# Synthesizing existing evidence to design future trials: survey of methodologists in Europe

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**Abstract**

*Background*: The potential of network meta-analysis to inform the design of future studies is largely underutilised. A suggested framework for efficiently planning clinical trials based on a network of interventions has been termed conditional trial design and consists of three parts. The first part pertains mainly to interpretation of meta-analysis and addresses whether *the existing evidence answers the research question*. The second part of the framework bears upon *how best to use the existing evidence to answer the research question,* and the third part addresses *how to use the existing evidence to plan future research.*

*Methods*: We conducted an online survey among trial statisticians, methodologists and users of evidence synthesis research to capture opinions about all parts of the conditional trial design framework and the practices among clinical researchers.

*Results*: In total, 76 contacted researchers completed the survey. We found that the level of acceptance of network meta-analysis is low to moderate. Three out of four survey participants were willing to consider using evidence synthesis to design a future clinical trial and around half of the participants would give priority to such a trial design. The median rating of the frequency of using it was 0.41 on a scale from 0, which stands for never, to 1, which stands for always. The major barrier in adopting conditional trial design is the current paradigm in regulatory setting, trial funding agencies and sponsors.

*Conclusions*: For the conditional trial design to be adopted by the clinical research community, cross-familiarization and collaboration between evidence synthesis and clinical trial design researchers is needed.

**Keywords**

Conditional trial design, sample size, meta-analysis, network of interventions

## *1 Introduction*

Systematic reviews can identify knowledge gaps that may direct the research agenda toward questions that need further investigation. Knowledge gaps may arise when the available data are insufficient, or when there is no evidence at all that can answer a research question. Once identified, primary research (e.g. trials) may be designed and conducted to fill such gaps.

Such considerations, along with implementation strategies, have appeared in the literature. The Agency of Healthcare Research and Quality developed a framework for determining research gaps using systematic reviews (1). Methods for informing aspects of trial design based on a pairwise meta-analysis have also been proposed and include powering a future trial based on a relevant existing meta-analysis (2–4) or highlighting the trial's impact on the summary effect obtained thus far (5–7). These methods are limited to situations in which existing evidence consists of two interventions. When existing evidence forms a network of interventions, synthesis of available trials can be done using network meta-analysis. Network meta-analysis is increasingly used in health technology assessment to summarize evidence and inform guidelines (8). However, its potential to inform trial design has not received much attention.

Methodological developments that use network meta-analysis as a basis for further research (3,7) have been recently collated to form a holistic framework for planning future trials based on a network of interventions (9). The framework, called *conditional trial design*, combines considerations relevant to both evidence synthesis and trial design, and consists of three parts. The first part pertains mainly to interpretation of meta-analysis and addresses the question, *does the existing evidence answer the research question?* The second part of the framework is related to *how best to use the existing evidence to answer the research question*. The third and last part of the framework addresses *how to use the existing evidence to plan future research*.

We conducted a survey to capture opinions and current practices among trial statisticians, methodologists and users of evidence synthesis research regarding different parts of conditional trial design. Assuming a starting research question for treatment decision we asked questions relevant to:

a. The decision about whether a meta-analysis answers the research question
b. The acceptability of network meta-analysis as a technique to enhance the evidence and answer the research question

c. The use of evidence synthesis in the planning of future clinical research

## *Methods*

### *1.1* Invited participants

Our convenience sample consisted of researchers working in Europe either in nonprofit organizations or in the pharmaceutical industry. We opted for researchers working in academic clinical trial units, evidence synthesis teams and major decision-making organizations such as WHO, and health technology assessment organizations. The full list of contacted organizations can be found in Appendix I. We sent a brief description and the link to the survey by email to key personnel within each organization, which included a request to forward it to anyone within their organization who might be interested, or we sent email messages to a mailing list or individuals. We did not track whether an invited person completed the survey, and sent no reminders.

### *1.2* Survey design

We designed a short online questionnaire using Survey Monkey (www.surveymonkey.com). We started with questions regarding principal affiliation, experience with systematic reviews, meta-analysis, network meta-analysis, guidelines, clinical trials, and involvement in research funding decisions. Implementation of the framework that we wanted to capture opinions about would require a collaborative process between experienced researchers in the areas of evidence synthesis and trial design. Participants were therefore directed to one or both of the survey's main parts, depending on their expertise, as shown schematically in Figure 1. For the majority of the questions, it was possible to select more than one answer. The full questionnaire is in Appendix II. The survey was open between October 10, 2016 and December 9, 2016. Responses were collected anonymously.

The first part of the survey was about current practices of deciding whether a meta-analysis answers the research question at hand. Only participants experienced in *evidence synthesis* and those who had been involved in deciding about funding clinical research were directed to this part. Certain questions asked participants to choose or report what they are actually *doing*, in practice, while others asked participants to choose what they *think* should be done. Topics related to interpretation of the meta-analysis results as such, how multiple outcomes are integrated, and issues concerning repeatedly conducting a meta-analysis. A separate section covered issues related to the acceptability of network meta-analysis.

The next part of the survey contained questions about the use of evidence synthesis, as pairwise or network meta-analysis, for the design of clinical trials. For all questions in this

part, the term *clinical trials* refers to randomized, post-marketing (e.g., phase IV) controlled clinical trials. Participants experienced in clinical trials and those who declared involvement in funding decisions were directed to this part (Figure 1). Some of the questions were formulated so that the participants answered them in their capacity as citizens who fund research (such as EU-funded clinical trials or other research funded by national funds through their taxation).

### *1.3* Analysis

We derived descriptive statistics as frequencies and percentages for participants' characteristics (affiliation, job role, experience in meta-analysis and clinical trials). Some questions allowed or requested free text answers by participants; these comments were summarized qualitatively. We present a sample of the written quotes regarding participants' willingness to consider a clinical trial design informed by meta-analysis and the biggest barrier to adopting such a design. Where a visual analogue scale was used, median and interquartile ranges are presented. For the question of rating clinical research proposals submitted for funding, rating averages are presented. We examined whether level of experience with evidence synthesis and clinical trials was related to different views on the acceptability of network meta-analysis and participants' likelihood to consider the use of conditional trial design using a chi-squared test or Fisher's exact test.

## *2 Results*

### *2.1* Participants characteristics

In total, 76 researchers completed the survey, of whom 29 (38%) were affiliated with a clinical trial unit and 15 (20%) with the pharmaceutical industry. Most participants appeared to be involved in several areas of clinical research. Fifty-three participants (70%) had performed and/or evaluated a systematic review, 46 (61%) had designed a clinical trial, and 36 participants (47%) had been involved in decisions about funding clinical research including reviewing grant applications.

The involvement of researchers in trials, meta-analyses, and network meta-analyses varied. A total of 63 researchers (83%) had been involved in at least one clinical trial, over half of whom (33) had been involved in more than 20 trials. Sixty-one researchers (80%) reported involvement in at least one pairwise meta-analysis, while 34 (45%) had participated in one or more network meta-analyses. The complete characteristics of participants can be found in Table 1.

### *2.2* Does the existing evidence answer the research question?

Among the 76 participants, 68 (89%) had experience in evidence synthesis and answered questions related to the interpretation of meta-analysis results (figure 1).

Asked about judging when a summary treatment effect is conclusive and when further research is needed, 39 of these 68 researchers (57%) examined the clinical importance of the summary effect, while slightly fewer (31) examined the statistical significance of the summary effect.

Participants were asked about adjustment for multiple testing issues when meta-analysis is updated with new studies. Twenty-two of the 68 participants (32%) indicated that adjustment for multiple testing is not required for a repeatedly updated meta-analysis, while 18 participants (22%) reported that such an adjustment is required. Participants were also asked about interpreting evidence from multiple outcomes that bears upon a preference for one of two treatments. Among the 68 participants, 25 (37%) reported involving stakeholders in deciding which outcomes are more important, while 22 participants (32%) used methods described in the recommendations of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

### *2.3* How best to use the existing evidence to answer the research question?

Asked whether they prefer network meta-analysis as an evidence synthesis method to pairwise meta-analysis, participants indicated a comparatively low preference for network meta-analysis. Among the 68 participants, 15 (22%) preferred network to pairwise meta-analysis. A total of 25 participants (37%) indicated that network meta-analysis should be considered when there are either no or very few direct studies (Table 1). Eight participants suggested other approaches as indicated by two of their responses: “I would look at both direct and indirect analysis,” and “I see the evaluation as one process and don't want to disregard one versus the other.”

Asking participants about their interpretation in a more specific scenario such as the one presented in Figure 2, nearly twice as many participants indicated that they trusted network meta-analysis more than pairwise meta-analysis when the results are more precise (23 versus 13 participants). A considerable subgroup of participants claimed that they do not know what to conclude, or they did not respond to the question (32 total participants, 48%) (Figure 2).

### *2.4* How to use the existing evidence to plan future research?

Among the total of 76 participants, 43 researchers experienced in clinical trial design (57%) were directed to questions related to practices and opinions about using meta-analysis to inform aspects of the design of future clinical trials (Figure 1).

**Practices of using meta-analysis in the design of clinical trials**

Participants rated their use of evidence synthesis in the design of clinical trials on a visual rating scale from 0, which indicated never, to 1, which indicated always. The median value was 0.41, with an interquartile range of 0.20 to 0.70. A total of 29 participants (67%) reported using meta-analyses of previous trials in the definition of other parameters involved in sample size calculations (such as standard deviations, baseline risk, etc.), 25 participants (58%) considered meta-analyses in defining alternative effect size in power calculations, and 22 (51%) used meta-analyses in the determination of health outcomes to be monitored (Table 1).

When asked about the best among five approaches to resolve uncertainty regarding the best pharmaceutical treatment for a given condition, a three-arm randomized trial comparing the two most promising interventions and standard treatment and a network meta-analysis comparing all treatment alternatives were the most popular options (rating averages 1.83 and 2.15, respectively). The least favorable research design was a large international registry (rating average 4.10, Table 1).

**Acceptability of sample size calculations based on an existing meta-analysis**

Twenty-six participants (60%) were aware of the methodology of explicitly incorporating results from a meta-analysis in the sample size calculation of a future trial (based on conditional power). Twenty-eight participants (65%) said they possibly or definitely would consider the approach when planning a trial in the future. When asked about reasons for not considering such a design, participants justified their answers with arguments mainly associated with concerns about the reliability and validity of meta-analysis as well as the paradigm of perceiving trials as independent pieces of evidence. Some sample answers are presented in Box 1. When asked to respond from the perspective as citizens supporting publicly funded research, 21 of the 43 participants (49%) indicated that priority should be given to conditional trial design compared to conventional sample size calculations. Changing the paradigm of funders and researchers was presented as the biggest barrier towards adopting such a trial design (16 participants, 37%) (Table 1).

### *2.5* Relation between level of experience with clinical trials/evidence synthesis and acceptability of network meta-analysis and conditional trial design

Experienced researchers in evidence synthesis were more likely to have confidence in network meta-analysis. Among the 27 participants with experience in evidence synthesis who indicated that they either can perform network meta-analysis themselves or have been involved in systematic reviews with network meta-analysis, 11 (41%) responded that, in general, network meta-analysis is preferable to pairwise meta-analysis. Among the 41 participants with little or no experience with network meta-analysis, only four (4%) said that network meta-analysis is to be preferred.

The willingness to consider the use of an existing meta-analysis to inform sample size calculations of a new study did not materially vary according to researchers' experience in clinical trials or evidence synthesis (Appendix Tables 4 and 5).

## *3 Discussion*

In this survey of methodologists based in Europe, participants reported low to moderate use of evidence synthesis methods in the design of future trials. Evidence synthesis is used for the design of approximately every other trial. The information most used is the parameters required for sample size calculations and outcome definitions. The proportion having used meta-analysis to inform a future trial was 50% in the survey conducted by Clayton et al. while only 32% thought that network meta-analysis should be used to inform whether a future trial is needed (10).

Empirical evidence has shown lower uptake of systematic reviews in planning new trial than the findings in the current survey and the survey conducted by Clayton et al. (11–19). Clarke et al. assessed reports of randomized trials published in Annals of Internal Medicine, BMJ, JAMA, The Lancet, and the New England Journal of Medicine in the month of May in the years 1997, 2001, 2005 and 2009; according to their findings, only a small proportion of trial reports attempted to integrate their findings with existing evidence (11,12,15,16). Out of 446 trial protocols submitted to the UK ethics committees in 2009, only four (less than 1%) used a meta-analysis and 92 (21%) used previous studies to set the treatment difference sought (20). A review of 1523 trials published from 1963 to 2004 showed that fewer than 25% of preceding RCTs were cited by subsequent RCTs (21).

Funders of clinical trials often emphasize the importance of using existing evidence in grant applications (14,22,23). A majority of 37 out of 48 trials funded by the National

Institute for Health Research Health Technology Assessment between 2006 and 2008 referenced a systematic review in the funding application; the percentage was 100% for trials funded in 2013 (24). Nasser et al. searched the websites of 11 research funding organizations, four of which require systematic reviews to show that new clinical trials are needed (22). The interest of funders in research synthesis dates back to the 1990s when several organizations responsible for funding clinical research started to require systematic reviews of existing research as a prerequisite for considering funding for new trials (14). But as Clayton et al. point out, it is not clear to what extent and in which way funders expect evidence synthesis to be used (10).

Our study has some limitations that render questionable the generalizability of its results. First, the sample size of our survey was 76 participants, which is relatively small. As well, having asked recipients of our email to forward it to people they thought would be interested we could not estimate the response rate for our survey. Second, we cannot exclude the possibility that the characteristics of participants systematically differed from those of nonparticipants. Such selection bias seems likely, considering that a relatively high proportion of participants knew about calculating sample size based on a meta-analysis (60%), despite the fact that the methods had only recently been developed (2,7,9) and are not widely used. This indicates that participants were probably a well-informed sample of methodologists who were up-to-date with recent developments.

We clarified in the survey that by the term "clinical trials" we mean "randomized, post-marketing controlled clinical trials." This clarification was made because in the context of designing trials for licensing it is unlikely that the conditional trial design would be appropriate since usually there will not be previously published trials. Phase III clinical trials, though, are the most common type of trial (25), and only around 25-30% of drugs move from phase III to phase IV (26). The design of trials supporting applications for a license came up quite often in free text answers (Box 1). It is possible that the unavailability of evidence (and thus its potential to inform clinical trial design) before licensing may be an important barrier to use the proposed method; this barrier may be particularly relevant for pharmaceutical industries. A clearer distinction and guidance on how comparative effectiveness can and should be used in the entire process of approval and adoption of new drugs would be of interest.

Despite its potential to reduce sample size and the moderate per se willingness to use it in this sample, conditional trial design has not yet been adopted by the clinical research community. This may partly be explained by the fact that researchers are usually familiar

either with evidence synthesis or with clinical trial design; in our sample only 22% of the participants had been involved in more than five trials and more than five meta-analyses. Cross-familiarization and collaboration between evidence synthesis and clinical trial design researchers is needed for conditional trial design to be adopted.

## 4 *Ethics approval and consent to participate*

Not applicable

## *5 Consent for publication*

Not applicable

## *6 Availability of data and material*

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## *7 Competing Interests*

The authors declare that they have no competing interests.


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## *9 Authors' contributions*

GS, AN and ME conceived the study and designed the survey questionnaire. ST critically revised the survey questionnaire. GS contacted the survey participants. AN designed the survey in Survey Monkey, performed the main analyses and wrote the first draft of the paper. All authors critically revised the manuscript, interpreted the results and performed a critical review of the manuscript for intellectual content. GS, AN and ME produced the final version of the submitted article and all co-authors approved it.


## *10 Acknowledgements*

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**Table 1 Opinions and practices of participants regarding evidence-based planning of future trials. Questions have been simplified for presentation purposes. The full text and questions are available in Appendix II. HTA: health technology assessment; WHO: World Health Organization; CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation**

| ***Question*** | Possible answers | Responses (% |
|---|---|---|
| ***Population characteristics (total participants: 76)*** | | |
| What is your primary affiliation? | Clinical trials unit | 29 (38%) |
| | A funding body | 3 (4%) |
| | Pharmaceutical industry | 15 (20%) |
| | HTA/Cochrane/WHO | 28 (37%) |
| | Missing | 1 (1%) |
| ***Does the existing evidence answer the research question? (total participants: 68)*** | | |
| How do you judge whether a summary treatment effect provides conclusive evidence or whether further research is needed (more than one choice allowed)? | I examine the statistical significance of the summary effect and its CI | 31 (46%) |
| | I examine the clinical importance of the summary effect and its CI | 39 (57%) |
| | I test whether future studies could change the statistical significance of the summary effect | 7 (10%) |
| | I follow the GRADE guidelines for judging imprecision | 19 (28%) |
| | Not involved in interpretation of meta-analysis results / Other / missing | 29 (43%) |
| ***How to use the existing evidence to answer the research question? (total participants: 68)*** | | |
| Do you think that network meta-analysis should be considered as the preferred evidence synthesis method instead of pairwise meta-analysis? | Yes, network meta-analysis should always be preferred | 15 (22%) |
| | No, network meta-analysis should not be considered | 5 (7%) |
| | It should be considered only if there are no or few direct studies | 25 (37%) |
| | Other / missing | 23 (34%) |
| ***How to use the existing evidence to plan future research? (total participants: 43)*** | | |
| According to your experience, results from relevant meta-analyses are considered to (more than one choice allowed): | Define the alternative effect size in power calculations | 25 (58%) |
| | Decide about the intervention in the comparator arm | 19 (44%) |
| | Define other parameters involved in sample size calculations | 29 (67%) |
| | Define health outcomes to be monitored | 22 (51%) |
| | Other / missing | 7 (16%) |
| What do you think is the biggest barrier towards adopting the conditional trial design in designing trials? | Lack of training | 6 (14%) |
| | Changing the paradigm of funders and researchers | 16 (37%) |
| | Lack of good-quality meta-analyses | 4 (9%) |
| | Other / missing | 17 (40%) |
| ***Question*** | Possible answers | Rank |

| | | |
|---|---|---|
| As a citizen supporting publicly funded research how would you rank (from 1 being the top priority to 5 being the least) the following proposals tackling the treatments for an important health condition? Consider also the cost for each research proposal (presented in parenthesis in arbitrary units). | A well-powered 3-arm randomized trial comparing the three most promising interventions (none of which is standard care) (100) | 3.77 |
| | A well-powered 3-arm randomized trial comparing the two most promising interventions and standard treatment (90) | 1.83 |
| | A well-powered 2-arm randomized trial comparing a newly launched treatment and standard treatment (70) | 3.10 |
| | A large registry involving many countries (40) | 4.10 |
| | A network meta-analysis comparing all available treatments using existing studies (10) | 2.15 |

**Box 1 Free texts explanations for not or possibly considering sample size calculations based on a meta-analysis when planning future trials, and on the biggest barrier for adopting the approach.**

**Quoted answers from those who replied "No" or "Possibly" to the question "Would you be willing to consider a conditional trial design next time you plan a trial?"**

Related to concerns on the reliability and validity of meta-analyses

- "Lots of examples where a large definitive trial has contradicted the results of a meta-analysis of smaller trials."
- "Any meta-analysis is observational research"
- "Because when you finalize the trial, the meta-analysis will be outdated. Your study should be a standalone trial."
- "Not enough faith in the homogeneity/comparability of the studies"
- "The assumptions behind a meta-analysis (homogeneity, no publication bias), are very rarely plausible, so a typical RCT has to offer a chance of providing a definitive conclusion on its own."

Related to concerns of changing the paradigm at licensing and health technology assessment agencies

- "Clinical trials are perceived as independent pieces of evidence. There would need to be a major shift by regulators, HTA bodies and physicians for companies to design trials in the context of meta-analyses"
- "Usually the context in which I work is of trials supporting applications for a license. Regulators require each study to be 'significant' independently of others."
- "Wonder whether it would be convincing to authorities"
- "In the regulatory context, meta-analyses are typically NOT considered for approval decisions, at least not directly. (Typically). I would answer differently for publicly funded studies. A newish suggestion - most of our trials are phase 2/3, where things are a little different."

**Quoted answers from those who replied "Other" to the question "What do you think is the biggest barrier towards adopting conditional trial design in designing trials?"**

- "Although trials can be planned to add just enough power to an existing meta-analysis, there is a high risk that such planning fails because of wrong assumptions, differences in study execution, or other reasons."
- "It is flawed and too risky (why give an experimental drug in an underpowered study)?"
- "Guidelines from important regulatory and health economic agencies"
- "Lack of dissemination"
- "Skepticism as trials should be powered to stand alone, I would think. All other studies in the MA may not be comparable or of high quality."
- "It's not necessarily logical."
- "I don't believe this is an appropriate way to design trials"

**Figure 1. Schematic representation of the parts of the survey to which participants were directed according to their involvement in several aspects of systematic reviews, guidelines and clinical trials production.**

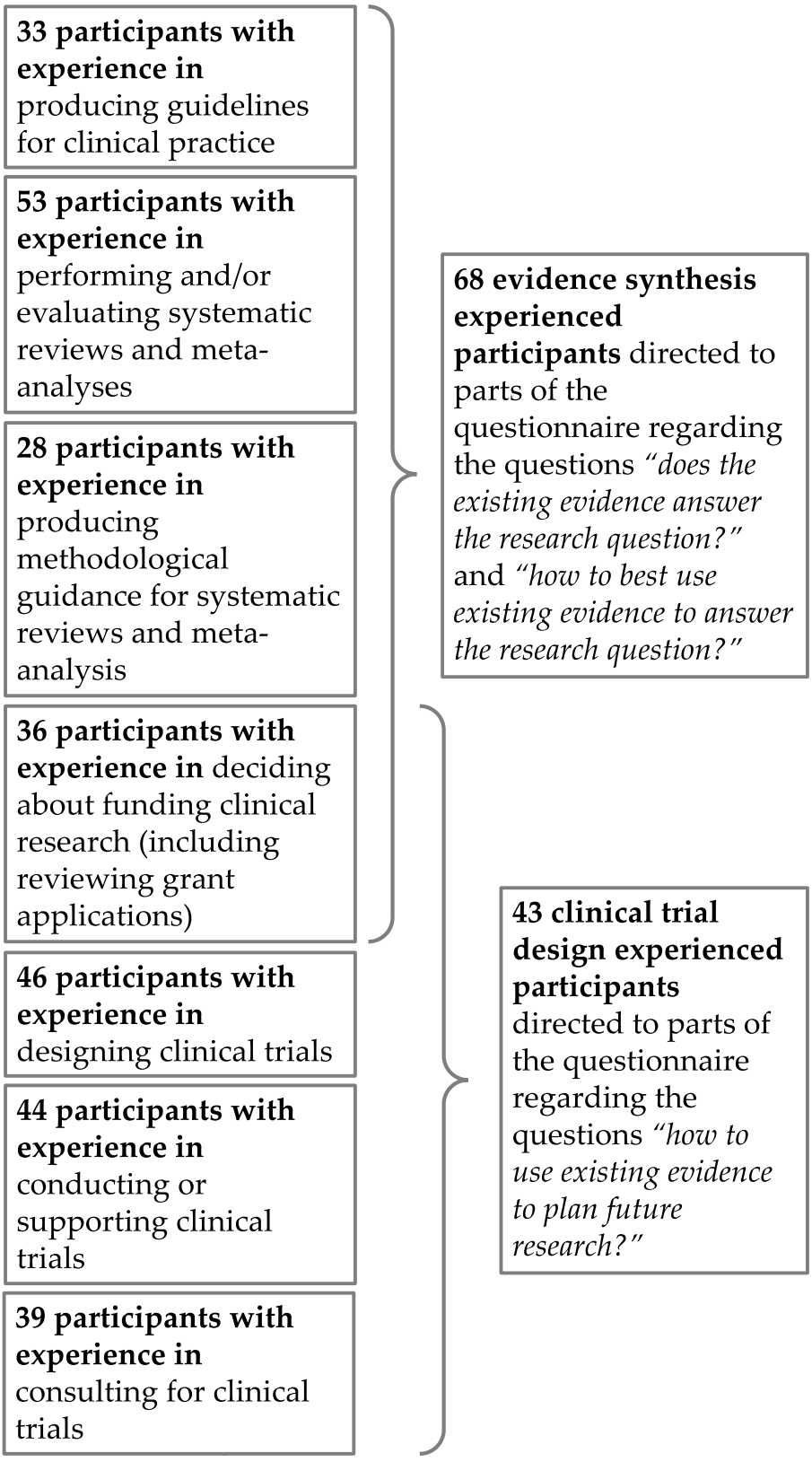
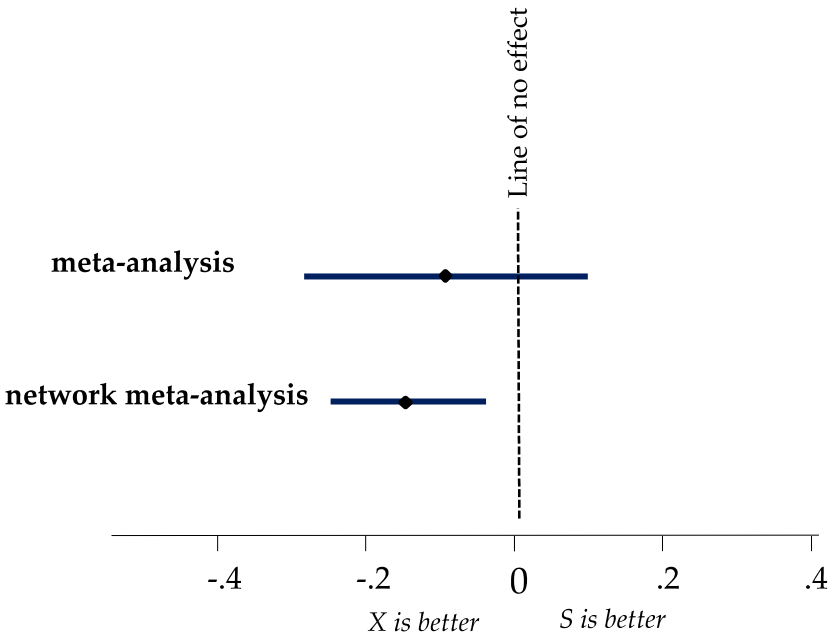


**Figure 2. Opinions among researchers on their interpretation of a hypothetical scenario where network meta-analysis provides conclusive evidence that treatment X is better than treatment S while pairwise meta-analysis indicates that further evidence is needed. The question was addressed to the subset of 68 'evidence synthesis experienced' participants.**




| "What do you conclude?" | Number of participants (%) |
|---|---|
| I trust the result from network meta-analysis | 23 (34%) |
| I trust the result from pairwise meta-analysis | 13 (19%) |
| I don't know what to conclude | 16 (24%) |
| Not responded | 16 (24%) |