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Kubesch, Nadine; Gaitonde, Sneha; Petriti, Uarda; Bakker, Elisabeth; Basu, Swati; Birks, Laura Ellen; Aubrun, Elodie; de Vries, Sieta T; Schneider, Rahel

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REVIEW

# Use cases of registry-based randomized controlled trials—A review of the registries' contributions and constraints

**Nadine Kubesch**[1] | **Sneha Gaitonde**[2,3] | **Uarda Petriti**[4] | **Elisabeth Bakker**[5] | **Swati Basu**[2] | **Laura Ellen Birks**[6] | **Elodie Aubrun**[7] | **Sieta T. de Vries**[5] | **Rahel Schneider**[7]

[1]Cognizant Technology Solutions, Barcelona, Spain

[2]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

[3]Rutgers University Ernest Mario School of Pharmacy, Piscataway, New Jersey, USA

[4]Cognizant Technology Solutions, Amsterdam, The Netherlands

[5]Department of Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[6]Novartis Farmacéutica, S.A., Barcelona, Spain

[7]Novartis Pharma AG, Basel, Switzerland

**Correspondence**
Rahel Schneider, Novartis Pharma AG, Fabrikstrasse 4, 4056 Basel, Switzerland.
Email: rahel.schneider@novartis.com

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## Abstract

Registry-based randomized controlled trials (RRCTs) can combine the advantages of registries with those of randomization. This review aimed to expand the current knowledge on RRCT utilization and implementation by providing a comprehensive overview of RRCT use cases. A targeted literature search was conducted through July 2023 to identify articles on RRCTs. Information regarding the RRCT characteristics, their utilization, and the registries' contributions and the constraints faced was extracted. Descriptive statistics were used. We identified 102 RRCTs in 110 publications. RRCTs were mostly performed for the assessment of medical devices or surgical/clinical procedures ($n = 45$), followed by drugs ($n = 30$). More than half of the RRCTs were conducted in the Nordic countries ($n = 58$) and the most used registry types were health service registries/administrative health data ($n = 63$), followed by disease registries ($n = 46$). Approximately half of the RRCTs ($n = 53$) utilized additional data sources aside from registry data. The contribution of a registry to the RRCT was mostly for data collection and study follow-up ($n = 90$–$92$), followed by patient recruitment ($n = 56$–$61$), and randomization ($n = 28$–$38$), with varying levels of transparency in reporting. We collated author-reported constraints related to the used registries into four overarching themes, that is, data availability and completeness, data quality, representativeness, and registry infrastructure and accessibility. This review shows that RRCTs are already used in different domains and geographic regions. Guidelines on structured and transparent reporting of RRCT methods and the optimal use are, however, needed to inform decision-making by health authorities and to reach their full potential.

Nadine Kubesch and Sneha Gaitonde shared first authorship.

## INTRODUCTION

Randomized controlled trials (RCTs) are considered the gold standard for obtaining high-quality clinical evidence to demonstrate therapeutic efficacy and improve clinical care. However, RCTs often face challenges including scientific and operational complexity, waning site and patient participation, burdensome regulatory and institutional requirements, and high costs.[1] Moreover, RCTs enroll a highly selected patient sample, which limits the generalizability of study results to the real-world patient population.[1,2] Due to the challenges of RCTs, researchers have explored alternative methodological approaches to obtain high-quality clinical evidence that is both affordable and generalizable.[3–5] One option is the registry-based randomized controlled trial (RRCT). RRCTs fall under the umbrella of "pragmatic trials" and have the potential to combine the advantages of registries (low expense, external validity) with the advantages of randomization (internal validity).

There are variable definitions of what constitutes an RRCT, depending on the methods used to recruit patients and the type of registry employed to collect data.[3,6–8] Registry data can be utilized in various ways in RRCTs, for example, for identification and recruitment of patients, collecting patients' baseline characteristics including medical history and data related to the intervention, identification of endpoints for outcomes ascertainment post-intervention, and guidance of trial design.[9] Recently, a review study identified six author-reported RRCT-specific strengths, that is, the ability to compare individuals in the registry who were or were not included in the trial, complete and high-quality trial information, existing data for feasibility estimations, large samples, enhanced efficiency, and enhanced generalizability.[10] However, despite these strengths, the European Medicines Agency (EMA) emphasizes in their guideline on registry-based studies that questions remain regarding the validity and relevance of RRCTs in scientific research.[9] Echoing the concerns of the EMA, the main author-reported limitations of RRCTs in the above-mentioned review study were incomplete or insufficient registry data, insufficient uniformity of measurement processes, insufficient generalizability, and inaccessible data due to privacy/consent issues.[10]

Other review studies have shown that RRCTs are mostly conducted in the disease area of cardiology,[3,7,11] that the included RRCTs were mostly comparative effectiveness studies,[3,7] and, indeed, generally have a large sample size.[3,7,11] In the current review study, we aimed to expand the knowledge about RRCTs by providing a comprehensive overview of RRCT characteristics and an in-depth exploration of their utilization, and the registries' contributions and the constraints faced in facilitating RRCT implementation.

## MATERIALS AND METHODS

### Study design and data sources

A review was conducted using a comprehensive search strategy in PubMed to obtain articles on RRCTs (e.g., RRCT study publications, study protocol publications, statistical analysis plan publications) published in the English language through 12 July 2023 (see Appendix S1 for search terms). The title and abstract of each identified article were screened, and all articles with relevant content were screened in full by one author (NK). In addition, a manual search was performed to follow up on allusions to registries or RRCTs mentioned within the identified literature and to find additional relevant articles from the publications' list of references. Once selected, further details (e.g., on methodology) of the RRCTs were extracted from clinicaltrials.gov, if relevant.

### Outcomes

The outcomes of this study were (1) characteristics of the RRCT and used registries, that is, study domain, geographical scope, total study size (if only the protocol was available, planned study size was reported), registry type, and whether or not the RRCT used a mixed approach to data collection (i.e., collection of part or entirety of data outside the registry), (2) contributions of the registry to the RRCT based on the categories mentioned in the EMA guideline on registry-based studies,[9] that is, sample size calculation, patient recruitment (e.g., to identify patients meeting inclusion and exclusion criteria), randomization allocation, endpoint identification (i.e., the process of selecting and defining the endpoints that will be used to evaluate the impact of the intervention being studied), and data collection and study follow-up, and (3) author-reported constraints related to the use of registries in the RRCT.

### Analyses

Descriptive analyses were conducted, and results were reported as frequencies and percentages. For the characteristics of the RRCTs and used registries, an inductive qualitative approach was used to identify the study domains and registry types. Two authors (NK and UP) independently classified each of the reviewed RRCTs into

categories and identified and classified the contributions of each of the registries mentioned in the publications. In case of discrepancies between the two authors, cases were discussed among coauthors until consensus was reached.

Regarding contributions of the registry to the RRCT, when trials could not be clearly allocated to one specific category (e.g., due to ambiguous reporting), we reported ranges to account for uncertainty. The lowest value of each range represents the number of RRCTs that were certainly assigned to the associated category, while the highest value includes the number of RRCTs that were considered likely but not certainly associated with the respective category.

Using an inductive qualitative approach, one of five authors (NK, UP, STdV, RS, or SG) identified author-reported registry-related constraints and collated them into overarching themes, which were subsequently verified by another author among the group.

Microsoft 365 Excel version 2312 (build 17126.20190) (Microsoft Corporation, Redmond, USA) was used for the analyses and for the graphical presentation of the results.

## RESULTS

Of 819 hits from PubMed and the manual search, 110 publications reporting on 102 RRCTs were included in the review. The dataset is accessible in Appendix S2. Information for 11 of the trials was retrieved from the clinicaltrials.gov website due to either missing[12–14] or incomplete[15–22] information regarding trial characteristics in the publications.

### RRCT characteristics

The characteristics of the 102 RRCTs are described in Table 1. Four main study domains were identified, that is, medical device or surgical/clinical procedures ($n=45$), drugs ($n=30$), health service/public health ($n=23$), and occupational health ($n=4$). Most RRCTs were conducted in the Nordic countries (Denmark, Norway, Sweden, Finland, and Iceland) ($n=58$), followed by the United States ($n=18$) and Canada ($n=9$). No RRCT was conducted solely in South or Central America. However, one of the six multinational RRCTs involved a total of 16 countries, including Argentina, Brazil, and Panama.[15] Of the RRCTs that mentioned the (planned) study size, most RRCTs ($n=52$ of 89) aimed to include over 1500 participants.

Four categories of registry types were created among the included RRCTs based on the registries' nature and aim for data collection: health service registries/administrative health data, disease registries, surgical/clinical procedure registries, and "other." The category of health service registries/administrative health data comprises databases that collect information on healthcare services provided, focusing on their utilization, resource allocation, and health outcomes. Disease registries aim to capture comprehensive information on specific diseases or medical

**TABLE 1** Characteristics of the registry-based randomized controlled trials (RRCT).

| Characteristic | RRCT, *n* (%) |
|---|---|
| *N* | 102 |
| Study domain | |
| Medical device or surgical/clinical procedures | 45 (44.1) |
| Drugs[a] | 30 (29.4) |
| Health service/public health | 23 (22.5) |
| Occupational health | 4 (3.9) |
| Geographical scope | |
| Nordic countries[b,c] | 58 (56.9) |
| United States of America | 18 (17.6) |
| Canada | 9 (8.8) |
| Multinational | 6 (5.9) |
| The Netherlands | 2 (2.0) |
| United Kingdom | 2 (2.0) |
| Australia | 2 (2.0) |
| Germany | 2 (2.0) |
| Italy | 1 (1.0) |
| Republic of Korea | 1 (1.0) |
| Japan | 1 (1.0) |
| Total (planned) study size | |
| ≤500 | 18 (17.6) |
| >500–1500 | 19 (18.6) |
| >1500–5000 | 31 (30.4) |
| >5000 | 21 (20.6) |
| Unknown | 13 (12.7) |
| Registry type[d] | |
| Health service registries/administrative health data | 63 (61.8) |
| Disease registries | 46 (45.1) |
| Surgical/clinical procedure registries | 21 (20.6) |
| Other | 16 (15.7) |
| Mixed approach to data collection[e] | 53 (52.0) |

[a]Including medical oxygen therapy, specific nutrition regimes in care settings, or vaccine administration.

[b]Denmark, Norway, Sweden, Finland, and/or Iceland.

[c]Seven RRCTs in this group were multinational (i.e., included several Nordic countries).

[d]Each RRCT can contribute to multiple categories (e.g., if several different registries were used).

[e]Defined as collection of part or entirety of data outside the registry.

conditions. The category of surgical/clinical procedure registries encompasses databases that collect information on surgical procedures, medical devices, or clinical interventions. The "other" category mostly comprises registries that originated from the merging of different registry types. The two most common categories of registry types were health service registries/administrative health data ($n = 63$) and disease registries ($n = 46$) (Table 1). Surgical/clinical procedure registries ($n = 21$) and registries falling into the "other" category ($n = 16$) were less commonly utilized (Table 1). The "other" category included 11 RRCTs using the SWEDEHEART registry, which combines a disease registry, surgical/clinical procedure registries, and immunization registries.[5,12,23–36]

About half of the RRCTs ($n = 53$) utilized a mixed approach to data collection. Among the reported additional data collection methods for supplementation of registry data were, for example, the administration of questionnaires and collection of patient-reported and/or provider-reported information,[17,37–44] telephone and in-person interview follow-ups,[20,45–47] and study visits, clinical exams, and other health check-ups.[38,45,48]

## Registry contributions to the RRCTs

In most of the RRCTs, the registry was used for data collection and study follow-up ($n = 90$–$92$) (Figure 1), which could include the collection of data at baseline and/or during follow-up. More than half of the RRCTs ($n = 56$–$61$) used the registry for patient identification and/or recruitment. About a third of the RRCTs ($n = 28$–$38$) used the registry for participants' randomization allocation (mainly based on integrated tools, such as web-based randomization modules). Due to a lack of clarity in the reporting, the randomization allocation had the largest width of the range of all contribution categories. The use of the registry for sample size calculation was reported for 7 to 13 RRCTs. None of the RRCTs used the registry data for endpoint identification.

Furthermore, 15 RRCTs[21,37,49–62] used registry data for other purposes, including the administration of the intervention itself, such as sending reminders to participants,[37,61,62] site identification,[59] intervention feedback,[21] or investigation of the generalizability of the study results.[37,49,55,56] One RRCT used a population-based register to create an external comparator group.[60]

In one use case, the contribution of the registry involved was not specified in the publication and could not be attributed to any of the predefined categories.[63]

## Constraints regarding the use of registries for RRCT conduct

We collated author-reported constraints into four overarching themes, that is, data availability and completeness, data quality and reliability, representativeness, and

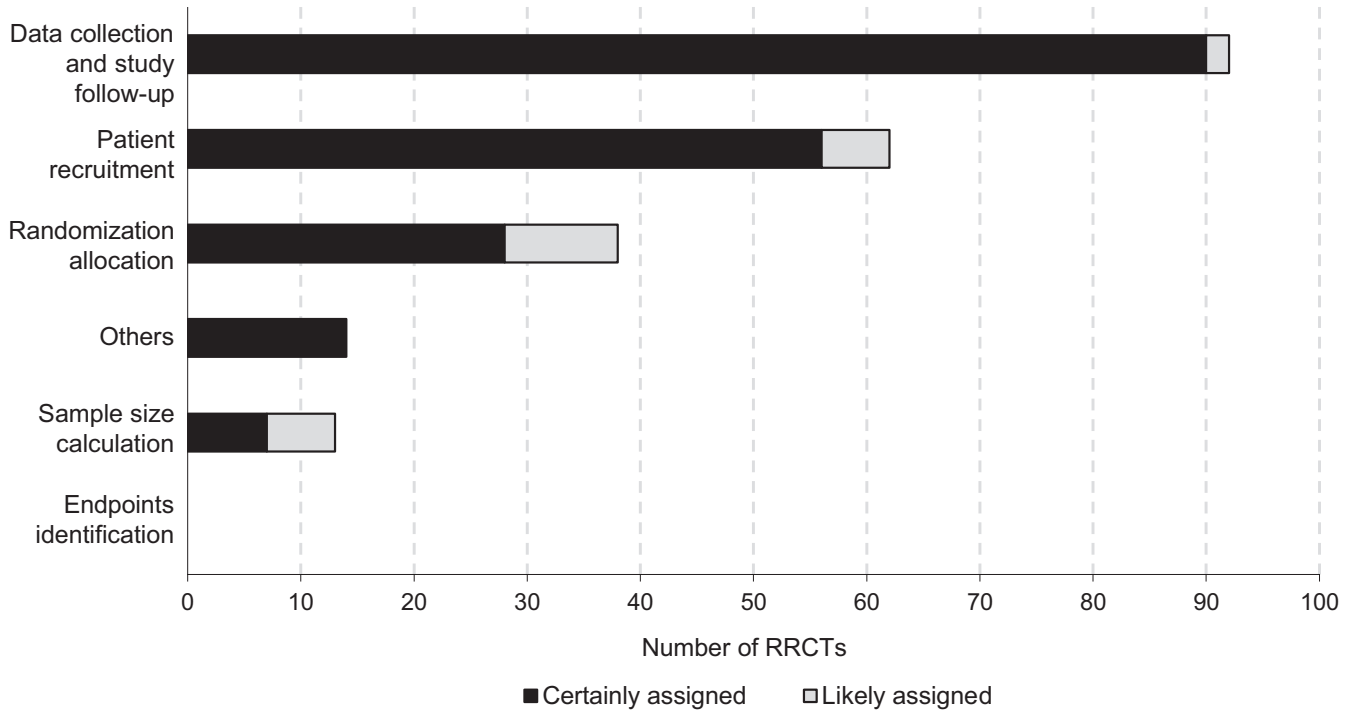


**FIGURE 1** Contribution of registries to the registry-based randomized controlled trials (RRCT).

**TABLE 2** Author-reported registry-related constraints in registry-based randomized controlled trials.

| Constraints related to | Examples with a supporting reference[a] |
|---|---|
| Data availability and completeness | • Absence of core variables[80]<br>• Missingness of data due to the registry context[55]<br>• Need for modification of outcome definition due to insufficient/lack of data availability in registry[59]<br>• Time lag in reporting[88] |
| Data quality | • Potential inaccuracy of data[89]<br>• Variation of accuracy or quality of coding between clinicians and/or sites[64]<br>• Variation of willingness and ability of healthcare providers to enter data in the registry between sites[64]<br>• Data inconsistencies due to use of different registries from different countries[36]<br>• Potential misclassification of outcome or exposure due to the lack of internal adjudication or validation[90]<br>• Potential misclassification of participant eligibility due to lack of (baseline) parameters needed for recruitment[65] |
| Representativeness | • Incomplete population capture[28]<br>• Registry sites may not be representative[16] |
| Registry infrastructure and accessibility | • Need for different randomization methods across involved countries due to lack of randomization modules within some registries[45]<br>• Technical complexity and extra work due to changes in the data system during the study period[43]<br>• Additional investment of time and effort due to establishment of data use agreements with registries[67]<br>• Collecting outcome data from routine administrative registers is not encouraged due to current norms of research ethics approvals[43] |

[a]The references provided are illustrative examples of articles mentioning the specified constraints and do not represent an exhaustive list.

registry infrastructure and accessibility. Specific examples are described in Table 2. Data availability and completeness issues of registry data included both the absence of data (i.e., variables not captured in the registry) and the missingness of data (i.e., missing observations among captured data). In addition, timeliness constraints regarding registry data were observed, for example, based on a time lag of data reporting, which impacted outcome assessment. This issue is closely linked with the challenge of an unclear temporal relationship between an intervention and the specific health outcomes reported to the registry as information regarding interventions or outcomes may not populate at the time of the event.[64]

Another overarching theme of constraints was related to the data quality (i.e., the extent to which the entered data are reliable, timely, and coherent, thus reflecting the validity of the information). For example, the ICD-10 coding may vary between clinicians and/or sites according to experience or knowledge of the illness and the quality framework in place or may not reflect all subtypes of a disease or condition.[41] Data reliability concerns stemming from a less rigorous or missing internal adjudication or validation of variables in RRCTs compared to conventional RCTs create concerns regarding misclassification of eligibility or of the outcome. For example, transplant-ineligible patients may be misclassified as eligible for transplant due to the lack of administrative health data on certain exclusion criteria (e.g., substance abuse[65]). To mitigate the consequences related to this constraint, some trials implemented external adjudication/validation practices.[31,66]

Constraints regarding representativeness were related to insufficient generalizability of the included registry sites and the incomplete population capture of the used registries (i.e., the extent to which all necessary individuals who could have been included have actually been included). An example of the latter, which was mentioned by authors of several RRCT publications, was that conservatively treated patients may have been missed because the used registry data were based on hospital admissions.[28] Several

authors reported a difference in baseline characteristics between participants who were enrolled into the RRCT and eligible non-enrolled participants within the registry. As a result, individuals participating in randomized trials may not fully represent the overall real-world patient population, even in a registry setting.[16,41,45,48,54,55,66]

Registry infrastructure and accessibility concerns related to the overall structure, organization, and availability of the registry system, including its technological capabilities, ease of use, and ability to be accessed by relevant stakeholders for data entry and retrieval. If, for example, the registry is not used routinely due to the registry interface being too burdensome to use, usability of data may be limited. In addition, it was noted that the establishment of data use agreements with registries should be considered when designing an RRCT as it may require additional investment of time and effort.[67] Another challenge includes the need for different randomization allocation methods among participating countries depending on the (un)availability of registry-embedded randomization modules.[45]

## DISCUSSION

This review provides a comprehensive overview of the characteristics of RRCTs, their registries' contributions and author-reported constraints.

Regarding the characteristics, we found that the RRCTs conducted so far have been more commonly conducted in the study domain of medical devices and surgical or clinical procedures than in other domains such as drugs. It is likely that RRCTs play a particularly important role in evaluating clinical questions where funding is difficult to access, which can be the case for the evaluation of medical devices and clinical procedures.[68] Other explanations could be the differences in the approval processes between the study domains and the recognition of the potential value of RRCTs in the specific field. Differences in requirements, classifications, and timelines of the approval processes of medical devices and drugs have for instance been observed.[69] Further studies are needed to investigate such potential explanations.

The majority of the RRCTs identified in our study were conducted in the Nordic countries. This has also been shown in previous review studies.[7,11] The accessibility of registries and the possibility of linkage to other data sources in these countries may have contributed to this finding. Of the RRCTs conducted in other countries, only two were conducted solely in Asian countries[16,60] and only one multinational RRCT included countries from South and Central America.[15] This may indicate, for instance, a potential lack of registries in these regions, a lack of possibilities to link data sources, less reliable health registers, less recognition for the registries' potential value, or differences in data protection laws, in cultural perceptions of health systems or in openness to health data sharing.

Various types of registries exist, including disease-, procedure-, or pathology-specific registries, administrative-, health-systems-based, or combined/linked registries, and product registries.[70] We found that health service registries/administrative health data are the registry type most often used in RRCTs (i.e., in 62% of the identified RRCTs). However, it is noteworthy that about half of the RRCTs in our review either could not or did not rely solely on the data available from registries. Additional data collection in conjunction with a registry may add complexity and cost to the RRCT. This shows the importance of an initial feasibility assessment and the inclusion of a fit-for-purpose registry.[9] Nevertheless, additional data collection can address several of the identified registry constraints by minimizing the occurrence of missing or inaccurate data and by enhancing the understanding of data validity and integrity. This is corroborated by a systematic review of RRCTs, indicating that the smallest amount of missing data was found in studies that combined different types of registries.[7] In this review, numerous RRCTs used multiple data sources merged into one registry or merged several registries involving a comprehensive data linkage to overcome data limitations. For RRCTs that were not conducted in Nordic countries, challenges to merging registry data included a lack of standardized data and the requirement of complex data pooling.[3,43] In general, a team of diverse stakeholders and experts on both RCTs and real-world data (including registry data) is vital in the set-up of RRCTs, which includes aligning on core data elements, to maximize their usability and impact.

The contribution of registries to RRCTs consisted most frequently of data collection and study follow-up, followed by patient recruitment and randomization. Recruitment and follow-up can be two of the most laborious and expensive parts of conducting RCTs.[71] Therefore, these are areas in which registry data use is highly advantageous for researchers.[70] Registries were not used for endpoint identification in any of the RRCTs found in our review. This may partly be attributed to the limited number of RRCTs observed in the field of rare diseases,[13,14,33] an area in which uncertainties in the choice of endpoints often arise and to which a registry could contribute.[72]

In about a third of the RRCTs, registries with integrated randomization tools were used to allocate interventions to the different groups. The methods used in RRCTs to randomize patients or investigational sites, however, were not always transparent in the publications. In the case of 10 RRCTs, it was likely, though not reported with enough

clarity whether the registry played a role in the randomization process.[19,21,22,36,64,73–78] Uncertainty regarding the use of registries was also observed for sample size calculation, patient recruitment, and data collection and study follow-up in six,[67] five,[18,19,45,64,79] and two[15,80] RRCTs, respectively. Such uncertainty is in line with the findings of another review, which called out a lack of information and transparency from RRCTs with respect to which datasets have been accessed and for what purposes.[81] Similarly, a large review study found that adequate reporting of critical features of RRCTs is often inadequate in biomedical journals, thereby hampering replicability, bias assessment, interpretation, and applicability of results.[6] Thus, clearly describing the registry contribution within the body of the publication is crucial for allowing transparency of methodology. Structural use of the Consolidated Standards of Reporting Trials (CONSORT) extension for randomized controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE)[82] could be a way forward. Moreover, it has been suggested that RRCTs should be registered as is the case for RCTs[3] and that guidance is needed for the critical appraisal and synthesis of evidence from RRCTs.[8]

As the concept of RRCTs lacks a clear definition,[3,6–8] RRCTs are expected to be treated like conventional RCTs by regulators. This means imposing strict rules and regulations that are either not applicable to RRCTs or may be challenging to follow.[83] The EMA provides general guidance on the conduct of registry-based observational studies.[9] Specific guidance on the conduct of RRCTs has been developed in Sweden. These national guidelines are freely available from the regional node for clinical studies or the regional office of the national registry center.[84] Moreover, a 5-year project that started in January 2023 aims to establish the value of registry-based real-world data in augmenting RCT data and enable the More Effective and ethical Use of Registry data to suppOrt PAtient-centered regulatory and health technology assessment (HTA) decision-making (More-EUROPA).[85] The project seeks in part to develop guidance and a protocol for RRCT conduct that could be used to answer questions posed by regulatory authorities and HTA bodies. How to evaluate and design RRCTs will also be part of the provided training program.

Guidance for RRCT conduct should not only consider the potential of RRCTs, but also their possible constraints and information on how to mitigate them. The author-reported constraints identified in our study were related to (a) data availability and completeness, (b) data quality and reliability, (c) representativeness, and (d) registry infrastructure and accessibility. These are in line with the concerns about registry-based studies reported in the EMA guideline as well as with constraints found in previous studies.[3,10,34,86]

While findings of RRCTs are deemed more generalizable to the real-world population than those of RCTs,[10] insufficient population capture or included registry sites that are not representative may still compromise external validity. In addition to reported issues regarding representativeness identified in this review, a survey study found that barriers to inhibit patients from joining a registry for RCTs include data safety concerns, potential side effects, and concerns that registry participation would impact current treatment. However, despite these concerns, roughly four of five patients were still willing to consent to have their data collected in a registry for conducting RCTs.[87]

Unless directly addressed within the study design, the identified author-reported constraints could lead to spurious associations between study interventions and outcomes, hindering the decision-making process. Especially, timeliness of data is a serious concern, since it is a core part of determining the causality of an outcome.[64] To ensure that RRCTs result in reliable and high-quality clinical evidence, the challenges of data integrity, data quality, and endpoint adjudication need to be addressed by incorporating quality assurance processes into the administration of registries.[3] RRCTs may also have repercussions for registry data that were originally meant to reflect routine clinical practice in a real-world setting. Due to the nature of RCTs, participants do not necessarily receive the current standard of care during RRCT participation. If these data are recorded within the registry and not specifically flagged as being used for an RCT, subsequent observational studies based on them may come to biased conclusions (e.g., in a study describing drug utilization). Registration of such information is needed so that it can be taken into account in observational studies by, for instance, excluding those participants or conducting sensitivity analyses.

The most important strength of the current review was the broad inclusion criteria resulting in a comprehensive overview of the current landscape of RRCTs. The following limitations should be considered when interpreting this review's findings. As there was a variety of specific methodologies used and a lack of literature describing them, the classification of study domains and registry types was done using an inductive qualitative approach. Thus, there is a risk of misclassification. However, this risk was minimized by having two reviewers independently perform the classification. In addition, for the registry contributions, the degree of uncertainty of the classification was reported, as reflected by the ranges introduced in the quantitative data. Moreover, we only considered author-reported registry-related constraints within included RRCT publications and provided a summary of the constraints in this review. As there may have been unreported constraints in working with registry data, we did not attempt to quantify them. Additionally, because this

review did not follow a systematic review approach but rather aimed to explore the breadth of RRCT applications, some publications may not have been identified in the search. Research that was unpublished or published in a language other than English may have been overlooked. Lastly, although our search strategy was broad, differences in terminology used in reporting RRCTs could have led to some publications not being identified in this review. This could have been the case if terms such as "pragmatic trials" or "registry-based clinical trials" had not been used in earlier publications. The use of different search terms, data sources and inclusion and exclusion criteria could also explain differences in included RRCTs across other review studies.[7,11]

In conclusion, this review study found that registries are used in a variety of ways in the RCT setting across many study domains, from drug-related research to public health research. Registry data were most frequently used for data collection, study follow-up, and patient recruitment. Yet, in about half of all RRCTs, additional data sources aside from registry data were utilized. To improve the suitability of registries for RRCTs, validation of outcomes and standardized processes to increase data quality and data completeness should be considered. Forthcoming discussions should include the establishment of guidelines on transparent reporting of RRCT methods and the optimal use of RRCTs to inform decision-making by health authorities.

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## CONFLICT OF INTEREST STATEMENT

EA, LB, SB, RS, and SG are Novartis employees and EA, LB, SB, and RS own shares in the company. NK and UP are employees at Cognizant Technology Solutions, which has a service agreement with Novartis Pharma AG. EB and STdV are employees at the University Medical Centre Groningen and declare no competing interests in this work.

## ORCID

*Nadine Kubesch* https://orcid.org/0000-0002-4929-3815
*Sneha Gaitonde* https://orcid.org/0009-0001-7028-7559
*Uarda Petriti* https://orcid.org/0009-0005-1933-2720
*Elisabeth Bakker* https://orcid.org/0000-0002-3359-9588
*Swati Basu* https://orcid.org/0009-0003-2739-7917
*Laura Ellen Birks* https://orcid.org/0000-0001-7024-9563
*Elodie Aubrun* https://orcid.org/0000-0002-1181-7265
*Sieta T. de Vries* https://orcid.org/0000-0001-6090-2434
*Rahel Schneider* https://orcid.org/0000-0002-2996-1409

## REFERENCES

1. Jones WS, Roe MT, Antman EM, et al. The changing landscape of randomized clinical trials in cardiovascular disease. *J Am Coll Cardiol*. 2016;68(17):1898-1907. doi:10.1016/j.jacc.2016.07.781
2. Lauer MS, D'Agostino RB Sr. The randomized registry trial – the next disruptive technology in clinical research? *N Engl J Med*. 2013;369(17):1579-1581. doi:10.1056/NEJMp1310102
3. Karanatsios B, Prang KH, Verbunt E, Yeung JM, Kelaher M, Gibbs P. Defining key design elements of registry-based randomised controlled trials: a scoping review. *Trials*. 2020;21(1):552. doi:10.1186/s13063-020-04459-z
4. Barnish MS, Turner S. The value of pragmatic and observational studies in health care and public health. *Pragmat Obs Res*. 2017;8:49-55. doi:10.2147/por.S137701
5. Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med*. 2017;377(12):1132-1142. doi:10.1056/NEJMoa1706443
6. Mc Cord KA, Al-Shahi Salman R, Treweek S, et al. Routinely collected data for randomized trials: promises, barriers, and implications. *Trials*. 2018;19(1):29. doi:10.1186/s13063-017-2394-5
7. Mathes T, Buehn S, Prengel P, Pieper D. Registry-based randomized controlled trials merged the strength of randomized controlled trails and observational studies and give rise to more pragmatic trials. *J Clin Epidemiol*. 2018;93:120-127. doi:10.1016/j.jclinepi.2017.09.017
8. Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials – what are the advantages, challenges, and areas for future research? *J Clin Epidemiol*. 2016;80:16-24. doi:10.1016/j.jclinepi.2016.08.003
9. European Medicines Agency. Guideline on registry-based studies. Updated 16 September 2021. Accessed 19 June 2024. https://www.ema.europa.eu/en/guideline-registry-based-studies-scientific-guideline
10. Krause KR, Tay J, Douglas WA, et al. Paper II: thematic framework analysis of registry-based randomized controlled trials provided insights for designing trial ready registries. *J Clin Epidemiol*. 2023;159:330-343. doi:10.1016/j.jclinepi.2023.04.015
11. Baba A, Tay J, Sammy A, et al. Paper I: heterogeneous use of registry data for participant identification and primary outcome ascertainment is found in registry-based randomized controlled trials: a scoping review. *J Clin Epidemiol*. 2023;159:289-299. doi:10.1016/j.jclinepi.2023.04.016
12. Jernberg T. Evaluation of decreased usage of betablockers after myocardial infarction in the SWEDEHEART registry (REDUCE-SWEDEHEART). ClinicalTrialsgov. Accessed 12 July 2023. https://clinicaltrials.gov/study/NCT03278509
13. Korngut L. A registry-based clinical trial of pimozide in patients with neuromuscular junction transmission dysfunction due to ALS. 26 October 2016. ClinicalTrialsgov. Accessed 12 July 2023. https://clinicaltrials.gov/study/NCT02463825

14. Korngut L. A clinical trial of pimozide in patients with amyotrophic lateral sclerosis (ALS) (Pimozide2). 28 May 2020. ClinicalTrialsgov. Accessed 12 July 2023. https://clinicaltrials.gov/study/NCT03272503
15. Heyland DK, Patel J, Compher C, et al. The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT protein): an international, multicentre, pragmatic, registry-based randomised trial. *Lancet*. 2023;401(10376):568-576. doi:10.1016/s0140-6736(22)02469-2
16. Park DW, Kang DY, Ahn JM, et al. Routine functional testing or standard care in high-risk patients after PCI. *N Engl J Med*. 2022;387(10):905-915. doi:10.1056/NEJMoa2208335
17. Roberge P, Houle J, Provost JR, et al. A pragmatic randomized controlled trial of a group self-management support program versus treatment-as-usual for anxiety disorders: study protocol. *BMC Psychiatry*. 2022;22(1):135. doi:10.1186/s12888-021-03675-4
18. Sundh J, Bornefalk-Hermansson A, Ahmadi Z, et al. REgistry-based randomized controlled trial of treatment and Duration and mortality in long-term OXygen therapy (REDOX) study protocol. *BMC Pulm Med*. 2019;19(1):50. doi:10.1186/s12890-019-0809-7
19. Ferreira-Legere LE, Chu A, Rashid M, et al. Making informed CHOICES: the launch of a "big data" pragmatic trial to improve cholesterol management and prevent heart disease in Ontario. *Healthc Q*. 2020;22(4):6-9. doi:10.12927/hcq.2020.26091
20. Lund LH, Oldgren J, James S. Registry-based pragmatic trials in heart failure: current experience and future directions. *Curr Heart Fail Rep*. 2017;14(2):59-70. doi:10.1007/s11897-017-0325-0
21. Alexander KP, Wang TY, Li S, et al. Randomized trial of targeted performance feedback to facilitate quality improvement in acute myocardial infarction care. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):129-135. doi:10.1161/circoutcomes.110.958470
22. Ecker BL, Brajcich BC, Ellis RJ, Ko CY, D'Angelica MI. Registry-based randomized clinical trials in surgery: working with ACS-NSQIP and the AHPBA to conduct pragmatic trials. *J Surg Oncol*. 2022;125(1):89-92. doi:10.1002/jso.26742
23. Nordenskjöld AM, Agewall S, Atar D, et al. Randomized evaluation of beta blocker and ACE-inhibitor/angiotensin receptor blocker treatment in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA-BAT): rationale and design. *Am Heart J*. 2021;231:96-104. doi:10.1016/j.ahj.2020.10.059
24. Pasupathy S, Lindahl B, Tavella R, et al. Randomized evaluation of beta blocker and ACE-inhibitor/angiotensin receptor blocker treatment for post infarct angina in patients with myocardial infarction with non-obstructive coronary arteries: a MINOCA-BAT sub study rationale and design. *Front Cardiovasc Med*. 2021;8:717526. doi:10.3389/fcvm.2021.717526
25. Bäck M, Leosdottir M, Ekström M, et al. The remote exercise SWEDEHEART study-rationale and design of a multicenter registry-based cluster randomized crossover clinical trial (RRCT). *Am Heart J*. 2023;262:110-118. doi:10.1016/j.ahj.2023.04.014
26. Böhm F, Mogensen B, Östlund O, et al. The Full Revasc (FfrgUidance for compLete non-cuLprit REVASCularization) Registry-based randomized clinical trial. *Am Heart J*. 2021;241:92-100. doi:10.1016/j.ahj.2021.07.007
27. Erlinge D, Koul S, Eriksson P, et al. Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction – a registry-based randomized clinical trial in the SWEDEHEART registry (the VALIDATE-SWEDEHEART trial). *Am Heart J*. 2016;175:36-46. doi:10.1016/j.ahj.2016.02.007
28. Götberg M, Berntorp K, Rylance R, et al. 5-year outcomes of PCI guided by measurement of instantaneous wave-free ratio versus fractional flow reserve. *J Am Coll Cardiol*. 2022;79(10):965-974. doi:10.1016/j.jacc.2021.12.030
29. Götberg M, Christiansen EH, Gudmundsdottir I, et al. Instantaneous wave-free ratio versus fractional flow reserve guided intervention (iFR-SWEDEHEART): rationale and design of a multicenter, prospective, registry-based randomized clinical trial. *Am Heart J*. 2015;170(5):945-950. doi:10.1016/j.ahj.2015.07.031
30. Hofmann R, Befekadu Abebe T, Herlitz J, et al. Routine oxygen therapy does not improve health-related quality of life in patients with acute myocardial infarction-insights from the randomized DETO2X-AMI trial. *Front Cardiovasc Med*. 2021;8:638829. doi:10.3389/fcvm.2021.638829
31. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med*. 2017;377(13):1240-1249. doi:10.1056/NEJMoa1706222
32. Omerovic E, Erlinge D, Koul S, et al. Rationale and design of switch Swedeheart: a registry-based, stepped-wedge, cluster-randomized, open-label multicenter trial to compare prasugrel and ticagrelor for treatment of patients with acute coronary syndrome. *Am Heart J*. 2022;251:70-77. doi:10.1016/j.ahj.2022.05.017
33. Omerovic E, James S, Erlinge D, et al. Rationale and design of BROKEN-SWEDEHEART: a registry-based, randomized, parallel, open-label multicenter trial to test pharmacological treatments for broken heart (takotsubo) syndrome. *Am Heart J*. 2023;257:33-40. doi:10.1016/j.ahj.2022.11.010
34. Foroughi S, Wong HL, Gately L, et al. Re-inventing the randomized controlled trial in medical oncology: the registry-based trial. *Asia Pac J Clin Oncol*. 2018;14(6):365-373. doi:10.1111/ajco.12992
35. Davies JE. iFR-SWEDEHEART: answering the questions of a decade of scientific debate about iFR and FFR. *J Am Coll Cardiol*. 2022;79(10):975-976. doi:10.1016/j.jacc.2022.01.009
36. Yndigegn T, Lindahl B, Alfredsson J, et al. Design and rationale of randomized evaluation of decreased usage of beta-blockers after acute myocardial infarction (REDUCE-AMI). *Eur Heart J Cardiovasc Pharmacother*. 2023;9(2):192-197. doi:10.1093/ehjcvp/pvac070
37. Jakobsen L, Christiansen EH, Freeman P, et al. Randomized clinical comparison of the dual-therapy CD34 antibody-covered Sirolimus-eluting combo stent with the sirolimus-eluting orsiro stent in patients treated with percutaneous coronary intervention: the SORT OUT X trial. *Circulation*. 2021;143(22):2155-2165. doi:10.1161/circulationaha.120.052766
38. Nilvér H, Wessberg A, Dencker A, et al. Women's childbirth experiences in the Swedish Post-Term Induction Study (SWEPIS): a multicentre, randomised, controlled trial. *BMJ Open*. 2021;11(4):e042340. doi:10.1136/bmjopen-2020-042340
39. Sjöberg V, Tseli E, Monnier A, et al. Effectiveness of the eVISualisation of physical activity and pain intervention (eVIS) in Swedish Interdisciplinary Pain Rehabilitation Programmes: study protocol for a registry-based randomised controlled

clinical trial. *BMJ Open*. 2022;12(4):e055071. doi:10.1136/bmjopen-2021-055071

40. Willert MV, Thulstrup AM, Bonde JP. Effects of a stress management intervention on absenteeism and return to work – results from a randomized wait-list controlled trial. *Scand J Work Environ Health*. 2011;37(3):186-195. doi:10.5271/sjweh.3130
41. Juul L, Maindal HT, Zoffmann V, Frydenberg M, Sandbaek A. A cluster randomised pragmatic trial applying self-determination theory to type 2 diabetes care in general practice. *BMC Fam Pract*. 2011;12:130. doi:10.1186/1471-2296-12-130
42. Tastaldi L, Bencsath K, Alaedeen D, et al. Telescopic dissection versus balloon dissection for laparoscopic totally extraperitoneal inguinal hernia repair (TEP): a registry-based randomized controlled trial. *Hernia*. 2019;23(6):1105-1113. doi:10.1007/s10029-019-02001-y
43. Hemminki E, Heikkilä K, Sevón T, Koponen P. Special features of health services and register based trials – experiences from a randomized trial of childbirth classes. *BMC Health Serv Res*. 2008;8:126. doi:10.1186/1472-6963-8-126
44. Elden H, Hagberg H, Wessberg A, et al. Study protocol of SWEPIS a Swedish multicentre register based randomised controlled trial to compare induction of labour at 41 completed gestational weeks versus expectant management and induction at 42 completed gestational weeks. *BMC Pregnancy Childbirth*. 2016;16:49. doi:10.1186/s12884-016-0836-9
45. Ragnarsson S, Janiec M, Modrau IS, et al. No-touch saphenous vein grafts in coronary artery surgery (SWEDEGRAFT): rationale and design of a multicenter, prospective, registry-based randomized clinical trial. *Am Heart J*. 2020;224:17-24. doi:10.1016/j.ahj.2020.03.009
46. Blixt S, Mukka S, Försth P, Westin O, Gerdhem P. Study protocol: the SunBurst trial – a register-based, randomized controlled trial on thoracolumbar burst fractures. *Acta Orthop*. Jan 24 2022;93:256-263. doi:10.2340/17453674.2022.1614
47. Zwisler AD, Soja AM, Rasmussen S, et al. Hospital-based comprehensive cardiac rehabilitation versus usual care among patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease: 12-month results of a randomized clinical trial. *Am Heart J*. 2008;155(6):1106-1113. doi:10.1016/j.ahj.2007.12.033
48. Saxon DR, Chaussee EL, Juarez-Colunga E, et al. A toolbox approach to obesity treatment in urban safety-net primary care clinics: a pragmatic clinical trial. *J Gen Intern Med*. 2019;34(11):2405-2413. doi:10.1007/s11606-019-05222-0
49. Hansen KN, Jensen LO, Maeng M, et al. Five-year clinical outcome of the biodegradable polymer ultrathin strut sirolimus-eluting stent compared to the biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: from the SORT OUT VII trial. *Circ Cardiovasc Interv*. 2023;16(1):e012332. doi:10.1161/circinterventions.122.012332
50. Jensen LO, Maeng M, Raungaard B, et al. Randomized comparison of the polymer-free biolimus-coated BioFreedom stent with the ultrathin strut biodegradable polymer sirolimus-eluting Orsiro stent in an all-comers population treated with percutaneous coronary intervention: the SORT OUT IX trial. *Circulation*. 2020;141(25):2052-2063. doi:10.1161/circulationaha.119.040241
51. Jensen LO, Thayssen P, Maeng M, et al. Randomized comparison of a sirolimus-eluting Orsiro stent with a biolimus-eluting Nobori stent in patients treated with percutaneous coronary intervention: rationale and study design of the Scandinavian Organization for Randomized Trials with Clinical Outcome VII trial. *Am Heart J*. 2015;170(2):210-215. doi:10.1016/j.ahj.2015.05.009
52. Jensen LO, Thayssen P, Maeng M, et al. Randomized comparison of a biodegradable polymer ultrathin strut sirolimus-eluting stent with a biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: the SORT OUT VII trial. *Circ Cardiovasc Interv*. 2016;9(7):e003610. doi:10.1161/circinterventions.115.003610
53. Christiansen EH, Jensen LO, Thayssen P, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. *Lancet*. 2013;381(9867):661-669. doi:10.1016/s0140-6736(12)61962-x
54. Raungaard B, Jensen LO, Tilsted HH, et al. Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. *Lancet*. 2015;385(9977):1527-1535. doi:10.1016/s0140-6736(14)61794-3
55. Rasmussen K, Maeng M, Kaltoft A, et al. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet*. 2010;375(9720):1090-9. doi:10.1016/s0140-6736(10)60208-5
56. Galløe AM, Thuesen L, Kelbaek H, et al. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA*. 2008;299(4):409-416. doi:10.1001/jama.299.4.409
57. Jakobsen L, Christiansen EH, Maeng M, et al. Randomized clinical comparison of the dual-therapy CD34 antibody-covered sirolimus-eluting combo stent with the sirolimus-eluting Orsiro stent in patients treated with percutaneous coronary intervention: rationale and study design of the Scandinavian Organization for Randomized Trials with clinical outcome (SORT OUT) X trial. *Am Heart J*. 2018;202:49-53. doi:10.1016/j.ahj.2018.04.019
58. Kempe A, Daley MF, Barrow J, et al. Implementation of universal influenza immunization recommendations for healthy young children: results of a randomized, controlled trial with registry-based recall. *Pediatrics*. 2005;115(1):146-154. doi:10.1542/peds.2004-1804
59. Rao SV, Hess CN, Barham B, et al. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial. *JACC Cardiovasc Interv*. 2014;7(8):857-867. doi:10.1016/j.jcin.2014.04.007
60. Miyagawa S, Kainuma S, Imanishi Y, et al. Prognosis of patients with heart failure receiving autologous myoblast patches – comparison of single-arm trial data to registry data. *Circ J*. 2023;87(4):481-486. doi:10.1253/circj.CJ-22-0319
61. van den Broek IV, van Bergen JE, Brouwers EE, et al. Effectiveness of yearly, register based screening for chlamydia in the Netherlands: controlled trial with randomised stepped wedge implementation. *BMJ*. 2012;345:e4316. doi:10.1136/bmj.e4316

62. Stolpe S, Choudhry NK. Effect of automated immunization registry-based telephonic interventions on adult vaccination rates in community pharmacies: a randomized controlled trial. *J Manag Care Spec Pharm*. 2019;25(9):989-994. doi:10.18553/jmcp.2019.25.9.989
63. Hegelund MH, Ritz C, Nielsen TL, et al. Multidimensional individualized nutritional therapy for individuals with severe chronic obstructive pulmonary disease: study protocol for a registry-based randomized controlled trial. *Trials*. 2023;24(1):86. doi:10.1186/s13063-023-07099-1
64. Hollingsworth R, Palmu A, Pepin S, et al. Effectiveness of the quadrivalent high-dose influenza vaccine for prevention of cardiovascular and respiratory events in people aged 65 years and above: rationale and design of a real-world pragmatic randomized clinical trial. *Am Heart J*. 2021;237:54-61. doi:10.1016/j.ahj.2021.03.007
65. Yohanna S, Naylor KL, Mucsi I, et al. A quality improvement intervention to enhance access to kidney transplantation and living kidney donation (EnAKT LKD) in patients with chronic kidney disease: clinical research protocol of a cluster-randomized clinical trial. *Can J Kidney Health Dis*. 2021;8:2054358121997266. doi:10.1177/2054358121997266
66. Fröbert O, Götberg M, Angerås O, et al. Design and rationale for the influenza vaccination after myocardial infarction (IAMI) trial. A registry-based randomized clinical trial. *Am Heart J*. 2017;189:94-102. doi:10.1016/j.ahj.2017.04.003
67. Zolin SJ, Petro CC, Prabhu AS, et al. Registry-based randomized controlled trials: a new paradigm for surgical research. *J Surg Res*. 2020;255:428-435. doi:10.1016/j.jss.2020.05.069
68. Doherty DA, Tong SYC, Reilly J, et al. Registry randomised trials: a methodological perspective. *BMJ Open*. 2023;13(3):e068057. doi:10.1136/bmjopen-2022-068057
69. Marshall J, Morrill K, Gobbe M, Blanchard L. The difference between approval processes for medicinal products and medical devices in Europe. *Ophthalmologica*. 2021;244(5):368-378. doi:10.1159/000517522
70. Rubinger L, Ekhtiari S, Gazendam A, Bhandari M. Registries: big data, bigger problems? *Injury*. 2023;54(Suppl 3):S39-S42. doi:10.1016/j.injury.2021.12.016
71. Anderson BR, Gotlieb EG, Hill K, et al. Registry-based trials: a potential model for cost savings? *Cardiol Young*. 2020;30(6):807-817. doi:10.1017/s1047951120001018
72. Jansen-van der Weide MC, Gaasterland CMW, Roes KCB, et al. Rare disease registries: potential applications towards impact on development of new drug treatments. *Orphanet J Rare Dis*. 2018;13(1):154. doi:10.1186/s13023-018-0836-0
73. Diederichsen AC, Rasmussen LM, Søgaard R, et al. The Danish Cardiovascular Screening Trial (DANCAVAS): study protocol for a randomized controlled trial. *Trials*. 2015;16:554. doi:10.1186/s13063-015-1082-6
74. Dombkowski KJ, Costello LE, Harrington LB, Dong S, Kolasa M, Clark SJ. Age-specific strategies for immunization reminders and recalls: a registry-based randomized trial. *Am J Prev Med*. 2014;47(1):1-8. doi:10.1016/j.amepre.2014.02.009
75. Dombkowski KJ, Harrington LB, Dong S, Clark SJ. Seasonal influenza vaccination reminders for children with high-risk conditions: a registry-based randomized trial. *Am J Prev Med*. 2012;42(1):71-75. doi:10.1016/j.amepre.2011.09.028
76. Nevarez NM, Brajcich BC, Liu J, et al. Cefoxitin versus piperacillin-tazobactam as surgical antibiotic prophylaxis in patients undergoing pancreatoduodenectomy: protocol for a randomised controlled trial. *BMJ Open*. 2021;11(3):e048398. doi:10.1136/bmjopen-2020-048398
77. Luijkx J, Winkler P, van 't Hof A. Clopidogrel or ticagrelor alongside dabigatran in acute coronary syndrome and indication for NOAC: a study rationale. *Future Cardiol*. 2022;18(4):265-274. doi:10.2217/fca-2021-0085
78. Nørgaard CH, Friedrich S, Hansen CT, et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. *Alzheimers Dement (N Y)*. 2022;8(1):e12268. doi:10.1002/trc2.12268
79. Panse J, Tölle D, Fiegle E, et al. Scheduled removal of central venous catheters (CVC) to prevent CVC-related bloodstream infections in patients with hematological disease or autologous stem cell transplantation: a registry-based randomized simulation-study. *Ann Hematol*. 2022;101(10):2317-2324. doi:10.1007/s00277-022-04958-w
80. van Diepen S, Norris CM, Zheng Y, et al. Comparison of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker management strategies before cardiac surgery: a pilot randomized controlled registry trial. *J Am Heart Assoc*. 2018;7(20):e009917. doi:10.1161/jaha.118.009917
81. Lensen S, Macnair A, Love SB, et al. Access to routinely collected health data for clinical trials – review of successful data requests to UK registries. *Trials*. 2020;21(1):398. doi:10.1186/s13063-020-04329-8
82. Kwakkenbos L, Imran M, McCall SJ, et al. CONSORT extension for the reporting of randomised controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE): checklist with explanation and elaboration. *BMJ*. 2021;373:n857. doi:10.1136/bmj.n857
83. Crona J, Baudin E, Terzolo M, et al. ENSAT registry-based randomized clinical trials for adrenocortical carcinoma. *Eur J Endocrinol*. 2021;184(2):R51-R59. doi:10.1530/eje-20-0800
84. Nyberg K, Hedman P. Swedish guidelines for registry-based randomized clinical trials. *Ups J Med Sci*. 2019;124(1):33-36. doi:10.1080/03009734.2018.1550453
85. More-EUROPA. Accessed January 1, 2023. https://umcgresearch.org/en-GB/more-europa
86. Prang KH, Karanatsios B, Verbunt E, et al. Clinical registries data quality attributes to support registry-based randomised controlled trials: a scoping review. *Contemp Clin Trials*. 2022;119:106843. doi:10.1016/j.cct.2022.106843
87. Murphy E, O'Keeffe A, O Shea N, Long E, Eustace JA, Shiely F. Patient perceptions of the challenges of recruitment to a renal randomised trial registry: a pilot questionnaire-based study. *Trials*. 2021;22(1):597. doi:10.1186/s13063-021-05526-9
88. Al-Jaishi AA, McIntyre CW, Sontrop JM, et al. Major Outcomes with Personalized Dialysate TEMPerature (MyTEMP): rationale and design of a pragmatic, registry-based, cluster randomized controlled trial. *Can J Kidney Health Dis*. 2020;7:2054358119887988. doi:10.1177/2054358119887988
89. Haile ST, Joelsson-Alm E, Johansson UB, et al. Effects of a person-centred, nurse-led follow-up programme on adherence to prescribed medication among patients surgically treated for intermittent claudication: randomized clinical trial. *Br J Surg*. 2022;109(9):846-856. doi:10.1093/bjs/znac241
90. Everett CC, Fox KAA, Reynolds C, et al. Evaluation of the impact of the GRACE risk score on the management and

outcome of patients hospitalised with non-ST elevation acute coronary syndrome in the UK: protocol of the UKGRIS cluster-randomised registry-based trial. *BMJ Open*. 2019;9(9):e032165. doi:10.1136/bmjopen-2019-032165

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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