

# Using evidence of multiple study designs in systematic reviews

Citation for published version (APA):

Peinemann, F. (2015). *Using evidence of multiple study designs in systematic reviews*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20150611fp>

## Document status and date:

Published: 01/01/2015

## DOI:

[10.26481/dis.20150611fp](https://doi.org/10.26481/dis.20150611fp)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

## General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

[www.umlib.nl/taverne-license](http://www.umlib.nl/taverne-license)

## Take down policy

If you believe that this document breaches copyright please contact us at:

[repository@maastrichtuniversity.nl](mailto:repository@maastrichtuniversity.nl)

providing details and we will investigate your claim.

# Summary

## **Background and rationale**

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. The most distinctive characteristics that are present in a systematic review and that are not present in a nonsystematic review may be a study protocol, an analysis plan, a literature search strategy, and a description of the selection of suitable studies in accordance with prospectively defined inclusion and exclusion criteria. The starting point and fundamental component of a systematic review of health care interventions is a structured clinical question.

A systematic review may evaluate benefit and harm of a health care intervention and may include a specific set of studies. Explanatory study designs address the question whether the intervention of interest can work in principle in the ideal study setting and typically provide a conclusion for an average patient only. The intervention and the control group may differ only with respect to the intervention of interest. Known and unknown characteristics are equally distributed among the two treatment groups. The resulting structural equality facilitates a decision whether an observed effect was actually caused by the intervention. Randomization may be the best approach to provide this structural equality and may provide a low risk of bias. However, in some situations, randomization is not feasible, not appropriate, or the results may not be applicable to everyday practice. Pragmatic study designs aim to show that interventions will work under every day circumstances but may have a high risk of bias. To accommodate the evaluation of various research questions, the inclusion of more than one study design appears to be necessary.

## **Research questions and answers**

The aim of this thesis is to investigate the advantages and disadvantages of using various study designs to answer specific clinical research questions within systematic reviews and to develop and pilot test an algorithm to guide systematic reviewers in their

decision to choose appropriate study designs. The following research questions are discussed in the present thesis:

*What is known in the published literature about the pros and cons of integration of multiple study types in systematic reviews?*

A review of 42 articles about the use of multiple study designs in systematic reviews of health care interventions showed a tendency that nonrandomized studies should be conducted and integrated in systematic reviews to complement available randomized controlled trials or replace lacking trials in 85% (36 of 42) of these articles. It was acknowledged that only randomized controlled trials can achieve the lowest risk of bias. Many papers highlighted that results of randomized trials may not be applicable to a considerable number of the actual target population. The risk of presenting uncertain results without knowing for sure the direction and magnitude of the effect holds true for both nonrandomized and randomized controlled trials.

*What can be learnt from conducting systematic reviews about topics that may require the inclusion of multiple study designs, assuming that more than one study design may be essential to gather sufficient data for answering the objectives of the review.*

If no comparative study is available, then the data of single-arm studies might provide, for example, an estimation of overall survival. Data on adverse events can be presented beyond the scope of a randomized controlled trial. Discussing the limitations of the results may bring the public attention to a lack of certain data, which might foster the conduction of a long desired trial. In another example, the test but not the control intervention may cure patients, however, the test intervention might be associated with a higher early treatment-related mortality than the control intervention. This situation might create a conflict. Ethical concerns may prevent trials with a random allocation of patients to the treatment groups. The principles of 'Mendelian randomization' could be applied for evaluating transplantation by restricting transplant donors to siblings. Another example shows that patients with a localized as opposed to an advanced cancer might have a very good overall survival regardless of the type of intervention. Though, the health-related quality of life as measured by patient-reported outcomes may vary considerably among the treatment options, which is caused by the varying degrees of their invasiveness. Reluctance of patients and physicians alike to participate in randomization corroborates the consideration of alternative approaches. A report on deaths was issued in connection with a particular medical device. It showed that the consideration of registry analyses and case reports can be very helpful to draw attention to possible dangerous and life-threatening events. It was also helpful to point at the home setting where a considerable number of deaths happened.

*What is the preferred content and format of a straightforward algorithm for integration of various study designs in a systematic review that incorporates major study characteristics as decision points and that allows consideration of practical concerns?*

A decision tree was constructed using length of follow-up, frequency of events, and type of outcomes as main decision points. It was ensured that the preset pathways retain sufficient flexibility to consider ethical and practical issues as well as unavailable best evidence. The outcomes may be evaluated after a short or long follow-up. The events of interest may be rare or frequent. The outcomes can be classified into the five major groups of death, disease, discomfort, disability, and dissatisfaction. Then, appropriate study designs are recommended with respect to the type of outcome. Practical or ethical concerns or lack of recommended study designs may emerge as reasons to override the earlier decisions or to switch to a more appropriate study design. Therefore, the reader is reminded to reconsider the chosen path.

*Can the algorithm hold its promise as a useful guide for choosing appropriate study designs by testing its feasibility and applying it to existing systematic reviews?*

The appropriateness of the pathways of the decision tree was confirmed during the application of the algorithm on four selected systematic reviews. These systematic reviews were conducted to evaluate the prospects of using multiple study designs and were well suited for a projection on the various pathways offered by the algorithm. The theory-based algorithm proved to be useful in various practical situations and helped to choose the appropriate study designs for inclusion in each tested systematic review.

## **Strengths and limitations**

One strength of the thesis lies in the broad search strategy. The retrieved information was designated to provide an objective view on the possible merits of every individual study design to support decision-making in health care. Nevertheless, personal preferences may have influenced the results in every step of acquisition and judgement of data. While reading through hundreds of papers, I perceived a polarized dispute on randomized versus nonrandomized and on experimental versus observational study designs among some authors. Thus, the inferences made in many included papers may be influenced by the authors' preoccupations.

The testing of the algorithm was conducted retrospectively by backtracing systematic reviews that were already completed. This approach is far from the everyday working condition. It may be considerably biased by my expectations that the algorithm should have been worked if applied prospectively. Thus, the results of this testing need to be confirmed by other systematic reviewers who plan to use the algorithm

from the start. The algorithm is not intended to be an absolute guide always leading to appropriate study designs. Disease-specific circumstances and aims of interventions always have to be taken into account during application of the algorithm.

## **Recommendations**

The algorithm is foreseen to function as a guide helping to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. It is recommended to confirm this assumption by its prospective application, possibly within a trial. It is also recommended to test its usefulness with respect to other types of population, intervention, comparator, and outcome than those contained in the systematic reviews of this thesis. The algorithm may help to reorientate oneself to major features of the studies eligible for an evaluation of a health care intervention. There might be an educational challenge of instructing end users of the algorithm. Persons who are planning to conduct a systematic review and use the algorithm should make themselves acquainted with the scope of possible study designs, their purposes, advantages, and drawbacks. Persons without extensive practice in conducting systematic reviews might be asked to share their opinion concerning its usefulness for beginners. In general, a flexible and pragmatic approach without the obligation to rigidly exclude study designs is recommended.