an EHR, where information can be exchanged in both directions (otherwise if the patient is simply adding data but not viewing any of his/her data, we consider it ePRO).
Telehealth	Telehealth is the use of telecommunication technologies (telemonitoring) to improve the provision of care. This allows for care to be provided at a distance and therefore to maintain clinical contact with patients at home without requiring the same amount of resources to be dispensed. Examples of telehealth are blood glucose monitoring machines tethered to an EHR that integrate blood glucose levels taken by the patient at home into the EHR automatically (and can send an alert in the EHR interface to the clinician if the values are out of a predefined range and action must be taken); and increasingly mobile health data collected by wearable devices.

Electronic Patient Reported Outcomes (ePRO)	ePROs are health related information recorded by the patient themselves in electronic form, often through a web page or application. While ePROs have often been utilized in clinical trials, we also consider ePROs any data that have been collected by the patients themselves and tethered to an EHR or PHR. An example would be a patient pain diary, in which a pain score and information are inputted daily on a webpage or via a smartphone app and these data are added to an EHR; where the clinician can monitor it and consult it during a visit.

These definitions are our own working definitions used for this project and have been adapted from HealthIT.gov(37) and CMS.gov(38).

Figure 1: Practical applications of EHR for randomized trials



EHR: electronic health record; CPOE: computerized physician order entering system; CDS: clinical decision support system.

4.4 Manuscript 4

Agreement of Treatment effects from Randomized Trials using Routinely collected data and traditional trials: A meta-epidemiological Analysis

Kimberly A. Mc Cord MSc[1], Hannah Ewald PhD[1,2], Arnav Agarwal MD[3], Dominik Glinz PhD[1], Soheila Aghlmandi PhD[1], John P.A. Ioannidis MD DSc[4-9]., Lars G. Hemkens MD MPH[1,9]

[1]*Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, 4031 Basel, Switzerland*

[2]*University Medical Library, University of Basel, 4051 Basel, Switzerland*

[3]*Department of Medicine, University of Toronto, Toronto, Ontario, Canada*

[4]*Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA*

[5]*Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Palo Alto, CA 94305, USA*

[6]*Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA 94305, USA*

[7]*Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA 94305, USA*

[8]*Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, CA 94305, USA*

[9]*Meta-Research Innovation Center Berlin (METRIC-B), Berlin Institute of Health, Berlin, Germany*

Status:

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Key Points

Question: Do randomized clinical trials using routinely collected data sources to ascertain outcomes estimate similar treatment effects as trials with traditional data collection?

Finding: In this systematic analysis of various clinical topics and outcomes, trials using routinely collected data provided on average 13% less favorable treatment effect estimates (ROR 0.87, CI 0.76 - 0.99) than trials actively collecting their data for the purpose of the clinical trial.

Meaning: Estimated benefits of treatments may be smaller when assessed in randomized trial designs utilizing routinely collected data. We need better understanding of factors driving the results of randomized trials providing real-world evidence.

Abstract

IMPORTANCE: Routinely collected data (RCD) are increasingly used in randomized clinical trials (RCTs) to provide real-world evidence. It is not known whether using this data for outcome measurement leads to different treatment effect estimates.

OBJECTIVE: To assess how effect estimates from RCTs using RCD for outcome ascertainment agree with those from traditional RCTs not using RCD.

DESIGN, SETTING, AND PARTICIPANTS: This analysis is based on systematically identified RCTs using any type of RCD, including registries, electronic health records (EHRs) and administrative databases for outcome ascertainment that were included in a meta-analysis of a Cochrane review on any clinical question and any health outcome together with traditional trials not using RCD for outcomes measurement. The effect estimates from trials using or not using RCD were summarized in random effects meta-analyses. Two investigators independently assessed the quality of each data source.

MAIN OUTCOME(S) AND MEASURE(S): The main outcome was the agreement of (summary) treatment effect estimates from trials using RCD and those not using RCD, expressed as ratio of odds ratios (ROR). Subgroup analyses explored effects in trials based on different types of RCD.

RESULTS: We included 87 RCD-RCTs and 477 traditional RCTs on 22 clinical questions. RCTs using RCD for outcome ascertainment showed 13% less favorable treatment effect estimates than traditional trials (ROR 0.87, CI 0.76 - 0.99, I^2=21%). Results were similar across various types of outcomes (mortality outcomes: ROR 0.92, 95% CI 0.77 - 1.10, I^2 =14%; non-mortality outcomes: ROR 0.83, 95% CI 0.67 – 1.03, I^2=24%), data sources (EHRs: ROR 0.86, 95% CI 0.57 - 1.28, I^2 =37%; registries: ROR 0.87, 95% CI 0.75 – 1.00, I^2=19%; administrative data: ROR 0.77, 95% CI 0.62 - 0.96, I^2=0%) and data quality (high data quality: ROR 0.86, 95% CI 0.75 – 0.99, I^2=23%).

CONCLUSIONS AND RELEVANCE: RCTs using RCD for outcome ascertainment show smaller treatment benefits than traditional trials. These differences may have implications for health care decision making and the application of real-world evidence.

Introduction

Health data that are not collected for the purpose of research are increasingly used for clinical trials[1,2]. Such routinely collected data (RCD) from registries, electronic health records (EHRs), administrative claims or even mobile devices may be used to identify trial participants and to assess treatment outcomes[2]. Readily available data are typically more affordable than actively collected research data[3]. Cost reduction may make larger and longer trials more feasible. Data collection during usual care also avoids artificial research settings, and this may increase pragmatism and applicability of trial results to routine care[4]. RCD databases include many outcomes that are relevant in practice and matter to clinicians and patients (e.g. mortality, disability or hospitalization), while they typically lack outcomes that are more relevant for explanatory trials aiming to understand the biological processes underpinning treatment effects (e.g. biomarkers)[5]. Cutting out research-driven follow-up visits and relying only on patient interaction during usual care probably better reflects "real-world" treatment effects, and patient adherence may be less faithful in such a setting as compared to traditional, more explanatory trials. Overall, trials embedded in existing data collection structures may provide real world evidence, being more informative for guiding treatment decisions and sharing more features of pragmatic trials than many traditional trials[6–8].

A key issue of using RCD for clinical research is data quality[1,2]. For some outcomes, data quality in RCD may be lower, in particular due to non-uniform data collection and potential measurement errors[9–13]. On the other hand, healthcare professionals collecting RCD during usual care may have more clinical expertise than research staff who often collects trial data only for a narrow time frame and scope, sometimes only for very few participants or even a single patient per center[14]. Since RCD is collected independently of the trial from people unaware of treatment allocations, biases related to outcome ascertainment might be even less likely than in traditional trials. Moreover, data quality in RCD can vary enormously for different outcomes. For mortality, the quality might be very high[15]: with proper linkage to death registries, complete, accurate information can be achieved, while other trials not linked to RCD sources may lack information on survival status for many participants. Conversely, data quality in RCD might be highly insufficient for other outcomes, such as specific adverse events or some

patient-reported endpoints. The impact of using RCD for outcome ascertainment and the impact of potential inaccuracies on trial results is unclear. Misclassification of clinical events or missing information that occurs randomly, for example due to coding errors or problems with database linkage[16], may diminish the treatment effect point estimates[17]. Larger sample sizes achieved by using RCD may increase precision of treatment effect estimates[18] but these may still be biased underestimations.

Here, we aimed to provide empirical insights on the agreement of findings from trials using RCD for measuring outcomes as compared to traditional RCTs.

Methods

We systematically obtained a large sample of RCTs that used RCD to measure study outcomes and identified RCTs that explored the same clinical question but used traditional ways (not based on RCD) to measure the outcomes. We defined RCD as any health information that wasn't collected primarily for research. We compared the treatment effects estimated in RCTs using routinely collected information (RCD-RCTs) with treatment effects estimated in RCTs with traditional data collection for the same clinical questions. We assumed that studies included in the same meta-analysis in a Cochrane review would be on the same clinical question.

We included RCTs that used RCD for measurement of any binary clinical outcome of any health intervention in any population. We did not consider outcomes that were uniquely cost related, but we kept outcomes measuring uptake of interventions, such as vaccinations, drug treatments or screening. There were no other eligibility criteria.

Identification and selection of RCD-RCTs and traditional RCTs

We searched PubMed using text words and medical subject headings focusing on terms around routine data (Appendix 1). We searched for RCTs published in English between 2000 and 2015 because of the emerging availability of EHRs and other sources of RCD in the last two decades and because more recent trials were less likely to be already included in Cochrane reviews. Two reviewers independently screened titles and abstracts (KAM and AL or HE). Any article that was found potentially eligible by one reviewer was considered for further analysis

We then identified Cochrane reviews citing any of the potentially eligible RCD-RCTs using the "cited in systematic reviews" function on PubMed. We also queried ISI Web of Science and perused the citing articles (from Web of Science Core Collection).

We obtained all full-texts of citing reviews and cited RCTs. One reviewer (KAM) determined if at least one outcome was measured with RCD in the RCT and if the RCD-RCT was included in a meta-analysis of the Cochrane review on that outcome together with other, i.e. traditional, RCTs. We obtained the full-texts for all these other trials. Whenever there was any uncertainty in these steps, a second reviewer was consulted (LGH) and the decision was made based on consensus.

One reviewer (KAM or DG) perused all full-texts and finally classified the RCTs as RCD-RCTs or as traditional RCTs actively collecting outcome data for the purpose of the trial. A second reviewer confirmed eligibility of all RCD-RCTs (LGH, AA, KAM). Any uncertainties were resolved by discussion.

Selection of clinical questions

From each Cochrane review, we selected one clinical question addressed by one meta-analysis including an RCD-RCT. In case there were multiple meta-analyses, we selected the meta-analysis with the largest number of RCTs (if there were still multiple ones, we selected the one that had the greatest total sample size). Some meta-analyses were reported with summary estimates for subsets of studies but without an overall summary effect. In such cases, we took the subset including the highest number of RCD-RCTs. In some cases, the same RCD-RCTs were included in multiple subsets (for example, for different lengths of follow-up) but there was an overall summary presented. Here we also used only the largest subset to avoid double counting of participants or events. We preferred any primary analysis over sensitivity or subgroup analyses if the former was present. Sensitivity analyses on methodological features (for example by publication year) were always excluded. For two secondary analyses, we applied a different selection approach: In one we considered only clinical questions with primary outcomes of the Cochrane review and in the other we only considered mortality outcomes.

The last searches for RCD-RCTs in literature databases and citing Cochrane reviews were in April 2016 and September 2017 (for details see appendix 1). We used the most recent updated version (last search January 2020) of each Cochrane review for all pertinent clinical questions and updated our searches, classifications and extractions using these most recent versions

Data extraction, risk of bias and data quality assessment

For each included trial, we extracted the treatment effects (i.e., number of events and no events per study arm).

For each eligible RCD-RCT, we extracted general characteristics and the types of RCD utilized. We also noted whether the RCD source was the only form of outcome data source, or if a hybrid approach was reported (i.e. where the RCD were complemented by additional active data collection). Trials using RCD within a hybrid approach were considered as RCD-RCTs but were excluded in a sensitivity analysis. We extracted the overall risk of bias assessment reported in the Cochrane reviews. For more detailed analyses, we specifically extracted the risk of bias due to the blinding status (or participant blinding when several blinding domains were presented). We deemed the overall risk of bias to be "high", if any bias domain was deemed by the authors "high risk"; "low" if all domains were deemed "low risk"; "unclear" in all other cases. All of these extractions were done by one reviewer (KM, LGH, AA or DG).

One reviewer (KAM or DG) extracted any statement on data quality of the RCD in the broader sense (e.g. statements related to measurement errors, reliability, accuracy or completeness) and a second reviewer (KAM or AA) verified the extractions. Both reviewers then independently assessed whether the RCD would be adequate to reliably measure the outcomes of interest. We fully acknowledge that such an assessment from the outside is difficult. When authors provided a statement that led us assume that the RCD would adequately measure the outcome of interest, a "high quality" mark was given. If this was not reported, but the source was specifically designed to collect the endpoint (e.g. breast cancer cases through a comprehensive national breast cancer registry), a "high quality" mark was still given. If a statement indicating "low quality" was provided (which we expected to be rare, but such statements could have been made in the limitation section of the studies) or the reviewer felt that the RCD source was

unlikely to specifically collect such outcome data with little missingness and little measurement error (e.g. adverse events extracted from administrative databases), a low mark was given. Other cases were rated "unclear". We quantified the agreement between the two reviewers (KAM vs AA or DG) using kappa statistics and the total agreement.

Statistical analysis

We calculated two summary odds ratios (sOR) for each clinical question: the sOR of the RCD-RCTs, and separately the sOR of all the traditional RCTs. In cases when there was only one trial, the "summary" OR was actually the OR of the trial. Subsequently, for each sOR pair, we calculated their respective ratio, i.e. ratio of odds ratio (ROR). We ensured that for all clinical questions ORs <1 indicate favorable effects for the evaluated treatment. We inverted effects where necessary (i.e. if a meta-analysis reported survival, we inverted the effect estimate by taking its reciprocal so that estimates <1 indicate mortality benefits). For consistency, we ensured that the second comparator was the control (i.e. no intervention or usual care, in three cases where two active interventions were compared[20–22], we defined the control as the older treatment; we left these cases out in a sensitivity analysis). Calculations were done after log-transformation of ORs. A ROR <1 indicated that the RCD-RCTs estimated a less favorable treatment effect for the evaluated treatment than the traditional RCTs. A meta-analysis of all RORs across all clinical questions provided an overall summary of the relationship of treatment effects obtained from trials using RCD vs trials not using RCD. Meta-analyses used random-effects models (Hartung-Knapp-Sidik-Jonkman method[23]).

We conducted several sensitivity analyses: including only RCD-RCTs with low risk of bias overall; including only RCD-RCTs with low risk of bias related to blinding; excluding RCD-RCTs with some active data collection (hybrid approaches); excluding older RCD-RCTs (published before 2005); stratified by number of participants and number of events (tertiles across all RCD trials); including only clinical questions on non-mortality outcomes; excluding clinical questions with active controls; using only clinical questions with effect estimates from RCD-RCTs and traditional-RCTs that had no largely different precision (i.e. ratio of sOR standard errors >0.33 and <3); using only

DerSimonian-Laird random effects meta-analyses; and using only fixed-effect meta-analyses.

For exploration, we conducted subgroup analyses including only RCD-RCTs using registries, EHR, or administrative data, and where RCD-RCTs data quality was assumed to be high.

We report medians with interquartile ranges if not stated otherwise. We used the meta package (version 4.9-7) for meta-analyses (RStudio version 1.2.1335; R version 3.6.1).

Results

Characteristics of trials using RCD and traditional RCTs

We included 87 RCD-RCTs with a median of 698 participants per trial (IQR 272 - 2430), the majority (59 of 87, 68%) originating from North America, followed by Scandinavia (14 of 87, 16%) (Table 1; Table 2; Appendix 2). They were published between 1976 and 2017 (median 2004). The RCD sources were registries (37 of 87, 42%), EHRs (33 of 87, 38%) and administrative databases (17 of 87, 20%). In 30 RCD-RCTs, a hybrid approach with elements of active data collection was applied (35%). The risk of bias was deemed overall low in 18 of 87 (21%) RCD-RCTs, and the risk of bias related to blinding was deemed low in 34 of 87 (39%). We deemed the quality of the data adequate for 57 of the 87 RCD-RCTs (moderate interrater agreement [74.4%; kappa 0.47; weighted kappa 0.47]).

Their results were compared across 22 clinical questions with 477 traditional RCTs (median 120 participants per trial; IQR 58 - 357). The clinical questions were related to screening and preventative medicine (n=8 of 22, 36%), community medicine (n=5, 23%), cardiology (n=5, 23%) and surgery (n=4, 18%) (Table 2). In 12 comparisons there was 1 RCD-RCT only, 2 comparisons had 2 RCD-RCTs, 3 comparisons had 3 RCD-RCTs, and 5 comparison had 4 or more. Outcomes were diverse, with a large proportion related to mortality (9 of 22 in the main analysis; 39%).

Agreement of treatment effect estimates

RCTs using RCD for outcome ascertainment systematically showed less favorable estimates of treatment effects than those from traditional RCTs not using RCD (ROR 0.87, 95% CI 0.76 - 0.99) (Figure 1; Figure 2; Table 3). In 3 of the 22 clinical questions ("intrauterine device for heavy menstrual bleeding", "breastfeeding support for healthy women", and "immunization reminders and recalls"), the 95% CIs of the RORs excluded the null and in all 3 clinical questions, RCTs with RCD had less favorable results than traditional RCTs.

The results were similar when including only any available primary outcomes of Cochrane reviews (ROR 0.88, 95% CI 0.78 - 1.00) or mortality outcomes (ROR 0.92, 95% CI 0.77 - 1.10), or studies with RCD where we deemed the data quality high (ROR 0.86, 95% CI 0.75 – 0.99). The results were also similar when analyzing EHRs (ROR 0.86 95%, CI 0.57 - 1.28), registries (ROR 0.87, 95% CI 0.75 – 1.00) or administrative data sources (ROR 0.77, 95% CI 0.62 - 0.96) (Table 3).

Discussion

RCTs using RCD for outcome ascertainment showed less favorable treatment effects than traditional trials not using RCD in this systematic analysis of various clinical topics and outcomes. This might be due to data quality issues and measurement errors leading to dilution of effects by misclassified outcomes. However, the results remained similar across sensitivity analyses addressing this possibility, including data source type and estimated data quality, or when including only mortality outcomes where misclassification is probably less likely. Thus, trials using RCD for outcome collection may have other features that are associated with less pronounced effect estimates[2]. For example, such trials might be more pragmatic than traditional trials[2,5,18,24]. More natural care settings with less eagerness to artificially increase treatment adherence may result in smaller treatment effect estimates.

This interpretation agrees with empirical research indicating that procedures to standardize and increase data quality may have smaller impact on trial effect estimates than often assumed: a review[25] indicated that central outcome adjudication committees used to increase data quality typically did not influence effect estimates compared to

onsite assessments in the very same trial. Of note, in contrast to such research, we did not aim to isolate the "clean" effect of using RCD versus not using RCD within the same trial as alternative data ascertainment methods. Conversely, we aimed to empirically describe how results from trials designed to provide randomized real-world evidence[26] (by using real-world data) agree with those from traditionally designed trials relying on their own, active data collection procedures.

We are aware of only one other similar study that compared effects from 30 registry-based trials with that from traditional trials on 12 different topics in cardiology or cancer screening[27]. The reported RORs were 0.97 (95% CI 0.92 - 1.03) for mortality and 0.95 (95% CI 0.89 - 1.02) for other outcomes (reported ROR inverted to facilitate comparison). However, some RCD-RCTs were double-counted. A sensitivity analysis using only unique RCD-RCTs (ROR 0.95, 95% CI 0.85 - 1.05 and ROR 0.95, 95% CI 0.89 - 1.02, respectively) provided results compatible with our findings for registry-based trials.

Several limitations need to be considered. First, while the outcome selected for our analysis was routinely collected in the RCD-RCTs, other outcomes within some of these RCD-RCTs were still determined traditionally, thus introducing artificial settings that deviate from routine care. Therefore, some of the RCD-RCTs may reflect the "real-world" more and others less.

Second, we did not directly evaluate the impact of trial pragmatism on treatment effects. A deeper investigation of all RCD-RCTs and their comparators would be far beyond the scope of this project and a valid retrospective assessment of each trial's pragmatism is difficult for researchers outside of the original trial team, requiring further information such as study protocols[28] that are typically unavailable.

Third, while we individually assessed and graded data quality and expected accuracies in duplicate, assessing the quality of RCD source is inherently subjective and we are not aware of an established instrument that would allow to unambiguously determine the "data quality" on an outcome level using trial reports. Thus, interpretations in this regard need to be cautious.

Fourth, while our topics were evaluated in Cochrane reviews and very likely explore questions of interest for healthcare decision makers, they do not cover the full spectrum of clinical research. The statistical heterogeneity across topics was moderate, and issues related to data quality and trial design vary across clinical fields. More evidence is needed to better assess the generalizability of our findings to specific medical fields.

Finally, some of our analyses rely on sometimes insufficiently reported details[29]. While we systematically ensured that the trials were actually measuring the analyzed outcomes through RCD, poor reporting of RCD use in the traditional RCTs could have led to some misclassification or we might have overlooked some hybrid approaches.

Conclusion

RCTs utilizing any form of RCD for their outcomes' ascertainment found systematically less favorable treatment effects than RCTs utilizing traditional methods. There may be differences between traditional trials and trial designs utilizing RCD beyond data quality issues that would explain this. We need a better understanding of these factors, to optimize the use of such emerging designs for comparative effectiveness research and to increase the applicability of real-world evidence derived from randomized trials.

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Contributors: Lars G. Hemkens conceived and designed the study. Kimberly Mc Cord, Hannah Ewald and Aviv Ladanie screened titles, abstracts and full-text publications. Kimberly Mc Cord, Arnav Agarwal, Lars G. Hemkens and Dominik Glinz extracted the data, and Kimberly Mc Cord and Lars G. Hemkens analyzed the data. Kimberly Mc Cord and Lars G. Hemkens drafted the manuscript. All of the authors interpreted the data, critically revised the manuscript for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Table and figures

Table 1: Overview of the characteristics of analyzed trials using Routinely Collected Data (main analysis)

Characteristic	No. (%) of overall RCD-RCTs	No. (%) Registry RCD-RCTs	No. (%) Admin RCD-RCTs	No. (%) EHR RCD-RCTs
Frequency	87 (100%)	37 (42%)	17 (20%)	33 (38%)
Publication year				
Median [IQR]	2004 [1998 - 2010]	2003 [1992 - 2009]	2007 [2003 - 2012]	2005 [2000- 2011]
Range (min - max)	1976 - 2017	1976 - 2015	1998 - 2015	1989 - 2017
Number of participants				
Median [IQR]	698 [272 - 2430]	2001 [511 - 16824]	878 [319 - 2471]	282 [142 - 575]
Range (min - max)	16 - 89699	99 - 89699	45 - 24743	16 - 12205
Number of events				
Median [IQR]	218 [60 - 1266]	401 [66 - 1367]	614 [109 - 1816]	121 [33 - 284]
Range (min - max)	0 - 86201	4 - 86201	13 - 18146	0 - 5562

Country				
North America	59 (68%)	17 (46%)	14 (82%)	28 (85%)
Scandinavia[1]	14 (16%)	13 (35%)	1 (6%)	0 (0%)
Continental Europe	4 (5%)	0 (0%)	1(6%)	3 (9%)
United Kingdom	5 (6%)	4 (11%)	0 (0%)	1 (3%)
Other[2]	5 (6%)	3 (8%)	1 (6%)	1 (3%)
Risk of bias				
Blinding				
High	20 (23%)	5 (14%)	2 (12%)	13 (39%)
Low	34 (39%)	18 (49%)	6 (35%)	10 (30%)
Unclear	33 (38%)	14 (38%)	9 (53%)	10 (30%)
Overall				
High	36 (41%)	17 (46%)	4 (24%)	15 (45%)
Low	18 (21%)	8 (22%)	3 (18%)	7 (21%)
Unclear	33 (38%)	12 (32%)	10 (66%)	11 (33%)

Estimated Data quality				
High	57(65%)	32 (86%)	8 (47%)	17 (52%)
Low	26 (30%)	3 (8%)	9 (53%)	14 (42%)
Unclear	4 (5%)	2 (5%)	0 (%)	2 (6%)
RCD collection level[3]				
Complete RCD	57 (65%)	32 (86%)	7 (41%)	18 (55%)
Hybrid	30 (35%)	5 (14%)	10 (59%)	15 (45%)

Admin: administrative; EHR: electronic health record; IQR: interquartile range.; RCT: randomized clinical trial; RCD: routinely collected data.

1) Scandinavia includes Sweden, Norway, Denmark, Finland and Iceland

2) Other includes Australia, China and New Zealand.

3) Complete RCD: fully RCD-based data collection; Hybrid: routine data collection with supportive active data collection.

Table 2: Clinical questions and corresponding trials (main analysis):

Clinical question[1]	Outcome	Cochrane review identifier; Meta-Analysis number	Number of trials	Median trial size of trial(s); IQR; Range
Individualized discharge plan for all hospitalized patients	Unscheduled readmissions[2]	CD000313[30]; 2.1.0	5 RCD-RCTs	414; 214 - 606; 96 - 698
			12 other RCTs	150; 93 - 297; 50 - 738
Breastfeeding support for healthy pregnant women intending to breastfeed or already breastfeeding	Stopping breastfeeding	CD001141[31]; 1.1.0	1 RCD-RCT	990
			51 other RCTs	300; 135 - 534; 41 - 1003
Mammography screening in women without previous breast cancer diagnosis	Breast cancer mortality[2]	CD001877[32]; 1.1.0	7 RCD-RCTs	39405; 24767 - 46357; 17793 - 59176
			4 other RCTs	62000; 59949 - 111420; 57897 - 160840
Anti-fibrinolytic agents in patients undergoing surgery	Need for allogeneic blood transfusion[2]	CD001886[33]; 1.1.0	1 RCD-RCT	16
			107 other RCTs	59; 40 - 98; 17 - 1784
Interventions to increase uptake of cervical cancer screening	Uptake of screening	CD002834[34]; 1.1.1	4 RCD-RCTs	1171; 393 - 2335; 349 - 89699
			8 other RCTs	482; 162 - 1317; 97 - 1794
Self-management interventions in patients with COPD	Hospital admissions (respiratory-related)	CD002990[35]; 1.7.0	1 RCD-RCT	191
			9 other RCTs	76; 62 - 143; 38 - 743
Exercised-based interventions in patients with heart failure	Hospital admissions	CD003331[36]; 1.4.0	1 RCD-RCT	2330
			6 other RCTs	99; 50 - 123; 43 - 200
Fast track interventions for early extubation (time-directed extubation protocol) in patients undergoing cardiac surgery	Mortality[2]	CD003587[21]; 2.1.4	3 RCD-RCTs	109; 63-186; 48-597

			3 other RCTs	98; 65-172; 60-404
Levonorgestrel-intrauterine device vs hysterectomy in women with heavy menstrual bleeding	Additional surgery received[4]	CD003855[20]; 2.13.0	1 RCD-RCT	225
			5 other RCTs	60; 57-63; 57-72
Reminder and recall immunization interventions in adults and children	Immunization rates	CD003941[37]; 1.1.0	32 RCD-RCTs	1724; 700-4591; 204-24743
			27 other RCTs	296; 173-505; 96-3006
Routine invasive vs conservative selective treatment in patients with unstable angina and non-ST elevation myocardial infarction	Mortality or non-fatal myocardial infarction[2]	CD004815[38]; 1.13.0	1 RCD-RCT	2457; 2457-2457; 2457-2457
			2 other RCTs	1505; 1352-1658; 1200-1810
Interventions to reduce falls in those aged 60 years or older in care facilities and hospitals	Falls	CD005465[40]; 4.2.0	1 RCD-RCT	48
			5 other RCTs	353; 114 - 594; 91 - 625
Collaborative care interventions for people with depression and anxiety	Antidepressant medication use[4]	CD006525[41]; 1.3.1	13 RCD-RCTs	208; 88 - 285; 45 - 372
			31 other RCTs	179; 83 - 292; 34 - 1570
Antioxidant supplementation in healthy participants and in patients with various stable diseases	Mortality[2]	CD007176[42]; 1.1.0	3 RCD-RCTs	910; 510 - 15022; 109 - 29133
			75 other RCTs	360; 98 - 1713; 19 - 39876
On-pump surgery in patients undergoing CABG	Mortality[2]	CD007224[43]; 2.1.0	1 RCD-RCT	339
			73 other RCTs	60; 40 - 120; 20 - 2203
Structured telephone support or non-invasive telemonitoring interventions in patients with heart failure	Mortality[2]	CD007228[44]; 1.2.0	3 RCD-RCTs	319; 263 - 515; 206 - 710
			14 other RCTs	160; 90 - 261; 20 - 460
Mycophenolic acid vs azathioprine as primary immunosuppression for adult and children kidney transplant recipients	Acute rejections[2,3]	CD007746[22]; 1.6.4	1 RCD-RCT	497

			21 other RCTs	71; 46 - 148; 16 - 495
Statins in patients with chronic kidney disease not requiring dialysis	Mortality[2]	CD007784[45]; 1.2.0	2 RCD-RCTs	9565; 5936 - 13194; 2306 - 16824
			8 other RCTs	722; 255 - 1472; 87 - 3267
Case management interventions in people with dementia	Hospital admissions	CD008345[46]; 1.5.2	2 RCD-RCTs	141; 133 - 149; 125 - 157
			3 other RCTs	89; 88 - 107; 88 - 126
Medication review in hospitalized patients	Mortality[2]	CD008986[47]; 1.1.0	1 RCD-RCT	99
			8 other RCTs	368; 120 - 485; 66 - 936
Interventions to reduce dietary salt in hypertensive patients	Mortality[2]	CD009217[48]; 1.1.0	1 RCD-RCT	1981
			6 other RCTs	519; 401 - 710; 67 - 2382
Fish oil for pregnant or breastfeeding women to prevent allergies in their children	Allergy rates	CD010085[49]; 6.2.1	1 RCD-RCT	528
			1 other RCTs	706

1) All comparators were no intervention or usual care if not stated otherwise.

2) Additionally, we used another, mortality outcome from this same Cochrane review for the secondary analysis on mortality outcomes.

3) Additionally, we used another, primary outcome from this same Cochrane review for the secondary analysis on primary outcomes.

4) Not a primary outcome of the Cochrane review; no primary outcomes from this same Cochrane review were eligible.

IQR: interquartile range; RCD: routinely collected data.

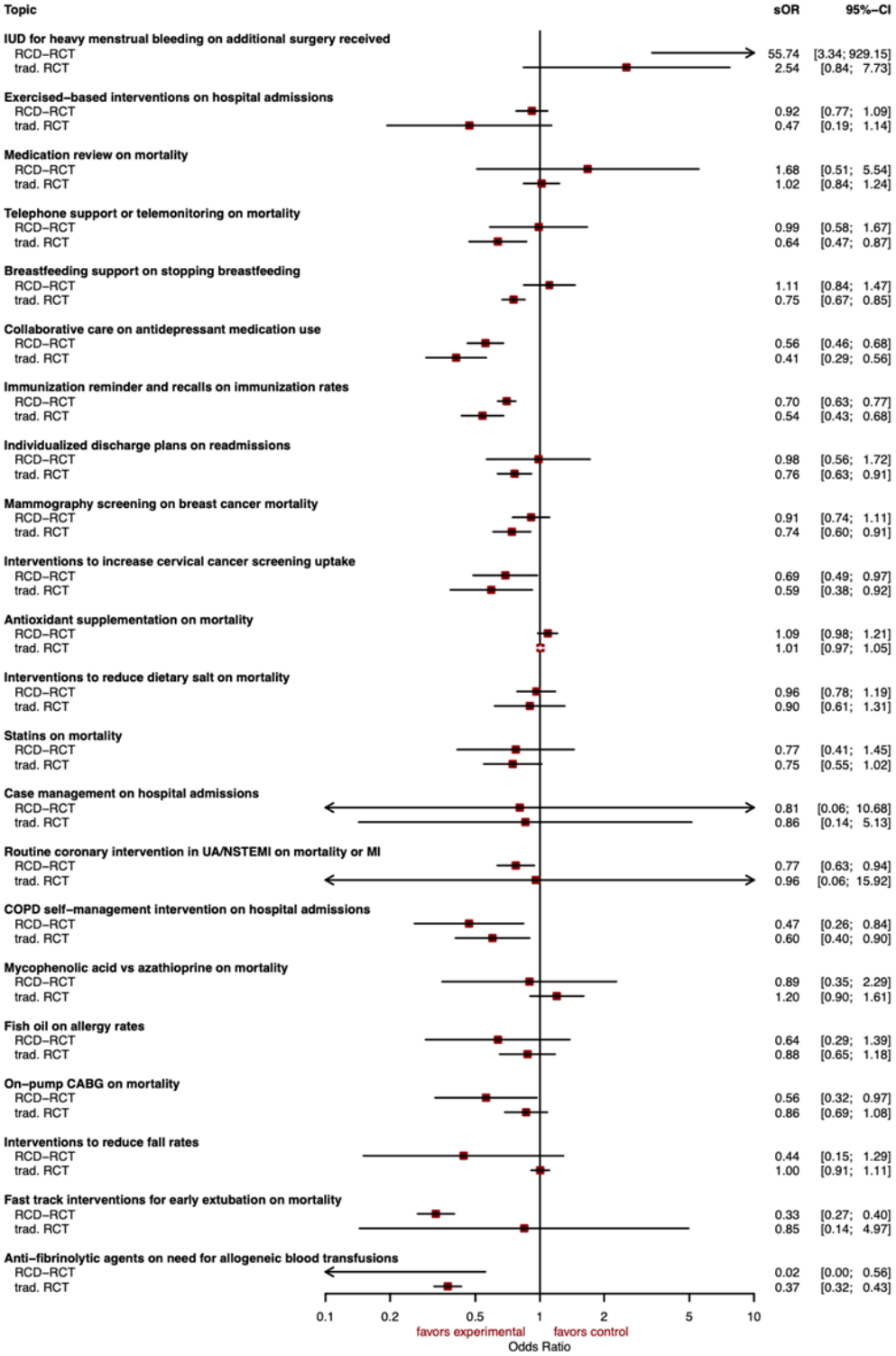
Table 3: Results of meta-epidemiologic analyses of the agreement of treatment effects measured with or without RCD in clinical trials

Analysis	No. of clinical questions	ROR (95% CI)	I^2 (95% CI)
Main analysis	22	0.87 (0.76 - 0.99)	21% (0-53%)
Other analyses			
Primary outcomes	20	0.88 (0.78 – 1.00)	13% (0-48%)
Mortality outcomes	12	0.92 (0.77 - 1.10)	14% (0-53%)
Sensitivity and subgroup analyses			
Non-mortality outcomes	14	0.83 (0.67 – 1.03)	24% (0-59%)
RCD-trials using registries only	14	0.87 (0.75 – 1.00)	19% (0-56%)
RCD-trials using EHRs only	9	0.86 (0.57 - 1.28)	37% (0-71%)
RCD-trials using administrative claims data only	8	0.77 (0.62 - 0.96)	0% (0-56%)
RCD-trials with high data quality only	17	0.86 (0.75 – 0.99)	23% (0-57%)
RCD-trials with hybrid data collection excluded	18	0.89 (0.75 – 1.05)	32% (0-62%)
RCD-trials published after 2005 only	15	0.81 (0.66 - 0.99)	15% (0-52%)
RCD-trials with low risk of bias (overall) only	10	0.90 (0.65 - 1.27)	41% (0-72%)

RCD-trials with low risk of bias (blinding) only	13	0.91 (0.76 - 1.09)	24% (0-60%)
Smallest trials (lowest tertile)[1]	13	1.00 (0.64 - 1.57)	22% (0-59%)
Medium trials (middle tertile)[1]	10	0.83 (0.68 - 1.01)	0% (0-49%)
Largest trials (largest tertile)[1]	5	0.92 (0.86 - 0.99)	0% (0-57%)
Lowest number of events (lowest tertile)[2]	12	1.09 (0.65 – 1.83)	46% (0-72%)
Medium number of events (middle tertile)[2]	8	0.84 (0.66 - 1.06)	0% (0-45%)
Largest number of events (largest tertile)[2]	5	0.91 (0.83 – 1.00)	0% (0-76%)
Excluding clinical questions with active comparators	19	0.86 (0.76 - 0.98)	18% (0-53%)
Excluding clinical questions with largely different precision per summary estimates	14	0.86 (0.75 – 0.98)	20% (0-58%)
DerSimonian-Laird random effects meta-analyses	22	0.86 (0.77 - 0.96)	37% (0-62%)
Fixed-effect meta-analyses	22	0.90 (0.86 – 0.93)	51% (20-70%)

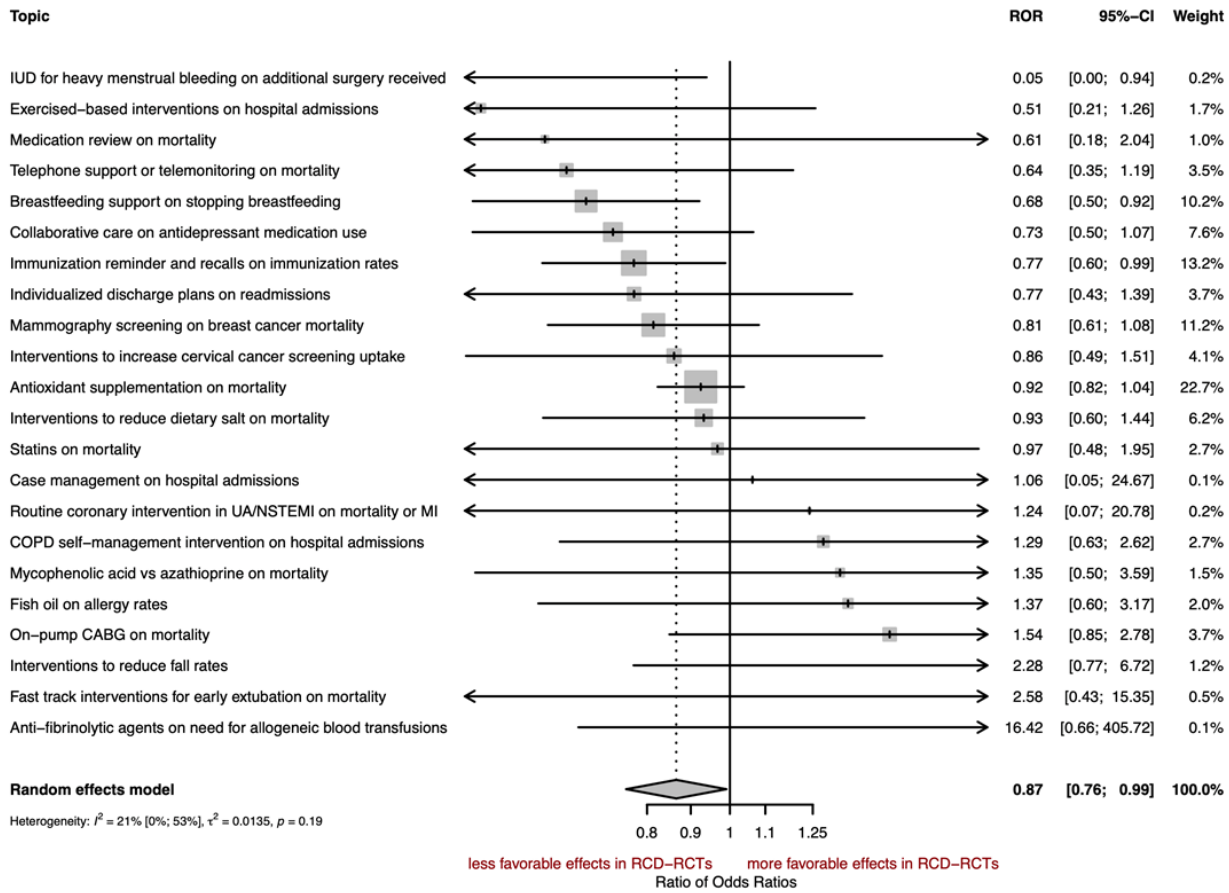
CI: Confidence interval; EHR: electronic health record; I^2: Heterogeneity; RCD: Routinely collected data; RCTs: Randomized clinical trials; ROR: Ratio of odds ratio.
1) Tertiles for participants were 343 and 1927.
2) Tertiles for events were 78 and 493.
A ROR <1 indicates that the RCD-RCT estimated a less favorable treatment effect of the evaluated treatment than the traditional RCT.

Figure 1: Treatment effects measured with or without RCD in clinical trials for 22 clinical questions. Overview of summary results (main analysis).



CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; IUD: Intrauterine device; sOR: summary odds ratio; RCD: routinely collected data; trad. RCT: traditional randomized controlled trial not using RCD for outcome collection; MI: Myocardial infarction; ROR: ratio of odds ratio; UA/NSTEMI: Unstable angina/Non-ST-elevation myocardial infarction. Ordered by ROR.

Figure 2: Agreement of treatment effects measured with or without RCD in clinical trials. Forest plot of main analysis.



CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; IUD: Intrauterine device; sOR: summary odds ratio; RCD: routinely collected data; trad. RCT: traditional randomized controlled trial not using RCD for outcome collection; MI: Myocardial infarction; ROR: ratio of odds ratio; UA/NSTEMI: Unstable angina/Non-ST-elevation myocardial infarction.

Ordered by ROR.

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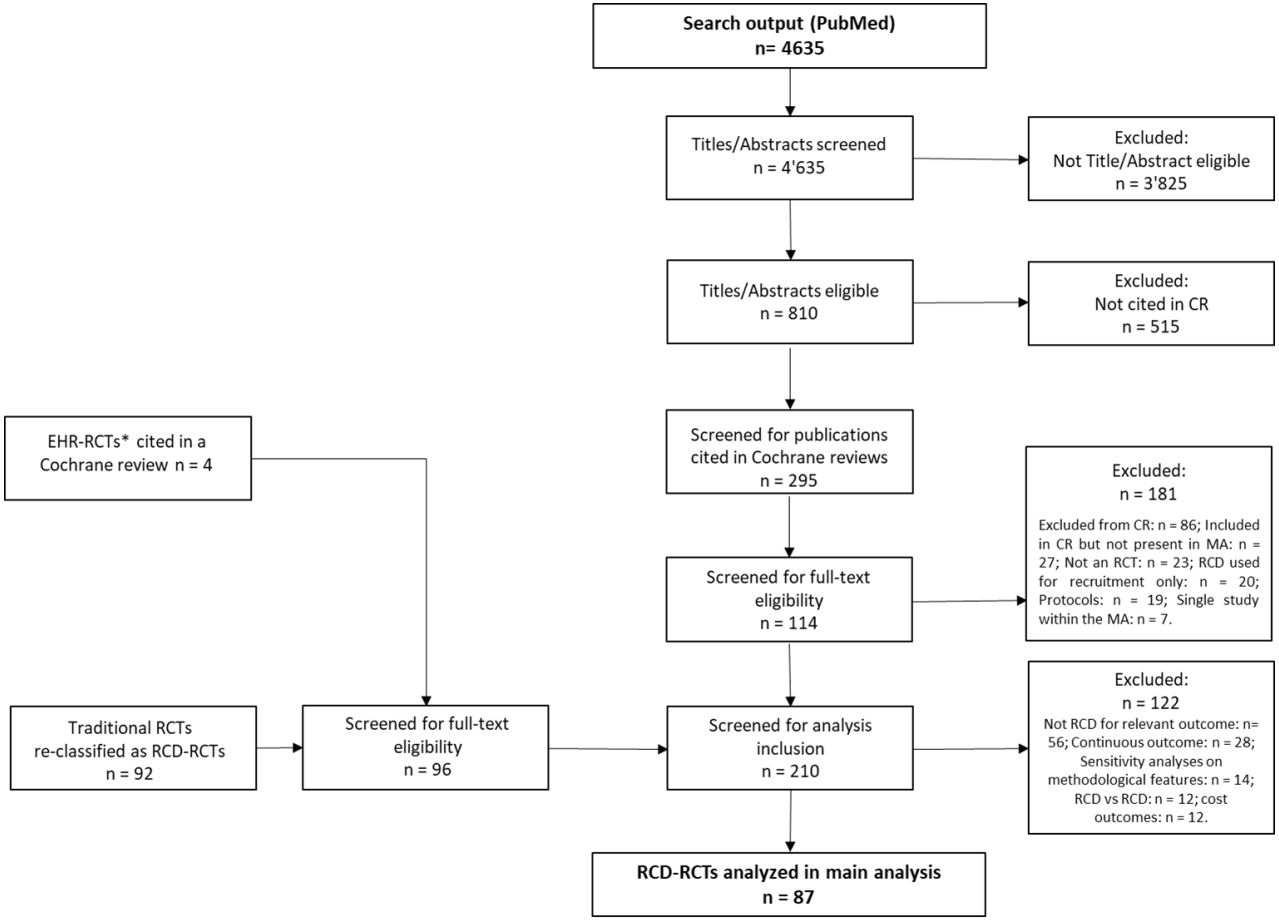
Appendices

Appendix 1: Search strategy

Search	Query	Items found
#4	#1 NOT #2 Filters: Randomized Controlled Trial; Publication date from 2000/01/01 to 2016/12/31	4635
#3	#1 NOT #2	446676
#2	animals[mh] NOT humans [mh]	4186023
#1	“routine data”[tiab] OR “routinely collected”[tiab] OR Administrative[tiab] OR Claims[tiab] OR "Registries"[mh] OR registry[tiab] OR registries[tiab] OR database*[tiab] OR "healthcare data"[All fields] OR "health care data"[All fields] OR "national database"[All fields] OR "Databases as Topic"[Mesh] OR "Administrative Claims, Healthcare"[Mesh]	464227

Interface: PubMed; Date of last search: 11 March 2016

Appendix 2: Study Flow diagram



CR = Cochrane review, EHR = electronic health record, MA = meta-analysis, RCD = routinely collected data, RCT = randomized clinical trial.

* EHR-RCTs that used EHR infrastructures for recruitment or outcome measurement but did not explore EHR technology itself (as here no traditional RCTs would be available), originating from a search described elsewhere which was specifically focused on EHR-RCTs (Mc Cord KA et al. CMAJ Open. 2019 Feb 3;7(1):E23-E32). Date of last search 13 Sep 2017

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4.5 Manuscript 5

Systematic Analysis of the Reporting Transparency and Completeness of Randomized Controlled Trials using Registries

Kimberly A. Mc Cord[1], Mahrukh Imran[2], Stephen J. McCall[3 4], Linda Kwakkenbos[5], Ole Fröbert[6], Chris Gale[7], Sinéad M Langan[8], David Moher[9], Clare Relton[10], Merrick Zwarenstein[11 12], Edmund Juszczak[3], Brett D Thombs[2 13 14 15 16] and Lars G. Hemkens[1] on behalf of the CONSORT Extension for Trials Conducted in Cohorts and Routinely Collected Data Group

[1]*Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland*

[2]*Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, Quebec, Canada*

[3]*National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU), Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Headington, Oxford*

[4]*Center for Research on Population and Health, Faculty of Health Sciences, American University of Beirut, Ras Beirut, Lebanon*

[5]*Behavioural Science Institute, Clinical Psychology, Radboud University, Nijmegen, the Netherlands*

[6]*Department of Cardiology, Faculty of Health, Örebro University, Örebro, UK*

[7]*Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK*

[8]*Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK*

[9]*Centre for Journalology, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*

[10]*Centre for Clinical Trials and Methodology, Barts Institute of Population Health Science, Queen Mary University, London, UK*

[11]*Centre for Studies in Family Medicine, Department of Family Medicine, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada*

[12]*Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada*

[13]*Department of Psychiatry, McGill University, Montreal, Quebec, Canada*

[14]*Departments of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada*

[15]*Department of Medicine, McGill University, Montreal, Quebec, Canada*

[16]*Departments of Educational and Counselling Psychology, McGill University, Montreal, Quebec, Canada*

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Abstract

BACKGROUND: Registries may be used to support randomized controlled trials (RCTs), but the reporting of how registries are used in RCTs may be insufficient. This motivated the development of a Consolidated Standards of Reporting Trials (CONSORT) extension for RCTs using Cohorts and Routinely Collected Health Data.

OBJECTIVES: To describe the current level of reporting of RCTs using registries after introduction of CONSORT but before the novel CONSORT extension.

METHODS: We used a database of trials using registries from a scoping review supporting the development of the CONSORT extension. We included primary and secondary publications of RCTs using registries for any purpose. The completeness and transparency of reporting based on established CONSORT items and novel CONSORT extension items was assessed.

RESULTS: We assessed reports of 47 registry RCTs (28% used registries to identify eligible trial participants, 51% to assess trial outcomes, and 21% for both). Most were performed in Scandinavian countries (45%), followed by the Unites States of America (25%) and Continental Europe (15%).

Of the CONSORT extension items, 5 out of 13 items were adequately reported in at least half of the 47 trial reports (2 in at least 80%). The 8 other items were related to RCD source eligibility (32% adequate), data linkage (9% adequate), validation and completeness of data used for outcome assessment (12% adequate), validation and completeness of data used for participant recruitment and inclusion (0% adequate), participant flow (9% adequate), allocation concealment (39% adequate), RCD source funding (6% adequate) and interpretation of results in consideration of RCD source use (25% adequate).

INTERPRETATION: The reporting of trials using registries was often poor, in particular details on data linkage and data quality were not sufficient in most trials. Better reporting is urgently needed for appropriate use of the results of these trials.

Background

Registries are repositories of health information with a common characteristic, such as a disease, a drug treatment or health exposure[1]. They can be used to monitor the progression of a health condition and are often utilized to explore etiology, progression and potential treatments or cures of diseases. Registries are a type of routinely collected data (RCD) source that is increasingly utilized as a framework to support randomized controlled trials (RCTs)[2–4]. Compared to traditional RCTs, trials conducted with RCD, including registries, may allow the exploration of pragmatic questions in so called "real world settings", potentially increasing the applicability of the results[5]. Furthermore, traditional RCTs are often expensive, particularly due to the costs of setting up a specific research and data collection infrastructure; leveraging the environment of a registry may greatly reduce expenditures associated with assessing a novel treatment or choosing the best among alternative treatment choices[6]. Nonetheless, designing and maintaining registries involves a considerable expense, and access to the registry data can have costs[7–9].

The novel use of RCD to conduct trials requires reporting of elements that are not part of traditional RCTs to allow replicability and sufficient assessment of biases and applicability. For example, consent processes may be much more complex and diverse than in traditional trials and the completeness and accuracy of data that are not collected for the purpose of a trial requires special consideration. The advantage of potentially better applicability of findings from such trials may be lost if there is a mismatch between key aspects of participants in the data source in relation to a target population[10], but for an assessment of this, adequate and complete reporting needs to be provided.

Traditional RCTs are often reported inadequately,[11]and with the added complexity in new RCD-based trial designs, reporting challenges increase. To address the novel reporting needs of trials conducted using RCDs, an extension of the Consolidated Standards of Reporting Trials (CONSORT) guideline[12] for Trials using Cohorts and Routinely Collected Data has been developed[13]. The present study used trial reports identified in a scoping review that aimed to inform the guideline development and provided various examples of trials using RCD.

We aimed to: (1) describe characteristics of RCTs conducted using registry data and published after the CONSORT 2010 statement; and (2) assess and describe the quality of reporting of the

trial's reports in peer-reviewed biomedical journals. Similar analyses for trials using electronic health records or administrative databases are reported elsewhere[14,15].

Methods

A protocol for this study was published in the Open Science Framework (https://osf.io/6ukem/).

A literature search was performed for the scoping review in the framework of the CONSORT 2010 Statement extension for Trials using Cohorts and Routinely Collected Health Data[14]. The aim of the working group was to extend the original CONSORT checklist to include features relating to the use of cohorts and routinely collected health data in RCTs. These items were developed through an international collaboration of experts in the field of clinical research, and through three stages of Delphi processes[16]. Briefly, the scoping review aimed to identify items important for reporting by trials conducted using cohorts and routinely collected health data, including registries, electronic health records, and administrative data as well as to identify examples of good reporting. Several databases were searched during the literature search, which was conducted by a librarian: Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE and EBM Reviews—Cochrane Methodology Registry (Final issue, third Quarter 2012). Using a systematic search strategy, two reviewers from the scoping team screened the titles and abstracts of publications and included reports on RCTs published between 2007 and 2018, using cohorts or routinely collected data for any purpose in any population. At this stage, the RCTs were classified and divided as those using cohorts, registries, administrative databases or EHRs.

For this project, only trials using registries were relevant.

Table 1: Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement extension for Trials using Cohorts and Routinely Collected Data – Coding manual for the quality of reporting.

ORIGINAL CONSORT Item			CONSORT for cohorts and routinely collected data	Adequately reported	Inadequately or Not reported
Title and abstract					
	1c		The abstract should specify that a cohort or routinely collected database(s) was used to conduct the trial and, if applicable, provide the name of the cohort or routinely collected database(s). (Additional)	Did the authors specify in the abstract that a registry was used to conduct the trial and is the data source name provided?	Did the authors not specify that a registry was used to conduct the trial and not provide the source name?
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio		Did the authors clearly describe the trial design including allocation ratio?	Did the authors not describe the trial design including allocation ratio?
			Description of trial design (such as parallel, factorial) **including allocation ratio, the cohort or routinely collected database(s) used to conduct the trial (such as cohort, registry) and how the data were used within the trial (such as identification of eligible trial participants, trial outcomes) (Modified)**	Did the authors clearly mention the (1) registry that was used within the trial and (2) how the data was used within the trial (i.e. identification of participants, outcome measurement, other)?	Did the authors not describe the registry that was used within the trial and not describe how the data were used within the trial (i.e. identification of participants, outcome measurement, other)?
Cohort or routinely collected data					
	4a		Name and description of the cohort or routinely collected database(s) used to	Did the authors clearly (1) name and (2) describe the registry and (3) provide	Did the authors not name and describe the registry and not provide information on the

			conduct the trial, including information on the setting (such as primary care), locations, and dates, (such as periods of recruitment, follow-up, and data collection) (Additional)	information on the setting, locations, and relevant dates (e.g. periods of recruitment, follow-up, and data collection)?	setting, locations, and relevant dates (e.g. periods of recruitment, follow-up, and data collection)?
	4b		Eligibility criteria for participants in the cohort or routinely collected database(s) (Additional)	Did the authors clearly describe eligibility criteria for the registry?	Did the authors not describe all eligibility criteria for the registry?
	4c		State whether the study included person-level, institutional-level, or other data linkage across two or more databases and, if so, linkage techniques and methods used to evaluate completeness and accuracy of linkage (Additional)	Did the authors clearly state whether the study included (1) person-level, institutional-level, or other data linkage across two or more registries or databases and (2) the methods of linkage and (3) methods used to evaluate completeness and accuracy of linkage?	Did the authors not state whether the study included person-level, institutional-level, or other data linkage across two or more registries or databases and not state the methods of linkage and methods used to evaluate completeness and accuracy of linkage?
Trial participants	5a	Eligibility criteria for participants		Did the authors clearly describe the eligibility for the trial participants?	Did the authors not describe all eligibility criteria for the trial participants?
			Eligibility criteria for trial participants, **including information on how to access the list of codes and algorithms used to identify eligible participants, including methods used to assess accuracy and completeness, if applicable (Modified)**	Did the authors provide information on (1) how to access the lists of codes and algorithms used to identify participants, including (2) methods used to assess accuracy and completeness, if applicable?	Did the authors not provide information on how to access the lists of codes and algorithms used to identify participants, and not provide the methods used to assess accuracy and completeness?
	5c		Describe whether and how consent was obtained (Additional)	Did the authors describe clearly whether and how consent was obtained?	Did the authors not describe whether and how consent was obtained?
Outcomes	7a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed		Did the authors clearly define the pre-specified primary and secondary outcome measures, including how and when they were assessed?	Did the authors not define the pre-specified primary and secondary outcome measures and not define how and when they were assessed?

			Completely defined pre-specified primary and secondary outcome measures, including **how and when they were ascertained and the cohort or routinely collected database(s) used to ascertain each outcome (Modified)**	Did the authors clearly describe (1) how and (2) when they ascertained the outcomes and (3) the registry used to ascertain each outcome?	Did the authors not describe how and when they ascertained the outcomes and not describe the registry used to ascertain each outcome?
	7b		Information on how to access the list of codes and algorithms used to define or derive the outcomes from the cohort or routinely collected database(s) used to conduct the trial, including methods used to assess accuracy and completeness, if applicable (Additional)	Did the authors clearly (1) describe information on how to access the list of codes and algorithms used to define or derive the outcomes from the registry, (2) including methods used to assess accuracy and completeness?	Did the authors not describe information on how to access the list of codes and algorithms used to define or derive the outcomes from registry, and not describe the methods used to assess accuracy and completeness?
Allocation concealment mechanism	10	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Mechanism used to implement the random allocation sequence (**such as embedding an automated randomizer within the cohort or routinely collected database(s))**, describing any steps taken to conceal the sequence until interventions were assigned **(Modified)**	Did the authors clearly describe the mechanism used to implement the random allocation sequence (such as embedding the random allocation sequence within the registry), describing any steps taken to conceal the sequence until interventions were assigned?	Did the authors not describe the mechanism used to implement the random allocation sequence (such as embedding the random allocation sequence within the registry), describing any steps taken to conceal the sequence until interventions were assigned?
Participant flow (a diagram is strongly recommended)	14a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome		Did the authors define clearly for each group, (1) the number of participants who were randomly assigned, (2) received intended treatment and (3) were analysed for the primary outcome?	Did the authors not describe clearly for each group, the number of participants who were randomly assigned, and not received intended treatment and not were analysed for the primary outcome?
			For each group, the number of participants **in the cohort or routinely collected database(s) used to conduct the trial and the numbers screened for eligibility, randomly assigned, offered and accepted interventions (e.g., cohort multiple RCTs)**, received intended treatment, and	Did the authors clearly define, for each group, the number of participants in the registry used to conduct the trial and the numbers screened for eligibility, randomly assigned, received intended treatment, and analysed for the primary outcome?	Did the authors not define, for each group, the number of participants in the registry used to conduct the trial and not define the numbers screened for eligibility, randomly assigned, received intended treatment, and analysed for the primary outcome

			analysed for the primary outcome **(Modified)**		
Discussion					
Interpretation	23	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		Did the authors clearly provide an interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence?	Did the authors not provide an interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence?
			Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence, including the implications of using data that were not collected to answer the **trial research questions** (Modified)	Did the authors (1) clearly provide an interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence and (2) describe the implications of using data that were not collected to answer the specific research question?	Did the authors not provide an interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence and not describe the implications of using data that were not collected to answer the specific research question?
Other information					
Funding	26	Sources of funding and other support (such as supply of drugs), role of funders		Did the authors clearly describe the sources of funding and the role of funders?	Did the authors not describe the sources of funding and other support for the trial and the role of the funders?
			Sources of funding and other support for both the trial **and the cohort or routinely collected database(s)**, role of funders (Modified)	Did the authors clearly describe the sources of funding for the registry and trial and the role of the funder of the trial?	Did the authors not describe the sources of funding for registry and trial and not describe the role of the funder of the trial?

Reporting transparency and completeness

Trials that utilized registries to select patients or ascertain outcomes were included (R-RCTs). We limited our sample to R-RCTs published after 2011 since we were basing the items from the CONSORT 2010 checklist version.

We applied 7 selected CONSORT items and all 13 newly developed CONSORT extension items for Cohorts and Routinely Collected Health Data (Table 1) to assess and evaluate the transparency and completeness of reporting in these publications. All literature screenings and data extractions were performed using Distiller SR (Evidence Partners, Ottawa, Canada[17]).

Data extraction

For all R-RCTs, two independent reviewers (KAM, MI) extracted whether the registry source was utilized (1) to identify and recruit patients only, (2) to ascertain outcomes only, (3) for both patient recruitment and outcome assessment. Furthermore, we extracted the R-RCTs' characteristics (publication year, sample size, country of data collection, randomization type, registry use) and PICO information (population, intervention, comparator and outcome) (Table 2). We also classified publications into primary and secondary reports to evaluate any differences in the quality of reporting. Primary publications were reports on the trial's primary patient outcome(s) and may also report other trial outcomes while secondary publications were reports on only secondary patient outcomes or other post-hoc outcomes (if a report referred to a previous publication or did not specify outcome status but referred to a previous publication of results, then the report was categorized as secondary). Any disagreements were resolved in consultation with a third reviewer.

Reporting assessment

Two independent reviewers (KAM, MI) assessed the reporting transparency and completeness for all additional (new) and modified items from the CONSORT Cohorts and Routinely Collected Health Data extension checklist. For the modified items, we additionally performed the reporting assessment for the original CONSORT version in an attempt to distinguish potential poor reporting of the trials in general from the RCD-specific one. We defined the completeness of reporting as "Adequately reported" when the reviewers could clearly identify the required details for each item in the R-RCT publication, "Partially reported" when parts of the details were clearly identifiable by the reviewers in the publication (but not all, when applicable) or if the information was implied but not clearly stated by the authors,

“Inadequately reported or Not reported” when the reviewers cannot identify the required details for the item in the publication, and “Not applicable” in cases where the reporting item was not relevant to the trial (for example, if the R-RCT only used the registry to ascertain outcomes, patient identification or participant flow items would not be relevant. Details in Table 1).

The original CONSORT and extension items were considered the minimum reported information to be present in each publication, therefore we did not search for additional publications to complement missing information even if the authors mentioned that such information was published elsewhere.

Any disagreements were resolved by consensus.

Data analysis

All data were reported as simple frequency statistics such as absolute frequencies, medians and interquartile ranges (IQRs). No formal test statistics were performed.

Results

Trial characteristics

Of the 47 included R-RCT publications (Figure 1), 51% described trials that used registries to assess outcomes only, 21% used them for both patient identification and outcome assessment and 28% of them used it for identification only (Table 2).

Several R-RCTs were performed in Scandinavian countries (45%), followed by the United States of America (25%) and Continental Europe (15%) (Table 2). The median sample size was 1826 participants [IQR 347-3618]. Five trials had a cluster design, and the median cluster sample size was 136 [IQR 17-312]. The most frequently researched medical specialties were cardiology (36%), oncology (25%) and internal medicine (17%). The interventions most frequently encountered were surgical procedures (30%), guidelines and reminders to clinicians (13%) and drugs (13%); while the comparators were usual care (62%), active comparators (30%) or placebo (8%) (Table 2).

Table 2: Characteristics of registry-based trials

	RCTs using registries for:			
	Patient identification (PI) N (%)	**Outcome assessment (OA) N (%)**	**Both PI and OA N (%)**	**Total N (%)**
	13 (28%)	24 (51%)	10 (21%)	47 (100%)
Registry used for primary outcome				
Yes	0 (0%)	21 (91%)	12 (86%)	33 (70%)
No	10 (100%)	2 (9%)	1 (7%)	13 (28%)
Unclear	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Publication type				
Primary	7 (70%)	14 (61%)	13 (93%)	34 (72%)
Secondary	3 (30%)	9 (39%)	1 (7%)	13 (28%)
Sample size (median [IQR])	737 [300-6846]	2029 [268-2774]	2722 [680-7736]	1826 [347-3618]
Year (median [IQR])	2015 [2013-2016]	2015 [2013-2016]	2015 [2013-2017]	2015 [2013-2016]
Setting				
Primary care	0 (0%)	3 (13%)	1 (7%)	4 (8%)
Inpatient	1 (10%)	14 (61%)	4 (29%)	19 (40%)
Outpatient	0 (0%)	1 (4%)	1 (7%)	2 (4%)
Community medicine	9 (90%)	5 (22%)	8 (57%)	22 (47%)

Country				
Scandinavia	1 (10%)	15 (65%)	5 (36%)	21 (45%)
USA	4 (40%)	4 (17%)	4 (29%)	12 (25%)
Continental Europe	3 (30%)	3 (13%)	1 (7%)	7 (15%)
Australia	1 (10%)	0 (0%)	2 (14%)	3 (6%)
UK	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Other[1]	1 (10%)	1 (4%)	1 (7%)	3 (6%)
Medical specialty				
Cardiology	-	12 (52%)	5 (36%)	17 (36%)
Oncology	7 (70%)	2 (9%)	3 (21%)	12 (25%)
Internal medicine	0 (0%)	3 (13%)	5 (36%)	8 (17%)
Neurology/Psychiatry	1 (10%)	3 (13%)	1 (7%)	5 (11%)
Pediatrics	1 (10%)	2 (9%)	0 (0%)	3 (6%)
Other[2]	1 (10%)	1 (4%)	0 (0%)	2 (4%)
Intervention				
Surgery	0 (0%)	10 (43%)	4 (29%)	14 (30%)
Guideline/reminder	0 (0%)	2 (9%)	4 (29%)	6 (13%)
Drug	1 (10%)	5 (22%)	-	6 (13%)
Screening	3 (30%)	1 (4%)	1 (7%)	5 (11%)
Education/coaching	2 (20%)	3 (13%)	1 (7%)	6 (13%)
Lifestyle	2 (20%)	1 (4%)	1 (7%)	4 (8%)
Multiple	0 (0%)	1 (4%)	1 (7%)	2 (4%)
Other[3]	2 (20%)	0 (0%)	2 (14%)	4 (8%)
Comparator				
Usual care	8 (80%)	9 (39%)	12 (86%)	29 (62%)
Active comparator	1 (10%)	11 (48%)	2 (14%)	14 (30%)
Placebo	1 (10%)	3 (13%)	0 (0%)	4 (8%)
Outcome				
Composite	0 (0%)	12 (52%)	1 (7%)	13 (28%)
Disease occurrence/AE	1 (10%)	4 (17%)	1 (7%)	6 (13%)
Mortality	-	3 (13%)	4 (29%)	7 (15%)
Self-reported	4 (40%)	0 (0%)	0 (0%)	4 (8%)
Uptake of treatment	2 (20%)	2 (9%)	3 (21%)	7 (15%)
Quality improvement	1 (10%)	0 (0%)	1 (7%)	2 (4%)
Other[4]	2 (20%)	2 (8%)	4 (28%)	8 (17%)

AE: adverse events; R-RCT: registry-based randomized controlled trial.

Other includes: [1]Iran and Israel; [2]Intensive care and Nephrology; [3]Networking intervention, oxygen therapy, enhanced invitation letter and quality improvement; [4]Surrogate, Fatigue Impact Scale (FIS) score, letter response rate, minimum differences of interest (MDI) of weight loss, time to hospitalization and management of key modifiable risk factors.

Reporting transparency and completeness

Original items

Of the 7 selected key original CONSORT items (Table 3), 5 items (on trial design, eligibility criteria, outcome, participant flow and interpretation) were adequately reported in over 90% of the trials. Details on allocation concealment (item 10) and funding (item 26) were reported adequately in only 55% and 58% of the trials.

Extension items

Of the CONSORT extension items, 5 out of 13 items were adequately reported in at least half of the 47 trial reports (2 in at least 80%), while the reporting was insufficient for the other items (Table 4).

Mentioning of the RCD source in the trial was adequate in the abstract for 85% of the publications (item 1c; 40 of 47) and the name and type of the registry source in the main text was clear in 98% of the publications (item 3a; 46 of 47). However, the description of the registry and its setting were often not well described (item 4a, adequately reported in 24 of 47 trials, 51%).

When the registry was used for outcome measurement, details on how and when it was used for each of the outcomes was adequately reported in 79% of the publications (item 7a; 27 of 34), but there was rarely information on the codes and algorithms used to define these outcomes (item 7b; inadequately reported in 15 of 34 trials, 44%).

The criteria defining eligibility for participation in the registry were adequately reported in only 32% of the publications (item 4b; 15 of 47). When the trial was used to identify eligible patients within the registry to facilitate recruitment, the codes and algorithms used were never adequately reported (item 5a, 0 of 23). While the participant flow was almost perfectly reported for the original CONSORT item, additional details from the extension (item 14a) were almost never adequately reported (2 of 23, 9%); meaning that it was difficult to determine which participants from the registry were randomized, excluded, lost to follow up or included in the analysis.

The description of informed consent was only adequately reported 70% of the times (item 5c; 33 of 47) to let readers know if, when and how informed consent was sought.

Information on the embedding of a random allocation sequence within the registry (item 10) would have been assessable in only about one third of the publications (adequately reported in 9 out of 23 trials, 39%). Furthermore, users of these publications wouldn't have had sufficient information on RCD data linkage (item 4c, adequately reported in 4 of 47 trials, 9%). Details of funding for the RCD source (item 23) were adequately reported in 6% (3 of 47) of the publications, leaving it often unclear if the funders of the registry had any involvement in the trial design and interpretation. Lastly, the implications of using an RCD source in the RCT and discussing its strengths and limitations (item 23), was adequately reported in a quarter of our sample, making it difficult to ascertain whether the authors considered and addressed such implications when designing and interpreting their trial (12 of 47, 25%).

Table 3: Reporting quality in registry-based trials for items from the original CONSORT statement

CONSORT Item	**Item (manuscript section)**	**Total [n]**	**Adequately reported** [n (%)]	**Partially reported** [n (%)]	**Inadequately reported** [n (%)]
3a	Description of trial design (Methods)	47	46 (98%)	0 (0%)	1 (2%)
5a	Eligibility criteria (Methods)	47	46 (98%)	1 (2%)	0 (0%)
7a	Outcomes (Methods)	47	44 (94%)	3 (6%)	0 (0%)
10	Allocation concealment (Methods)	47	26 (55%)	3 (6%)	18 (38%)
14a	Participant flow (Results)	47	46 (98%)	1 (2%)	0 (0%)
23	Interpretation (Discussion)	47	46 (98%)	1 (2%)	0 (0%)
26	Funding (Other information)	47	32 (58%)	5 (11%)	10 (21%)

Table 4: Reporting quality in registry-based trials for items from the CONSORT Extension

CONSORT Extension Item	Item (manuscript section)	Total [n]*	Adequately reported [n (%)]	Partially reported [n (%)]	Inadequately reported [n (%)]
1c	Registry mentioned in abstract (Abstract)	47	40 (85%)	1 (2%)	6 (13%)
3a	Description of trial design and RCD use (Methods)	47	46 (98%)	1 (2%)	0 (0%)
4a	RCD description and settings (Methods)	47	24 (51%)	21 (45%)	2 (4%)
4b	RCD eligibility criteria (Methods)	47	15 (32%)	15 (32%)	17 (36%)
4c	RCD data linkage (Methods)	47	4 (9%)	15 (32%)	28 (59%)
5a	RCD eligibility criteria: coding & algorithms (Methods)	23	0 (0%)	4 (17%)	19 (83%)
5c	Informed consent (Methods)	47	33 (70%)	5 (11%)	9 (19%)
7a	RCD outcome: description (Methods)	34	27 (79%)	7 (21%)	0 (0%)
7b	RCD outcome: coding & algorithms (Methods)	34	4 (12%)	15 (44%)	15 (44%)
10	RCD allocation concealment (Methods)	23	9 (39%)	3 (13%)	11 (48%)
14a	RCD participant flow (Results)	23	2 (9%)	20 (87%)	1 (4%)
23	RCD trial interpretation (Discussion)	47	12 (25%)	8 (17%)	27 (57%)
26	RCD source funding (Other information)	47	3 (6%)	25 (53%)	19 (40%)

*As not all items are applicable to all 47 trials. Items 5a, 10 and 14a are only relevant to trials using registries to identify, recruit and randomize participants (n = 23); items 7a and 7b are only relevant to trials measuring outcomes using a registry (n = 34).

Discussion

Our systematic assessment of the reporting of 47 systematically identified articles on RCTs that used registries in any capacity showed that key information addressed by established CONSORT items is often adequately reported, while crucial details that are deemed essential for trials using registry data are lacking for most of them. Critical information on data linkage and data quality are typically missing.

Issues of data validation and endpoint adjudication, while often being considered the Achilles heel of using RCD, were not reported well in the trials that we assessed. Additionally, issues of applicability and generalizability were difficult to interpret since the RCD source eligibility was rarely reported. Details on linkage methodology between registries or other RCD sources, which can add errors and biases due to incomplete or incorrect matching of the participant, were pervasively difficult to ascertain.

Since the interpretation of the strengths and limitations of R-RCTs is evaluated through all of these items, this level of improper reporting introduces clearly avoidable limitations of such research, some of them may render this trial research useless and the related investments and resources might be research waste[18].

Our results for the original CONSORT items are in line with previously published data on the insufficient quality of reporting in biomedicine, although the reporting quality of the original CONSORT items in our sample was markedly higher than previously published [11,19,20]. This is the first evaluation of RCD-specific reporting in RCTs, but the findings are comparable to those observed in non-randomized studies[18]: the use of RCD was often described in titles or abstracts (72%), and the characteristics of the data source were adequately reported in most studies (60.5%), but details on the coding of participants and outcomes (adequate in 42% and 54%), validation of classification algorithms (20%) and issues of data linkages (29%) were not sufficiently reported in many studies.

There are a several limitations with our study.

Firstly, we performed an assessment of the reporting quality, which is to some degree subjective. We aimed to address this by using prespecified criteria and we performed all extractions systematically and in duplicate.

Secondly, the search strategy was developed for a different scope than that of this specific study, which may have rendered our sample less representative. The identification of the trials used for this sample depended on information in the abstract or in keywords which probably has led to an overestimation of this item (item 1c; this item would almost always be reported in our sample or we would have identified the trial only via keywords). To determine overall eligibility, we had to know that a registry was used – this implies an overestimation of the reporting quality overall for any item that relates to the general use of a registry.

Thirdly, a third of our sample included publications that were not the main publications, and we did not consider alternative publications even when authors reported that additional information could be found elsewhere. We believe that the minimum reporting standards as developed in the extension should be accessible in all primary and secondary R-RCT publications for adequate reporting.

Conclusion

In conclusion, our assessment of the reporting transparency and completeness indicates that R-RCTs are currently inadequately reported for several critical details. The implications are that the user of such a trial report wouldn't have sufficient information to replicate the trial, assess potential biases or to apply the trial findings. This highlights the urgent need for an RCD-specific reporting guideline and its uptake by all involved stakeholders, including authors, peer-reviewers and journals editors.

Acknowledgments

Data sharing

No additional data available.

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare no financial relationships with any organization that might have an interest in the submitted work in the previous three years.

KAM and LGH support the RCD for RCT initiative, which aims to explore the use of routinely collected data for clinical trials. They are members of the MARTA-Group, which aims to explore how to Make Randomized Trials more Affordable.

They have no other relationships or activities that could appear to have influenced the submitted work

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Transparency declaration

The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

Not required, this article does not contain any personal medical information about any identifiable living individuals.

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Supplemental information

Appendix 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 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="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

Appendix 2

Inclusion criteria

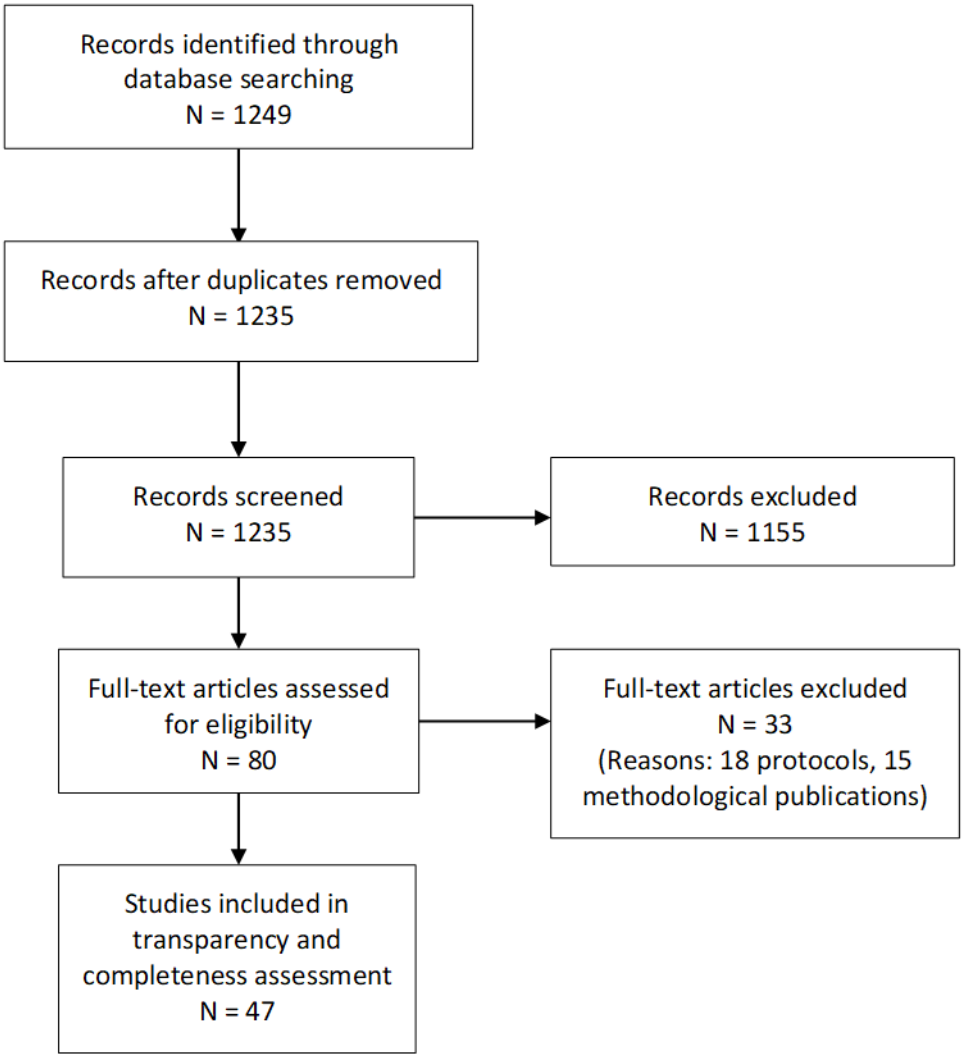
No: not an RCT using registry data. Only publications on RCTs that use registry data for conducting the trial, including activities such as identifying eligible participants for the trial or as an intervention or collecting trial outcomes, are eligible. If the publication only reports (1) issues related to methods or reporting of RCTs conducted using registry data, or (2) a protocol from an RCT conducted using registry data, it is excluded. If the RCT did not randomize humans, it is excluded.

Yes: the registry is used for identifying eligible participants. If the publication describes a trial in which the registry database was used to identify eligible trial participants, it will be included.

Yes: the registry data is used to ascertain health outcomes. If the publication describes a trial that uses registry database to ascertain health outcomes, as trial endpoints, it will be included.

Appendix 3

Figure 1: PRISMA[21] 2009 Flow Diagram



5 Discussion

In this thesis I investigated the characteristics of RCD-RCTs and explored their potential and their limitations.

5.1.1 Electronic Health Records and Costs

One of the biggest advantages of RCD-RCTs are the costs that can be saved when utilizing data not actively collected to perform the RCT. But whether the cost reduction is actually achieved when performing RCD-RCTs was not clear. We attempted to empirically observe the costs of RCD-RCTs in an effort to compare them to the frequently observed high costs associated with traditional RCTs.

In the EHR-related projects (sections 4.2 and 4.3) we observed that EHR-based trials were different than RCD-RCTs from other sources, because EHRs did not only offer information for participant recruitment and outcome assessment, but in the vast majority of such trials they also served as the intervention itself. Approximately 90% of the EHR-RCTs in our systematically derived sample deployed an EHR add-on or alert which served as the intervention evaluated within the trial, opening the doors to the so-called point-of-care trials (POC-R). Examples of POC-R in our sample include trials where EHR displayed alerts or recommendations when ordered medications where incompatible or when suggesting guideline-concordant care if certain elements in the patient's chart indicate that guidelines are not being followed[86,87].

We identified a trend in trial cost reduction when any form of automation was implemented in data extraction or patient identification via the EHR. The per-patient costs varied from 44 USD in a fully automated extraction to 2000 USD in a manual extraction. This indicates that EHRs have potential in saving resources when conducting randomized experiments, but further augmentation on the application are often needed to reduce costs compared to traditional RCTs. Simply querying the EHR list may not be a cost-effective measure.

In the limited sample we obtained, we noticed a trend of cost savings, because the costs of RCD-RCTs were clearly below the observed costs of traditional RCTs (although the empirical evidence for this is also quite scarce[88]), and because) the greater the automation in retrieving the RCD, the lower the costs(even less than 50 USD per patient).

Furthermore, we found that RCD-RCTs are valuable as they allow to perform investigations normally not amenable without using RCD. In this aspect, EHR shine, as they can be leveraged in the trial as the modality of intervention, by alerting clinicians, modifying prescription behavior and educating on guideline concordant care. By interaction during the care delivery, many novel interventions are now possible. We showed empirically that RCD-RCTs possess great value when performing avant-garde trials, as well as supporting more traditional ones.

5.1.2 Data Quality and Agreement of Treatment Effects

While RCD used to augment RCTs is a favorable idea for practical reasons, it is also possible that RCD-RCTs detect outcomes systematically differently than traditional RCTs. In addition to assessing the benefits associated with performing RCD-RCTs, we also addressed one of their often-cited limitation: the quality of the data.

There may be a great uncertainty when considering data quality of data collected routinely, fearing misclassification or mis-recorded data. While argument can be made that RCD could offer similar data quality levels as actively collected data since health professional are gathering this data while delivering care and thus at high stakes; it is also true that actively collected data in clinical trials is subject to more quality standards and regulations.

Difficulties in accessing missing or improperly recorded data in routine sources could lead to biases, but to minimize these, researchers can attempt to evenly distribute errors among treatment arms by compensating with larger sample sizes. However, if these differences were due to other factors inherently bound to the RCD-RCT trial design, such as the tendency of such trials of being more pragmatic in nature, then comparing results of traditional RCTs to RCD-RCTs might be closer to comparing pragmatic and explanatory trials.

To obtain an initial insight into this matter, we performed a meta-epidemiological analysis comparing treatment effects estimates of RCD-RCTs with traditional RCTs investigating the same research question (section 4.4).We found a 13% difference in their effect estimates (the RCD-RCTs showed less pronounced treatment benefits). This is relevant because the indicated magnitude was never previously empirically quantified. Additionally, we attempted to characterize the possible features of the RCTs that could have impacted these results and our ability to make this determination. We found that the data source type (i.e. EHR vs registry vs administrative data) and data quality seem to have little impact on the treatment effects

estimates. We did not assess the level of trial pragmatism and cannot determine its influence on treatment effect estimates; although future assessments are warranted to clearly differentiate between data-driven or pragmatism-driven variations. Our analysis of the impact of data quality was hindered by poor reporting. Future studies aiming to closer assess these differences might be possible once there is an improved RCD-RCT reporting quality.

We now know that a moderate deviation in treatment effect estimates does indeed exist, and next steps would be to validate our findings, including another meta-epidemiological analysis encompassing pragmatism as a variable, or to perform a study within a trial (SWAT[89]). SWATs occur when an hypothesis is assessed within the framework of a clinical study[89], such as comparing different data collection methods in a RCT estimating the effectiveness of a new drug. If we could split the intervention and control arms so that some participants' treatment effects are measured with RCD and others with actively collected, we would have a clearer picture of whether trial pragmatism or settings are the reason for any discrepancy rather than data source type.

5.1.3 Reporting Quality

In order to ensure replicability and assessment of RCD-RCTs and to effectively monitor the evolution of this study design, the quality of reporting of these trials needs to be at par. We know that RCD-RCTs are criticized for using low quality data and commended for their potential in cost reduction, but neither of this information was forthrightly reported and evaluable in the publications screened throughout the projects included in this thesis.

The current reporting guideline for RCD, the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD-statement[90]) focuses only on observational studies, and as such there is a great need for an RCD-RCT reporting guideline. While insufficient reporting of RCTs is not novel and it's a well-known limitation in assessing the quality of the evidence, we found in the various projects that this was even more difficult with RCD-RCTs. Within the CONSORT extension framework, aiming to support the development of a novel reporting guideline specifically for RCD-RCTs, a transparency and completeness of reporting quality assessment was performed. We assessed reports of 47 registry RCTs and showed that of the 13 novel CONSORT extension items, only 6 were adequately reported in at least half of the 47 trial reports (and only 3 in at least 80%).

Information pertaining to the quality of the RCD source (endpoint adjudication, incomplete data, etc.) and linkage among data sources was inadequately reported in most of the trials. In particular, reporting items that are really essential to determining the trial's internal and external validity were the worst reported. This provided a baseline assessment of the reporting quality and underlined the urgency to develop a specific reporting guideline which is aimed to be published in the near future[83].

5.2 Future Insights

5.2.1 RCD-RCD Research Needs

To fully leverage RCD-RCTs and progress towards a learning and dynamic healthcare system[91], there are several matters that will require further exploration.

In particular, the trial pragmatism of RCD-RCTs should be further explored and kept in context when assessing the impact of using RCD for trial results. An assessment of pragmatism level, such as with the PRECIS-2 tool (PRagmatic Explanatory Continuum Indicator Summary[1]), could shed light on variations of the effect estimates between RCD-RCTs and traditional trials.

In addition, a better estimate of costs of running RCD-RCTs as compared to traditional RCTs is necessary. Several factors will influence the affordability of RCD-RCTs, such as the cost of accessing the data (for example, the cost of obtaining access to a registry) and the amount of data curating necessary to deploy the data. For healthcare stakeholder responsible for the EHR or registry implementation, the cost of implementing and running these systems may have to be factored in.

Ideally, a more thorough investigation of the costs of conducting an RCD-RCT would be performed, by either systematically obtaining a larger amount of RCD-RCT and traditional RCT cost data, or by performing a SWAT. One could compare the costs of actively collecting certain or all endpoints in one arm, and using RCD for the other arm, and precisely determine if the costs were similar at the end of the trial.

In terms of reporting quality, the CONSORT extension for trials cohorts and routinely collected data[83] will guide researchers towards greater reporting transparency. In the future, repeated monitoring will be needed to determine the quality of reporting after dissemination and

integration of the reporting guideline and its uptake by researchers and other stakeholders in the publication process.

5.2.2 RCD Developments

A major driver in the expansion of RCD and RWE in clinical research are pharmaceutical companies and supporting industry providing data and analysis infrastructures. In the US, the establishment of the 21st Century Cures Act (Cures Act)[92], aims for discovery and approval of drug products in a quicker fashion. Cures Act is a law that was passed by the US congress in 2016, and it is described by the FDA as follows *"The 21st Century Cures Act, signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. The law builds on FDA's ongoing work to incorporate the perspectives of patients into the development of drugs, biological products, and devices in FDA's decision-making process. Cures Act enhances our ability to modernize clinical trial designs, including the use of real-world evidence, and clinical outcome assessments, which will speed the development and review of novel medical products, including medical countermeasures*"[93].

The major aspects of this law for drug development are the inclusion of novel trial designs and RWE to support the timely approval of drugs and devices. The implications are vast, and there were many opponents to this bill passing, including some consumer advocacy groups such as the National Center for Health Research[94]. While using RWD to generate RWE has several potential benefits, such as lowering the costs and efforts of conducting RCTs and exploring research questions where RCTs may be unfeasible, the Cures Act can also pose a threat to the methodological and safety standards currently employed by the FDA during the evidence reviewal process[92].

Using RCD-RCTs would be ideal, but now pharmaceutical companies can bypass gold standard RCT by providing observational RWD

While including patient reported outcomes or RWD from smartphones is an ideal step towards including patients in research and expanding the digital medicine framework, the Cures Act also promotes the use of surrogate outcomes and biomarkers, which may not be the ideal choice in terms of measured effects[95].

Furthermore, the Cures Act relaxed the drug approval requirements of new indications for the FDA, by stating that "data summaries" can be submitted instead of a formal RCT report when satisfactory drug safety evidence is already present. This opens the door for the submission of low quality, observational data rather than the uptake of RCD-RCTs by the system. While integrating RCD in clinical trials leads to similarly robust evidence (as shown in this thesis; section 4.4) , using RCD alone maintains the methodological difficulties in determining causal relationships and treatment effect estimates and may hinder the quality of evidence behind future approved treatments.

The Institute for Quality and Efficiency in Health Care (IQWiG), the agency responsible for assessing the benefits and harms of medical treatments to support reimbursement decisions in Germany, has published a report assessing the use of RWE for drug assessment and approval[96]. In contrast to the FDA, IQWiQ's perspective remains unconvinced of the current capacity of using RWD outside of a randomized framework, and they mention that this should only occur when the data quality is flawless (acknowledging that this is rarely the case). Nonetheless, IQWiG supports the use of RWD within randomized trials and found registry-based RCD-RCTs particularly promising for the future of long-term benefit assessment of marketed drugs, as their data quality was deemed consistently higher[97].

This scenario highlights the difficulty in progressing the RCD agenda in clinical research, since we wish to expand innovation while limiting laxer interpretation of findings. The uptake of RWD in generating medical evidence must also be understood, accepted and supported by patients and consumers.

A recent publication[1] reporting on a RWE roundtable with patients, highlighted several issues including the fact that not all patients were aware of the existence of real-world evidence and were overwhelmed by the many definitions in existence. Nonetheless, they expressed positive sentiment in the existence of RWE, especially since it can provide information on other patients with similar conditions and provide a sense of reassurance[98]. It will be only through inclusion of patients and consumers in the RWE discussion, legislation and deployment that positive and sustainable changes can emerge.

5.3 Closing Remarks

In this thesis work, we have initially confirmed the value of RCD-RCTs by not only providing several examples of their current application in clinical research, but also by providing insights on their cost reduction potential. Additionally, our methodological work has shed some light on the treatment effect estimates of RCD-RCTs in comparisons to traditional trials and clarified the magnitude in their difference. Both in the difficulty of obtaining the information for the projects, as well as by performing a direct assessment of RCD-RCTs, we have offered an understanding of the current reporting level and challenges that will need to be addressed with future research.

The next steps in the RCD-RCT research agenda are to understand why there is a difference in treatment effect estimates, especially considering trial pragmatism; and to determine what their precise cost reduction potential is.

We have helped conceptualizing RCD-RCTs, exploring their potential and limitations, and assessed their current use by performing a literature review of RCD-RCTs. We compared the treatment effects estimates of RCD-RCTs with those of RCTs actively collecting their data and did not find clear evidence of data quality impacting such difference. Rather, we found that these differences might be more related to other factors, and further research will be needed to expand our knowledge on this matter. Finally, we assessed the reporting quality of RCD-RCTs, which was generally insufficient, supporting the need for an RCD-specific reporting guideline.

The impact of these research efforts is a clearer understanding of the RCD-RCT landscape, and it is now possible to set a clearer research agenda on the future research needs. The vision for the future of RCD in clinical research is one where simple, point-of-care trials can be continuously performed to optimize care, not unlike A/B testing in technology companies, until we reach equal and evidence-based care for all.

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7 Further Publications

7.1 Published Original Articles (co-author)

7.1.1.1 Protocol for the development of a CONSORT extension for RCTs using cohorts and routinely collected health data

Linda Kwakkenbos, Edmund Juszczak, Lars G Hemkens, Margaret Sampson, Ole Fröbert, Clare Relton, Chris Gale, Merrick Zwarenstein, Sinéad M Langan, David Moher, Isabelle Boutron, Philippe Ravaud, Marion K Campbell, Kimberly A Mc Cord, Tjeerd P van Staa, Lehana Thabane, Rudolf Uher, Helena M Verkooijen, Eric I Benchimol, David Erlinge, Maureen Sauvé, David Torgerson and Brett D Thombs.

Res Integr Peer Rev. 2018 Oct 29;3:9. doi: 10.1186/s41073-018-0053-3.

BACKGROUND: Randomized controlled trials (RCTs) are often complex and expensive to perform. Less than one third achieve planned recruitment targets, follow-up can be labor-intensive, and many have limited real-world generalizability. Designs for RCTs conducted using cohorts and routinely collected health data, including registries, electronic health

records, and administrative databases, have been proposed to address these challenges and are being rapidly adopted. These designs, however, are relatively recent innovations, and published RCT reports often do not describe important aspects of their methodology in a standardized way. Our objective is to extend the Consolidated Standards of Reporting

Trials (CONSORT) statement with a consensus-driven reporting guideline for RCTs using cohorts and routinely collected health data.

METHODS: The development of this CONSORT extension will consist of five phases. Phase 1 (completed) consisted of the project launch, including fundraising, the establishment of a research team, and development of a conceptual framework. In phase 2, a systematic review will be performed to identify publications (1) that describe methods or reporting

considerations for RCTs conducted using cohorts and routinely collected health data or (2) that are protocols or report results from such RCTs. An initial "long list" of possible modifications to CONSORT checklist items and possible new items for the reporting guideline will be generated based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statements. Additional possible modifications and new items will be identified based on the results of the systematic review. Phase 3 will consist of a three-round Delphi exercise with methods and content experts to

evaluate the "long list" and generate a "short list" of key items. In phase 4, these items will serve as the basis for an inperson consensus meeting to finalize a core set of items to be included in the reporting guideline and checklist. Phase 5 will involve drafting the checklist and elaboration-explanation documents, and dissemination and implementation of the guideline.

DISCUSSION: Development of this CONSORT extension will contribute to more transparent reporting of RCTs conducted using cohorts and routinely collected health data.

7.1.1.2 Protocol for a scoping review to support development of a CONSORT extension for randomised controlled trials using cohorts and routinely collected health data

Linda Kwakkenbos, Mahrukh Imran, Kimberly A McCord, Margaret Sampson, Ole Fröbert, Chris Gale, Lars G Hemkens, Sinead M Langan, David Moher, Clare Relton, Merrick Zwarenstein, Eric I Benchimol, Isabelle Boutron, Marion K Campbell, David Erlinge, Sena Jawad, Philippe Ravaud, Danielle B Rice, Maureen Sauve, Tjeerd P van Staa, Lehana Thabane, Rudolf Uher, Helena M Verkooijen, Edmund Juszczak, Brett D Thombs.

BMJ Open. 2018 Aug 5;8(8):e025266. doi: 10.1136/bmjopen-2018-025266.

INTRODUCTION: Randomised controlled trials (RCTs) conducted using cohorts and routinely collected health data, including registries, electronic health records and administrative databases, are increasingly used in healthcare 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 or REporting of studies Conducted using Observational Routinely collected health Data 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.

7.1.1.3 Resource use, costs, and approval times for planning and preparing a randomized clinical trial before and after the implementation of the new Swiss human research legislation

Benjamin Speich, Nadine Schur, Dmitry Gryaznov, Belinda von Niederhäusern, Lars G. Hemkens, Stefan Schandelmaier, Alain Amstutz, Benjamin Kasenda, Christiane Pauli-Magnus, Elena Ojeda-Ruiz, Yuki Tomonaga, Kimberly Mc Cord, Alain Nordmann, Erik von Elm, Matthias Briel, Matthias Schwenkglenks, a collaboration of the MARTA (MAking Randomized Trials Affordable) and

ASPIRE (Adherence to Standard Protocol Items: REcommendations for interventional trials) Study Groups.

PLoS One. 2019 Jan 11;14(1):e0210669. doi: 10.1371/journal.pone.0210669

BACKGROUND: The preparation of a randomized controlled trial (RCT) requires substantial resources and the administrative processes can be burdensome. To facilitate the conduct of RCTs it is important to better understand cost drivers. In January 2014 the enactment of the new Swiss Legislation on Human Research (LHR) considerably changed the regulatory framework in Switzerland. We assess if the new LHR was associated with change in (i) resource use and costs to prepare an RCT, and (ii) approval times with research ethics committees (RECs) and the regulatory authority Swissmedic.

METHODS: We surveyed investigators of RCTs which were approved by RECs in 2012 or in 2016 and asked for RCT preparation costs using a pre-specified item list. Additionally, we collected approval times from RECs and Swissmedic.

RESULTS: The response rates of the investigator survey were 8.3% (19/228) for 2012 and 16.5% (47/285) in 2016. The median preparation cost of an RCT was USD 72,400 (interquartile range [IQR]: USD 59,500–87,700; n = 18) in 2012 and USD 72,600 (IQR: USD 42,800–169,600; n = 35) in 2016. For single centre RCTs a median REC approval time of 82 (IQR: 49–107; n = 38) days in 2012 and 92 (IQR: 65–131; n = 63) days in 2016 was observed. The median Swissmedic approval time for any clinical trial was 27 (IQR: 19–51; n = 213) days in 2012 and 49 (IQR: 36–67; n = 179) days in 2016. The total duration for achieving RCT approval from both authorities (REC and Swissmedic) in the parallel submission procedure applied in 2016 could not be assessed.

CONCLUSION: Based on limited data the costs to plan and prepare RCTs in Switzerland were approximately USD 72,000 in 2012 and 2016. For effective and valid research on costs and approval times of RCTs a greater willingness to share cost information among investigators and more collaboration between stakeholders with data linkage is necessary.

7.1.1.4 Contrasting evidence to reimbursement reality for off-label use (OLU) of drug treatments in cancer care: rationale and design of the CEIT-OLU project

Amanda Katherina Herbrand, Andreas Michael Schmitt, Matthias Briel, Stefan Diem, Hannah Ewald, Anouk Hoogkamer, Markus Joerger, Kimberly Alba Mc Cord, Urban Novak, Sirintip Sricharoenchai, Lars G Hemkens, Benjamin Kasenda.

ESMO Open. 2019 Dec 1;4(6):e000596. doi: 10.1136/esmoopen-2019-000596.

BACKGROUND: Off-label use (OLU) of a drug reflects a perceived unmet medical need, which is common in oncology. Cancer drugs are often highly expensive and their reimbursement is a challenge for many healthcare systems. OLU is frequently regulated by reimbursement restrictions. For evidence-based healthcare, treatment ought to be reimbursed if there is sufficient clinical evidence for treatment benefit independently of patient factors not related to the treatment indication. However, little is known

about the reality of OLU reimbursement and its association with the underlying clinical evidence. Here, we aim to investigate the relationship of reimbursement decisions with the underlying clinical evidence.

METHODS/ DESIGN: We will extract patient characteristics and details on treatment and reimbursement of cancer drugs from over 3000 patients treated in three Swiss hospitals. We will systematically search for clinical trial evidence on benefits associated with OLU in the most common indications. We will describe the prevalence of OLU in Switzerland and its reimbursement in cancer care, and use multivariable logistic regression techniques to investigate the association of approval/rejection of a reimbursement requests to the evidence on treatment effects and to further factors, including type of drug, molecular predictive markers and the health insurer.

DISCUSSION: Our study will provide a systematic overview and assessment of OLU and its reimbursement reality in Switzerland. We may provide a better understanding of the access to cancer care that is regulated by health insurers and we hope to identify factors that determine the level of evidence-based cancer care in a highly diverse western healthcare system.

7.1.1.5 Reporting Quality of Journal Abstracts for Surgical Randomized Controlled Trials Before and After the Implementation of the CONSORT Extension for Abstracts

Benjamin Speich, Kimberly A. Mc Cord, Arnav Agarwal, Viktoria Gloy, Dmitry Gryaznov, Giusi Moffa, Sally Hopewell, Matthias Briel.

World J Surg. 2019 Jun 20:2371-2378. doi: 10.1007/s00268-019-05064-1.

BACKGROUND: Adequate reporting is crucial in full-text publications but even more so in abstracts because they are the most frequently read part of a publication. In 2008, an extension for abstracts of the Consolidated Standards of Reporting Trials (CONSORT-A) statement was published, defining which items should be reported in abstracts of randomized controlled trials (RCTs). Therefore, we compared the adherence of RCT abstracts to CONSORT-A before and after the publication of CONSORT-A.

METHODS: RCTs published in the five surgical journals with the highest impact factor were identified through PubMed for 2005–2007 and 2014–2016. Adherence to 15 CONSORT-A items and two additional items for abstracts of non-pharmacological trials was assessed in duplicate. We compared the overall adherence to CONSORT-A between the two time periods using an unpaired t test and explored adherence to specific items.

RESULTS: A total of 192 and 164 surgical RCT abstracts were assessed (2005–2007 and 2014–2016, respectively). In the pre-CONSORT-A phase, the mean score of adequately reported items was 6.14 (95% confidence interval [CI] 5.90–6.38) and 8.11 in the post-CONSORT-A phase (95% CI 7.83–8.39; mean difference 1.97, 95% CI 1.60–2.34; $p < 0.0001$). The comparison of individual items indicated a significant improvement in 9 of the 15 items. The three least reported items in the post-CONSORT-A phase were randomization (2.4%), blinding (13.4%), and funding (0.0%). Specific items for non-pharmacological trials were rarely reported (approximately 10%).

CONCLUSION: The reporting in abstracts of surgical RCTs has improved after the implementation of CONSORT-A. More importantly, there is still ample room for improvement.

7.1.1.6 Nonrandomized studies using causal-modeling may give different answers than RCTs: a meta-epidemiological study

Hannah Ewald, John P. A. Ioannidis, Aviv Ladanie, Kimberly Mc Cord, Heiner C. Bucher, Lars G. Hemkens.

J Clin Epidemiol. 2020 Feb;118:29-41. doi: 10.1016/j.jclinepi.2019.10.012.

OBJECTIVES: To evaluate how estimated treatment effects agree between nonrandomized studies using causal modeling with marginal structural models (MSM-studies) and randomized trials (RCTs).

STUDY DESIGN: Meta-epidemiological study.

SETTING: MSM-studies providing effect estimates on any healthcare outcome of any treatment were eligible. We systematically sought RCTs on the same clinical question and compared the direction of treatment effects, effect sizes, and confidence intervals.

RESULTS: The main analysis included 19 MSM-studies (1,039,570 patients) and 141 RCTs (120,669 patients). MSM-studies indicated effect estimates in the opposite direction from RCTs for eight clinical questions (42%), and their 95% CI (confidence interval) did not include the RCT estimate in nine clinical questions (47%). The effect estimates deviated 1.58-fold between the study designs (median absolute deviation OR [odds ratio] 1.58; IQR [interquartile range] 1.37 to 2.16). Overall, we found no systematic disagreement regarding benefit or harm but confidence intervals were wide (summary ratio of odds ratios [sROR] 1.04; 95% CI 0.88 to 1.23). The subset of MSM-studies focusing on healthcare decision-making tended to overestimate experimental treatment benefits (sROR 1.44; 95% CI 0.99 to 2.09).

CONCLUSION: Nonrandomized studies using causal modeling with MSM may give different answers than RCTs. Caution is still required when nonrandomized “real world” evidence is used for healthcare decisions.

7.1.1.7 Acetylcholinesterase inhibitors combined with memantine for moderate to severe Alzheimer's disease: a meta-analysis

Glinz Dominik, Gloy Viktoria L., Monsch Andreas U., Kressig Reto W., Patel Chandni, Mc Cord Kimberly Alba, Ademi Zanfina, Tomonaga Yuki, Schwenkglenks Matthias, Bucher Heiner C., Raatz Heike

Swiss Med Wkly. 2019 Jun 30;149:w20093. doi: 10.4414/.

BACKGROUND: The clinical efficacy and safety of combination therapy with acetylcholinesterase inhibitor (AChEI) and memantine compared to AChEI or memantine alone in patients with Alzheimer’s disease is inconclusive.

AIMS OF THE STUDY: We conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) comparing the clinical efficacy and safety of combination therapy of AChEI and memantine to monotherapy with either substance in patients with moderate to severe Alzheimer's disease (Mini-Mental State Examination score is <20).

METHODS: We systematically searched EMBASE, Medline and CENTRAL until February 2018 for eligible RCTs. We pooled the outcome data using inverse variance weighting models assuming random effects, and assessed the quality of evidence (QoE) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

RESULTS: We included nine RCTs (2604 patients). At short-term follow-up (closest to 6 months), combination therapy compared to AChEI monotherapy had a significantly greater effect on cognition than AChEI monotherapy (standardised mean difference [SMD] 0.20, 95% confidence interval [CI] 0.05 to 0.35, 7 RCTs, low QoE) and clinical global impression (SMD −0.15, 95% CI −0.28 to −0.01, 4 RCTs, moderate QoE), but not on activities of daily living (SMD 0.09, 95% CI −0.01 to 0.18, 5 RCTs, moderate QoE) or behavioural and psychological symptoms of dementia (mean difference −3.07, 95% CI −6.53 to 0.38, 6 RCT, low QoE). There was no significant difference in adverse events (relative risk ratio 1.05, 95% CI 0.98 to 1.12, 4 RCTs, low QoE). Evidence for long-term follow-up (≥ 9 months) or nursing home placement was sparse. Only two studies compared combination therapy with memantine monotherapy.

CONCLUSIONS: Combination therapy had statistically significant effects on cognition and clinical global impression. The clinical relevance of these effects is uncertain. The overall QoE was very low. With the current evidence, it remains unclear whether combination therapy adds any benefit. Large pragmatic RCTs with long-term follow-up and focus on functional outcomes, delay in nursing home placement and adverse events are needed.

8 Curriculum Vitae

Personal information

Name:	Kimberly Mc Cord – De Iaco
Hometown:	Lugano, TI
Nationality:	CH and USA
Address:	14 Cornelius way, 02141 Cambridge, MA
Contact:	+1 (801) 683 9771 – kima.mccord@gmail.com
LinkedIn:	linkedin.com/in/kimberlymccord
ORCID ID:	orcid.org/0000-0002-2147-3160

Education

March 2017- Current: Doctoral student at the University of Basel in Epidemiology/Public Health (Faculty of Medicine). Research project at the Basel Institute for Clinical Epidemiology and Biostatistics (CEB) – University Hospital Basel

- The PhD work focuses on the application of routinely collected data (RCD) in clinical research, through the collaboration in a pragmatic randomized clinical trial (RCT) based on health insurance claims, through an international collaboration for the development of an routinely collected data reporting guideline (CONSORT extension), and through two meta-epidemiologic reviews assessing the impact and utilization of RCD in clinical trial research.

2015-2017: Master of Science (MSc) in Epidemiology at the Swiss tropical and Public Health Institute (Swiss TPH)

- The master thesis project involved conducting a systematic review on electronic health records (EHRs) and other RWD sources in clinical trials, at the Basel Institute for Clinical Epidemiology and Biostatistics (CEB).

2009-2013: Bachelor of Science (BS) in Health Promotion and Education at the University of Utah School of Public Health and Pre-Medicine Bachelor of science

- Fulfilled the requirements for attending medical school and majored in Health Promotion and Education with an emphasis in consumer health.

2008-2009: Emergency Medical Technician training at Utah Academy of Emergency Medicine (Mt. Nebo School in Provo, Utah - EMT-A and EMT- B Licenses)

2003-2007: Scuola di Operatore Socio-Sanitario (OSS) in Trevano, Switzerland (parallel to the High School diploma)

Employment history

March 2017 – December 2019: Doctoral candidate at the Institute for Clinical Epidemiology and Biostatistics (CEB) at the University Hospital of Basel

April 2016 – February 2017: Employed as a Junior Research Fellow at the Institute for Clinical Epidemiology and Biostatistics (CEB) at the University Hospital of Basel

- In the health technology assessment team (HTA), assisting with the performance of systematic reviews and other HTA-related tasks.

2014 – 2016: Employed as a Licensed Nurse practitioner (LPN/OSS) at Associazione di Cure Domiciliari del Mendrisiotto e Basso Ceresio (ACD), Ticino

- Performance of nursing duties and patient care within the homecare setting.

2010-2013: Employed at the University of Utah Hospital at 5 West Psychiatry unit as a Psychiatric Technician

- Supervision and encouragement of individuals with acute psychiatric conditions, as well as rendering of daily support groups.

2009-2010: Employed at Intermountain Healthcare's McKay-Dee Emergency Room as a Critical Care Technician

- Assistance of the physician in delivering emergency medical care, including the insertion of intravenous catheters (IVs), execution of advanced cardiac life support (ACLS) and aiding in wound care and casting/splinting.

Supervision of students/ Teaching activities

- Supported my supervisor (PD Dr. Lars G. Hemkens) in the supervision of Master student Sirintip Sricharoenchai between June 2018 and June 2019. Coordinated project deadlines, supervised data extraction, and offered support of methodological and other practical aspects.
- Attended Transferable Skills course “Becoming a good PhD supervisor”.
- Several years of patient education and teaching such as explaining and supervising self-care activities, including disease monitoring and procedures (for example, blood glucose testing, injections, urinary catheter care, parenteral feedings, etc.).

Memberships in panels, boards and individual scientific reviewing activities

- October 2016 – July 2019: Editor at the Young Researcher editorial (YRE).
  YRE is a student-edited editorial series of the International Journal of Public Health (IJPH), managed by an editorial board formed of doctoral students from the Swiss School of Public Health + (SSPH+).

- Founded the Real-World Data Alliance (www.RWDalliance.com) in an effort to bring together RWD stakeholders and academics; planning to seek funding for a conference and workshop in 2020.

Prizes, awards, fellowships

- February 2018: Awarded University of Basel excellence grant (Antelope program, University track). Grant value - approximately 8’000 CHF.
- May 2018: Awarded competitive stipend for top-up project, awarded by PhD Program in Health Sciences. Grant value - 4'125 CHF.

Personal skills

- Languages: Italian (native speaker), English (native speaker), French (Advanced proficiency – C1 level) and German (basic proficiency).
- IT: R and Python programming (intermediate level), Linux (Ubuntu) and Git (basic level), Stata and SPSS software (basic level), Microsoft Office (advanced level).