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ORIGINAL RESEARCH

# Both clinical trial register and electronic bibliographic database searches were needed to identify randomized clinical trials for systematic reviews: an evaluation study

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## Abstract

**Objectives:** To determine whether clinical trial register (CTR) searches can accurately identify a greater number of completed randomized clinical trials (RCTs) than electronic bibliographic database (EBD) searches for systematic reviews of interventions, and to quantify the number of eligible ongoing trials.

**Study Design and Setting:** We performed an evaluation study and based our search for RCTs on the eligibility criteria of a systematic review that focused on the underrepresentation of people with chronic kidney disease in cardiovascular RCTs. We conducted a combined search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform through the Cochrane Central Register of Controlled Trials to identify eligible RCTs registered up to June 1, 2023. We searched Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE for publications of eligible RCTs published up to June 5, 2023. Finally, we compared the search results to determine the extent to which the two sources identified the same RCTs.

**Results:** We included 92 completed RCTs. Of these, 81 had results available. Sixty-six completed RCTs with available results were identified by both sources (81% agreement [95% CI: 71−88]). We identified seven completed RCTs with results exclusively by CTR search (9% [95% CI: 4−17]) and eight exclusively by EBD search (10% [95% CI: 5−18]). Eleven RCTs were completed but lacked results (four identified by both sources (36% [95% CI: 15−65]), one exclusively by EBD search (9% [95% CI: 1−38]), and six exclusively by CTR search (55% [95% CI: 28−79])). Also, we identified 42 eligible ongoing RCTs: 16 by both sources (38% [95% CI: 25−53]) and 26 exclusively by CTR search (62% [95% CI: 47−75]). Lastly, we identified four RCTs of unknown status by both sources.

**Conclusion:** CTR searches identify a greater number of completed RCTs than EBD searches. Both searches missed some included RCTs. Based on our case study, researchers (eg, information specialists, systematic reviewers) aiming to identify all available RCTs should continue to search both sources. Once the barriers to performing CTR searches alone are targeted, CTR searches may be a suitable alternative. 

*Keywords:* Clinical trial register search; Clinical trial registry; Systematic review; Randomized clinical trials; Randomized controlled trials; Information retrieval

## 1. Introduction

Randomized clinical trials (RCTs) are pivotal in providing robust evidence on treatment effectiveness [1]. RCTs inform interventional systematic reviews and meta-analysis and are key to clinical guideline development. To identify RCTs, methodological guidelines for systematic reviews (ie, Chapter 4: Searching for and selecting studies, *Cochrane Handbook for Systematic Reviews of Interventions*) recommend combining electronic bibliographic

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**What is new?**

**Key findings**

- In this case study of cardiovascular randomized clinical trials (RCTs), clinical trial register (CTR) searches identify a higher number of completed RCTs than electronic bibliographic database (EBD) searches for systematic reviews of interventions.
- There is substantial agreement (81%) between CTR and EBD searches in identifying completed RCTs with available results, and both uniquely identify completed RCTs not found by the other source.

**What this adds to what was known?**

- In this case study, most completed RCTs exclusively identified by EBD search were not registered.

**What is the implication and what should change now?**

- Researchers, including librarians, information specialists, and systematic reviewers, who wish to identify all relevant RCTs should adopt a dual search strategy using both CTRs and EBDs to ensure comprehensive identification, and the validity of these results may be confirmed in other clinical areas.
- Searching in CTRs alone for RCTs may be possible once the barriers of CTR searches are properly tackled, particularly through ensuring results reporting and implementing simplified retrieval mechanisms of results and publications linked to clinical trial records.

database (EBD) searches with clinical trial register (CTR) searches [2]. Searching both sources minimizes the risk of missing relevant RCTs; while searches for RCTs in EBDs are limited to the identification of published articles, CTRs allow the identification of RCTs regardless of their publication status [3−7].

RCTs may be missed for various reasons, such as incorrect indexing in search databases, publication in journals not included in the systematic search, or papers not being published at all [8−10]. Consequently, the effect estimates identified by the systematic review may be biased [8−12]. Another issue contributing to biased effect estimates in systematic reviews is publication bias: the selective publication of studies due to the strength or direction of the results [5,8,13−17]. This might result in distorted effect sizes and incorrect conclusions in systematic reviews [5,11,12].

Exclusively searching CTRs for RCTs may be a suitable alternative to the current recommendation. Clinical trial (CT) registration is typically performed a priori, enabling CTR searches to identify both completed and ongoing trials that lack a published article, and which might have otherwise been missed with an EBD search alone [3,7,8]. Consequently, CTR searches help to assess and potentially minimize the impact of publication bias on systematic review findings. Furthermore, while completed RCTs directly inform systematic reviews, the identification of ongoing trials serves as a useful indicator for determining the timing of systematic review updates [7].

Inconsistent CT registration and inadequate results reporting (ie, no link to published article or posting in CT record) can hinder exclusively performing CTR searches for systematic reviews [18−20]. A study from 2014 which compared systematic review search strategies reported a low yield of identified RCTs from CTR searches and inadequate adherence to CT registration, while a review from 2018 on RCTs of newly developed drugs suggested that the completeness of CT registers improved in recent years [18,19]. This development led us to reevaluate current search approaches for identifying RCTs for systematic reviews of interventions.

In this study, we aimed to determine whether CTR searches can accurately identify a greater number of completed RCTs than EBD searches for systematic reviews of interventions, and to quantify the number of eligible ongoing trials. Based on a case study of cardiovascular RCTs, we conducted similar searches, adjusting them accordingly to the specific source, in both CTRs and EBDs, and compared the search results.

## 2. Methods

### 2.1. Study design

We performed an evaluation study based on a case study to assess the accuracy of CTR and EBD searches in identifying RCTs for systematic reviews of interventions. We registered our study protocol on the Open Science Framework [21].

### 2.2. Case study

This is a substudy of a systematic review that assessed the underrepresentation of people with chronic kidney disease in cardiovascular RCTs [22]. The systematic review searched for eligible RCTs in ClinicalTrials.gov through the Cochrane Central Register of Controlled Trials (CENTRAL) with a combination of keywords for cardiovascular diseases, cardiovascular risk factors, and the interventions of interest [23−25]. The systematic review's aim and protocol have been reported previously [22]. The protocol is registered in the International Prospective Register for Systematic Reviews (PROSPERO CRD42022296746).

**Table 1.** PICOS

| Elements | Description | |
|---|---|---|
| Population | Adults with a history of CVD [22]:<br>• Coronary artery disease<br>• Atrial fibrillation<br>• Congestive heart failure<br>• Peripheral arterial disease<br>• Stroke | Adults with ≥1 cardiovascular risk factor [26–28]:<br>• Overweight and obesity<br>• Hypertension<br>• Hyperglycemia and diabetes mellitus<br>• Chronic or end-stage kidney disease |
| Intervention[a] | Direct factor Xa inhibitors (B01AF):<br>• Apixaban (B01AF02)<br>• Betrixaban (B01AF04)<br>• Edoxaban (B01AF03)<br>• Rivaroxaban (B01AF01) | Direct thrombin inhibitors (B01AE):<br>• Argatroban (B01AE03)<br>• Dabigatran (B01AE07) |
| Comparator | • No treatment<br>• Placebo<br>• Standard of care | • Another treatment<br>• Different dosage |
| Outcome | • All-cause mortality<br>• Cardiovascular mortality<br>• Major cardiovascular event (MACE)/ another composite cardiovascular endpoint<br>• Coronary artery disease | • Cerebrovascular disease<br>• Peripheral arterial disease<br>• Hospitalization for heart failure<br>• Development of heart failure stage III or IV (New York Heart Association classification)<br>• End-stage kidney disease |
| Study type | RCTs with at least 100 participants | |

CVD, cardiovascular disease; RCT, randomized clinical trial.
[a] The interventions are listed with their Anatomical Therapeutic Chemical (ATC) code in brackets.

### 2.3. Eligibility criteria

The eligibility criteria of our study were identical to the case study [22]. Due to the proof-of-concept character of our study, we limited our search to RCTs evaluating direct anticoagulants. Table 1 shows the Population, Intervention, Comparison, Outcome and Study Design of our study.

### 2.4. Information sources

We based our search on the databases recommended by "Chapter 4: Searching for and selecting studies" of the *Cochrane Handbook of Systematic Reviews of Interventions* [7]. To identify trial registration records of eligible RCTs, we performed a search for ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP) records within CENTRAL as part of the Cochrane library (https://www.cochranelibrary.com/) on June 1, 2023 [24,25,29]. We obtained the published reports from the completed CT records by following the provided link or by manual search. For the EBD search, we searched CENTRAL (https://www.cochranelibrary.com/), EMBASE (embase.com; 1947-), and MEDLINE (Ovid MEDLINE(R) ALL 1946) on June 5, 2023, for published articles of RCTs either describing a study protocol or reporting the main results of the RCT [23,30,31]. No limitations on publication year were applied to either search (supplementary material, Sections A and B).

### 2.5. Screening and data collection

#### 2.5.1. Screening

*2.5.1.1. CTR search.* Two reviewers (TK, DI) screened the CT records in duplicate. The same two reviewers performed full-text screening to determine whether a trial met the inclusion criteria. We based our decision on the CT record only in case no published article was available. Any disagreements were resolved through discussion to reach consensus or by involving a third reviewer.

*2.5.1.2. EBD search.* One reviewer (TK) performed title-abstract screening, while a second reviewer (DI) screened a 20% random sample. Any disagreements were resolved through discussion to reach consensus or by involving a third reviewer. We regarded an inter-rater reliability of 0.7 of Cohen's κ as sufficient for agreement between the two reviewers [32,33]. Before full-text screening, we held a calibration session. In this session, the reviewers screened 20 full-texts and discussed whether to include a published article. Then, one reviewer (TK, DI, or LHV) proceeded independently with the remaining set for full-text screening.

#### 2.5.2. Data collection

For both approaches, one reviewer extracted the data (TK, DI, or LHV), while a second (TK, DI, or LHV) verified them. Collected items included CT registration

number, name of CT registry, study acronym, first author, last author, contact details, study year, study location/s, funding, and intervention (supplementary material, Section C).

### 2.6. Comparison of the search strategies

#### 2.6.1. Matching procedure

To compare the accuracy of the search strategies, we retrieved the CT registration numbers (if any) from the published articles retrieved by EBD search, and combined them with the records retrieved by CTR search in one spreadsheet in Microsoft Excel (version 16.68) [34]. Then, we compared the identified RCTs by CT registration number, study acronym, study location, and intervention.

*2.6.1.1. Matched RCTs.* We considered an RCT as ''identified by both sources'' if the same CT registration number was present in both sets or if the study acronym and/or study location and/or intervention presented itself as identical (supplementary material, Section D).

*2.6.1.2. Unmatched RCTs*

*2.6.1.2.1. RCTs identified by CTR search only.* For unmatched RCTs identified exclusively by CTR search, we first checked whether the CT record referred to a published article. If not, we manually searched CENTRAL, EMBASE, and MEDLINE using the CT registration number, the study acronym, first and last authors, study location, and/or intervention. If we identified a published article, we classified the RCT as ''only identified by CTR search and published in indexed journals'' (falsely missed by EBD search) (supplementary material, Section D). Additionally, we checked (ie, by Google search) whether an article had been published in a journal not indexed by CENTRAL, EMBASE, or MEDLINE (not indexed in searched EBDs). Otherwise, we considered the RCT as ''only available in CT record'' (supplementary material, Section D).

*2.6.1.2.2. RCTs identified by EBD search only.* For unmatched RCTs identified exclusively by EBD search, we manually searched ClinicalTrials.gov and the ICTRP using the CT registration number (if provided), the study acronym, the study location, and/or the intervention. If we identified a CT registration, we considered the RCT as ''identified by EBD search only and registered'' (falsely missed by CTR search) (supplementary material, Section D). In case we failed to identify a CT registration by manual search, we contacted study authors for more information. If we did not receive a reply to our enquiries, we considered the RCT as ''nonregistered'' (not included in CTRs) (supplementary material, Section D).

#### 2.6.2. Classification of identified RCTs

After the matching, we classified RCTs according to their completion status and their results availability as either ''completed with(out) results'' or ''ongoing,'' based on the (planned) study completion date available in the CT record (supplementary material, Section D). We classified RCTs with a study completion date before January 1, 2022, as ''completed with results,'' if any results were available. In case no results were available, we contacted study authors for more information. In case we did not receive a reply to our enquiries, we considered the RCT as ''completed without results'' (protocol only) (supplementary material, Section D). Ongoing RCTs had a planned study completion recorded in their CT record after December 31, 2021. We chose December 31, 2021, as a cut-off as we anticipated that the main results would be published within 12 months after study completion [35–37]. In case we identified RCTs of unknown completion status, we contacted study authors for more information on the respective RCTs. In case we did not receive a response to our enquiries, we categorized these RCTs as ''RCTs of unknown status'' (supplementary material, Section D).

### 2.7. Statistical analysis

For our analysis, we focused on completed RCTs, since we expected these to be available in both sources. We treated ongoing RCTs as a separate outcome because we assumed that they would be available primarily in CTRs. RCTs of unknown status were reported as exploratory outcomes (supplementary material, Section D).

We calculated counts and percentages or median and range to describe the characteristics of the included RCTs. We calculated counts, percentages, and the corresponding 95% CI for the outcomes using the Wilson score interval [38]. We performed all statistical analyses in RStudio, version 2022.07.2 [39].

## 3. Results

### 3.1. Study flow and sample characteristics

The EBD search identified a total of 9395 records for screening. We excluded 8648 of these records during title-abstract screening as they did not meet the eligibility criteria. We excluded 396 records of these because they were conference abstracts or secondary analyses. We screened 351 reports on full-text for eligibility and finally included 97 RCTs by EBD search (Fig 1). The CTR search identified a total of 523 records. We excluded 214 of these records during record screening, assessed 309 reports for eligibility and finally included 129 eligible RCTs (Fig 2).

After the comparison (Section 2.6 Comparison of the search strategies), we identified a total of 138 unique RCTs from both sources. Of these, 92 were completed (Table 2). Eighty-one completed RCTs had results available, while 11 did not. We included 42 ongoing RCTs and four of unknown study status (Tables 3 and 4). Most RCTs were from Asia (38%) and funded by industry (53%) (Table 5). The

median year of publication for published articles ($n$ = 101) was 2018 (range: 2007−2023). The median (planned) completion year of RCTs without published articles as listed in the CT record ($n$ = 21) was 2021 (IQR: 2015−2026) (Table 5).

### 3.2. Comparison of the search strategies

#### 3.2.1. Completed RCTs with results

We included a total of 81 completed RCTs with results. Out of these, we identified 66 RCTs in both sources (representing 81% agreement [95% CI: 71−88]) (Table 2). We also identified eight eligible RCTs by EBD search only, accounting for 10% of the total (95% CI: 5−18) (Table 2). Among these, three RCTs (4% [95% CI: 1−10]) had a CT registration while five did not (6% [95% CI: 3−14]) (Table 2). We were unable to obtain information regarding the missing CT registration from the study authors upon request. Two of the ClinicalTrials.gov-registered RCTs were not present in the Cochrane CENTRAL database at the time of searching, while one was available, but our CTR search strategy did not identify it (supplementary material, Section E). Moreover, we identified 7 eligible RCTs exclusively by CTR search, constituting 9% of the total (95% CI: 4−17) (Table 3). Among these, one RCT (1% [95% CI: 0−7]) had an article published in indexed journals but was not identified by the EBD search strategy we employed (thus falsely missed by EBD search; supplementary material, Section E), zero in non-indexed journals (0% [95% CI: 0−1]), and six had results only available in their CT record (not available in EBDs) (8% [95% CI: 3−15]) (Table 2).

#### 3.2.2. Completed RCTs without results

We included a total of 11 completed RCTs without results. Out of these, we identified four RCTs by both sources (representing 36% agreement [95% CI: 15−65]) (Table 2). We also identified one RCT exclusively by EBD search, accounting for 9% of the total (95% CI: 1−38) (Table 2). Moreover, we identified six eligible RCTs exclusively by CTR search, constituting 58% of the total (95% CI: 28−79) (Table 2). Among these, all six only had a CT

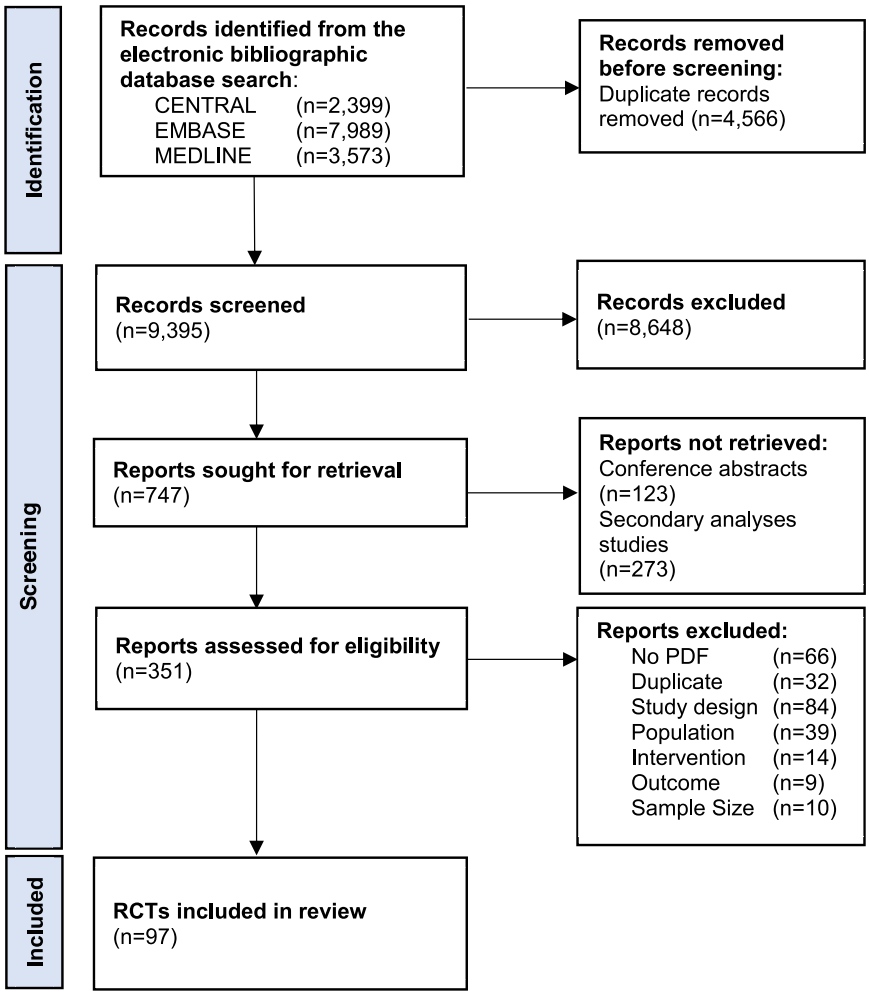


**Figure 1.** Flow diagram of the electronic bibliographic database search. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

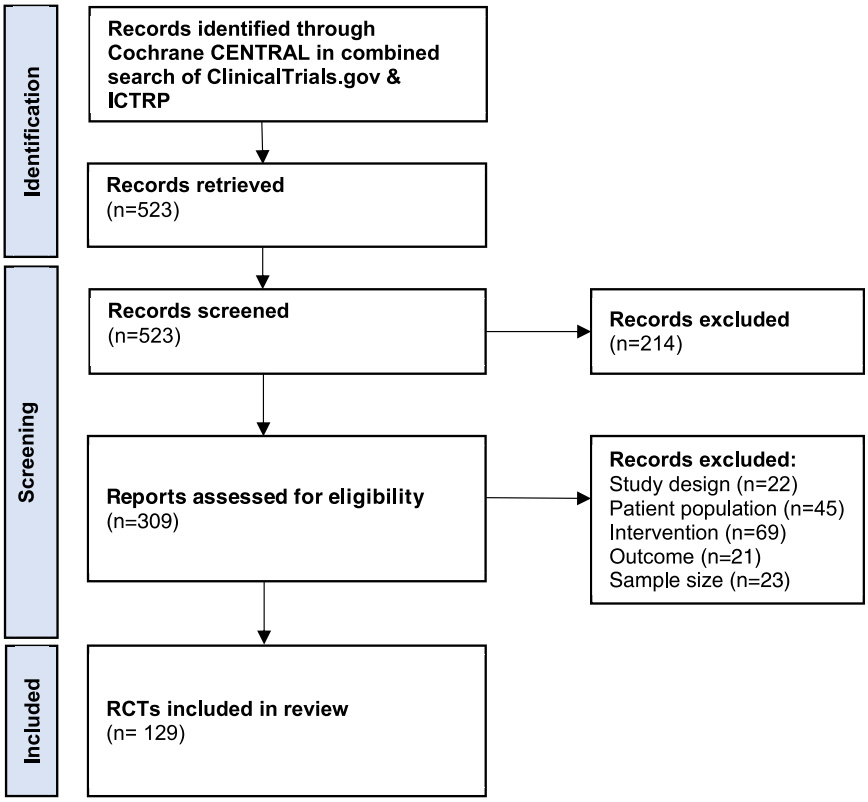


**Figure 2.** Flow diagram of the clinical trial register search. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

record available (protocol only, without results) (55% [95% CI: 28−79]) (Table 2). None of our requests for information on the completed RCTs without results succeeded.

#### 3.2.3. Ongoing RCTs

We included 42 eligible ongoing RCTs (Table 3). We identified 16 of these by both sources (representing 38% agreement [95% CI: 25−53]). The remaining 26 were identified through CTR search and only available as CT records, accounting for 62% of the total (95% CI: 47−75).

#### 3.2.4. RCTs of unknown status

We identified 4 RCTs of unknown status by both sources (100% [95% CI: 51−100]) (Table 4). None of our request for information on these trials succeeded.

## 4. Discussion

We conducted an evaluation study based on a case study of cardiovascular RCTs to determine whether CTR searches can accurately identify a greater number of completed RCTs than EBD searches and quantified the number of eligible ongoing RCTs. Our results indeed showed that CTR searches identify a greater number of completed RCTs compared to EBD searches ($n$ = 83 vs $n$ = 79). However, this was mainly due to completed RCTs for which results were not published. Moreover, we found a high agreement of completed RCTs with published results between the two searches (81%). We identified some completed RCTs exclusively by one source. Furthermore, we identified all ongoing trials either by both sources or exclusively by CTR search. Our findings support methodological guidelines recommending the inclusion of CTR searches in systematic review search strategies and align with previous study results showing that CTR searches identify additional RCTs for systematic reviews of interventions [2,4,40].

### 4.1. Comparison to previous studies

In recent years, a priori CT registration has significantly improved and has contributed to the increased accuracy of CTR searches. In our study, 96% of the included RCTs were registered in a CTR. These results differ from previous findings by Glanville et al. in 2014, which indicated low compliance with CT registration but align with findings by Knelangen et al. in 2018 which indicated high adherence to CT registration, particularly in RCTs that focus on new drugs [19]. Moreover, our study confirms the observations of Glanville et al. and Knelangen et al. that the CTR search primarily overlooks unregistered trials [18,19]. Nevertheless, it is worth noting that in Glanville et al.'s study, RCTs were still missed even after 2005, whereas Knelangen et al. found that the non-registered studies were either pre-2005 or non-RCTs. In contrast, our study found that all five

**Table 2.** Identification source of completed RCTs per results availability

| Completed RCTs | n(%) | [95% CI] |
|---|---|---|
| With results ($n$ = 81) | | |
| *Identified by both sources*[a] | 66 (81) | 71–88 |
| *Identified by EBD search only*[a] | 8 (10) | 5–18 |
| Registered RCT[a,c] | 3 (4) | 1–10 |
| Non-registered RCT[a] | 5 (6) | 3–14 |
| *Identified by CTR search only*[a] | 7 (9) | 4–17 |
| Results published in indexed journals[a,c] | 1 (1) | 0–7 |
| Results published in nonindexed journals[a] | 0 (0) | 0–1 |
| Results available in clinical trial record only[a] | 6 (8) | 3–15 |
| Without results ($n$ = 11) | | |
| *Identified by both sources*[b] | 4 (36) | 15–65 |
| *Identified by EBD search only*[b,c] | 1 (9) | 1–38 |
| *Identified by CTR search only*[b] | 6 (55) | 28–79 |
| Protocol published in indexed journals[b] | 0 (0) | 0–79 |
| Protocol published in non-indexed journals[b] | 0 (0) | 0–79 |
| Protocol available in clinical trial record only[b] | 6 (55) | 28–79 |

CTR, clinical trial register; EBD, electronic bibliographic database; RCT, randomized clinical trial.
[a] Denominator: completed RCTs with results ($n$ = 81).
[b] Denominator: completed RCTs without results ($n$ = 11).
[c] Additional information provided in Section E of the supplementary material.

RCTs lacking CT registration were conducted after 2005. While Knelangen et al. predominately analyzed pivotal trials conducted within the context of drug approval in Europe, Glanville et al. and our study included RCTs from a broader geographical context. This may explain the difference in findings between our study and the more recent findings by Knelangen et al.

Lacking CT registration presents a major challenge to exclusively performing CTR searches. Universal coverage of a CT registration mandate and better adherence to the already existing ones are important pillars for exclusively performing CTR searches in the future [3,41,42]. Furthermore, the CT search missed a few trials in our study, despite being available in ClinicalTrials.gov, simply because they were not included in CENTRAL. A search directly through ClinicalTrials.gov or the ICTRP would have likely led to the identification of these trials.

Retrieving results from CT records requires additional effort. Most CT records do not have any results posted or provide links to published articles [20,43]. In our study, this was especially the case for ICTRP records. Results reporting items in the CT record were nearly always incomplete, making manual searches to obtain the published article or contacting study authors for information necessary. ClinicalTrials.gov–registered trials, on the other hand,

**Table 3.** Identification source of ongoing RCTs

| Ongoing RCTs | n(%) | [95% CI] |
|---|---|---|
| Protocol identified by both sources | 16 (38) | 25–53 |
| Protocol identified by EBD search only | 0 (0) | 0–1 |
| Registered RCT | 0 (0) | 0–1 |
| Non-registered RCT | 0 (0) | 0–1 |
| Protocol identified by CTR search only | 26 (62) | 47–75 |
| Protocol published in indexed journal | 0 (0) | 0–1 |
| Protocol published in nonindexed journal | 0 (0) | 0–1 |
| Protocol available in clinical trial record only | 26 (62) | 47–75 |

Denominator: ongoing RCTs ($n$ = 42).
CTR, clinical trial register; EBD, electronic bibliographic database; RCT, randomized clinical trial.

**Table 4.** Identification source of RCTs of unknown status

| RCTs of unknown status | n (%) | [95% CI] |
|---|---|---|
| Protocol identified by both sources | 4 (100) | 51–100 |
| Protocol identified by EBD search only | 0 (0) | 0–49 |
| Protocol identified by CTR search only | 0 (0) | 0–49 |

Denominator: RCTs of unknown status ($n$ = 4).
CTR, clinical trial register; EBD, electronic bibliographic database; RCT, randomized clinical trial.

**Table 5.** Characteristics of included RCTs

| Characteristics | n (%) |
|---|---|
| Study location | |
| Africa | 0 |
| Asia | 54 (38) |
| Australia | 1 (1) |
| Europe | 25 (18) |
| North America | 11 (9) |
| South America | 3 (2) |
| Multicontinental | 44 (32) |
| Funding | |
| Government | 9 (7) |
| Industry | 73 (53) |
| Institutional | 28 (20) |
| Unspecified/miscellaneous | 8 (6) |
| Government, institutional | 3 (2) |
| Industry, institutional | 16 (11) |
| Industry, government | 1 (1) |
| Year of publication (median, range)[a] | 2018 (2007–2023) |
| Year of planned completion (median, range)[b] | 2021 (2015–2026) |

RCT, randomized clinical trial.
[a] RCTs with published articles ($n$ = 101).
[b] RCTs without published articles and (planned) completion date available in CT record ($n$ = 21).

provided CT data as well as links to the published articles more frequently.

CTR searches remain the most important tool to explore the presence of publication bias on systematic review findings. In our study, we found that searching CTRs led to the identification of additional RCTs that are not included in EBDs yet (Tables 2–4). Nearly half of the unpublished trials had results posted in their CT record. Systematic review findings may be greatly impacted by publication bias if only EBDs are searched and unpublished trials not identified [11,12].

The screening effort for eligible RCTs is significantly reduced with a CTR search compared to that of an EBD search. In our study, we needed to screen one-twentieth of records identified by CTR search compared to the number of records identified by EBD search ($n$ = 523 vs $n$ = 9,395), while identifying more eligible completed RCTs with the CTR search ($n$ = 83 vs $n$ = 79).

### 4.2. Implications

CTR searches are valuable for identifying completed RCTs without published articles and ongoing RCTs. In our study, the CTR search identified more completed trials than the EBD search and identified all eligible ongoing trials. Nevertheless, the CTR search did not identify all completed RCTs with available results. Therefore, researchers (ie, librarians/information specialists and systematic reviewers) aiming to identify all RCTs with available results should continue to search both CTRs and EBDs.

CTR searches have the advantage of significantly reducing the screening effort. For systematic searches where the absence of a few RCTs (ie, unregistered RCTs) is acceptable, performing only CTR searches is a good alternative to the combined search approach. Nevertheless, an important disadvantage of performing CTR searches is the current infrastructure of most CTRs. To make CTR searches more user-friendly for researchers (ie, librarians/information specialists, systematic reviewers), some important issues need to be addressed. First, results reporting in the CT records need to be improved significantly. Most completed RCTs did not report any results in their CT record. Second, links to the published articles need to be added to the CT records. These were not provided in most cases, especially for ICTRP records. The manual search for results and published articles contributed significantly to the workload of our project. Finally, we also found that it was impossible to download all published articles from the CT record at once or to load them directly into our systematic review software. Addressing these issues will greatly improve the efficiency of CTR searches and make it more feasible to search CTRs alone for RCTs for systematic reviews.

### 4.3. Strengths and limitations

Our study has several strengths. We followed recommended methodological guidelines to identify RCTs for systematic reviews of interventions [2,44]. Moreover, we searched multiple databases with different combinations of search terms [23,25,29–31]. Also, we contacted study authors for information on missing trial information. Besides, our search represented a research question from clinical practice. Nevertheless, our study has some important limitations. First, CT registration has only been mandated for publication in major medical journals since 2005 [3]. CTR searches may not identify older trials since these may have fewer registrations available [3,18]. However, we specifically focused on direct anticoagulants since they emerged relatively recently, and we expected a larger amount of RCTs identifiable by both sources than with any (older) medication group included in the systematic review on which the case study was based upon [22]. Second, we performed our evaluation based on a specific subset of cardiovascular RCTs. Although the proof-of-concept nature of our study allowed for this, our results may differ from other clinical fields and may require confirmation. Third, although CTRs include all types of intervention studies, we specifically focused on RCTs. This design limitation means that our conclusions are not applicable to CTR searches of other study designs. Nonetheless, other study designs are less frequently registered than RCTs and therefore less relevant for CTR searches [3,45–47]. Fourth, we only screened some records in duplicate. However, we held a calibration session before full-text screening, and the reviewers achieved our prespecified interrater reliability threshold of 0.7. In addition, we checked for the presence of unmatched RCTs in the original datasets to ensure

that incorrectly excluded RCTs were rightfully included in the final analysis.

## 5. Conclusion

Our study findings show that CTR searches identify a greater number of completed RCTs compared to EBD searches. In addition, CTR searches allowed us to identify all eligible ongoing RCTs. Of note, CTR searches also identify RCTs that have been completed but not yet published. Nevertheless, we found that some RCTs were identified exclusively by either CTR or EBD search. Hence, if the goal is to identify all RCTs with available results, both CTRs and EBDs should continue to be searched. Once the barriers to conducting CTR searches alone are removed, CTR searches will be a more suitable alternative to the combined approach of searching both EBDs and CTRs. Therefore, improving the usability and infrastructure of CTRs would be beneficial to facilitate the review process and enable the assessment of critical information.

## CRediT authorship contribution statement

**Tabea Kaul:** Writing − original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julia M.T. Colombijn:** Writing − review & editing, Methodology, Investigation, Conceptualization. **Robin W.M. Vernooij:** Writing − review & editing, Methodology, Conceptualization. **Rene Spijker:** Writing − review & editing, Software, Resources, Methodology, Conceptualization. **Demy L. Idema:** Investigation, Data curation. **Linde F. Huis in 't Veld:** Investigation, Data curation. **Johanna A.A. Damen:** Writing − review & editing, Supervision, Methodology, Investigation, Conceptualization. **Lotty Hooft:** Writing − review & editing, Supervision, Methodology, Conceptualization.

## Data availability

Data will be made available on request.

## Declaration of competing interest

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## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2024.111300.

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