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Influence and management of conflicts of interest in randomised clinical trials: qualitative interview study

Lasse Østengaard,[1,2,3,4] Andreas Lundh,[1,2,3,5] Tine Tjørnhøj-Thomsen,[6] Suhayb Abdi,[1] Mustafe H A Gelle,[1] Lesley A Stewart,[7] Isabelle Boutron,[8] Asbjørn Hróbjartsson[1,2,3]

For numbered affiliations see end of the article.

Correspondence to: L Østengaard lasseoestengaard@bib.sdu.dk (or @LasseOstengaard on Twitter: ORCID 0000-0001-7033-3722)

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ABSTRACT

OBJECTIVE

To characterise and analyse the experiences of trial researchers of if and how conflicts of interest had unduly influenced clinical trials they had worked on, what management strategies they had used to minimise any potential influence, and their experiences and views on conflicts of interest more generally.

DESIGN

Qualitative interview study.

PARTICIPANTS

Trial researchers who had participated in at least 10 clinical trials with methodological or statistical expertise. Researchers differed by geographical location, educational background, and experience with different types of funders. Interviewees were identified by searches on Web of Science and snowball sampling. 52 trial researchers were approached by email; 20 agreed to be interviewed.

SETTING

Interviews conducted by telephone, recorded, transcribed verbatim, imported to NVivo 12, and analysed by systematic text condensation. Semistructured interviews focused on financial and non-financial conflicts of interest.

RESULTS

The interviewees had participated in a median of 37.5 trials and were mainly male physicians who had experience with commercial and non-commercial trial funders. Two predefined themes (influence of conflicts of interest and management strategies) and two additional themes (definition and reporting of conflicts of interest) emerged. Examples of perceived influence of conflicts of interest were: choice of inferior comparator, manipulation of the randomisation process, prematurely stopping the trials, fabrication of data, blocking access to data, and spin (eg, overly favourable interpretation of the results). Examples of strategies to manage conflicts of interest were: disclosure procedures, exclusion of the funder from design and analysis, independent committees, contracts ensuring complete access to the data, and no restriction by the funder on analysis and reporting. Interviewees used different definitions or thresholds for what they considered to be conflicts of interest, and they described different criteria for when to report them. Some interviewees considered non-commercial financial conflicts of interest (eg, funding of trials by governmental health agencies with a political agenda) to be equally or more important than commercial financial conflicts of interest (eg, funding by drug and device companies), but more challenging to report and manage.

CONCLUSION

This study described how trial researchers perceive conflicts of interest unduly influencing clinical trials they had worked on, and the management strategies they used to prevent these influences. The results indicated considerable variability in researchers' understanding of what conflicts of interest are and when they should be reported.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Funding by a commercial source and authors' financial conflicts of interest are associated with statistically significant results and favourable trial conclusions being reported more frequently

Concern that conflicts of interest might influence how trials are designed, conducted, analysed, and reported is widespread

The mechanisms linking undue influence of conflicts of interest on specific design features or bias of trials, and management strategies to minimise the problems, are not fully understood

WHAT THIS STUDY ADDS

Our study described how trial researchers perceive conflicts of interest unduly influencing clinical trials that they had worked on and the management strategies they used to prevent these influences; detailed examples of perceived influence of conflicts of interest were provided

Considerable variability was found between trial researchers of what they considered to be conflicts of interest and when they should be reported

Financial conflicts of interest related to non-commercial funders (eg, governmental health agencies with a political agenda) were considered equally or more important than commercial financial conflicts of interest (eg, drug and device companies), but more challenging to report and manage

Introduction

Clinical trials are considered to be the most reliable method of evaluating the effect of healthcare interventions, but trials can be biased or might investigate a question of little clinical relevance.[1 2] Conflicts of interest can influence how trials are designed, conducted, analysed, and reported,[3 4] and journal editors routinely ask authors of trial reports (and authors of other study publications) to declare conflicts of interest and the role of the funder in the trial.[5 6]

Conflicts of interest are often defined as "a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest."[6] The primary interest of researchers in a clinical trial should be to conduct a relevant and unbiased investigation. A conflict of interest is a risk of influence by a secondary interest (eg, if a funder or a researcher involved in how

a trial is designed, conducted, or reported stands to gain financially, depending on the published results of the trial).

To minimise undue influence from conflicts of interest and facilitate impartiality, and to be seen as free from conflicts, trial planners might include various management strategies: employ an independent trial statistician, establish an independent data safety and monitoring board, or exclude people working for a commercial funder from direct involvement in the trial.

Funding by a commercial source (eg, a pharmaceutical or medical device company) and authors' financial conflicts of interest have been shown to be associated with statistically significant results and favourable trial conclusions being reported more frequently.[3 7] Examples of academic trials with flawed results where non-financial conflicts of interest might have a role also exist (eg, because of unduly strong affiliations to a specialty, to a scientific theory, or to academic appearance).[8-11]

We are not aware of any empirical studies that have investigated the mechanisms linking undue influence of conflicts of interest to biased trial results or to specific trial design features, or studies on management strategies to minimise the problem. We wanted to explore the experiences and views of trial researchers on conflicts of interest because many of the known cases of flawed trials associated with conflicts of interest have been exposed by trial researchers.[12 13]

Therefore, we conducted a qualitative interview study of experienced trial researchers. Our main objectives were to characterise and analyse trial researchers' experiences of financial and non-financial conflicts of interest, and if and how they had unduly influenced clinical trials they had worked on. We also explored their experiences of management strategies that had been used to minimise the potential influence of conflicts of interest, and their experiences and views more generally.

Methods

Identification of candidates

We identified candidates by snowball and purposive sampling. In the initial screening process, we mainly used snowball sampling based on our personal networks and suggestions from interviewees. Our original plan was to search for candidates on Web of Science but this recruitment method was inefficient, and we shifted to snowball sampling, which identified 15 of the final 20 interviewees included in the study (fig 1 in the appendix).

In the next step, we deliberately selected information rich researchers. We defined information rich researchers by experience (10 trials or more) and author role (trial researchers with methodological and statistical expertise). The experience criterion facilitated saturation by focusing on individuals who were more likely to have experienced the influence of conflicts of interest in trials. The author role criterion allowed us to include interviewees with more knowledge of conflicts of interest and trial methodology, and perhaps more likely to have seen and remembered the issues we wanted to explore. We also wanted diversity in geography and professional background, and experience with different types of funders; these factors were defined a priori based on our knowledge of trial methodology and conflicts of interest, and on previous research.[3 14-16] These criteria were used consistently throughout the study.

We sent email invitations to candidates describing our study and providing the option to access our protocol (appendix). We sent one reminder if candidates did not reply. We did not set a time limit on responding to the emails. We stopped inclusion of new interviewees at the point of saturation—that is, when an informal preliminary assessment of the interviews showed no new major themes, evaluated each time five new interviews had been conducted.[17]

Interview procedures and content

Semistructured interviews[18] were conducted by telephone with an interview guide (fig 2 in the appendix). The interview guide was developed based on previous research,[19 20] our knowledge of the specialty, and suggestions by the interviewees from a pilot test. The pilot test involved three trial researchers (not included in our sample) and resulted in minor adjustments (adding one question on declaration of conflicts of interest). We conducted the interviews by telephone because we wanted to include trial researchers from different countries and continents. Telephone interviews are also suitable when dealing with topics that might be regarded as socially sensitive.[21 22]

The interviewer was guided by open ended questions structured around the trial researchers' experiences with: trial collaborators with conflicts of interest; undue influence of conflicts of interest on the design, conduct, analysis, and reporting of trials; and management of the undue influence. If the answers to the questions were brief, we used specific prompts from the interview guide to help the interviewees elaborate on examples and thoughts (fig 2 in the appendix). The interviewer made notes of the examples and comments of the trial researchers to help further elaboration. We emphasised that we were interested in their personal experiences of trials they had worked on. Also, we asked the interviewees about their educational background and general trial experience.

We informed the interviewees that all information would be handled confidentially and published in an anonymous format. The interviewees consented to audio recorded interviews that two of the authors (SA and MHAG) transcribed verbatim. We shared the transcript of our findings with one interviewee who asked to read them to ensure that they were not recognisable.

The interviewer

The interviewer (LØ) has a master's degree in physical therapy and was working as a research assistant and research librarian at the time of the interviews. He had

formal training in qualitative research and interview techniques but was not experienced in conducting qualitative research and had no strong beliefs about the topic of the interviews. He briefly introduced himself to the interviewees but gave no further details on his background unless asked during the interview.

Analysis and reporting

We analysed the interview transcriptions with systematic text condensation for thematic cross case analysis.[23] This analysis was a four step procedure: (1) all transcribed interviews were read for an overview of the data; (2) meaning units were identified in the texts, representing different aspects of the trial researchers' experiences of conflicts of interest in clinical trials, followed by coding into groups; (3) to clarify different aspects in the code groups, subgroups were created, from which condensates were produced, and illustrative quotations were identified; and (4) trial researchers' experiences with conflicts of interest based on the condensates were described. Two of the authors (LØ and AL) conducted the first step; the other three steps were conducted by the first author (LØ). Figure 3 in the appendix shows the coding tree. We used the software NVivo 12 (Alfasoft) for the analysis. In response to peer review comments, we conducted a secondary analysis of the transcripts focusing on potential differences in interview responses between men and women. We used the COREQ (consolidated criteria for reporting qualitative research) checklist for reporting qualitative research.[24]

Patient and public involvement

We did not engage patients or the public in our study because our focus was on research methodology and trial researchers.

Results

We emailed 52 interview candidates of whom 27 did not respond, five declined to participate (two did not have time to participate and three gave no reason), and 20 (38%) agreed to be interviewed. The 20 interviews were conducted from December 2017 to July 2018 and lasted a median of 24 minutes (range 15-58). The characteristics of the interviewees are reported in table 1 and the characteristics of the non-respondents are reported in table 1 in the appendix. In addition to the two predefined themes (influence of conflicts of interest on trials and management strategies), we found two more themes: definition and reporting of conflicts of interest.

Theme 1: influence of conflicts of interest on trials

Eight of the 20 interviewees had been involved in trials where they believed someone had tried to influence the trial because of conflicts of interest. The interviewees gave various examples of undue influence for financial and non-financial conflicts of interest. Table 2 describes all the perceived mechanisms of influence (with illustrative quotes) as a result of conflicts of interest experienced by the interviewees. We divided this theme into three subthemes: academic researchers, commercial funders (eg, a pharmaceutical company), and non-commercial funders (eg, a governmental agency).

Conflicts of interest related to academic researchers

One interviewee reported that surgeons with a strong belief in the beneficial effect of a procedure tampered with the randomisation process in a multicentre study. The interviewee explained: "What [several] centres did was open the envelopes in advance and gave the younger patients the new treatment and the older patients the old treatment" (interviewee 5).

Another interviewee, a biostatistician, experienced lead academic researchers asking for additional unplanned analyses or ways to present their data more positively to further their career. The interviewee said that the lead academic researchers made comments such as: "Well, if we want to get in the *New England Journal of Medicine*, which will make my career, then we got to have something to show" (interviewee 10).

In summary, the interviewees described a strong preference for one of the trial interventions by some researchers, and how the researchers might subconsciously or consciously try to manipulate a trial. The preferences might be linked to financial conflicts of interests (eg, if the researcher had close ties to a trial funder) or non-financial conflicts of interest (eg, if the researcher had a strong personal affiliation with a theoretical position or type of intervention). In both instances, these strong preferences might give rise to manipulations by different mechanisms, by cherry picking results from unplanned multiple analyses, or by not complying with the randomisation schedule so that patients with a good prognosis are selected for the experimental group.

Commercial financial conflicts of interest

One interviewee described the influence of pharmaceutical companies on which trials receive funding: "I actually think that the biggest place where conflicts come up . . . is in deciding which studies get done. I mean . . . once you have decided to do the trial the conflicts sort of become a side issue. But the much bigger issue is that there might be trials that I think we should do that industry doesn't want to fund" (interviewee 7). The same interviewee reflected on the interaction between trial design, pharmaceutical company, and regulatory authorities: "There is a big role that industry has in shaping what trials get done. And often in the United States, often those trials are driven by what the regulators, what the Food and Drug Administration, requires for approval" (interviewee 7).

Two interviewees said that pharmaceutical companies had tried to end the trials prematurely. According to one of the interviewees: "The trial was negative, and the company refused once they had an early look at the data, which they weren't supposed to do . . . they basically stopped the support and follow-up, so we had an incomplete database and we actually had a lot

Table 1 | Characteristics of the 20 interviewees

Characteristics	No of interviewees (%)
Educational background	
Physician	12 (60)
Other healthcare profession	2 (10)
Biostatistician	4 (20)
Other professions	2 (10)
Sex	
Men	18 (90)
Women	2 (10)
Location of primary institution	
Europe	9 (45)
North America	7 (35)
South America	1 (5)
Africa	1 (5)
Asia	1 (5)
Oceania	1 (5)
Type of primary institution	
University	8 (40)
Hospital	2 (10)
University and hospital	6 (30)
Private for-profit company	1 (5)
Private not-for-profit organisation	3 (15)
Financial conflicts of interest of the interviewees*	
Yes	8 (40)
No	12 (60)
Trial funding source experience†	
Industry funded with company involvement in trial	10 (50)
Industry funded but independently run academic trials	19 (95)
Non-commercially funded trials	18 (90)
Main type of trial the interviewees have participated in	
Drug trials	11 (55)
Non-drug trials	6 (30)
Similar proportion of drug trials and non-drug trials	3 (15)
Median (interquartile range) No of trials interviewees have participated in‡	37.5 (20-100)

*Disclosed in the two most recent PubMed indexed trials.
†More than one category possible.
‡If a range was given, instead of an approximate number, the mean was used.

of trouble getting the database from them to report it" (interviewee 12).

One interviewee described how pharmaceutical companies influenced follow-up analyses: "We often get supplemental contracts with industry to do secondary analyses of clinical trials . . . so, if the trial is positive and the drug is going to be approved, they will fund lots of secondary analyses . . . if the trial is negative they won't" (interviewee 7). Another interviewee described a situation where an academic researcher, a specialist in the intervention tested in the trial, tried to spin (eg, overly favourable interpretation) the trial report. The trial found no effect of the intervention, and the researcher repeatedly suggested explanations for why the trial had failed to detect the effect of the intervention. The academic researcher eventually removed themselves from authorship on the paper after the other authors refused to agree to spin the trial report. The interviewee reflected on the event: "Well, I think, because the research department from [their] institution received a lot of funding for training fees [from a company] . . . , a negative trial with [them] being one of the authors would be detrimental in terms of money" (interviewee 11).

In summary, the interviewees described how some drug and device company funders, or researchers with strong ties to a company, tried to manipulate a trial. Commercial financial conflicts of interest might drive different manipulation mechanisms, such as shaping the research agenda of a specialty, using an inferior comparator, accessing preliminary trial results, not publishing negative results of interventions, performing multiple analyses of a positive trial, and spin of the trial results (table 2).

Non-commercial financial conflicts of interest

One interviewee explained how representatives from governmental health departments, when negotiating a contract for a trial, wanted the option to prohibit papers from being published if they did not like the results: "We have done a few policy trials . . . We have had long and hard contract negotiations . . . where they felt they should be able to veto papers being published if they don't like the results" (interviewee 10). Another interviewee said: "I mean, the whole conflict of interest issue has not dealt with the fact that the most powerful organisations in the world are governments, and when I say governments it's the health part of it, and the health funding parts of it, and they have more conflicts of interest than others. With industry it's transparent and you can set up mechanisms to deal with it, with governments they pretend they're in for the public good, which they ought to be, but you know, people in governments make careers" (interviewee 17).

In summary, the interviewees described how some non-commercial funders will try to manipulate a trial. Non-commercial financial conflicts of interest might result in manipulation by mechanisms also seen with commercial financial conflicts of interest, such as not publishing negative results.

Theme 2: management strategies for conflicts of interest

Multiple strategies were mentioned to manage conflicts of interest in clinical trials. Table 3 reports a list of management strategies with illustrative quotes. Disclosure of conflicts of interest was mentioned by almost all interviewees as important for managing conflicts of interest in clinical trials. Making conflicts of interest transparent, and discussing the potential influence of these interests, was the first step to manage them for the trial collaborators. Conflicts of interest were disclosed at various times: when designing the trial, when preparing a grant application, once a year during the running of the trial, and when submitting the trial for publication.

One interviewee noted that at their institution, they carefully considered the value of the scientific question in relation to the conflicts of interest before deciding whether to participate in a trial: "We really try to decide not to participate in trials that do not have any type of scientific question or contribution that we think is important. I think that identifying clearly what is conflict, what's the potential competing interest, then you can decide if your scientific question is more important or not, and that's in all's interest. And we have refused participation in some trials that have

Table 2 | Examples of how conflicts of interest might unduly influence different stages of clinical trials

Stage of the trial and example of mechanism of influence	Quotes
Design	
Inferior comparator—the funder proposed comparing the intervention to a control treatment that was inferior to standard care	"For example, there are times where sponsors will propose comparing to an inferior control therapy, which may be approved for that indication, but it is no longer considered the standard care, no longer consider optimal" (interviewee 12)
Suboptimal primary outcome—the funder wanted to use an outcome that was easy to measure but was not directly clinically relevant	"The outcome that is selected may not necessarily be the outcome that I think should be the primary outcome, and a lot of times you don't have much control. You can make a suggestion and they will say: 'no we're going to do it this way', and that's it" (interviewee 20)
Choice of research agenda—pharmaceutical and device companies funded trials that potentially provide a positive result that they consider commercially interesting	"You know, the sponsors clearly have a result that they want to get . . . we work together to design trials that will answer the questions that they want to answer. They have a certain answer that they want. I have never felt pressured into getting that answer. But we only conduct trials that will potentially answer the questions that industry wants to answer" (interviewee 7)
Conduct	
Manipulation of the randomisation process—trial collaborators opened envelopes before the patients were enrolled	"What [several]*† centres did was open the envelopes in advance and gave the younger patients the new treatment and the older patients the old treatment" (interviewee 5)
Prematurely stopped the trial—the funder terminated a trial early	"They wanted to save money because they didn't see the drug being a big seller and so they tried to shut the study down" (interviewee 17)
Analysis	
Blocking data access—the funders blocked the academic researchers' access to the trial database	"The trial was prematurely terminated by the data safety monitoring board because of the drug actually was harmful and the company refused . . . to transfer the database to us. They basically blocked our access to the data" (interviewee 18)
Multiple unplanned analysis—the lead academic researcher wanted additional analyses to be conducted so that results would look more positive	"I have had examples of . . . chief investigators who have kind of come back and asked for additional analysis or ways of presenting data that would make it look more positive then it was" (interviewee 10)
Fabrication of data—the lead academic researcher wanted to insert fabricated values in trial database	"The administrator . . . came to see me and said; 'I have just been told by the chief investigator if there was a missing rating, I should just copy in the other rating'" (interviewee 10)
Reporting	
Spin—one of the academic researchers wanted to present the trial result in an overly positive way	"And then this researcher . . . [started] to make a lot of issues [as] to why we are writing the trial, so trying to find excuses for not having positive results" (interviewee 11)
Premature release of results—the funder released interim data to stockholders prematurely	"The company deliberately broke the confidentiality of the study and actually released the interim data" (interviewee 18)
Prevention of publication—the funders did not want the academic researchers to publish the results because they were unfavourable to their product	"It was an approved drug that was harmful, compared to the comparator, where industry didn't want us to publish the results" (interviewee 7)
Contractual constraints—the funder wanted contractual rights to prohibit a paper from being published	"We have done a few policy trials . . . we have had long and hard contract negotiations . . . where they felt they should be able to veto papers being published if they don't like the results" (interviewee 10)

*The text is anonymised by deleting the specific numbers of centres.
†Explanatory text inserted in brackets.

been proposed that we clearly found there is only a financial interest" (interviewee 9).

Some trials prohibited academic researchers with conflicts of interest; academic researchers were allowed to participate only if they had not received payments from companies that produced the drug under consideration or competitor drugs. Some of the interviewees had chosen not to receive any money from drug companies (eg, when sitting on advisory boards), and one of them said: "It allows me to speak freely. If I really think they're coming up with a design that is suboptimal or biased, or otherwise one I am not comfortable with, I can easily say so" (interviewee 15).

In summary, the interviewees described the procedures that were in place for handling conflicts of interest. Some type of procedure was in place in most trials, but practices differed greatly and focused mainly on commercial financial conflicts of interest (table 3).

Theme 3: definition of conflicts of interest

Some interviewees described it as a challenge to distinguish a conflict of interest from related but distinct phenomena (eg, anticipation of an effect of an intervention) and from ignorance (eg, being unaware of the problems involved in selective reporting of results). One interviewee remarked: "Sometimes it is difficult to know why people do things. Sometimes it is just ignorance . . . they think they're doing the right thing, but they're not doing it because they want a particular treatment to win, they're just doing it because they're stupid. And then there are others who know what they're doing, and they're doing it to try and make sure the results favour their point of view" (interviewee 5).

Interviewees had different thresholds for what they considered to be conflicts of interest. Two interviewees described comparable situations where commercial funders stopped the trials early. One interviewee considered this action to be a result of conflicts of interest, although the other interviewee did not, and instead characterised the company's decision to stop the trial as a "business decision" (which they did not consider a conflict of interest).

One interviewee said that they believed that many researchers have conflicts of interest: "I think it is true that most people are doing clinical trials or studying something for a reason. They typically believe it [the intervention] has an effect. They want to see whether or not that is actually true. So, I think the best way that we have come up with is to try and put in place design issues to minimise any potential subconscious influence on results" (interviewee 14).

In summary, the interviewees described the difficulties in defining conflicts of interest, especially the vagueness of the concept of non-financial conflicts

Table 3 | Strategies for managing conflicts of interest in different stages of clinical trials

Stage of the trial and example of strategy	Quotes
Design	
Declaration procedures*—sufficiently declared conflicts of interest	"I would say, step one is disclosure of potential conflicts of interest at various stages during the trial. Sometimes early on, and sometimes relatively late . . . [during the course of]† the trial" (interviewee 16)
No direct payments—payments went to the research departments and not to the academic researchers	"In terms of compensation for participation in clinical trials, our hospital does not accept direct compensation for the investigator . . . So, the payment for clinical trials comes to the hospital usually, not directly to the investigators" (interviewee 9)
Preplanned methods—a detailed protocol (including data management plan and statistical analysis plan)	"[to manage conflicts of interest, it is good] to have a very good protocol for the trial, where people are in agreement on what is going to be conducted, and what is going to be the primary outcome or outcomes, and what is going to be the secondary and tertiary outcomes, and a good data plan for data management, and a good plan for statistical analysis, and a recording of the trial design in a paper as early as possible after starting the trial, and a report of the statistical analysis plan before any data have been looked at" (interviewee 2)
Decline participation—academic researchers refused to participate in trials designed by the industry	"The way these trials are done is the company picks the steering committee, they pick a principal investigator, the company writes the protocol, the company analyses the data and the company provides data tables to the investigators . . . we will not participate in . . . such trials, we call them 'rent-a-doc trials'" (interviewee 18)
Exclusion—trial collaborators with conflicts of interest were not allowed to contribute to designing the trial	"I think the best examples I have were in industry sponsored academically run trials, where the industry sponsor was . . . excluded from the design . . . , analysis and recording of the study. They funded it and they approved the general research questions, but they were not involved in anything further" (interviewee 16)
Conduct	
Adequate randomisation procedures—a web based system for randomisation minimises the risk of someone tampering with the randomisation	"Well, for randomisation we use a web-based system for all our trials" (interviewee 5)
Adequate blinding procedures—trial researchers were blinded and a plan of action described the procedure if blinding of the trial collaborators was broken	"The main way that we're trying to address the potential influences of our intellectual conflicts . . . is just through design issues . . . ideally in almost all of our trials we blind" (interviewee 14) "We also make extensive effort to specify in our charters and executive committees etc, that blinding be maintained, to detail the few exclusions in which blinding may be broken, and also to isolate any personnel, who for whatever reason have their blinding broken" (interviewee 12)
Independent committees—independent data monitoring and trial steering committees are used to give unbiased recommendations	"If there is an independent committee that isn't going to get its name on the paper anyway and isn't going to have a better association with the pharma company if the trial is positive, and whose career ultimately doesn't depend on the results, then that committee . . . is more likely to give an unbiased answer" (interviewee 15)
Exclusion—trial collaborators with conflicts of interest (strong belief in the effect of the experimental intervention) were excluded from also delivering the control intervention	"These guys [trial collaborators] are usually the treatment providers, so we try to ask them . . . not providing treatment for the control group . . . because the enthusiasm would be different" (interviewee 11)
Analysis	
Data access—a copy of the entire database was sent to the academic researcher	"Our contracts with the sponsor, the pharmaceutical company, usually state . . . that we will get a copy of the database" (interviewee 7)
Independent analysis—analysis was done by an independent academic statistician	"We're going to give the data . . . to independent academics who have absolutely nothing to do with the trial" (interviewee 4)
Exclusion—trial collaborators with conflicts of interest were excluded from involvement in the analysis	"We cannot use tables that they [pharmaceutical company] provide, they [the tables] have to be done by our statisticians" (interviewee 18)
Reporting	
Transparency—detailed reporting if the protocol was not adhered to	"Sometimes you will do analyses that are not pre-specified . . . you'll just be honest about it and say it is not pre-specified" (interviewee 17)
Exclusion—trial collaborators with conflicts of interest were excluded from manuscript writing	"We will not allow the company to write any portion of the manuscript, they can comment on the manuscript that we write, but they cannot write any portion of the manuscript" (interviewee 18) "The industry has the right to look at the draft of the manuscript and make any comments on areas of facts but not interpretation" (interviewee 5)
Authorship—a researcher with conflicts of interest was given a less important authorship position	"They [researchers with conflicts of interest] will be positioned in the middle of authorship rather than in top and tail" (interviewee 4)
Absence of contractual constraints on publication—the funders were not allowed to prohibit papers from being published	"I would also tend to pay quite a lot attention to contracts . . . whether they put any limitation on our ability to publish findings" (interviewee 10)

*Disclosure can be seen as a preventive step, as knowledge of the need to disclose conflicts of interest might prevent some researchers with strong conflicts of interest from participating in a trial, and if they participate, it might modify their behaviour or assessments when conflicts of interest are known. Also, disclosed conflicts of interest might influence the threshold for when the author group decides on an action to manage the conflicts of interest.
†Explanatory text inserted in brackets.

of interest, the difference between risk of influence and actual influence because of a secondary interest, and the difficulties in deciding when a person with conflicts of interest acts because of these conflicts or for other reasons.

Theme 4: reporting of conflicts of interest

Non-financial conflicts of interest (intellectual conflicts of interest or fixated and strong personal beliefs) were considered harder to detect and therefore difficult to report. Commercial financial conflicts of interest, on the other hand, were considered easier to detect because of the money flow and hence easier to report. Reporting of financial conflicts of interests was not always straightforward, however. One interviewee had participated in a trial funded by the World Health Organization where the funding was from a pharmaceutical company. Another interviewee had experienced a similar situation: "It raises interesting questions if you know some of the money is coming from somewhere else. Is that an additional conflict that you should report?" (interviewee 7).

Financial conflicts of interest in relation to non-commercial funders, such as governmental health departments or charitable foundations, were considered difficult to detect by some interviewees. One

interviewee said: "There has to be system in place to avoid competing interests at governments, at charitable foundations, at journals. It is not just an industry issue" (interviewee 17). Some of the interviewees mentioned variation in the standards for declaring conflicts of interest between scientific journals. They also reflected on the time period before conflicts of interest were regarded as outdated; three years for the International Committee of Medical Journal Editors (ICMJE),[25] and four or five years for some of the interviewees.

Most interviewees agreed that when reporting conflicts of interest, full details should be disclosed. One interviewee remarked: "I have generally taken the position that it is better to over-report. There are definitely variations across journals, in terms of what they say is actually required. So, some will say: report any financial relations you have had with any company in the last 2 years. I just reported any I have ever had at any time in my career" (interviewee 14).

In summary, the interviewees stated the importance of declaring all conflicts of interest, but also noted that declaration procedures differed and were focused mainly on commercial financial conflicts of interest.

Secondary analysis

We explored how men and women interviewees responded but found no differences.

Discussion

Our study described how trial researchers perceive conflicts of interest unduly influencing their trials and how they managed those conflicts of interests. Two more interview themes emerged: definition and reporting of conflicts of interest. Examples of perceived undue influence of conflicts of interest included the choice of comparator, manipulation of the randomisation process, prematurely stopping trials, fabrication of data, blocking access to data, and spin of trial results. Interviewees had many methodological strategies for managing conflicts of interest at different stages of their trials. They used different definitions or thresholds for what they considered to be conflicts of interest, and some considered non-commercial financial conflicts of interest (eg, funding of trials by governmental health agencies with an agenda) as equally or more important than commercial financial conflicts of interest (eg, funding by drug and device companies), but more challenging to report and manage.

Strengths and limitations of the study

A strength of our study was the use of qualitative interviews to study the influence and management of conflicts of interest in clinical trials. This design allowed us to explore trial researchers' subtle reflections on conflicts of interest in clinical trials with a focused analysis of their experiences based on their own trials. Trial researchers described their experiences of specific mechanisms for how conflicts of interest had affected trials and which management strategies had been implemented to minimise the influence of these conflicts. We included all experiences reported by the interviewees, regardless of when they occurred, to create a more detailed overview. Recent experiences might be remembered more clearly, and therefore were probably more commonly reported in our interviews.

Most of the interviewees (90%) were men. When we planned our study, we prioritised our sampling based on geography, professional background, and experience with different types of funders. The factors were selected based on our knowledge of trial methodology and conflicts of interest, and previous research.[3 14-16] We acknowledge the gender bias in the career path to becoming an experienced trialist.[26-28] Our aim was not to look at gender bias in academic careers, however, but to explore how trialists reported their experiences and views on conflicts of interest in trials. We looked at how men (n=18) and women (n=2) interviewees responded to our questions but no difference was detected.

We sampled experienced trialists (defined as having participated in 10 or more trials), and the median number of trials the interviewees had participated in was 37.5. Including experienced trialists could have resulted in a conservative description of the problems involved because conflicts of interests might have more influence on smaller trials conducted by less experienced trialists and with less efficient management practices in place.

Our qualitative investigation should not be interpreted in the same way as a quantitative study. Qualitative studies cannot establish how often the reported examples and events occur. Sampling of interviewees was based mainly on snowball suggestions from other interviewees and was not random or independent. The proportion of trial researchers that declined to participate or did not reply to our invitation was high (>60%). Trial researchers with repeated experiences of problems in their trials because of conflicts of interest are likely to more often decline participating in an interview study. Also, what constituted conflicts of interest, how problems were perceived, and how strong the links were between the two varied between interviewees. We noticed that some of the interviewees considered conflicts of interest to be present only if a clear influence was apparent whereas other interviewees considered conflicts of interest as a set of circumstances that creates a risk of influence.

Other studies

To our knowledge, no previous qualitative interview study has investigated how conflicts of interest might influence clinical trials. Qualitative interview studies are rare in clinical trial methodology, but we were encouraged by a previous study describing trial researchers' views on their motives for selective outcome reporting.[29] Also, qualitative interview studies have investigated attitudes to universities' policies on conflicts of interest (for clinical trials) and views on different strategies for handling conflicts of interest in clinical guidelines.[30 31] In agreement with our results, a study reported that some content experts regarded

intellectual conflicts of interest as more important than financial conflicts of interest.[30]

The results of our qualitative study complement previous case stories,[8-10] theoretical considerations, systematic and narrative reviews,[3 32] and meta-epidemiological studies.[33] Our results suggest mechanisms that might explain the differences between commercially and non-commercially funded trials that other studies have reported in relation to trial characteristics,[34] results, and conclusions.[3 33] Our study also emphasises the vagueness of the concept of non-financial conflicts of interest, and adds to the ongoing debate about the meaningfulness of the concept.[35] Our interviewees also had concerns about the role of non-commercial financial conflicts of interests in clinical trials. We could not identify any empirical study of the influence of governmental or other non-commercial funders on trial design, conduct, analysis, or reporting.

Meaning of the study: possible explanations and implications for clinicians and policy makers

We found many examples of problems in clinical trials perceived to have arisen from conflicts of interest. We were surprised, however, that only eight of the 20 interviewees reported that they had experienced what they considered as undue influence. This finding could imply that in many trials conflicts of interest is not a problem. Another explanation could be related to the different thresholds researchers use to define conflicts of interest, or problems, and when conflicts of interest are considered to cause a problem. The non-random selection process in recruiting the trial researchers could also explain this finding.

General concern exists among users of trial results that trial researchers' conflicts of interest and commercial funding might unduly influence trials.[3 7] In some trials, the funder's influence is considerable. One of the interviewees used the term "rent-a-doc trial" and explained that a pharmaceutical company picks the steering committee and a principal investigator, writes the protocol, analyses the data, and provides data tables to the investigators. Other mechanisms of influence are use of inferior comparators, surrogate outcomes, limited access to data, and constraints on publication rights.[36 37] Our study corroborates these findings and gives more examples, such as fabrication of data and spin of the results, in research publications.

We found that some of the interviewees regarded non-commercial financial conflicts of interest as important. The reason could be that in the past decades, the primary focus of the debate on conflicts of interest in trials has been on the influence of commercial drug and device companies.[35] Financial conflicts of interest related to non-commercial funders, such as foundations or governmental agencies, has received little attention. We did note, however, that some of the interviewees had experienced that governmental health department funders, with a perceived policy agenda for a specific trial result, had tried to impose restrictions on publication rights. The interviewees also reflected on non-financial conflicts of interest (eg, academic or specialty conflicts of interests). In general, these non-commercial conflicts of interest were regarded as more difficult to define, report, detect, and handle.[38]

The interviewees described mechanisms where conflicts of interest unduly influenced the design, conduct, analysis, and reporting of randomised trials. The mechanisms could be considered in three broad categories: applicability of a trial result, risk of bias in a published trial result, and missing trial results or spin of the results. An example of a mechanism related to the applicability of a trial result is choosing an inferior control group. Choosing an inferior control group is problematic for external validity[39] and more generally for the relevance and completeness of the evidence within a specialty. An example of a mechanism related to the risk of bias of a trial result is tampering with randomisation envelopes which is problematic for internal validity.[40] An example of a mechanism related to risk of bias because of missing trial results is not publishing the results of a trial or not publishing a specific outcome of a trial because of "uninteresting" results. Missing uninteresting trial results will bias a meta-analysis (that would have included the trial results had they been available).[41] Also, incomplete reporting or spin of the results will reduce the transparency of the methods and results.[42 43] Thus the influence of conflicts of interest on trials included effects on external validity, internal validity, and risk of non-reporting bias and spin.

We hope the results of our study will help interpretation of results from trials with conflicts of interest.[44] Many of the examples of undue influence from conflicts of interest that we found would not be described in a typical trial report. Our study supports the general awareness of potential problems in trials with conflicts of interests, however. A trial report might include suggestions of a conflict of interest, which could be interpreted more cautiously given our results. For example, a reader of a trial report funded by a non-commercial source investigating a politically sensitive issue could look more carefully for signs of undue influence, and be more concerned about an unclear description of the funder's role. A reader of trial reports might be more vigilant in assessing whether appropriate management strategies were in place to minimise possible undue influence of conflicts of interest. We also hope that our results will further discussions on the policies of journals and funding agencies for managing and reporting conflicts of interest in trials, and inform the development of trial protocols.[45]

Unanswered questions and future research

Our results are part of the evidence base for the development of a tool for looking at conflicts of interest in clinical trials.[46 47] TACIT (tool for addressing conflicts of interest in trials) aims to guide readers of trial reports on where to access information on conflicts of interest and how to process the information. TACIT gives a structure for how to interpret results from trials

with conflicts of interest, especially when conducting a systematic review.[47] Our results will inform the main framework components of TACIT: trial design, conduct, analysis and reporting. We can offer the tool developers a range of problematic issues and mechanisms related to conflicts of interest, which the tool could aim to manage. A follow-up questionnaire on the frequency of the events and mechanisms reported by the interviewees could be useful, as would an in-depth exploration of an academic's legitimate interest in their research (including hopes for an effect of an intervention tested in a clinical trial) and non-financial conflicts of interest.

In conclusion, our study described how trial researchers perceive conflicts of interest having unduly influenced clinical trials and the management strategies they used to prevent these influences. We found considerable variability between trial researchers in their understanding of what are conflicts of interests and when they should be reported.

AUTHOR AFFILIATIONS

[1]Centre for Evidence-Based Medicine Odense (CEBMO), Odense University Hospital, Kløvervænget 10, 13th floor, 5000 Odense C, Denmark

[2]Open Patient data Exploratory Network (OPEN), Odense University Hospital, Odense, Denmark

[3]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[4]University Library of Southern Denmark, Odense, Denmark

[5]Department of Infectious Diseases, Hvidovre Hospital, Hvidovre, Denmark

[6]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[7]Centre for Reviews and Dissemination, University of York, York, UK

[8]Université de Paris, CRESS, Inserm, INRA, F-75004, Paris, France

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Contributors: LØ, AH, AL, LAS, and IB designed the study. LØ conducted the interviews, and SA and MHAG transcribed the interviews. LØ, AH, AL, and TT-T were involved in the analysis of the interviews. LØ and AH wrote the first draft of the manuscript, which was then critically reviewed and revised by the other authors. All authors approved the final version of the manuscript for submission. The lead author (LØ) is the guarantor, had the final responsibility for the decision to submit for publication and accepts full responsibility for the work and the conduct of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: To preserve the anonymity of the interviewees, the transcribed interviews are not available for sharing.

The lead author (LØ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained. The study protocol is in the appendix.

Dissemination to participants and related patient and public communities: An email to the participants will be sent, with a link to the published study.

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1 Evans I, Thornton H, Chalmers I, et al. *Testing treatments. Better research for better healthcare.* 2nd ed. Pinter & Martin Ltd, 2011.
2 Page MJ, Higgins JPT, Clayton G, Sterne JA, Hróbjartsson A, Savović J. Empirical evidence of study design biases in randomized trials: systematic review of meta-epidemiological studies. *PLoS One* 2016;11:e0159267. doi:10.1371/journal.pone.0159267
3 Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2017;2:MR000033. doi:10.1002/14651858.MR000033.pub3
4 Rochon PA, Sekeres M, Hoey J, et al. Investigator experiences with financial conflicts of interest in clinical trials. *Trials* 2011;12:9-9. doi:10.1186/1745-6215-12-9
5 Campbell MK, Piaggio G, Elbourne DR, Altman DG, CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661
6 Institute of Medicine. *Conflict of interest in medical research, education and practice.* National Academies Press, 2009.
7 Ahn R, Woodbridge A, Abraham A, et al. Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study. *BMJ* 2017;356:i6770. doi:10.1136/bmj.i6770
8 Marret E, Elia N, Dahl JB, et al. Susceptibility to fraud in systematic reviews: lessons from the Reuben case. *Anesthesiology* 2009;111:1279-89. doi:10.1097/ALN.0b013e3181c14c3d
9 Wise J. Boldt: the great pretender. *BMJ* 2013;346:f1738. doi:10.1136/bmj.f1738
10 Horton R. Expression of concern: non-steroidal anti-inflammatory drugs and the risk of oral cancer. *Lancet* 2006;367:196. doi:10.1016/S0140-6736(06)68014-8
11 Berendt L, Callréus T, Petersen LG, Bach KF, Poulsen HE, Dalhoff K. From protocol to published report: a study of consistency in the reporting of academic drug trials. *Trials* 2016;17:100. doi:10.1186/s13063-016-1189-4
12 Jüni P, Rutjes AWS, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs?*BMJ* 2002;324:1287-8. doi:10.1136/bmj.324.7349.1287
13 Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015;351:h4320. doi:10.1136/bmj.h4320
14 Panagiotou OA, Contopoulos-Ioannidis DG, Ioannidis JPA. Comparative effect sizes in randomised trials from less developed and more developed countries: meta-epidemiological assessment. *BMJ* 2013;346:f707. doi:10.1136/bmj.f707
15 Norris SL, Burda BU, Holmer HK, et al. Author's specialty and conflicts of interest contribute to conflicting guidelines for screening mammography. *J Clin Epidemiol* 2012;65:725-33. doi:10.1016/j.jclinepi.2011.12.011
16 Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA* 2012;307:1838-47. doi:10.1001/jama.2012.3424
17 Saunders B, Sim J, Kingstone T, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant* 2018;52:1893-907. doi:10.1007/s11135-017-0574-8
18 Brinkmann S, Kvale S. *Interviews: learning the craft of qualitative research interviewing.* 3rd ed. Sage, 2014.
19 Bero L. Addressing bias and conflict of interest among biomedical researchers. *JAMA* 2017;317:1723-4. doi:10.1001/jama.2017.3854
20 Lundh A, Bero L. The ties that bind. *BMJ* 2017;356:j176. doi:10.1136/bmj.j176
21 Novick G. Is there a bias against telephone interviews in qualitative research?*Res Nurs Health* 2008;31:391-8. doi:10.1002/nur.20259.
22 Opdenakker R. Advantages and disadvantages of four interview techniques in qualitative research. Forum Qualitative Sozialforschung/Forum: Qualitative Social Research, volume 7(4), article 11. 2006;7. doi:10.17169/fqs-7.4.175. http://nbn-resolving.de/urn:nbn:de:0114-fqs0604118.
23 Malterud K. Systematic text condensation: a strategy for qualitative analysis. *Scand J Public Health* 2012;40:795-805. doi:10.1177/1403494812465030
24 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349-57. doi:10.1093/intqhc/mzm042

25 International Committee of Medical Journal Editors. Conflicts of interest form. http://www.icmje.org/conflicts-of-interest/.
26 Ludmir EB, Mainwaring W, Miller AB, et al. Women's representation among lead investigators of clinical trials in oncology. *JAMA Oncol* 2019;5:1501-2. doi:10.1001/jamaoncol.2019.2196
27 Filardo G, da Graca B, Sass DM, Pollock BD, Smith EB, Martinez MA. Trends and comparison of female first authorship in high impact medical journals: observational study (1994-2014). *BMJ* 2016;352:i847. doi:10.1136/bmj.i847
28 Hamel MB, Ingelfinger JR, Phimister E, Solomon CG. Women in academic medicine--progress and challenges. *N Engl J Med* 2006;355:310-2. doi:10.1056/NEJMe068143
29 Smyth RMD, Kirkham JJ, Jacoby A, Altman DG, Gamble C, Williamson PR. Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists. *BMJ* 2011;342:c7153. doi:10.1136/bmj.c7153
30 Akl EA, Karl R, Guyatt GH. Methodologists and context experts disagreed regarding managing conflicts of interest of clinical practice guidelines panels. *J Clin Epidemiol* 2012;65:734-9. doi:10.1016/j.jclinepi.2011.12.013
31 Boyd EA, Cho MK, Bero LA. Financial conflict-of-interest policies in clinical research: issues for clinical investigators. *Acad Med* 2003;78:769-74. doi:10.1097/00001888-200308000-00002
32 McGauran N, Wieseler B, Kreis J, Schüler YB, Kölsch H, Kaiser T. Reporting bias in medical research - a narrative review. *Trials* 2010;11:37. doi:10.1186/1745-6215-11-37
33 Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events?*JAMA* 2003;290:921-8. doi:10.1001/jama.290.7.921
34 Zwierzyna M, Davies M, Hingorani AD, Hunter J. Clinical trial design and dissemination: comprehensive analysis of clinicaltrials.gov and PubMed data since 2005. *BMJ* 2018;361:k2130. doi:10.1136/bmj.k2130
35 Bero LA, Grundy Q. Why having a (nonfinancial) interest is not a conflict of interest. *PLoS Biol* 2016;14:e2001221. doi:10.1371/journal.pbio.2001221
36 Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Constraints on publication rights in industry-initiated clinical trials. *JAMA* 2006;295:1645-6. doi:10.1001/jama.295.14.1645
37 Lundh A, Krogsbøll LT, Gøtzsche PC. Access to data in industry-sponsored trials. *Lancet* 2011;378:1995-6. doi:10.1016/S0140-6736(11)61871-0
38 Wiersma M, Kerridge I, Lipworth W. Dangers of neglecting non-financial conflicts of interest in health and medicine. *J Med Ethics* 2018;44:319-22. doi:10.1136/medethics-2017-104530
39 Rothwell PM. Factors that can affect the external validity of randomised controlled trials. *PLoS Clin Trials* 2006;1:e9. doi:10.1371/journal.pctr.0010009
40 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898
41 Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. Cochrane Handbook for Systematic Reviews of Interventions version 6.0. 2019. https://www.training.cochrane.org/handbook.
42 Boutron I, Altman DG, Hopewell S, Vera-Badillo F, Tannock I, Ravaud P. Impact of spin in the abstracts of articles reporting results of randomized controlled trials in the field of cancer: the SPIIN randomized controlled trial. *J Clin Oncol* 2014;32:4120-6. doi:10.1200/JCO.2014.56.7503
43 Yavchitz A, Boutron I, Bafeta A, et al. Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study. *PLoS Med* 2012;9:e1001308. doi:10.1371/journal.pmed.1001308
44 Lundh A, Rasmussen K, Østengaard L, Boutron I, Stewart LA, Hróbjartsson A. Systematic review finds that appraisal tools for medical research studies address conflicts of interest superficially. *J Clin Epidemiol* 2020;120:104-15. doi:10.1016/j.jclinepi.2019.12.005
45 Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7. doi:10.7326/0003-4819-158-3-201302050-00583
46 Page MJ, Boutron I, Hansen C, Altman DG, Hróbjartsson A. Assessing risk of bias in studies that evaluate health care interventions: recommendations in the misinformation age. *J Clin Epidemiol* 2018;97:133-6. doi:10.1016/j.jclinepi.2018.01.004
47 Lundh A, Boutron I, Stewart L, et al. *What to do with a clinical trial with conflicts of interest.* BMJ Evidence-Based Medicine, 2019. doi:10.1136/bmjebm-2019-111230

Web appendix: Appendix