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ORIGINAL ARTICLE

Registered trials address questions already answered with high-certainty evidence: A sample of current redundant research

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Abstract

Objective: To identify clinical trials registered later than 2015, that study the effect of an intervention on a primary outcome whose "Certainty of Evidence" (CoE) has already been rated "high" in a Cochrane SR.

Study Design and Setting: We searched the Cochrane Library for all SRs from 2015. We analyzed SRs of interventions and excluded withdrawn reviews or those with no Summary of Findings (SoF) table. We retrieved the GRADE CoE ratings of each SR's primary outcomes in the SoF tables and identified those rated "high." We searched the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials to identify records of clinical studies that tackled those outcomes and were registered after the date of publication of the respective 2015 SR.

Results: We selected 602 SRs. Eighty-one contained a "high" CoE rating on at least one primary outcome, totaling 152 primary outcomes rated "high." We found 39 clinical trials registered for primary outcomes with evidence already rated as "high" in a 2015 Cochrane SR.

Conclusion: This study shows the existence of clinical trials registered to study primary outcomes whose CoE has already been rated "high" in a Cochrane SR.

Keywords: Clinical trials as topic; Systematic reviews as topic; Research; GRADE

What is new?

Key findings

- We found registered RCTs that research questions that have already been answered.

What this adds to what is known?

- Redundant trials waste research resources and may harm the involved patients. Our work reveals that redundant trials still exist, despite sustained efforts and mechanisms aimed to stop them.

What is the implication, what should change now

- We suggest that researchers do a systematic review of the literature before planning a new RCT. We encourage ethics committees either to ensure this happens or to conduct a systematic review themselves before approving an RCT protocol.

1. Introduction

Clinical trials should focus on testing interventions for which evidence is either lacking (they have not been tested yet) or low-quality (they need further assessment). So, when a new trial is planned, researchers should conduct an extensive literature search in order to identify the existent

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trials or systematic reviews (SRs) that tackle the topic they are about to investigate [1]. Then, when writing the trial's protocol, they should take into consideration all the findings from the literature they reviewed. Furthermore, as the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement indicates it in its "Background and Rationale" item, trial protocols should include a "Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished), examining benefits and harms for each intervention" [2].

The literature search concludes whether the intervention has been tested before. If the intervention has been tested, then the quality of the existing evidence should be assessed. The GRADE rating system [3,4] provides a method for conducting such assessment. The ratings are usually presented in 'Summary of Findings' (SoF) tables [5,6], which make it easier for the reader to understand the quality of the evidence for each specific outcome. If the evidence related to an outcome is rated as "very low," it means the reviewers take the estimate of effect to be very uncertain [3]. Hence, "very low" quality of evidence could help to justify the undertaking of a new trial. In contrast, if the evidence related to an outcome is rated as "high," it means that the reviewers have confidence that the true effect of the intervention is close to the one presented in the table and therefore is unlikely to change with further research [3].

Despite the recommendations such as SPIRIT's and the availability of "high" GRADE rating evidence provided by a systematic review, clinical research - for example, new trials - may continue all the same. This kind of research, which ignores the known evidence when planning a study, may lead to redundant results, waste of resources and overexploitation of participants [7–9]. A well-known example of evidence ignorance is the case of the 33 trials that, between 1959 and 1988, evaluated the use of intravenous streptokinase as thrombolytic therapy for acute infarction. The first eight trials demonstrated a consistent and precise estimate of the effect of reducing total mortality; the subsequent 25 trials - with a total participation of 34,542 patients - evaluated an intervention already proved to be useful [10].

Our objective was to identify redundant research: research that is conducted despite the availability of high-certainty, easy-to-access evidence. In order to accomplish it, we searched for clinical trials registered later than 2015 that set up to study the effect of an intervention on a primary outcome whose "Certainty of Evidence" (CoE) has already been rated 'high' in a 2015 Cochrane SR.

2. Methods

We conducted this study at the end of 2018 and chose a 3-year period as a reasonable period from which to collect data on prospectively registered trials. First, we searched the Cochrane Database of Systematic Reviews for all the Cochrane Systematic Reviews published in 2015. We ran a pilot selection and data extraction because the process would not be done by duplicate; this allowed us to ensure consistency among the researchers. We excluded editorials, overviews, and diagnostic, qualitative and methodological reviews. We also excluded systematic reviews that had been withdrawn and those without SoF tables. We identified and extracted the GRADE rating of each of the primary outcomes included in the SoF tables of the included SRs and selected those whose evidence quality rated "high" in the GRADE scale.

After selecting the outcomes, we searched for clinical trials that tackled those outcomes. We proceeded by executing search strategies in ClinicalTrials (https://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/en/) for each review title having at least one primary outcome rated "high." We used the same search strategy established in the search methods and/or the appendix section of each selected systematic review and we adapted them to the requirements of each database. We describe our search strategies in Appendix 1. The results obtained from both resources were filtered by registration date, selecting all those registered between the respective Cochrane SR publication date and September 2019.

2.1. Inclusion criteria

We extracted RCT records that fulfilled all inclusion criteria listed below.

1) RCT met criteria to be included in a SR update (i.e., same population, same intervention, same outcome).
2) RCT had the same primary outcome as the SR.
3) Whenever an intervention was pharmacological, doses had to be the same as the one used in the SR.
4) RCT was registered after the Cochrane SR publication date.

We selected the records by reading the title, abstract, and, if doubts remained, by checking the full entry in the registry platform.

We extracted RCT records for each primary outcome. If different outcomes shared the same record, we only included the record once. We then eliminated duplicated RCT records. Finally, we assessed the study state of the remaining records, checking the registry platform and searching in PubMed by the registry's identifier.

3. Results

We found a total of 1,006 SRs published during 2015. Nine hundred sixty-one of these SRs were interventional, with 909 were active and 52 withdrawn. Of the active intervention SRs, 602 had a "Summary of Findings" table. In total, 81 SRs had at least one primary outcome (PO)

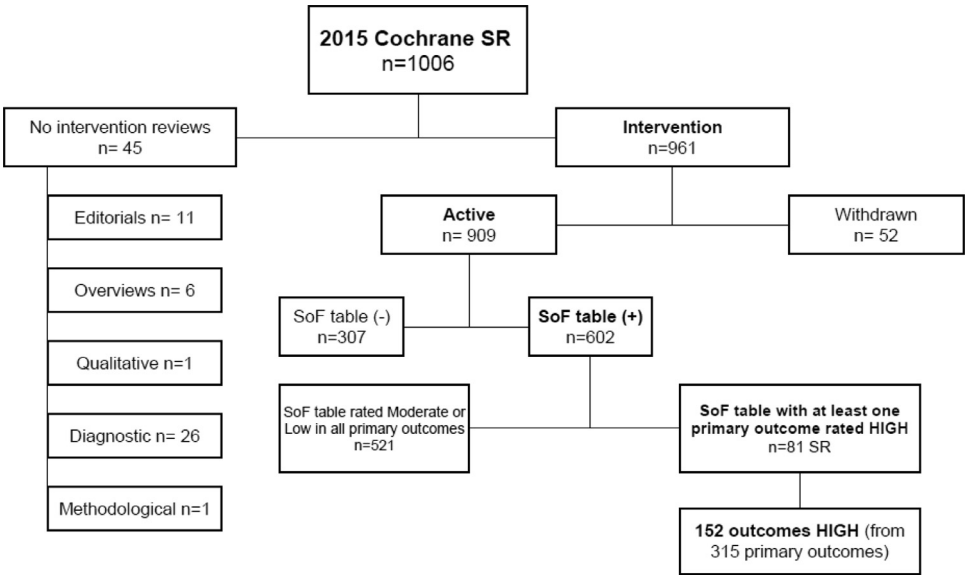

Fig. 1. Primary outcomes rated "high" selection flowchart.

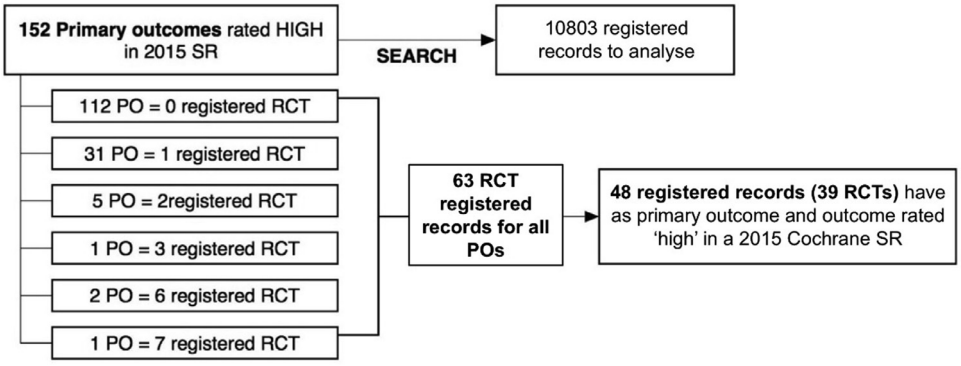

Fig. 2. Registered records for primary outcomes rated 'high'. PO, primary outcome; SR, systematic review; RCT, randomized clinical trial.

rated "high," with a total of 152 outcomes rated "high" (Fig. 1). We present all these SRs and POs in Appendix 2.

We ran the searches used in each of the 81 SRs both in ClinicalTrials and ICTRP, and looked for registered clinical trials assessing the 152 POs rated "high." Our search obtained 10803 RCTs registries to analyze. One hundred twelve POs had zero registered RCTs eligible, 31 POs had one registered RCT each, five POs had two registered RCTs each, one PO had three registered RCTs, two POs had six registered RCTs each, and one PO had seven registered RCTs eligible. This sums up a total of 63 RCT records, considering all POs. However, if an RCT record included more than one of the 152 POs rated "high," then the RCT record would appear more than once in our record search. So we eliminated the repeated RCT records, obtaining 48 unique RCT records. These records corresponded to 39 RCTs, since nine records were duplicates (Fig. 2). The list of the 39 RCTs is included in Appendix 2.

Finally, we assessed the state of the RCTs that were identified from the selected records. The state of the selected RCTs is shown in Table 1.

Table 1. Current state of randomized clinical trials (May 2020)

Study state	Number of studies
Ongoing	18
Completed, not published	10
Completed and published	7
Discontinued	2
Uncertain	2

4. Discussion

We found 48 RCTs records (39 RCTs) for primary outcomes whose evidence has already been rated as "high" in a 2015 Cochrane SR. This may have several ethical and economic implications.

First, there are ethical implications because of the patients' participation in medical research [11]. The Helsinki declaration states that "Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its

potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects" [12]. If the adverse effects are equal, then researchers still should not involve patients in testing treatments if there exists an alternative that offers higher therapeutic value. In 1987, Freedman defined "equipoise" as the "state of genuine uncertainty regarding the comparative merits of treatments", and said that it is necessary for researchers to be in that state when conducting a trial, because, "If a physician knows that these treatments are not equivalent, it is an ethic requirement that the superior treatment be recommended" [13]. Equipoise allows randomization to be done ethically, because a "patient can enroll in a trial without worrying about being disadvantaged and physicians can include patients without compromising their duty of care" [14]. Involving a patient in a trial that tests an intervention already studied and proved with high-quality evidence may lead to two undesirable situations: exposing the patient to an intervention known to be harmful or denying the patient an intervention known to be useful.

Second, there are economic implications. If a trial is repeated, human and material resources that could be used for other purposes are wasted. Instead, they could be used, for example, in conducting well-planned trials that generate useful new evidence, in improving health care delivery, or in creating new public health policies. This point is specifically relevant when public resources are invested in medical research [7]. Here, too, equipoise is the desired state for the researcher. Without genuine uncertainty, there is a waste of resources and "the scientific and social value of the study is questionable" [14].

Several reasons might explain why redundant trials are still current. One is that if researchers conduct inadequate reviews and syntheses of the existing literature then they cannot identify research gaps and needs properly. Another explanation is that many of the redundant trials are industry-funded trials, which seek generating profits rather than advancing knowledge as in the case of me-too drugs [15,16].

Efforts should be made to avoid redundant RCTs. Although the recommendation is that the protocol of an RCT should summarize and cite an up-to-date systematic review of relevant studies [2], it is not regulated. For example, a 2019 study found that, in Denmark, an ethics committee's approval of an RCT does not ensure that a systematic review was done before the protocol's writing and registration [17]. We propose that regulators either ensure that the investigators have already ran a systematic review prior to beginning a trial or run a systematic review themselves before approving a trial to be registered. The clear candidates to perform these tasks are the Institutional Review Boards or ethics committees, given they are the only entities that analyze protocols before trials start. We propose they follow the SPIRIT statement [2] recommendations, which provides an evidence-based list of items that should be part of every protocol.

It is desirable that researchers planning a clinical trial use existing systematic reviews to inform the choice of their research question or, if they are not available, to conduct their own, high-quality systematic review of the evidence. This would avoid research waste [18] and, ideally, encourage researchers to meta-analyze their own, new data with the pre-existing evidence providing updated conclusions [19,20].

Another interesting finding of this study was the number of 2015 Cochrane SRs that do not use a SoF table to present their results (307 SRs). These SRs were published after the release in 2011 of the Cochrane Handbook and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) statement, which established the use of SoF tables in all Cochrane SRs [21].

This study has certain limitations. First, we neither selected nor extracted data by duplicate. Also, we did not identify the number of registered clinical trials whose primary outcomes have already been assessed as having "low" certainty of evidence. So, we could not compare that number with the number of outcomes with a "high" rating. If we had, we could have determined the extent to which researchers are working on updating and improving uncertain evidence. This is an important task, because it would be desirable to know if larger efforts are being made for relevant new evidence, translating to an adequate and ethical participation of patients and use of resources. Additionally, because we did not analyze systematic reviews that did not have a SoF table, we could not establish the total number of trials that ignore high-quality evidence from Cochrane SRs. Also, we did not run a search for unregistered trials, which means that the number of trials that meet our criteria for redundancy could be higher.

A limiting factor in this analysis is the reliability and accuracy of the GRADE ratings informed by the authors of the selected 2015 Cochrane SRs. Since 2015, several efforts have been made to improve the GRADE method, including the formatting of SoF tables and the guidance for SR authors [22–24]. Furthermore, GRADE ratings might not predict accurately the stability of effect estimates [25], as we assume in this study. In fact, we found updates of Cochrane SRs which, after incorporating new evidence, changed the "high" rating assigned to certain primary outcomes to "moderate" or "low" CoE [26–28].

Another limiting factor is that RCT registries may lack specificity. The search strategies used in SRs - which we used when searching the registry platforms - were sensitive, so our inclusion criteria should have added specificity to select the correct registries. If a registry is not specific enough - and answers a different clinical question from the one presented as a SR's primary outcome - then it may be taken to be redundant when it actually is not. Nevertheless, our focus on a framework as widely accepted as GRADE and our use of an exhaustive search strategy let us retrieve

enough data to illustrate the ongoing research of outcomes of "high" CoE, as ascertained by Cochrane SR.

We believe our findings highlight the persistence of redundant trials - a form of research waste that may overexploit trial participants, especially in low-resources settings. A substantial reduction in research redundancy can be achieved by improving clinical researchers' education in evidence search and synthesis and will also lead to better healthcare.

5. Conclusions

We found prospectively registered trials that addressed questions already answered with high-certainty evidence by Cochrane SRs. In order to avoid redundant trials in the future, ethical committees should either ensure that every clinical trial protocol includes a systematic search or run such systematic search themselves. We also recommend that potential investigators be educated in evidence search, and encourage researchers to perform systematic reviews before (and after) carrying out a new trial. We must improve our efforts to avoid redundant trials, for the benefit of patients and a more efficient and responsible use of healthcare resources worldwide.

Author Contributions

Laura Vergara Merino: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Visualization, Project administration. Catalina Verdejo: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - Original Draft, Visualization, Project administration. Juan Franco: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft. Camila Escobar Liquitay: Methodology, Investigation, Writing - Review and Editing. Gerard Urrútia: Methodology, Investigation, Writing - Review and Editing. Rachel Klabunde: Methodology, Investigation, Writing - Review and Editing. Paulina Pérez: Investigation, Writing - Review and Editing. Luna Sánchez: Investigation, Writing - Review and Editing. Eva Madrid: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft.

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Supplementary materials

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