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Inclusion of nonrandomized studies in Cochrane systematic reviews was found to be in need of improvement

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Abstract

Objectives: Nonrandomized studies (NRSs) are considered to provide less reliable evidence for intervention effects. However, these are included in Cochrane reviews, despite discouragement. There has been no evaluation of when and how these designs are used. Therefore, we conducted an overview of current practice.

Study Design and Setting: We included all Cochrane reviews that considered NRS, conducting inclusions and data extraction in duplicate.

Results: Of the included 202 reviews, 114 (56%) did not cite a reason for including NRS. The reasons were divided into two major categories: NRS were included because randomized controlled trials (RCTs) are wanted ($N = 81$, 92%) but not feasible, lacking, or insufficient alone or because RCTs are not needed ($N = 7$, 8%). A range of designs were included with controlled before-after studies as the most common. Most interventions were nonpharmaceutical and the settings nonmedical. For risk of bias assessment, Cochrane Effective Practice and Organisation of Care Group's checklists were used by most reviewers (38%), whereas others used a variety of checklists and self-constructed tools.

Conclusion: Most Cochrane reviews do not justify including NRS. When they do, most are not in line with Cochrane recommendations. Risk of bias assessment varies across reviews and needs improvement.

Keywords: Review; Systematic reviews; Meta-analysis; Intervention studies; Epidemiologic bias; Comparative effectiveness research

1. Introduction

The randomized controlled trial (RCT) is the gold standard for evaluating effects of treatment (intervention) in health care. The main reason is that randomization and concealment of the intervention allocation protect against selection bias and confounding and justify the application of statistical theory [1,2]. However, there are occasions when RCTs could be replaced by nonrandomized studies (NRSs) [1,3,4]. In such cases, NRSs are best defined as all studies that intend to evaluate the effect of an intervention but that do not use randomization to allocate the intervention [5]. The term ''nonrandomized studies,'' thus, covers a wide range of study designs that can contain almost all or very few elements of an RCT. Shadish et al. [6] gave an excellent overview of possible nonrandomized designs and described them as experimental and quasi-experimental studies for causal inference. However, there is no consensus on what are appropriate indications for using NRSs for evaluating the effects of health-care interventions. This becomes more important when conducting systematic reviews of interventions because methods for RCT-based reviews are well understood and accepted but not when NRSs are included.

In general, threats to internal validity are greater for NRSs compared with randomized trials, and results can only be interpreted with caution [7]. There are also other problems with using NRSs in a systematic review. NRSs are more difficult to locate with a search because there is no agreed nomenclature [8]. In case of a systematic review, this means that searches that are sensitive are nonspecific and yield a very large number of references. For the same reason, it is difficult to define nonrandomized study designs and to be sure what type of studies to include [9]. Consensus on the reporting of observational designs (STROBE) was developed fairly recently. This means that inadequate

Conflict of interest: J.H.V. and J.R. have authored Cochrane reviews including nonrandomized studies and are coordinating and managing editors of the OSH CRG in Kuopio. They were not involved in inclusion assessment and coding of the reviews in which they were authors. Data were extracted in duplicate by trained personnel not part of the OSH CRG (Prince Dadson and Tero Kankaanperä), and S.I. resolved disagreements.

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What is new?

Key findings

- In 56% of the Cochrane reviews including nonrandomized studies (NRSs), no reason or justification is provided for their inclusion. In the rest, reasons for inclusion were either a need of RCTs or not. These reasons were not always underpinned with valid arguments. Risk of bias assessment of NRSs varied to a large extent.

What this adds to what was known?

- When and how to include and assess NRSs in Cochrane reviews requires better guidance for authors to ensure optimal use of these studies in the future.

What is the implication and what should change now?

- We provide recommendations based on existing Cochrane review data on what make good justifications for including nonrandomized designs in a Cochrane review, with examples. Using these, review authors can balance the risk of bias that NRSs bring to their review against the possibility of RCT evidence being available before they start a review. This will lead to more appropriate inclusion and analysis of these studies within Cochrane reviews, enhancing their applicability. Better tools for risk of bias assessment for some nonrandomized designs are needed.

reporting may be more common in NRSs, which further hinders assessments of risk of bias [7]. Nevertheless, the need for including these studies for certain important questions in terms of interventions and outcomes cannot be denied [10]. This is reflected in the fact that these studies have also regularly been included in Cochrane reviews in spite of the cautionary advice regarding their inclusion.

The Cochrane Collaboration encourages using only RCTs in systematic reviews because they are more likely to provide unbiased information. However, some Cochrane reviews may include NRSs if the review question cannot be answered with an RCT. The Cochrane handbook advises including NRSs only when interventions cannot be randomized, when long-term or rare outcomes are studied, and when authors want to point out the weaknesses of NRSs and make a case for an RCT [11,12].

Other researchers looked at the inclusion of NRSs in systematic reviews of intervention studies commissioned by the Agency for Healthcare Research and Quality [10]. Based on this study and a Delphi process, they offered recommendations to authors of systematic reviews of comparative effectiveness [13]. They argue that observational studies are additional to RCTs and should be included if there are "gaps in the RCT evidence," for example, because RCTs are inappropriate, unnecessary, difficult, or infeasible. However, none of these studies gives a clear guidance on when, how, and which of these NRSs should be used in a systematic review of intervention.

Cochrane reviews are highly valued as evidence of health-care interventions and form a homogenous and high-quality sample that can provide valuable information about the practice of inclusion of NRSs. There is no study, to our knowledge, taking stock of the practice of inclusion of NRSs within Cochrane reviews. Therefore, we wanted to locate all Cochrane reviews that included NRSs to answer the question of when, how, and which NRSs are included in Cochrane reviews. Based on this analysis, we wanted to identify areas needing improvement and to make recommendations for researchers to guide future reviews intending to use NRSs.

2. Methods

We aimed to include all Cochrane reviews that mentioned in the methods section that one or more NRS designs were considered for inclusion. This approach included reviews that set out to include NRSs but did not find any. The most recent update of a review was included in case multiple versions were available. When the most recent update did not include NRSs, we excluded the review.

A problem with the naming of study designs is the quasi-randomized trials. These are usually defined as trials that use a method that is not random and therefore predictable such as alternation or using day of birth. Many authors, probably because of the advice in the *Cochrane Handbook* in chapter 6, consider including these trials alongside RCTs. The same holds for what is called controlled clinical trials (CCTs). Therefore, we excluded reviews that considered RCTs and quasi-randomized trials or CCTs only. We also excluded reviews that stated in the methods section that NRSs were excluded. Thus, we increased the efficiency of our overview by excluding reviews that would have provided very little information on NRSs.

We searched the Cochrane Database of Systematic Reviews via PubMed with the following search strategy to find relevant reviews up to May 2012: ("case-control" [tiab] OR "quasi random"[tiab] OR "quasi experimental" [tiab] OR ecological[tiab] OR "non-random"[tiab] OR "interrupted-time-series"[tiab] OR "before-after"[tiab] OR "before-and-after"[tiab] OR "cohort"[tiab]) AND Cochrane Database Syst Rev[ta].

When inclusion of NRSs was not clear from abstracts, we assessed full texts of these reviews to make our decision. Study selection and data collection were done in duplicate (Tero Kankaanperä, Prince Dadson, S.I., C.M., J.H.V., and J.R.), and when disagreement occurred, we sought a third person's opinion. We extracted the following data in a