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PhD Thesis

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Conflicts of Interest in Scientific Articles

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Preface

The studies included in this PhD thesis were conducted at Nordic Cochrane Centre as well as in my spare time while completing an MSc in Epidemiology and working as a clinical research fellow at Imperial College London, United Kingdom and while training to become a GP in Region Hovedstaden, Denmark. This thesis is a synopsis based on the following three papers:

1. Rasmussen K, Jørgensen KJ, Gøtzsche PC. Citations of scientific results and conflicts of interest: the case of mammography screening. Evid Based Med. 2013;18(3):83-9.
2. Rasmussen K, Schroll J, Gøtzsche PC, Lundh A. Under-reporting of conflicts of interest among trialists: a cross-sectional study. J R Soc Med. 2015;108(3):101-7.
3. Rasmussen K, Bero L, Redberg R, Gøtzsche PC, Lundh A. Collaboration between academics and industry in clinical trials: a cross-sectional study and survey of lead academic investigators. *Submitted*.

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English summary

Conflicts of interest can affect our ability to remain open-minded and may lead to a subconscious urge to reciprocate the kind gestures and donations of a funder. Furthermore, they can draw attention away from what is in the patients' best interest and instead serve the doctors' or researchers' other interests.

Objectives and methods

The overall aim of this PhD was to examine conflicts of interest in scientific articles within the medical field. This was done in three separate studies. In our first study, we assessed what general medical journal and specialty journal authors' positions were relating to one of three versions of an independent and comprehensive Cochrane systematic review on mammography screening, whether there were geographical differences, and whether acceptance of the review had changed over time. In our second study we examined the prevalence of conflicts of interest among Danish doctors who were authors on clinical randomised controlled trials and determined the extent of under-reporting of conflicts of interest. Finally, in our third study, we determined the involvement of academic authors of industry-funded clinical randomised controlled trials in the design, conduct, data analysis and reporting. Furthermore, we assessed what their experiences were with industry collaboration.

Results

In our first study, we found that authors of publications in general medical journals were more accepting of and less likely to reject the results and methods of the systematic Cochrane review of mammography screening compared to authors of publications in specialty journals. We found no geographical differences, but there was a tendency towards greater acceptance of the systematic review over time.

In our second study, we found that one in three Danish doctors who were authors on clinical drug trial publications had declared financial conflicts of interest with a pharmaceutical industry company. We also found that one in eight doctors failed to declare financial conflicts of interest with the industry funder of the trial and that conflicts of interest with other pharmaceutical companies often remained undeclared.

In our third study, we found that academic authors on industry-funded clinical trials mostly collaborated with industry employees on the trial design, conduct and reporting,

but the data analysis was most often conducted by industry statisticians. Most lead academic authors reported that the collaboration was beneficial and access to funding, publications in high-impact journals and prestige were among important benefits reported. However, some authors reported disagreements with the industry funder typically concerning trial design or reporting.

Conclusions

Authors of publications in general medical journals showed greater acceptance of the results and methods in the systematic review on mammography screening compared to authors from specialty journals. The difference in acceptance could be related to specialty journal authors' affiliation and conflicts of interest.

Self-declared conflicts of interest statements in trial publications are often unreliable. Public registries of doctors' collaboration with pharmaceutical industry companies can help achieve a more comprehensive declaration of conflicts of interest.

Industry-funded trials were often designed, conducted, analysed and reported with funder influence. While many of the lead academic authors found the collaboration with industry beneficial, some authors reported loss of academic freedom.

Danish summary

Interessekonflikter kan påvirke vores evne til at forholde os åbensindede og kan resultere i, at vi underbevidst føler gengældelsestrang overfor en sponsors venlige donationer og handlinger. Ydermere kan interessekonflikter flytte fokus væk fra, hvad der er bedst for patienterne, til hvad der er bedst for lægen eller forskeren.

Formål og metode

Det overordnede formål med denne PhD var at undersøge interessekonflikter indenfor medicinske forskningsartikler. Dette blev gjort i tre separate studier. I vores første studie vurderede vi, hvorledes forfattere i generelle medicinske tidskrifter og speciale tidskrifter forholdte sig til en uafhængig og omfattende Cochrane systematisk oversigtsartikel om mammografiscreening, om holdninger var forskellige afhængigt af geografisk lokalisation, og om der var sket ændringer over tid. I vores andet studie undersøgte vi prævalensen af interesse konflikter blandt danske læger, der er forfattere på kliniske

lægemiddelstudier og bestemte udbredelsen af udeklarerede interessekonflikter i publikationerne. I vores tredje studie vurderede vi, hvilken rolle akademiske forfattere har i kliniske randomiserede forsøg sponsoreret af lægemiddel- eller medico-industrien. Derudover undersøgte vi, hvad deres erfaringer var med at samarbejde med en industrisponsor.

Resultater

I vores første studie fandt vi, at forfattere i generelle medicinske tidskrifter var mere accepterende og mindre afvisende over for resultaterne og metoden i den systematiske oversigtsartikel sammenlignet med forfattere i speciale tidskrifter. Vi fandt ingen geografiske forskelle, men muligvis en tendens til større accept af oversigtsartiklen over tid.

I vores andet studie fandt vi, at hver tredje danske læge, der var forfattere på kliniske lægemiddelstudier havde deklareret finansielle interessekonflikter med lægemiddel- eller medico-virksomheder. Desuden fandt vi, at hver ottende læge havde undladt at deklarere deres finansielle interessekonflikter med industrisponsoren af forsøget og at interessekonflikter med andre lægemiddel- eller medico-virksomheder hyppigt var udeklarerede.

I vores tredje studie fandt vi, at akademiske forfattere på industrisponsorerede kliniske randomiserede studier generelt samarbejdede med industri-ansatte om design, udførelse og rapportering af studierne, men at data analysen oftest blev udført af en industriansat. Derudover fandt vi, at de ledende akademiske forfattere ofte så mange fordele i samarbejdet, bl.a. økonomiske fordele, publikationer i velansete medicinske tidskrifter og anerkendelse. Der var dog nogle forfattere, der oplevede konflikter med industrisponsoren oftest i forhold til design og rapportering.

Konklusion

Forfattere fra generelle medicinske tidskrifter udviste større accept af resultaterne og metoden i oversigtsartiklen om mammografiscreening sammenlignet med forfattere fra speciale tidskrifter. Forskellen i accept kan skyldes interessekonflikter hos forfatterne på publikationer i speciale tidskrifter.

Selv-deklarerede interesse konflikter er ofte upålidelige. Offentlige registre kan bidrage til en mere fuldstændig deklarering af interesse konflikter.

Industrisponsoren havde indflydelse på design, udførelse og rapportering i størstedelen af de inkluderede industrisponsorerede kliniske randomiserede studier. Mens mange af de akademiske forfattere betragtede samarbejdet med industrien som fordelagtigt, var der nogle som oplevede, at det begrænsede deres akademiske frihed.

Introduction

Psychology of Objectivity

"*Anyone who has made a decision is usually extremely reluctant to change it, even in the face of overwhelming evidence that it is wrong*" reports Sutherland (1). This insightful quote by Sutherland is a key element of how we make decisions as humans. It is particularly pertinent to the field of medicine because medicine should be underpinned by evidence based decision making. Nonetheless, changing our minds about a well-established treatment, diagnostic test, or screening programme remains difficult even when new, solid evidence against it prevails. This can be due to many doctors finding it difficult to convince themselves that what they have been practising for years, leads to more harm than benefit. An example that this bias affects even the greatest minds, is the double Nobel Prize winner Linus Pauling who refused to change his mind about the beneficial effects of vitamin C on anything from colds to cancer, despite a vast and growing amount of evidence contradicting his thesis. Furthermore, people seek confirmation of their current hypotheses and in the process fail to take new evidence into account and change their beliefs (1-3). Within the field of practising medicine and conducting research, having worked in a specific field for a while could impair your ability to remain completely objective and open to new evidence. These unacknowledged influences on objective decision-making are examples of intellectual conflicts of interest (COIs), an area that is much harder to study than the more readily recognised conflicts related to financial interests.

Conflicts of Interest

A CoI can contribute to the issue with doctors remaining objective. A CoI was defined by the American Institute of Medicine 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"* (4). This broad definition includes both financial and non-financial conflicts. Financial CoIs are easily identifiable circumstances such as stock ownership, reimbursement for consultancy or honoraria. Conversely, non-financial CoIs (i.e. intellectual CoIs) can be harder to identify and represent circumstances such as strong personal beliefs, academic competition or personal relationships (5).
The Hippocratic Oath entails that doctors first and foremost act to benefit their patients, but this oath may be set aside if there are competing financial interest such as a doctor

collaborating closely with or having shares in a company. Kassirer explains that when doctors collaborate with industry there is a shift and increase in doctors' financial expectations and that impaired professional judgements can result (3). Furthermore, examples of doctors being given disproportionate sums of money for expert advice or when serving as investigators on industry-funded trials are prolific and help explain how doctors' professional conduct gets corrupted by the companies (6-8).

Industry gifts and disproportionate payments are effective at altering professional habits because of individuals' urge to reciprocate. Notably, this urge is not correlated with the size of the gift or payment (3, 9). Cialdini explains that the reciprocation rule is one of the most influential weapons in the world, as it exists in all societies and is widely abused. By not reciprocating a gift, one risks being looked down upon and individuals are willing to go to great lengths to avoid being seen as a moocher (10). Even if doctors are aware if this intrinsic urge to reciprocate, the art of self-reflection is often not sufficient to appreciate how our conscience works and though some may be immune to their CoIs, many are likely to be affected (3).

CoIs are common amongst trialists and "key opinion leaders" as the vast majority of clinical trials today are industry sponsored (11). This can lead to bias in the interpretation and reporting of results (4). In a random sample of randomised controlled trials (RCTs) published in core clinical journals in 2015, 57% of the RCTs had one or more authors with reported CoIs (12). Similarly, Ahn et al. found a prevalence of disclosed CoIs amongst principal investigators of 50% (13). A recent study found that 99% of RCTs funded by for-profit companies had at least one author with CoIs, whereas this was only the case for 8% of not-for-profit funded RCTs (14). The study also found an association between disclosed stock ownership in the company funding the trial and favourable results, nevertheless, an association cannot reveal if the authors concluded positively because of their stock ownership, or if they bought stocks in the company because they believed in the product (14). However, other studies have found that other financial CoIs (e.g. reimbursement for consultancy) are also associated with positive results (13, 15).

Financial CoIs have the potential to affect clinical practice. A large systematic review of doctors' interaction with the pharmaceutical industry reconfirmed previous studies' findings that doctors' prescribing patterns are inappropriately changed by contact with industry (9). The extent to which industry collaboration is problematic was questioned by

the New England Journal of Medicine (NEJM) in three editorials suggesting that collaboration is mostly beneficial and unproblematic (16-18). However, the editorials resulted in many comments and papers arguing that CoIs with industry remain a major problem in evidence based medicine (19, 20).

Additionally, some medical journal editors also have CoIs. A study using the US Open Payments Database found that 51% of medical journal editors had received payments from industry and that the payments were especially high for specialty journals (21).

Under-reporting

The International Committee of Medical Journal Editors (ICMJE) consider not only actual, but also perceived CoIs as important and recommend that both types of CoIs are declared in journals. They describe both financial and non-financial CoIs as factors that can affect an author's credibility (5). Despite these unambiguous recommendations, it is still debated whether researchers are under-reporting their CoIs when reporting results (22). Ahn et al. found 15% undisclosed financial CoIs amongst primary investigators by searching CoIs statements in the investigators' other trial publications, Google, ProPublica's Dollars for Docs data base, and the US Patent Office (13). A study investigating disclosure of CoIs amongst the most highly cited American authors in clinical medicine found that most of the authors were often not fully disclosing their financial ties with industry either (23).

Mammography Screening

Not only financial but also non-financial CoIs (i.e. intellectual conflicts of interest) can affect the way authors interpret results. This was shown in a cross-sectional study of mammography screening papers. The study showed that harms were often downplayed or rejected compared to the benefits and this imbalance was greater if the authors were affiliated with mammography screening (24). Reasons for the affiliation bias include financial incentives and the effect of being surrounded by people who share your views (1, 3). Bero et al. argue that the focus on non-financial CoIs serves to obfuscate and draw attention away from financial CoIs that have a well-documented effect on research (25). Arguably, all researchers have intellectual CoIs. But some are more evident than others, for example, personal responsibility for a healthcare intervention may make it more difficult to acknowledge its harms.

Funder

In addition to the authors' individual CoIs, the study funder also plays an important role. The industry has become a significant source of funding for medical research (11). Nevertheless, the funding may come at price, as it has previously been shown that industry funders often influence choice of research topic, confidentiality, and time of publication and additionally the researchers involved often have individual CoIs (26). Furthermore, industry-funded drug and device trials report more positive results and conclusions compared with non-industry-funded trials and this cannot be explained by generic risk of bias assessments (26, 27). Funders' impact on our research has driven a UK project to study responsible research innovation that first and foremost serves public interests rather than financial ones (28).

Objectives

Three studies were carried out relating to CoIs in scientific articles.

The objective of our first study was to explore if authors of articles in general medical and specialty journals differed in whether they accepted the results and methods of three versions of a systematic Cochrane review on mammography screening (one original publication and two updates) (29-32). We also wanted to explore if there were geographical differences and whether acceptance of the Cochrane review increased over time.

The objective of our second study was to determine the prevalence of disclosed CoIs among Danish doctors who were authors of clinical drug trial reports irrespective of who sponsored the trial. Furthermore, we wanted to determine the extent of undisclosed CoIs in trial publications by comparing CoI statements in the publications to the CoIs listed on the Danish Medicines Agency's public disclosure list (33).

The objective of our third study was to determine the role of academic authors, funders and contract research organisations (CROs) in industry-funded vaccine, drug and device trials. Additionally, we wanted to understand lead academic authors' experiences with industry funder collaborations.

Description of the Research Project

Paper 1: Citations of Scientific Results and Conflicts of Interest

In our first study we explored the way that results and methods of three versions of a systematic Cochrane review (one original publication and two updates) on mammography screening were cited by authors of publications in general medical journals compared to specialty journals and whether the three versions of the review received greater acceptance over time.

Using Web of Science we systematically identified the relevant citations of the three versions of the review. Today retrieval of publication citations could also be done using google scholar, which has improved significantly since the study was conducted (34, 35).

We focussed on five specific topics of the systematic Cochrane review:

- Results regarding overdiagnosis
- Results regarding overtreatment
- Results regarding breast cancer mortality
- Results regarding overall mortality
- Methods used in the systematic review

One data extractor copied relevant paragraphs that cited the Cochrane review into a word document, standardised the font, and labelled the documents with a random number. Thus, the two other independent data extractors who performed the assessment of approval or rejections of results and methods had no knowledge of who authored the paragraph or where it was published. Therefore, the assessment was done in a blinded fashion. Similar methods of blinding have been used by Bernal-Delgado et al. to assess reporting of harms in abstracts (36).

Paper 2: Under-reporting of Conflicts of Interest Among Trialists

In our second study, we explored the prevalence of CoIs among Danish doctors who were authors of clinical trial publications. We included trial publications from journals listed as ICMJE journals to ensure that declarations of CoIs and stipulations of the funding source were available from the publications (37). Similarly, Grundy et al. have previously assessed the prevalence of disclosed CoIs in ICMJE publications (38).

Our study also explored the prevalence of undisclosed CoIs in the trial publications by comparing CoI statements from included publications with CoIs listed on the Danish Medicines Agency's public disclosure list. Previous studies have used a wide range of sources such as Google and cross-linking CoI statements in different publications to determine the prevalence of undisclosed CoIs (13, 15). However, the CoI data they employ suffers from the lack of information on when these CoIs were relevant and whether they were relevant to a specific publication. ICMJE recommends that CoIs are disclosed 36 months prior to submission of the manuscript and the papers could thus be overestimating the prevalence of undisclosed CoIs (39). Norris et al. used the Dollars for Docs database which only included data on CoIs from seven pharmaceutical companies at the time, and thus likely underestimated the prevalence of undisclosed CoIs (40). In our study we used a data source which provided dates indicating when CoIs were relevant, included all medical industry companies, and furthermore both the companies and doctors were legally required to submit information to the database (41). Since the publication of this study it has become possible to conduct similar research in the USA by using the open payments database (23, 42).

Paper 3: Collaboration Between Academics and Industry in Clinical Trials

In our third study, we used a retrospective cohort of 200 fully industry-funded clinical phase III-IV trials to assess the role that academic authors, funders and CROs have in the trial design, conduct, analysis and reporting. We included the most recent vaccine, drug and device trials published in one of the top seven high-impact general medical journals (i.e. NEJM, Lancet, JAMA, BMJ, Annals of Internal Medicine, JAMA Internal Medicine and PLoS Medicine). Two authors independently extracted data from the publications. Early in the data extraction we discovered that NEJM publications in particular suffered from very poor reporting of the role of the funder and occasionally also inadequate reporting of author contributions. We therefore broadened our extraction to include supplementary material for NEJM publications in order not to overlook important information. Hakoum et al. recently published a cross-sectional study where they in the same way found poor reporting of role of funder in 119 core clinical journals, with 50% not reporting the funder's role at all (43).

To further explore the roles of academic authors, funders and CROs in vaccine, drug and device trials we sent a pilot-tested survey to one of the lead academic authors from each included publication. We determined who the lead academic author was according to the following ranking system: Corresponding author, first author, last author, second author, etc. A similar approach was undertaken by Rochon et al., who surveyed Canadian academics on adherence to good clinical trial practices (44). However, the Rochon et al. survey asked more generally about trial experiences on multiple trials, while we specifically asked about the lead academics' latest clinical trial and therefore could match our extracted data with our survey data.

Additionally, we asked the lead academic authors about their experiences with the collaboration with the industry funder. To our knowledge this is the first study to specifically ask the lead academic authors about their experiences with a specific trial. Other publications have reported more anecdotal information about academics' past experiences (44, 45).

Summary of Results and Discussion

Paper 1: Citations of Scientific Results and Conflicts of Interest

Our first study was based on 171 publications citing one of the three versions of the systematic Cochrane review on mammography screening. Of these publications, 63 (37%) were published in a general medical journal and 108 (63%) published in a specialty journal. Eighty (47%) of the publications were published in European journals and 91 (53%) in North American journals. We found that publications in general medical journals were more likely to accept the results and methods (i.e. wrote statements indicating approval) of one of the three versions of the systematic Cochrane review compared to publications in specialty journals. Conversely, we found that the publications in specialty journals were more likely to reject the results and methods compared to general medical journals. This difference between general medical and specialty journals is likely due to the authors' affiliation and CoIs differing by journal type. Since general medical journals allow publications from a wider range of topics they have a less selected group of readers and authors compared to specialty journals. There were no differences between European and North American journal publications regarding their likelihood to either accept or reject. We found a tendency towards

greater acceptance of the later versions of the Cochrane review than the original publication and this could indicate a growing acceptance of the results and methods over time. Nevertheless, many publications were classified as unclear or not applicable regarding whether they accepted or rejected the content of the Cochrane review in one or more of the categories (overdiagnosis, overtreatment, breast cancer mortality, overall mortality and methods of the systematic review) and the number of citations that allowed for clear interpretation was low. Therefore, the results should be interpreted with caution.

Strengths and Limitations of our Study

One of the major strengths of this study is the blinded assessment of the paragraphs from the relevant citing papers. Another important strength was the independent assessment by two data extractors. Both of these design elements are likely to have reduced bias in the assessment process. We included publications from both European and North American journals and our results are thus applicable to those regions.

A limitation of this study is that we looked at the affiliation of the journals with clinical specialties rather than at the individual authors' affiliation. Therefore, our results may be a conservative estimate of intellectual biases as authors affiliated with mammography screening also publish in general medical journals. Although we are aware of publications were this has occurred we did not find a single article that directly rejected the existence of overdiagnosis. This is likely due to the fact that authors expressing such beliefs are unlikely to cite a comprehensive and independent systematic review where a central finding was the identification of overdiagnosis as a major harm. Jørgensen et al. found similar results with mammography specialists not mentioning or downplaying the harms of mammography screening (24). However, Bernal-Delgado found that harms were downplayed not only in high impact specialty journals, but also in high impact general medical journals (36). Surprisingly, a lot of the citations were categorised as not applicable due to the publications citing the controversy that arose as a result of the findings of the Cochrane review or the authors were referencing false positives or other outcomes. This questions whether authors are representing and discussing the benefits and harms of mammography screening in a balanced fashion.

The differences we found between how publications in general medical journals and specialty journals cited the Cochrane review could have been influenced by the fact that it is more difficult to get published in high impact general medical journals compared to

specialty journals and thus the general medical journals may have a higher standard for editorial and peer review. Furthermore, in contrast to general medical journal editors, the specialty journal editors are often appointed because they are leading researchers in their field and may therefore share the same views and intellectual CoIs as the specialists who publish in their journals (46). Additionally, CoIs at specialty journals such as representing specialty societies with vested interests could have influenced the discourse in these publications (46).

Comparisons with Other Studies

Our first study's findings are consistent with findings of the effects of CoIs on the interpretation of treatment benefits and harms in other specialties (15, 47). Furthermore, Norris et al. explored the effects of affiliation and CoIs on mammography screening guideline recommendations and found that the recommendations may be influenced by the specialty and intellectual interests of the guideline authors (48). This highlights the importance of having independent researchers review the evidence.

Perhaps, clinicians with vested interests worry that by informing the public about harms of the intervention, they decrease participation in mammography screening. A study using people imagining themselves as patients (i.e. mock patients) found that doctor disclosure of CoIs resulted in less acceptability of a low value health intervention whereas doctors who did not disclose CoIs had more mock patients choose the low value health intervention (49). In 2016 Esserman called for doctors to be more honest towards themselves and their patients about what is known and what is unknown about precursors and cancer (50). Similarly, others have called for shared decision making and better patient information on overdiagnosis (51). The evidence base for the existence of overdiagnosis in mammography screening is growing and a recent study estimated the overdiagnosis rate at 24% (including ductal carcinoma in situ) (52).

Parker et al. highlighted that downplaying harms and lack of participant autonomy in the decision to enter into a screening programme is still a problem today. Furthermore, they highlight that the views of experts in screening committees highly influence evidence based decision making (53).

Recently a Cochrane review on the treatment of ADHD triggered strong reactions from psychiatrists. Analogous to the systematic review on mammography screening, there was criticism of the methods of the systematic review and the quality of the evidence

with many of those criticising having intellectual or financial CoIs (54). Additionally, Olsen found in a qualitative study of GPs that the results of a Cochrane review assessing the safety of homebirth triggered strong emotions and it was difficult to change GPs' minds despite convincing evidence that showed their view was unfounded (55). A paper on polarised, scientific research using mammography as an example highlighted how far apart experts can be, and that the controversy over the benefits and harms of screening with mammography is still ongoing (56). Myers et al. underline the fact that there is still no consensus on how overdiagnosis should be estimated and how this harm should be compared to the benefits of screening programs (57). This lack of consensus is likely to be one of the main causes of the ongoing controversy.

Paper 2: Under-reporting of Conflicts of Interest Among Trialists

Our second study included 100 trial publications with 318 Danish academic authors, of which there were 241 individual Danish authors. Therefore, 47 authors contributed to more than one of the included publications. Forty-nine (49%) of the 100 trials were fully industry-funded; 30 (30%) reported mixed funding (i.e. both for-profit and not-for-profit funding); 19 were non-industry funded; and two did not report the funding source in the trial publication. We found a prevalence of disclosed CoIs of 27% (86 out of 318) among the trialists with 23% (72 out of 318) disclosing one or more CoIs with the trial's industry funder.

Forty (13%) of the 318 academic authors had undisclosed CoIs with the trial industry funder, identified through cross-checking with the CoI registry of the Danish Medicines Agency. In total 137 (43%) authors had undisclosed CoIs with any industry company. However, our sensitivity analysis of authors with only a single authorship in one of the 100 included trial publications reduced the undisclosed CoIs with the industry funder from 13% to 5% and similarly undisclosed CoIs with any industry company was reduced from 43% to 31%. This means that a few authors with strong industry involvement were responsible for the majority of missing CoI declarations. Furthermore, the proportion of authors with no CoIs at all was higher in the group of single publication authors. Thus, we found that the most prolific authors had the highest rate of both disclosed and undisclosed CoIs.

Strengths and Limitations of our Study

A major strength of our study is the use of an outside data source regulated by law to determine the prevalence of undisclosed CoIs. Since the publication of our study, this database has been improved to also include the specific amount of money paid to the doctor (33). However, in 2017 the declaration rules also changed so that the investigator's role in an industry-funded study no longer requires disclosure unless the doctor is a primary investigator or otherwise has a key role in the study conduct or receives reimbursement from the company for the role as an investigator (41). Another important strength of the study is that we focussed on clinical trials in general and did not limit our study to a single specialty. Thus, our results are applicable to drug trials in general.

One of the limitations of our study is the fact that we only focused on Danish doctors. Therefore, this may limit generalisability of the findings outside Denmark. However, we only included trial publications from international journals, and it is plausible that Danish authors will disclose CoIs more frequently than authors from other countries as the information is already publically accessible. Therefore, our findings may be conservatively estimating the prevalence of under-reported CoIs. Furthermore, data availability limitations from the Danish Medicines Agency meant we could not assess undisclosed CoIs more than two years prior to publication of the included trial reports meaning the number of undisclosed CoIs may have been underestimated.

Comparisons with Other Studies

Accessing information on potential CoIs in other countries can be difficult. Kesselheim et al. used whistleblower complaints alleging illegal off-label marketing to examine potential undisclosed CoIs, and found much more sobering results than our study. Only 15% of doctors accused of promoting off-label use had adequate disclosure statements of their industry ties in journal publications (58). The higher rate of undisclosed CoIs compared to our findings could be explained by the cohort of doctors being involved in promotion of off-label use, while our study included a less selected group of doctors based on the 100 most recent trial publications.

More recently a study of the most highly-cited authors in clinical medicine in the USA found that only 11% of their publications had CoI declarations that were in concordance with the Open Payments database (23). Similarly, a study of authors related to pulmonology, haematology, orthopaedics, cardiac surgery, and otorhinolaryngology found equally high rates of under-reporting of CoIs with pulmonology and haematology

publications having no publications with full disclosures of CoIs (59). This is a much higher rate of undisclosed CoIs than our results showed, however, not dissimilar to our subgroup of prolific authors, who also had a higher rate of undisclosed CoIs compared to single publication authors. Kaestner et al. used the Open Payments database to examine prolific authors' CoIs and the correlation between number of publications and industry payments and found an increase of 1.99 papers per $10 000 in payments from industry (60).

Rather surprisingly, a survey of Cochrane systematic review authors from low- and middle-income countries showed that 13% of the authors found it acceptable to not declare CoIs with a company involved in the research project. Furthermore, 40% of responders were aware that under-reporting of CoIs with funders had taken place at their institution (61). Transparency is not a given. Eisner et al. also found high rates of under-reporting of CoIs in journal articles on psychosocial interventions and concluded that journal CoI statements are unreliable (62).

The ICMJE only require disclosure of CoIs 36 months prior to publication (39). However, many authors get reimbursed by the industry funder for consultancy and other roles just after trial publication and such CoIs will not be disclosed and are thus not available to the readers of the publications. The prospect of near-future collaboration with industry funders is a potential CoI. While public registries, which are regularly updated, will provide some transparency with regard to this, the registries are unlikely to have this information at the time of publication.

Despite calls for the UK General Medical Council (GMC) to create a registry of doctors collaborating with industry, very little has changed since the publication of our second study (63). A small step was taken by the Association of the British Pharmaceutical Industry (ABPI) who now have a public list of doctors collaborating with industry companies (64). However, the doctors listed on the ABPI list volunteer the information and therefore the list is unreliable, incomplete and has received lots of criticism (65-67). In 2016 Dunn et al. proposed the development of a public registry for CoI disclosure that the ICMJE journals could require be updated prior to publication of a paper (68). Mandatory disclosure of CoIs in public registries is, nevertheless, likely to be insufficient to change doctors' prescribing practices to cheaper and generic drugs (69). However, public registries of CoIs can promote transparency and public trust, and they place the

decision of whether CoIs are important or not on the public, rather than in the hands of individual doctors who may be unreliable judges.

Paper 3: Collaboration Between Academics and Industry in Clinical Trials

In our third study, we found that most of the 200 included industry-funded trials were designed, conducted and reported by both academic and industry authors. Reporting also often involved a CRO. The data analysis in the trials was most often carried out by industry statisticians and/or a CRO employee without involvement of an academic author. In only 13% (26 out of 200) of the trials the data analysis was conducted solely by academic authors without funder involvement. It was often unclear who and how many authors conducted the statistical analysis as the publications used terms like "*all authors"* or "*the funder"* rather than names or initials.

The median number of authors per trial was 19 (range 5-103). One or more industry employees co-authored 87% (173 of 200) of the trials. However, they seldom had first, last or corresponding authorship despite having key roles in the study and writing process. We found that the lead academic author had disclosed CoIs with the industry funder in 83% (165 of 200) of the trials.

Only eight (4%) of the trials were classified as independent, with all aspects of the trial carried out by academic authors without involvement of the industry funder or a CRO. Nevertheless, in four of the eight independent trials the lead academic authors still declared CoIs with the industry funder.

We contacted the 200 lead academic authors and received a response from 106 (53%) of them, of which 80 (40%) completed the survey. Three lead academic authors were unreachable via email, post and telephone due to change of employer and/or country of residence. The survey showed that the lead academic authors generally found the collaboration beneficial and especially acknowledged the funding as a benefit. A few authors reported problems mostly in terms of disagreements over study design and reporting. Ten trials used a funder and/or CRO, who was not a named contributor or author on the trial publication, to conduct the statistical analysis and/or draft the manuscript.

Strengths and Limitations of our Study

To our knowledge this is the first study that links survey responses from lead academic authors to the trials they were involved in. We included international trials for interventions from a wide range of indications as well as lead academic authors from many different countries. Therefore, we believe the findings have broad generalisability. Another strength of this study is the careful design of the survey which included input from all co-authors of our study - one who is a journal editor, and together we have many years of experience with investigating industry-funded trials. Furthermore, we piloted the survey on academics with past investigator experience from industry-funded trials.

Since we used survey data there is a risk of recall bias. However, it is plausible recall bias would have had minor impact on the findings as we gave lead academic authors the option of answering "Do not know" or skipping the question without leaving a response if they could not remember. Furthermore, we only included the most recent trials and therefore the authors are likely to remember the details of the trial design, conduct, analysis and reporting. Another limitation in this study is the fact that we did not ask the lead academics whether they stored and owned the entire trial dataset themselves or if this was done by the funder or a CRO. This question was removed from the survey in the design phase due to concerns with the length of the survey. However, two lead academic authors highlighted in their survey responses that storing and ownership of the data is important for academic freedom. Despite different attempts (i.e. email reminders, contact via post and telephone) to encourage lead academic authors to reply, we only received responses from 40%. Nevertheless, we explored differences between responders and non-responders in terms of trial and author characteristics, and found no important differences, signalling minimal risk of selection bias. The 200 lead academic authors we contacted were generally very homogenous in terms of involvement in the trials and CoIs with the funder. Furthermore, we received responses at both extremes of the spectrum indicating that there was not a particular group of authors who did not respond.

Comparisons with Other Studies

In 2001 editors on behalf of ICMJE stated: *"We will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication." (70).* Unfortunately, our cross-sectional study and survey of lead academic authors found that the editors have not been able to

change this practice in studies published in their journals, as data access and control is often still the funder's prerogative and the publication of results is not without funder influence.

It was often unclear what type of data the lead academic authors had access to. The ICMJE recommend that authors state the following: *"I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis." (39).* However, in the survey responses it became clear that all data sometimes meant all analyses rather than individual patient data. DeAngelis et al. underlined that by stating the above, the academic authors are accountable should the publication be scrutinised in relation to selective reporting (71). Thus, it appears the academic authors are running a huge risk by allowing the industry funder to only give them limited access to the data.

Despite the fact that we only included high impact journals adhering to ICMJEs reporting requirements, we found many trials where the role of the funder was difficult to determine (5). For all the NEJM trials we had to assess supplementary material which occasionally provided a bit more information about the role of the funder and academic authors. A recent cross-sectional study of RCTs published in core clinical journals found similar problems with a lack of reporting of the role of the funding source (43). Guidance to improve the reporting of funding sources and the funder's role has been proposed (43). Additionally, we found problems with transparency regarding who conducted the statistical analyses of the trial and who had access to what type of data. Multiple authors often claimed involvement in data analysis, but it was frequently impossible to tell who performed the actual statistical analysis. Pyke et al. argue that more scrutiny of statistical analyses in clinical trials will help ensure better research integrity and honest reporting of trial results (72). JAMA has previously been a leader in this area by requiring independent statistical analyses of all industry-funded trials (71).

A recent epidemiological study found that industry-funded trials dominate the world, are more often international and are conducted primarily in high-income countries (11). Therefore, it is important that the academics who are involved in industry-funded trials take control of and responsibility for trial design, conduct, data analysis and reporting to uphold responsible research conduct.

Until now, far too little attention has been paid to the fact that industry-funded trials may be of great advantage to the academics involved in the trials. This can be in terms of

career advancement by facilitating high impact journal publications, international networking opportunities and future profitable consultancy jobs, and thus industry collaboration has the potential to become an important CoI for the academic authors. In 1992 Topol et al. published their strict rules for academic investigators on the GUSTO trial (73). The academic investigators were banned from owning stock, receiving remuneration for consultancy, expertise or services, being paid honoraria by the trial sponsors for educational activities or lectures, and being reimbursed for travel expenses until one year after publication of primary results (73). This truly forward thinking approach to dealing with CoIs amongst trialists has, however, not been adopted by researchers on a larger scale. It is likely that only policies at the ICMJE journals, ethical review boards, regulatory agencies, and/or national legislation can lead to wider adoption of such vigilant handling of potential CoIs.

Conclusions and perspectives for further research

CoIs, both financial and non-financial, can affect the way we view and scrutinise benefits and harms of interventions. From our first study we highlight how independent evidence can be interpreted differently by individuals publishing in different types of journals, with implications for the different groups' use and appreciation of evidence. The finding that publications in speciality journals were more likely to reject independent evidence suggests that intellectual biases persist despite robust counter evidence. Whilst, independent systematic reviews of evidence are of great importance for clinical practice, more appreciation of the effects of intellectual biases and potential CoIs are needed.

Our second study supports myriads of studies documenting the high prevalence of financial CoIs amongst trialists, but demonstrates that additionally there are many undisclosed financial CoIs. Under-reporting of CoIs in trial publications is common and ICMJE declarations of potential CoIs are often unreliable. More effort is needed to address this problem in order to support independent and ethical decision-making in medicine. One solution is mandatory public registries that can provide more reliable information of financial CoIs. Publications could link to these registries rather than depend on voluntary author disclosure.

Our third study highlights how ingrained industry funders are within academic research and how they have large implications for both intellectual and financial CoIs. Industry-funded trials are mostly conducted in a collaborative fashion with academic researchers, while industry employees mostly conduct the data analyses in trials. Being a lead academic author on an industry-funded trial provides several benefits for the academic author, but industry influence can also put restrictions on their academic freedom. Industry funders may control study design, data analyses and reporting, or may undertake more subtle approaches such as evoking feelings of obligation or reciprocation. There is evidence that industry funders are providing input to trials without being conspicuous, and whilst journals are increasingly paying attention to CoIs – particularly financial – a deeper look at the whole decision-making process within the trial is needed. We cannot expect editors and peer reviewers to police this field alone. Journals, ethical review boards and regulatory agencies could demand independent planning, conduct, analysis, and reporting of industry-funded trials to circumvent industry-introduced bias and CoIs.

People are very aware of CoIs – both disclosed and undisclosed, and although intellectual CoIs should be recognised, they must not be prioritised over financial ones. Efforts to address CoIs should take a more “bottom-up” approach rather than addressing them when they arrive in the journal’s inbox. Stricter CoI guidelines at medical schools, universities, hospitals and clinics are needed. Additionally, better understanding and encouragement of strong research integrity can be enhanced at all levels of the research pathways. Further research is needed on academic authors’ data access, storage and ownership of trial data when involved in industry funded trials. Furthermore, since many lead academic authors mention that regulatory agencies have great influence on the design of the clinical trials, research should examine how to enhance regulatory agencies’ ability to improve trial design, ensure patient safety, and safeguard ethical standards.

List of abbreviations

CoI – conflict of interest

CRO – contract research organisation

GMC – General Medical Council, UK

ICMJE – International Committee of Medical Journal Editors

RCT – randomised controlled trial

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The Three Papers

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Citations of scientific results and conflicts of interest: the case of mammography screening

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Abstract

Introduction In 2001, a Cochrane review of mammography screening questioned whether screening reduces breast cancer mortality, and a more comprehensive review in *Lancet*, also in 2001, reported considerable overdiagnosis and overtreatment. This led to a heated debate and a recent review of the evidence by UK experts intended to be independent.

Objective To explore if general medical and specialty journals differed in accepting the results and methods of three Cochrane reviews on mammography screening.

Methods We identified articles citing the *Lancet* review from 2001 or updated versions of the Cochrane review (last search 20 April 2012). We explored which results were quoted, whether the methods and results were accepted (explicit agreement or quoted without caveats), differences between general and specialty journals, and change over time.

Results We included 171 articles. The results for overdiagnosis were not quoted in 87% (148/171) of included articles and the results for breast cancer mortality were not quoted in 53% (91/171) of articles. 11% (7/63) of articles in general medical journals accepted the results for overdiagnosis compared with 3% (3/108) in specialty journals (p=0.05). 14% (9/63) of articles in general medical journals accepted the methods of the review compared with 1% (1/108) in specialty journals (p=0.001). Specialty journals were more likely to explicitly reject the estimated effect on breast cancer mortality 26% (28/108), compared with 8% (5/63) in general medical journals, p=0.02.

Conclusions Articles in specialty journals were more likely to explicitly reject results from the Cochrane reviews, and less likely to accept the results and methods, than articles in general medical journals. Several specialty journals are published by interest groups and some authors have vested interests in mammography screening.

Introduction

In October 2001, the Nordic Cochrane Centre published a Cochrane review of mammography screening, which questioned whether screening reduces breast cancer mortality.[1] Within the same month, the Centre published a more comprehensive review in *Lancet* that also reported on the harms of screening and found considerable overdiagnosis and overtreatment (a 30% increase in the number of mastectomies and tumourectomies).[2] This resulted in a heated debate, which is still ongoing.[3] The Cochrane review was updated in 2006,[4] to include overdiagnosis, and again in 2009.[5]

Recently, several studies have questioned whether screening is as beneficial as originally claimed,[6–8] and confirmed that overdiagnosis is a major harm of breast cancer screening.[9–11] The US Preventive Services Task Force published updated screening recommendations in November 2009 and asserted that the benefit is smaller than previously thought and that the harms include overdiagnosis and overtreatment, but it did not quantify these harms.[12] The task force changed its previous recommendations and now recommends that women aged 40–49 years discuss with their physician whether breast screening is right for them, and it further recommends biennial screening instead of annual screening for all age groups.[12] These recommendations were repeated in the 2011 Canadian guidelines for breast screening.[13]

Screening is likely to miss aggressive cancers because they grow fast, leaving little time to detect them in their preclinical phases.[6] Further, the basic assumption that finding and treating early-stage disease will prevent late stage or metastatic disease may not be correct, as breast cancer screening has not reduced the occurrence of large breast cancers[14] or late-stage breast cancers,[11] despite the large and sustained increases in early invasive cancers and ductal carcinoma in situ with screening.

A systematic review from 2009 showed that the rate of overdiagnosis in organised breast screening programmes was 52%, which means that one in three cancers diagnosed in a screened population is overdiagnosed.[9] It is quite likely that many screen-detected cancers would have regressed spontaneously in the absence of screening.[15 16]

We explored how the first comprehensive systematic review on mammography screening ever performed, the one from 2001 published in *Lancet*,[2] and the subsequent systematic Cochrane reviews from 2006[4] and 2009[5] have been cited from 2001 to April 2012. We investigated whether there were differences between general medical journals and specialty journals regarding which results were mentioned and how overdiagnosis, overtreatment, breast cancer mortality, total mortality, and the methods of the reviews were described. Vested interests on behalf of both journals and contributing authors may be more pronounced in specialty journals, and this may influence views on specific interventions, such as mammography screening.

Methods

We searched for articles quoting one of the three versions of the review[2 4 5] (date of last search 20 April 2012). We used the 'source titles function' in the Institute for Scientific Information (ISI) Web of Knowledge to count the number of times each review had been cited in individual journals. We only included journals in which four or more articles had cited one of the three versions of the review. This criterion led to the exclusion of specialty journals of little relevance for our study, for example, *Nephrology* and *Research in*

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Gerontological Nursing. Articles written by authors affiliated with the Nordic Cochrane Centre were also excluded.

We could not include the 2001 Cochrane review[1] because it was not indexed by the ISI Web of Knowledge. Furthermore, even if it had been indexed, we would have excluded it. This version of the review[1] is not comparable to the other three versions,[2–5] as the editors of the Cochrane Breast Cancer Group had refused to publish these data on overdiagnosis and overtreatment.

A journal was classified as a general medical journal if it did not preferentially publish papers from a particular medical specialty. A journal was classified as a specialty journal if it preferentially published articles from a particular medical specialty or topic.

When we rated how the papers cited the review, we looked for statements applicable to the following categories:

- Overdiagnosis
- Overtreatment
- Breast cancer mortality
- Total mortality
- Methods used in the review

We rated the quoting articles' general opinions about the results and methods of the review using the labels—accept, neutral, reject, unclear, or not applicable, using the following definitions:

Accept: the authors explicitly agreed with the results or methods, or quoted the numerical results without comments.

Neutral: the results or methods were mentioned and the author presented arguments both for and against them.

Reject: the authors explicitly stated that the results or methods were flawed, wrong, or false, or only presented arguments against them. Only reporting a result from a favourable subgroup analysis was also classified as rejected.

Unclear: the results or methods were mentioned, but it was not possible to tell if the authors agreed with them or not, or the results were only mentioned qualitatively. If several conflicting opinions were presented, it would also be classified as unclear.

Not applicable: the review was quoted for something else than its results or methods.

The articles quoting the review were assessed in relation to the five categories (overdiagnosis, overtreatment, breast cancer mortality, total mortality and methods) separately, and no overall assessment of the articles' general opinion about the review was made.

Texts classified as not applicable regarding any of the five categories were reread to determine and note which topics were discussed.

Two researchers (KR, Andreas Brønden Petersen, see Acknowledgements) assessed the text independently. Disagreements were settled by discussion.

In order to ensure blinded data extraction, an assistant (Mads Clausen, see Acknowledgements) not involved with data extraction identified the text sections citing one of the three review versions and copied them into a Microsoft Word document. Only this text was copied, and the two data extractors were therefore unaware of the author and journal names, time of publication and the title of the article. The fonts of the copied text were converted into Times New Roman, saved in a new document and the text labelled with a random number using the 'Rand function' in Microsoft Excel. The key to matching the text with the articles was not available to data extractors until the assessments had been completed. The person responsible for copying the text made sure it did not contain any information that might reveal which of the three versions of the review had been cited. When there was more than one reference within the copied text, the reference to the review was highlighted to make it clear which statements referred to the review.

All article types, as well as letters to the editor, were included and were classified as research papers, systematic reviews, editorials, letters, guidelines and narratives.

p Values were calculated using Fisher's exact test (two-tailed p values (http://www.swogstat.org/stat/public/fisher.htm)).

Results

In total, 523 articles cited one of the three versions of the review: 360 cited the 2001 *Lancet* review,[2] 123 the 2006 Cochrane review[4] and 40 the 2009 Cochrane review.[5] Three articles cited both the 2001 and the 2006 versions of the review; for these, we only used information related to the 2001 citation.

Including only journals that had published at least four articles, which cited one or more of the three versions of the review, the search identified 151, 27 and 15 articles, respectively (193 in total, or 37% of the total of 523 articles). A flow chart is shown in figure 1.

We excluded 22 additional articles, two because there was no reference to the review in the text, even though the review was listed as a reference,[17 18] and 20 (10, 5 and 5 citing the 2001, 2006 and 2009 versions, respectively) because they had one or more authors affiliated with the Nordic Cochrane Centre.

Thus, 171 articles were included for assessment. In total, 63 articles (37%) were from general medical journals and 108 (63%) from specialty journals. A total of 80 (47%) were from European journals and 91 (53%) from North American journals. No journals from other regions contained at least four articles citing the review.

The general medical journals included were *Lancet* (21 articles), *BMJ* (13 articles), *Annals of Internal Medicine* (13 articles), *Journal of the American Medical Association* (7 articles), *New England Journal of Medicine* (5 articles) and *International Journal of Epidemiology* (4 articles). The specialty journals included *Journal of the National Cancer Institute* (13 articles), *Cancer* (13 articles), *American Journal of Roentgenology* (7 articles) and 15 others (see box 1). Most of the included articles were either research papers (n=63, 37%) or narrative articles (n=44, 26%; table 1).

The text of 32 of the 171 included articles (19%) was rated as not applicable for all the five categories (overdiagnosis, overtreatment, breast cancer mortality, total mortality and methods). In total, 15 of these 32 articles discussed the controversy when the first review was published, without specifically mentioning any of the categories. Other subjects discussed were screening of

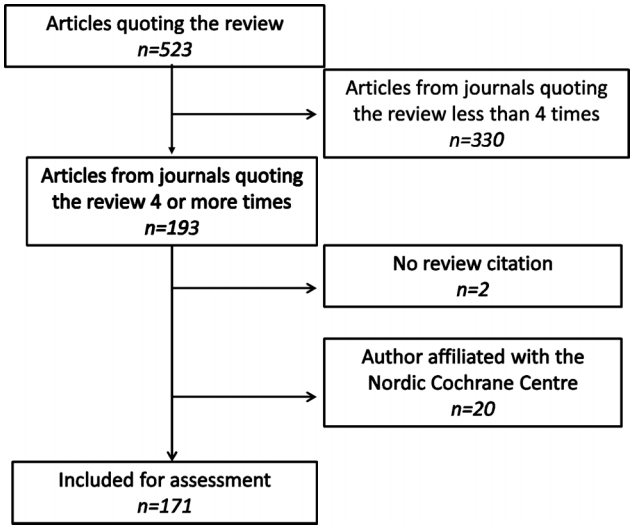

Figure 1 Flow diagram of article exclusion.

women under the age of 50 (two articles), and benefits of breast cancer screening other than those in our categories (two articles; see online supplementary appendix 1 for a full list of topics).

The review's conclusions regarding overdiagnosis were not quoted in 87% (149/171) of the included articles and the results for breast cancer mortality were not quoted in 53% (91/171) of the included articles.

General medical journals were more likely to accept the results or methods of systematic reviews than specialty journals, for example, overdiagnosis was classified as accepted in 11% (7/63) of articles in general medical journals, but in only 3% (3/108) of the articles in specialty journals (p=0.05), and the methods were accepted in 14% (9/63) of articles in general medical journals, but only in 1% (1/108) of articles in specialty journals (p=0.001). Specialty journals were also more likely to reject the results for breast cancer mortality, namely for 26% (28/108) of articles compared with 8% (5/63; p=0.02) in general medical journals. The differences between general medical and specialty journals in relation to rejecting the categories overdiagnosis, overtreatment, total mortality and methods were small (table 2).

The European and North American journals were equally likely to reject or accept the review's methods or results (data not shown).

The number of citations of the three versions of the review differed a lot over time (see table 3). Some years had very few citations, the lowest being 2012 and 2006 where the review was cited only 1 and 6 times, respectively. The highest number of citations was in 2002 (42 citations). There were no clear trends over time regarding the number of articles accepting or rejecting the methods and conclusions of the reviews, although the breast cancer mortality results may have received greater acceptance in recent years, for example, in 2002, there was no acceptance of the breast cancer mortality results (0 of 42), whereas 19% (3/16) explicitly accepted them in 2010 (p=0.02; data not shown).

The 2001 version of the review had more categories rejected and fewer categories accepted than the 2006 and 2009 versions, for example, 30% (3/10) accepted the results for breast cancer mortality presented in the 2009 version of the review, compared with 0 (0/140) in the 2001 version (p=0.0002; see table 4).

Box 1 The specialty journals included in this study

- Specialty journals included
- Journal of the National Cancer Institute (13)
- Cancer (13)
- European Journal of Cancer (7)
- British Journal of Cancer (7)
- American Journal of Roentgenology (7)
- Cancer Causes and Control (6)
- Annals of Oncology (6)
- European Journal of Surgical Oncology (6)
- Journal of Medical Screening (5)
- Cancer Epidemiology, Biomarkers and Prevention (5)
- CA: a Cancer Journal for Clinicians (5)
- Journal of Clinical Oncology (5)
- Radiologic Clinics of North America (5)
- Oncologist (4)
- Breast Cancer Research and Treatment (4)
- Breast (4)
- Radiology (3)
- Journal of Surgical Oncology (3)

Discussion

Although we deliberately reduced the sample size by requiring at least four citations for each included journal, we had enough articles that quoted the review for our comparisons.

Specialty journals were more likely to reject the estimate of the effect of screening on breast cancer mortality than the six general medical journals we included.

Table 1 The article types included in this study

	Article type					
	Research	Letter	Editorial	Guideline	Narrative	Review
General EU	8	17	1	0	12	1
General NA	8	5	4	1	5	2
Special EU	27	4	4	0	6	0
Special NA	20	4	14	2	21	5
Total	63	30	23	3	44	8

EU, European; NA, North American.

Articles in general medical journals were also more approving of four of the five individual categories we assessed (overdiagnosis, overtreatment, total mortality and methods) than the specialty journals were and the difference was statistically significant for all the categories, except for breast cancer mortality.

We have previously found that scientific articles on breast screening tend to emphasise the major benefits of mammography screening over its major harms and that overdiagnosis was more often downplayed or rejected in articles written by authors affiliated with screening by specialty or funding, compared with authors unrelated with screening.[19] Recommendations in guidelines for breast screening are also influenced by the authors' medical specialty.[20]

The difference we found between the general medical and specialty journals could be explained by conflicts of interest, which are likely to be more prevalent in specialty journals owned by political interest groups such as the American Cancer Society or by medical societies with members whose income may depend on the intervention. All the six general medical journals, but only 22% (4/18) of the specialty journals follow the International Committee of Medical Journal Editors' (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[21] Even though journals have conflict of interest reporting policies, the conflicts of interest reported are not always reliable.[22]

All the general medical journals included are members of the World Association of Medical Editors (WAME); however, this is only the case for 22% (4/18) of the specialty journals included. WAME aims to improve the editorial standards and, among other things, to ensure a balanced debate on controversial issues.[23] Being a member of WAME helps with transparency in terms of their guidelines for conflicts of interest, but it also reminds editors to ensure that their journals are covering both sides of a debate.

Development over time

The results and conclusions on breast cancer mortality and overdiagnosis were more often accepted in 2010 than in any other year (data not shown). This may reflect that the criticism of breast screening is becoming more widespread. The ongoing independent review of the National Health Service (NHS) Breast Screening Programme announced by Mike Richards, the UK National Clinical Director for Cancer and End of Life Care, Department of Health, in October 2011 is a further indication of this development.[24] Also, the US Preventive Services Task Force changed its recommendations for breast screening in 2009.[12] Though our data did not show strong time trends, we believe that these developments demonstrate a growing acceptance of the results and conclusions of our systematic review. In support of this, the 2009 version of the Cochrane review has received more approval than disapproval, for example, 30% (3/10) accepted the results for breast cancer mortality presented in the 2009 version of the review, compared with 0 (0/140) in the 2001 version.[25–31] The US Preventive Services Task Force was heavily criticised after the publication of its new recommendations in 2009,[29 32] but the criticism came from people with vested interests, and the independent Canadian Task Force supported the conclusions of the US Preventive Services Task Force and the 2009 Cochrane review[5] in 2011.[13]

The 2001 review published in *Lancet* was by far the most cited of the three reviews. It was 5 years older than the Cochrane review from 2006, but the vast majority of the citations came within the first year of publication. It was unique at the time, as it questioned whether mammography screening was effective, based on a thorough quality assessment of all the randomised controlled trials, and also was the first systematic review to quantify overdiagnosis.

Limitations

A minor part of the included articles (19%, 32/171) did not refer to any of our five specified outcomes. In nearly half of the cases (47%), this was due to the article referring only to the debate that followed the first review,[33] and not its results or methods. The texts also dealt with topics such as false positives or screening women under the age of 50 years. The articles also simply stated that mammography screening was beneficial without further specification. The most frequently used classification for each of our specified categories was not applicable. This was the case for articles in both the general medical and specialty journals, and for articles in the European and North American journals. The text typically dealt with only one or two of our categories, for example, overdiagnosis, and did not mention overtreatment or any other categories.

None of the articles rejected overdiagnosis (0 of 171 articles), which could be because they did not mention the issue at all. This was the case in 76% of scientific articles on breast screening in a previous study by Jørgensen *et al*.[19]

Our definition of rejection was that the author should explicitly state that the review's estimate was flawed, wrong or false, or that they should in some way argue against it. With this strict definition, we did not

Table 2 General medical journals compared with specialty journals. Column percentages in brackets

	Overdiagnosis			Overtreatment			Breast cancer mortality			Total mortality			Methods		
	General	Special	p Value	General	Special	p Value	General	Special	p Value	General	Special	p Value	General	Special	p Value
Accept	7 (11%)	3 (3%)	0.05	7 (11%)	1 (1%)	0.01	4 (6%)	2 (2%)	0.20	6 (10%)	0	0.00	9 (14%)	1 (1%)	0.00
Neutral	1 (2%)	0	0.37	2 (3%)	0	0.14	4 (6%)	3 (3%)	0.43	1 (2%)	0	0.37	3 (5%)	1 (1%)	0.15
Reject	0	0	1.00	1 (2%)	4 (4%)	0.65	5 (8%)	28 (26%)	0.02	3 (5%)	6 (6%)	1.00	10 (16%)	19 (17%)	1.00
Unclear	2 (3%)	10 (9%)	0.22	4 (6%)	11 (10%)	0.58	12 (19%)	23 (21%)	0.85	9 (14%)	19 (18%)	0.68	10 (16%)	13 (12%)	0.65
Not applicable	53 (84%)	95 (88%)	0.91	49 (78%)	92 (85%)	0.72	38 (60%)	53 (49%)	0.43	44 (70%)	83 (77%)	0.72	31 (49%)	74 (69%)	0.24

Two-tailed p values are used.

capture authors who have consistently stated over the years in other articles than those we included that they do not believe that overdiagnosis is a problem, and we also did not present their views on the subject.

Numerous articles were classified as unclear for one or more of our categories. The texts in question did not allow an interpretation in any direction and we did not rate the articles as accepting or rejecting the review's results and methods unless it was perfectly clear what the authors meant. This reflects that authors often do not present clear opinions of the intervention which they discuss. An additional explanation for the many articles found to be unclear could be that we did not assess the entire article, and arguments could have been presented elsewhere in the text.

Letters were included in this study, which could explain why some of the articles were classified as not applicable in all the five categories. The specialists who read and respond to letters in their own journals might be more likely to react negatively towards the review because of conflicts of interest.[19] Specialists with a connection to mammography screening also reply to articles in general medical journals when they concern mammography screening. Therefore, it is quite likely that there is a greater difference between the specialists involved with the screening programmes and the doctors not involved in breast cancer screening, in terms of accepting and rejecting the results and methods, than we have found in this study.

Conclusion

Articles in specialty journals were less approving of the results and methods of the systematic review of breast screening than those in general medical journals. This may be explained by conflicts of interest, as several specialty journals were published by groups with vested interests in breast screening, and several articles had authors with vested interests.

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Table 3 Number of citations of one of the three reviews per year

Number of citations per year	
2001	8
2002	42
2003	28
2004	22
2005	13
2006	6
2007	9
2008	10
2009	10
2010	15
2011	7
2012	1

Table 4 Comparison of the three versions of the review in terms of accepting or rejecting the five categories

	Overdiagnosis			Overtreatment			Breast cancer mortality			Total mortality			Methods		
Comparing 2001–2006	2001	2006	p	2001	2006	p	2001	2006	p	2001	2006	p	2001	2006	p
Accepted	4 (3%)	4 (19%)	0.02	5 (4%)	2 (10%)	0.25	0	3 (14%)	0.00	4 (3%)	0	1.00	8 (6%)	1 (5%)	1.00
Rejected	0	0	1.00	4 (3%)	0	1.00	29 (21%)	2 (10%)	0.38	9 (6%)	0	0.60	29 (21%)	0	0.05
Comparing 2001–2009	2001	2009	p	2001	2009	p	2001	2009	p	2001	2009	p	2001	2009	p
Accepted	4 (3%)	3 (30%)	0.01	5 (4%)	2 (20%)	0.09	0	3 (30%)	0.00	4 (3%)	2 (20%)	0.07	8 (6%)	1 (10%)	0.48
Rejected	0	0	1.00	4 (3%)	1 (10%)	0.31	29 (21%)	2 (20%)	1.00	9 (6%)	0	1.00	29 (21%)	0	0.37
Comparing 2006–2009	2006	2009	p	2006	2009	p	2006	2009	p	2006	2009	p	2006	2009	p
Accepted	4 (19%)	3 (30%)	0.67	2 (10%)	2 (20%)	0.59	3 (14%)	3 (30%)	0.64	0	2 (20%)	0.13	1 (5%)	1 (10%)	1.00
Rejected	0	0	1.00	0	1 (10%)	0.34	2 (10%)	2 (20%)	0.59	0	0	1.00	0	0	1.00

Percentages in brackets are calculated from the total number of articles cited in that version of the review. The total number of articles cited in the 2001 version: 140. The total number of articles cited in the 2006 version: 22. The total number of articles cited in the 2009 version: 10. Two tailed p values are shown.

Contributors KR participated in the design of the study, carried out data analysis, performed statistical analysis and drafted the manuscript. KJJ and PCG both participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests None.

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Under-reporting of conflicts of interest among trialists: a cross-sectional study

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Under-reporting of conflicts of interest among trialists: a cross-sectional study

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Abstract

Objectives: To determine the prevalence of conflicts of interest (COIs) among Danish physicians who are authors of clinical drug trial reports and determine the extent of undisclosed COIs in trial publications.

Design: Cross-sectional study.

Setting: The 100 most recent drug trial reports with at least one Danish non-industry employed physician author published in a journal adhering to the International Committee of Medical Journal Editors' (ICMJE) manuscript guidelines. For each article, two observers independently extracted trial characteristics and the authors' COIs. Disclosed COIs were compared to what was registered on the Danish Health and Medicines Authority's public disclosure list.

Participants: Trial authors who are Danish physicians.

Main outcome measures: Number of disclosed and undisclosed COIs.

Results: One observer screened 928 articles and two observers assessed 120 articles for eligibility. The 100 included trials were published from February 2011 to May 2013 and included 318 Danish non-industry employed authors. Eighty-six of the 318 authors (27%) reported one or more COIs in the journal article. We found undisclosed COIs for 40 of 318 authors (13%) related to the trial sponsor or manufacturer of trial drugs. Seventy-nine of 318 authors (25%) had undisclosed COIs related to competing companies manufacturing drugs for the same indication and 136 (43%) had undisclosed COIs with any drug manufacturer.

Conclusions: Almost half of all authors had undisclosed COIs in clinical trials reported in journals adhering to the International Committee of Medical Journal Editors' manuscript guidelines. Self-declared COIs cannot be trusted, but public registries may assist editors in ensuring that more COIs are being reported.

Keywords

clinical trials, conflicts of interest, drug industry, disclosure

Introduction

Clinical trials are essential for evaluating effects of medical interventions.[1] Most trials test drugs and around half of all trials are industry sponsored.[2] Sponsorship by the drug industry is not without problems, as it may lead to bias in the design, conduct and reporting of the trials.[3] Non-industry sponsored trials may also be biased, particularly if the trialists have affiliations with the companies whose products are being tested. Such relationships create a conflict of interest (COI) and may lead authors to perceive drugs to be more beneficial and less harmful than they really are.[4–6]

COIs are acknowledged as an important source of bias,[7] and medical journals usually require authors to disclose their COIs, for example by using the Disclosure Form of the International Committee of Medical Journal Editors (ICMJE).[8] However, journals rely on voluntary disclosure by authors and the ICMJE's criteria are not entirely clear, e.g. 'relevant financial activities' may be interpreted differently by authors resulting in some COIs being undisclosed.[9] Thus, it is imperative that we quantify the amount of under-reporting of COIs in medical journals.

In Denmark, physicians who wish to engage in collaboration with a pharmaceutical company are required by law to apply for permission from the Danish Health and Medicines Authority. More specifically, all Danish physicians who have permission to prescribe medication to patients and who wish to engage in paid collaboration or have long-term, unpaid collaboration (e.g. the equivalent of full-time work for 4 weeks) have to seek permission with the Danish Health and Medicines Authority before initiation of the collaboration. Furthermore, all pharmaceutical companies are required to report names and social security numbers of Danish physicians who are affiliated with the company. Failure to seek permission for a collaboration will result in a fine. All physicians with permissions are named on a publicly available list,[10] similar to the US Physician Payments Sunshine Act.[11] Travel expenses and honoraria covering the provision of meals that do not exceed what is reasonable for the service the doctor

provided do not require permission from the Danish Health and Medicines Authority and are therefore not published on the list. The Danish Health and Medicines Authority list provides the names and specialty of the Danish physicians, the name of the pharmaceutical company, the type of collaboration, e.g. advisory board member and the expiration date for the collaboration. The amount paid by the pharmaceutical company to the physician is not published on the list. The Danish Health and Medicines Authority's list made it possible to study the level of underreporting of COIs in trials published in biomedical journals.[12]

The objectives are:

- To determine the prevalence of COIs among Danish physicians who are authors of clinical drug trial reports irrespective of who sponsored the trial.
- To determine the extent of undisclosed COIs in trial publications.

Methods

On 12 May 2013, we searched EMBASE using the limits function for 'randomised controlled trials' (RCTs) and 'article', and the index term 'Denmark' under Institutional Address for the 100 most recent and eligible drug trials.

Inclusion criteria

Eligible articles had to be reports of randomised drug trials with at least one Danish non-industry employed physician author (determined using the institutional address) and published in a journal that adheres to the ICMJE's Uniform Requirements for Manuscripts Submitted to Biomedical Journals (identified via http://www.icmje.org/journals.html). The latter criterion was used to ensure that included articles contained COI statements. Both primary publications and secondary analyses (e.g. follow-up studies or subgroups) of trials were included.

Exclusion criteria

Trials were excluded if all Danish physician authors were employed by a drug company or a commercial contract research organisation, determined using the institution address reported in the journal. Trials of fluid therapy, vaccines and dietary supplements were excluded, as companies producing these products are not listed on the Danish Health and Medicines Authority's list. Trials not related to specific drugs, but to general treatment strategies (e.g. initiation of antiretroviral therapy using a different cut-off for CD4 cell counts) were also excluded.

One observer (KR) screened title and abstract of articles, and final inclusion was based on full text screening conducted independently by two observers (AL, KR). Disagreements were settled by discussion.

Data extraction

Two observers (AL, KR) independently extracted trial characteristics and disclosed COIs for each included article into a pilot tested spreadsheet. Characteristics included name of first author, title of article, journal name, type of journal (general or specialist), journal Impact Factor (according to Journal Citation Reports 2011), publication date, generic names of drugs used in the trial, and type of comparator drug (placebo, active, multiple arms, non-drug comparator or no treatment).

We also extracted information on sponsorship and used four categories: industry sponsorship, mixed sponsorship, non-industry sponsorship and not stated. We extracted the name of the manufacturers of the tested trial drugs (both test drug and comparators) and if it was not stated in the article, we identified the manufacturer using the Danish Pharmaceutical Information's website (www.pro.medicin.dk). If the study drug had multiple manufacturers, all names were extracted. We also extracted statements about industry sponsor's involvement in the trial (e.g. industry employed co-authors, assistance with data analysis or writing of manuscript, including statements in acknowledgements like 'XX provided editorial assistance').

We extracted number of authors, industry employed authors (with company affiliation in their address) and Danish non-industry employed physician authors (registered as a physician by the Danish Registry of Authorization to Practice Medicine[13] and with an affiliation to a non-industry institution, e.g. hospital, stated in their address). The names and COI statements of the Danish non-industry employed physician authors were also extracted.

Identification of conflicts of interest

We focused only on financial COIs and defined a COI as a paid or unpaid, but long-term affiliation with a drug company excluding affiliations that only consisted of honoraria for travel expenses and provision of meals. For each of the Danish non-industry employed physicians, two observers (JS, KR) independently categorised each disclosed COI as related to the trial industry sponsor or manufacturer of trial

drug being studied, related to a competing drug manufacturer or as related to any drug manufacturer.

COIs related to the trial sponsor or manufacturer were categorised as:

- Consultant/advisory board member/employee
- Speaker/educational activities
- Investigator/research collaboration/grants
- Equity/stockholder
- Other (e.g. provided legal testimony for the sponsor)

Two observers (JS, KR) independently compared the disclosed COIs with information about industry collaboration (type and drug company) on the Danish Health and Medicines Authority's public disclosure list.[10] Being an investigator for the trial sponsor or manufacturer of the drug being studied was not considered an undisclosed COI, as we could not determine whether the investigator role related to the included trial or a different trial reported elsewhere. Receiving reimbursement for conference expenses and travel expenses for single activities are not listed on the Danish Health and Medicines list and thus could not be identified as undisclosed COIs. Only the COIs that were present at the time of publication or three years prior, similar to ICMJE's criteria, were included (we used multiple editions of the disclosure lists from June 2010 and forward). If there was any doubt about the start date of the involvement with the pharmaceutical company, we contacted the Danish Health and Medicines Authority and the dates were specified further to allow for a precise classification.

Undisclosed COIs were categorised as related to the trial sponsor or manufacturer of the trial drug, to a competing manufacturer or to any drug manufacturer. COIs related to a competing manufacturer of a drug with the same indication as the drug being studied was classified using the Danish Pharmaceutical Information's website (www.pro.medicin.dk). This is a similar methodology as that employed by other studies.[4,5] For example, in a trial of the beta-blocker metoprolol for heart failure, heart failure drugs from other companies were considered, whereas in a trial of beta-blockers for hypertension, antihypertensives from other companies were considered.

Data analysis

We calculated the number of Danish non-industry physician authors with one or more disclosed and undisclosed COIs related to trial sponsor or manufacturer, to competing manufacturers and to any manufacturer. The number of disclosed COIs that were not listed on the Danish Health and Medicines Authority's website[10] was also calculated.

Sensitivity analysis

We re-analysed the results using a more conservative approach where undisclosed COIs were excluded if the author's only industry affiliation was participating as an investigator in an industry trial for a competing manufacturer or any manufacturer, as it is unclear whether such affiliation requires disclosure according to the ICMJE criteria.[8] To avoid clustering due to some authors (prolific authors) having co-authored multiple articles, we conducted a second sensitivity analysis restricted to authors of single articles.

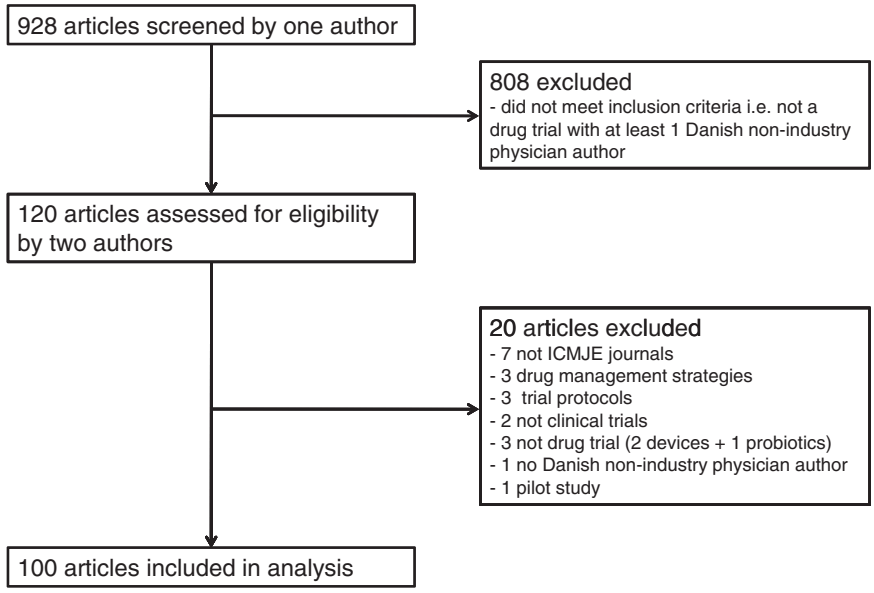
Results

One observer screened 928 articles and two observers assessed 120 for eligibility of which 100 were included (Figure 1).

The 100 articles included 318 Danish non-industry employed physician authors (median 1.5 per trial) (Table 1). There were 241 unique authors: 194 being of a single article and 47 of multiple articles (the maximum was 8 articles). Seventy articles were published in specialist journals, the median Impact Factor for the 100 included articles was 5.97 (IQR: 4.09 to 14.09), and 68 articles reported the analysis of primary results. Sixty-three trials were placebo controlled, 22 used an active comparator drug, four had several arms, one used a non-drug comparator, three were unclear and seven had a no-treatment control group. For the three trials classified as unclear, we could not determine whether the comparator was a placebo or no-treatment. Forty-nine trials were solely industry sponsored, 30 received both industry and public funding, 19 were non-industry sponsored and two did not report on sponsorship. We contacted the Danish Health and Medicines Authority to obtain information about start dates of collaborations for 11 of the 318 physicians, as it was unclear whether the publication of the paper had occurred before the collaboration started.

Eighty-six of the 318 authors (27%) disclosed one or more COIs in the article (Table 2). Seventy-two authors (23%) disclosed one or more COIs related to the trial sponsor or manufacturer of the trial drugs. Of these 72 authors, 58 had COIs related to consultancy or advisory board membership, 39 received grants, worked as investigator or received honoraria, 36 were paid for educational activities and 1 was a stockholder. Forty authors out of

Figure 1. Inclusion of drug trials for analysis.



318 (13%) had disclosed COIs related to a competing company manufacturing drugs for the same indication.

We found undisclosed COIs for 40 of 318 authors (13%) related to the trial sponsor or manufacturer of trial drugs. Seventy-nine of 318 authors (25%) had undisclosed COIs related to competing companies manufacturing drugs for the same indication and 137 (43%) had undisclosed COIs with any drug manufacturer. For example, one author disclosed that he received advisory board fees from AstraZeneca (trial sponsor and manufacturer), Bristol-Myers Squibb and Bayer, but did not disclose that he was a speaker for AstraZeneca and that he was on the advisory board for Eli Lilly, a company manufacturing drugs for the same indication, and had additional undisclosed COIs related to six other drug companies. Thirty-five of 115 authors (30%) from non-industry sponsored trials had any undisclosed COI whereas 102 of 203 authors (50%) from industry sponsored trials had any undisclosed COI.

A sensitivity analysis excluding all undisclosed COIs in the investigator role showed similar results. There were no changes to the COIs related to trial sponsor or manufacturer, as these did not include investigator COIs. The undisclosed COIs related to a competing manufacturer were reduced from 25% to 20% and any COI was reduced from 43% to 38%, see Supporting Information Table S1. A second sensitivity analysis restricted to 194 authors of single articles had some effect on our results. The undisclosed COIs related to sponsor or manufacturer was reduced from 13% to 5%, COIs related to a competing manufacturer from 25% to 13%, and COIs related to any manufacturer from 43% to 31%. Additionally, the proportion of authors with no COIs related to the sponsor, competing manufacturers and any manufacturer was higher for the group of single article authors, see Supporting Information Table S2.

Forty-five (14%) authors disclosed COIs in the journal that were not found on the Danish Health and Medicines Authority's list. Twenty-four authors had COIs related to a single company missing from the list and 21 related to several companies.

Discussion

Statement of principal findings

Almost half of all authors had undisclosed financial COIs in clinical trials reported in journals that adhere to the ICMJE's manuscript guidelines, and one of eight authors had not even disclosed COIs related to the trial sponsor or manufacturer of the drug being studied.

Strengths and weaknesses of the study

A major strength of our study is the use of a list where authors and companies are required by law to report their type of collaboration. Failure to report collaboration will result in a fine.[14] Our

Table 1. Trial characteristics ($n = 100$).

Characteristics	
Journal type, *n*	
General medical journal	30
Specialist journal	70
Journal impact factor, median (IQR)	5.97 (4.09–14.09)
Publication type, *n*	
Primary results	68
Secondary analyses	32
Comparator drug, *n*	
Active	22
Placebo	63
Multiple	4
Other*	11
Trial sponsorship, *n*	
Industry	49
Mixed	30
Non-industry	19
Not stated	2
Number of authors per trial, median (IQR)	
All authors	10 (7–13.25)
Danish non-industry physician authors	1.5 (1–5)
Industry employed authors	0 (0–2)

*Other includes 1 non-drug comparator, 3 unclear and 7 no comparator drug.

sample of 100 recent drug trials represents international publications of clinical trials in a wide range of journals and specialties. We discovered that 14% of authors declared COIs that were not listed on the Danish Health and Medicines Authority's list. This could be due to the fact that we only looked at lists that were published up to two years prior to the publication date of the study in question, as earlier lists were not available to us. The lists provide an 'up-to-the-minute account' and do not provide information on collaborations that have expired years before the current version. Thus, the lack of knowledge about COIs that were present more than two years prior to publication could potentially give an underestimation on the amount of under-reporting. As Denmark has been rated the least corrupt country in the world,[15] it is likely that the results we have reported here provide a 'best case scenario'.

Two observers independently undertook data extraction, and disagreements were discussed so consensus could be reached. The comparison of COIs between trial publications and the Danish Health and Medicines Authority's list was done using objective criteria pre-specified in the study protocol. However, this procedure could not be blinded, which could potentially have lead to bias.

Strengths and weaknesses in relation to other studies

Norris et al.[16] also found a high rate of under-reporting of COIs, with two-thirds of US physicians not disclosing COIs listed in ProPublica's Dollars for Docs database. However, this database only contains COIs related to 15 companies and it relies on voluntary information published on these companies' websites. Thus, it is highly likely that the results underestimate the amount of under-reporting.[16] A similar strategy was employed by Chimonas et al.[17] in a study of COIs related to five orthopaedic device companies, whereas Wang et al.[4] and Neuman et al.[9] identified additional COIs with Google searches and by retrieving COI statements in previous articles by the authors. The Danish Health and Medicines Authority's list provides us with more accurate and comprehensive data, as all Danish physicians are legally responsible for the reporting of the collaboration with the industry.

Interestingly, we found that a considerable proportion of COIs related to a competing manufacturer were undisclosed despite the fact that the ICMJE guidelines state that these COIs should be disclosed. To our knowledge, this finding has not previously been described.

Our definition of COIs could have influenced our results. However, our sensitivity analysis, where all COIs that were categorised as investigator role or research grants were excluded, gave similar results. We considered working as an investigator and receiving grants from the pharmaceutical industry as a COI, but some might consider it a less important relationship. However, we could not identify undisclosed COIs related to receiving reimbursement for

Table 2. Overview of disclosed, undisclosed and no conflicts of interest for all Danish non-industry physician authors.

	All conflicts of interest disclosed *n* (%)	Some conflicts of interest undisclosed *n* (%)	All conflicts of interest undisclosed *n* (%)	No conflicts of interest identified* *n* (%)	Total (%)
COI related to trial sponsor or manufacturer	44 (14%)	28 (9%)	12 (4%)	234 (74%)	318 (100%)
COI related to competing manufacturer	10 (3%)	30 (9%)	49 (15%)	229 (72%)	318 (100%)
COI related to any drug manufacturer	15 (5%)	71 (22%)	66 (21%)	166 (52%)	318 (100%)

*No conflicts of interest identified either in publication or in Danish Health Authority's list.

conference and travel expenses because the Danish list currently does not contain this information.

Our second sensitivity analysis showed that the proportion of undisclosed COIs decreased when we restricted our sample to authors of single articles. This suggests that COIs and lack of disclosure may be particularly prevalent among the group of authors of multiple articles, likely representing key opinion leaders in their field. This finding of a higher non-disclosure rate among prolific authors is a concerning result, as prolific authors dominate the literature and the lack of disclosure misleads the readers.

Meaning of the study

Our results show that COIs reported in ICMJE journals by trialists are not reliable. The Institute of Medicine emphasises that transparency of COIs is an important, but limited first step in dealing with COIs.[7] Public registries where both physicians and the drug companies are legally responsible for disclosure of their collaboration such as the Danish Health and Medicines Authority's list are a model for other countries. With the Physicians Payments Sunshine act,[12] it will become possible to get reasonably accurate information in the United States, similar to what is possible in Denmark. In a recent open letter to the General Medical Council (GMC) in the UK, the authors requested a similar registry where physicians can disclose all their COIs to ensure transparency in any collaboration with the industry.[18] The GMC reports that the matter of a UK register for mandatory declaration of COIs is still 'a work in progress'. Relying solely on the disclosures by the pharmaceutical industry such as the Association of the British Pharmaceutical Industry's disclosures is not reliable and will miss COIs such as shares in pharmaceutical companies.[19] However, a public registry cannot combat the bias that COIs can result in, but it can make physicians and the public aware of them.[20]

To ensure accurate and complete disclosure of financial COIs in the future, journals could require a report from a public registry providing information on paid collaboration for the past three years instead of relying on the authors' voluntary disclosures.

Conclusions

Under-reporting of COIs is common in clinical trials reported in journals adhering to the ICMJE's manuscript guidelines. Self-declared COIs cannot be trusted, but public registries may assist editors in ensuring that more COIs are being reported.

Declarations

Competing interests: None declared

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Guarantor: KR

Contributorship: AL conceived the idea for the study and developed the protocol with contributions from KR, JS and PCG. KR identified trials and AL verified the selection. AL and KR extracted trial data, and KR and JS identified conflicts of interest. All authors participated in data analysis and writing of the paper. All authors had full access to all the data in the study.

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Collaboration Between Academics and Industry in Clinical Trials: cross-sectional study of publications and survey of lead academic authors

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ABSTRACT

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Objective: To determine the role of academic authors, funders and contract research organisations in industry-funded vaccine, drug and device trials, and to determine lead academic authors' experiences with industry funder collaborations.

Design: Cross-sectional analysis of trial publications and survey of lead academic authors.

Eligibility criteria for selecting studies: We included the most recent 200 phase III and IV vaccine, drug and device trials with full industry funding, at least one academic author, published in one of the top seven high impact general medical journals (NEJM, Lancet, JAMA, BMJ, Annals of Internal Medicine, JAMA Internal Medicine and PLoS Medicine).

Results: Employees of industry funders co-authored 173 (87%) of publications. We found 183 (92%) trials reported funder involvement in design and 167 (84%) academic author involvement. Data analysis involved the funder in 146 (73%) trials and the academic authors in 79 (40%). Trial reporting involved the funder in 173 (87%) trials and academic authors in 197 (99%). Contract research organisations were involved in the reporting of 123 (62%) trials.

Eighty of 200 lead academic authors (40%) responded to the survey. Twenty-nine (33%) of the 80 responders reported that academics had final say on the design. Seven (9%) responders reported an unacknowledged funder or contract research organisation employee did the data analysis and 5 (6%) reported an unacknowledged funder or contract research organisation employee drafted the manuscript. Most academic authors found the collaboration with industry funder beneficial, but 3 (4%) experienced delay in publication due to the industry funder and 9 (11%) reported disagreements with the industry funder mostly concerning trial design and reporting.

Conclusions: Academic authors are involved in the design and reporting of most industry trials in high impact journals, but to a lesser degree in data analysis. Academics view the collaboration as beneficial, but some report loss of academic freedom.

INTRODUCTION

Collaboration between industry and academics is common in vaccine, drug and device development, as it can be mutually beneficial. The academics provide access to trial participants and methodological expertise, and industry provides funding and expertise. The degree of independence and roles of academics and industry varies across trials. Trials may be completely run by academic trial units with unrestricted industry funding or solely provision of study medication (1, 2). Alternatively, academics are involved in trials as honorary authors in order to give a trial scientific credibility and downplay the role of industry funder (3, 4).

Based on previous work and examples, collaboration between academics and industry may result in commercial considerations outweighing science and constraints on academic freedom. For example, previous studies have found some trial agreements permit funders to block publication (5-8). Furthermore, academics have reported problems with stalling of publications, restriction of publication rights and threats to never fund their institution again due to reporting of negative results or adverse events (9). A survey of Canadian trial investigators found problems in relation to control over study design, data ownership, data access and analysis (10).

Although most clinical drug and device trials are industry funded, the nature of the collaboration between industry and academics has received little attention (11). Previous studies have addressed the issue on a general level (5-10, 12). To our knowledge, no contemporary studies have surveyed the role and practices of academics, industry, and contract research organisations (CROs) when collaborating in clinical vaccine, drug or device trials.

Objective

- To determine the role of academic authors, funders and CROs in industry-funded vaccine, drug and device trials.
- To determine lead academic authors' experiences with industry funder collaborations.

METHODS

This study was in two parts: 1) a cross-sectional study of trial publications and 2) a survey of the lead academic authors of the 200 most recent industry-funded vaccine, drug and device trials published in one of the top seven high impact general medical journals.

Cross-sectional Study

Search

One author (KR) manually searched the top seven general and internal medical journals according to the impact factor of the 2015 Journal Citation Report (New England Journal of Medicine (NEJM), Lancet, JAMA, BMJ, Annals of Internal Medicine, JAMA Internal Medicine and PLoS Medicine) for the most recent trial publications meeting our inclusion criteria (13).

Inclusion Criteria

We included publications of phase III and IV trials with one or more academic authors (determined using the institutional address) that disclosed full industry funding. We defined full industry funding as any trial with funding exclusively from one or more vaccine, pharmaceutical or device companies. We included industry-supported trials described as investigator-initiated if the only funding was from industry sources (14).

We defined academic authors as authors whose affiliation in the publication was a clinic, hospital, university or non-profit academic research centre. The lead academic author was selected according to the following rank: corresponding author, first author, last author, second author, third author, etc. If there were more than one academic corresponding author, the lead academic would be deemed according to the following rank: first author, last author, second author, third author, etc.

Exclusion Criteria

- Trials of fluid therapy and dietary supplements.
- Trials with mixed funding (public and industry-funded, including free provision of study drug or device only).
- Secondary publications (e.g. subgroup analysis).
- If two publications of the same trials were identified (e.g. an interim analysis and the planned analysis) only the most recent publication was included.
- If a lead academic author had published more than one eligible trial, we only included the most recent trial.

A second author (AL) confirmed that the 200 trial publications met the inclusion and exclusion criteria. Disagreements were resolved by discussion.

Data Extraction

For each trial publication, two authors (AL, KR) independently extracted data into a standardised data sheet. We extracted data on the role of the academic authors, funder and CRO with regard to trial design, conduct, data analysis and reporting. We also extracted data on access to data, trial agreements and the lead academic author's reported conflicts of interest (COIs). Being an investigator or receiving a grant from the trial funder in relation to the included trial was not considered a COI (Appendix for full details). Disagreements were resolved by discussion.

During the initiation of the data extraction, we found that the contribution of individual authors and role of the funder was often not clear from the publications in NEJM, as roles were typically described in broad terms (e.g. the trial was designed by a steering committee of academics and funder representatives, but the publication did not describe which authors were members). We therefore decided to include supplementary material (e.g. lists of steering committee members and contributions statements) for data extraction of NEJM publications, if available.

Survey

We designed our survey using Qualtrics® (15). Each lead academic author was tracked by a unique identifier to allow matching of the survey response to the publication and in order to track authors who had not responded. Results were reported in an anonymised form and the identity of the academic authors was only known to two of us (AL, KR).

Survey questions were designed, ordered and sent out in a fashion recommended for increasing the response rate and the reliability of the responses (16, 17). The survey included 20 questions with possible answers in tick boxes and the possibility of writing a more detailed comment. The questions addressed design, analysis and reporting of the trial, data access, trial agreements, and experience with the collaboration (Appendix).

We pilot tested the survey on seven academics identified from our network who had previously collaborated with industry and modified the survey slightly according to their advice.

We emailed the survey to the 200 lead academic authors in June 2017 and reminders were emailed twice monthly until the end of September 2017 (seven reminder emails). Thereafter, we contacted non-responders by letter in October 2017 and by phone in November 2017.

If a survey response had a conflicting comment, e.g. the lead academic author had chosen "funder" in response to a question while it was clear in the comments that the academic authors were also involved, this would be reclassified after discussion between two authors (AL, KR). Responses were reclassified due to comments for 16 responders.

Data Analysis

We used only descriptive statistics. Responder comments were reported in a collated fashion where possible. Discrepancies between survey and trial publication were reported. For trial characteristics, we also stratified characteristics by vaccine, drug and device trials and survey response type (i.e. responders, declined via email, accessed survey, but did not respond, and non-responders).

For the survey, we stratified responses by vaccine, drug and device trials. We also stratified survey responses into those still collaborating with the funder or who would collaborate in the future and those no longer collaborating with the funder to assess whether these had important differences.

For both trial characteristics and survey responses, we stratified results into groups of independent trials and industry trials as we hypothesised that these groups would differ. Trials were classified as independent if neither funder nor a CRO was involved in design, conduct, analysis, or reporting.

To assess the impact of COIs in relation to two survey questions on "funder problems" we stratified responses by lead academic authors with COIs related to the funder and by lead academic authors without COIs.

RESULTS

Cross-sectional Study

We identified 1139 publications and included 200 trials published between July 2014 and April 2017 (Figure 1). We included trials from all selected journals except PLoS Medicine where no trials met our inclusion criteria because none were solely industry-funded.

Trial Characteristics

All trials but 7 were published in NEJM (53%), Lancet (31%) and JAMA (13%) and 165 trials (83%) were drug trials (Table 1 and Appendix for stratified analyses). The median number of authors was 19 (range 5-103), with one trial, published in JAMA, having a study group listed as authors, which consisted of 103 people. In 173 (87%) of the trials, there was one or more co-authors who were employees of the funder. The corresponding author was an academic author in 192 (96%) trials. The lead academic author had COIs with the trial funder in 165 (83%) trials.

Involvement of Funder, Academic Authors and CROs as Reported in Trial Publications

In 137 (69%) trials, both funder and academic authors were involved in the design and in 129 (65%) trials in conduct (Figure 2). In 109 (55%) trials, data analysis was done by the funder and/or a CRO without the involvement of academic authors and only 26 (13%) trials had data analysis done solely by academic authors. In 117 (59%) trials, the reporting involved the funder, academic authors and a CRO, primarily a medical writer. Only 8 (4%) trials were classified as independent trials (i.e. all aspects of the industry-funded trial were carried out by academic authors without involvement of the funder or a CRO). In 4 of these 8 trials the lead academic author had disclosed COIs with the funder.

The data analysis was done by a median of 3 (range 1-31) authors with the involvement of a median of 1 (range 0-11) funder employee. In 95 trial publications, we were unable to identify the exact number of authors involved in data analysis. Although we aimed to extract data on who performed the actual statistical analysis, this was often difficult, as publications used phrases such as *"All authors analysed and interpreted the data"* even though a publication might have 18 authors. Other publications used a phrase from the ICMJE requirements for authorship describing individual authors involvement in *"Acquisition, analysis, or interpretation of data",* and thus grouped three very different processes making it impossible to assess who performed the statistical analysis (18). In 10 trials, it was stated that the funder had no role in the data analysis, but it was unclear who else was involved (e.g. a CRO).

Data Access and Trial Agreements

All authors declared access to data in 77 (39%) trials and some academic authors did so in an additional 67 (34%) trials. For the remaining trials, 52 (26%) stated that authors vouched for the data without specifying who had access and 4 (2%) had no description of data access. The type of data available to authors was not specified in 135 (94%) of the 144 trials reporting data access, 3 (2%) reported access to analysed data only, 2 (1%) access to raw data, 1 (1%) access to summary data for all patients, but only individual patient data from own institution, and 3 (2%) access to data used in the publication.

In 16 (8%) trial publications, confidentiality agreements with the funder were described and 4 (2%) publications described that there were no such agreements. For the remaining 180 (90%) trials, there was no mention of confidentiality agreements in the publication.

Survey

We received responses from 106 (53%) lead academic authors (Figure 1). Three lead academic authors were unreachable by email, post, and telephone. Eighty out of 200 (40%) responded to survey questions, 10 (5%) accessed the survey without providing any response and 16 (8%) replied that they did not want to participate (Appendix). Our comparison of trial and author characteristics between those who responded to those who did not, revealed no important differences (Appendix).

Decisions and Involvement in Trial Design, Analysis and Reporting, as Reported by Lead Academic Authors

Twenty-six (33%) of the 80 responders reported, academic authors solely decided which comparator treatment to include whereas this was only the case for choice of outcomes in 4 (5%) of the responders' trials (Figure 3 for all responses, Figure 4 for selected author comments, and Appendix for additional author comments). Twenty-nine (36%) responders reported the academic authors had the final say in trial design. One responder reported the funder was involved in the design, but this was not described in the publication. Ten lead academic authors (6 from North America and 4 from Europe) acknowledged a drug regulatory agency as having the main decision power on choice of comparator, outcome and/or final say on the trial design. However, the corresponding publications only acknowledged regulator input in 2 of the 10 trials.

Four (5%) responders reported funder involvement in data analysis, but according to the responder the funder employee was not named in the trial publication. Three (4%) other responders reported, the funder was involved in data analysis, but this was not described at all in the trial publication.

Four (5%) responders reported CRO involvement in data analysis, but the CRO employee who did the analysis was not named in the publication.

Fifty-three (66%) responders reported that the manuscript was drafted solely by academic authors. However, 27 (51%) of these responders' trials had writing assistance from a CRO according to the corresponding publication. Four (5%) responders reported the manuscript was drafted by a funder employee who was not a co-author or a named contributor in the trial publication. One responder reported an unnamed CRO employee drafted the manuscript together with academic authors and another responder did not know who drafted the manuscript. One responder reported CRO involvement in reporting, while the corresponding publication did not describe this involvement. Fifty-two (65%) responders reported academic authors solely had final say on the published manuscript. However, 40 of these 52 trials included funder employed co-authors.

In total, 10 lead academic authors described involvement of an unnamed funder and/or CRO employee in the data analysis and/or reporting. An additional 8 responders described funder and/or CRO employee involvement in trial design, data analysis, or reporting which was not reported in the corresponding publication.

Trial Agreements and Data Access

Sixty-three (79%) responders reported a trial agreement was signed and 46 (73%) of these 63 included a publication agreement, 33 (52%) a presentation agreement and 39 (62%) a confidentiality agreement (Table 2). Eight lead academic authors commented that the contract they signed with the industry funder gave the funder the right to review and comment on the manuscript and presentations, but did not give the funder approval rights. However, six of these responders' eight trials had funder employed co-authors thereby indirectly giving funder approval right (Appendix) and one of these authors also described disagreements with the funder over manuscript content. Only 4 (6%) of these 63 trials with agreements, had a description of a confidentiality agreement in the trial publication. Another trial publication reported there was no confidentiality agreement, but the survey contradicted this and described that the data was 100% embargoed prior to publication suggesting the existence of a confidentiality agreement.

According to the survey, 63 (79%) of the lead academic authors had access to the entire dataset and in 56 (89%) of these trials, the access was used. Seventy-three of the trials allowed for a comparison of data access between survey responses and statements in trial publications. In 5 (7%) trials, the lead academic author had data access according to the publication, but they denied such access in the survey. In 3 trial publications that used the phrase: *"the authors vouch for the data,"* the lead academic author did not have data access according to the survey.

Experience with Collaboration

Three (4%) responders had experienced publication delay and 9 (11%) had disagreements with the funder, mostly concerning trial design and reporting (Table 2). Disagreements were generally described as minor (Figure 3 and Appendix for detailed comments).

Sixty-seven (84%) of lead academic authors were still collaborating with the industry funder or would like to collaborate with the funder again. The most commonly reported benefit of collaborating with the industry funder was funding (reported by 33 responders and by 18 (23%) responders as the only benefit). Thirteen (16%) responders found the fact that they were contributing new research a benefit of the collaboration. Eight (10%) responders reported the trial publication and subsequent publications using the same dataset as a benefit to the collaboration (Figure 4 and Appendix).

In our subgroup analyses we did not find any differences in trial characteristics or survey responses in relation to COIs, type of intervention, industry involvement and collaboration status (Appendix).

DISCUSSION

We found that industry-funded trials were mostly conducted in a collaborative fashion. Nevertheless, the role of academic authors, funders and CROs varied greatly. Generally, both academic authors and funders were involved in the trial design, conduct and reporting. However, the actual data analysis was most often conducted by funder or CRO employees. Few industry-funded trials were completely independently conducted by academics and sometimes industry involvement was downplayed or omitted in trial publications. The lead academic authors frequently found the collaboration beneficial, particularly in relation to funding of the trial. However, some

academic authors reported disagreements with the funder, mostly concerning trial design and reporting.

Context

Lundh et al. analysed trials published in the Lancet in 2008-9 and had access to trial protocols (12). Our findings of extensive involvement of industry funders and that the role of funders and CROs were sometimes downplayed in the trial publications are similar to the findings of Lundh et al. Data is often stored and owned by the industry funder and similar to Lundh et al. we found that trial publications rarely described what type of data the academic authors had access to and whether they used this access (19, 20). We believe that descriptions of data access in publications may not be accurate. In 67 of the 69 Lancet protocols, there was no information on academic authors' access to data, in striking contrast to the papers, which indicated that one or more academic authors had access to the data in 64 trials (12).

Ghost authorship, where individuals are involved in important aspects of clinical trials without the involvement being disclosed in the publications, has been well described (10, 21). We found evidence of ghost authorship in 18 trials, but this is likely an underestimate as some lead academic authors had a small role in the conduct, analysis and reporting of the trial. Thus, "ghost-authoring" could have taken place without the lead academic authors being aware. Gøtzsche et al. found a much higher prevalence of 75% of ghost authorship in trials, particular in relation to data analysis (21). However, prevalence of ghost authorship may have diminished over time since we found that 87% of trials had industry co-authors compared to 64% in the study by Gøtzsche et al (21).

Some academic authors reported that having a high impact publication was a benefit from the collaboration and academic authors were frequently (96%) prominently placed as corresponding authors. Our findings are consistent with previous studies which found high prevalences of industry ties among lead academic authors of industry-funded trials (22, 23). These financial COIs may impact on trial results. Industry-funded trials by lead academic authors with company ties are more often favourable compared to trials without authors' with financial COIs and it has been suggested that key opinion leaders with industry ties may be more willing to accept commercial pressure (22, 24, 25).Previous studies have found that some COIs are under-reported in publications (26, 27), so the actual figures may be even higher.

Strengths and Weaknesses

To our knowledge, this is the first study that directly surveyed a large cohort of international academic authors involved in industry-funded trials published in high impact general medical journals. A major strength of our study is the fact that we included trials from all over the world and thus our results are applicable at an international level. Our usage of data from both trial publications and survey responses allowed us more comprehensive data compared with studies solely based on a single information source (8, 10). Furthermore, the anonymised format of the survey is likely to have provided us with more truthful responses, especially with regard to sensitive topics. Our findings may be somewhat limited by the retrospective nature of the survey. However, we only included the most recent trials and therefore the authors are likely to remember the details compared to studies focusing on past experience of academics in general (10). Another possible limitation is the mixture of industry-funded trials initiated by academics and company trials initiated for regulatory purposes. It was not possible from trial publications to completely distinguish between these types of trials and funder involvement is likely more pronounced in industry-funded trials conducted for regulatory purposes. Additionally, we only assessed the supplementary material for trials published in NEJM. Academic authors with industry ties are more likely to be favourable towards industry involvement in research than those without ties, and thus our survey results may exhibit this bias (28). Finally, despite many reminders we only received survey responses from 80 (40%) academic authors which was somewhat lower than previous surveys of academic authors, but similar to Smyth et al (10, 19, 29). Nevertheless, the trial and author characteristics did not differ amongst responders and non-responders.

Meaning of the Study

We found that there is room for more accurate reporting of authors' contribution in industry-funded trials published in high impact general medical journals. A solution could be that guidelines such as ICMJE and CONSORT require more detailed reporting, particularly related to data analysis, data ownership and access (18, 30). Furthermore, journals could refuse publication when these elements are not clearly reported. Trials from high impact journals have important impact on clinical decisions (31, 32). Nevertheless, only a few of our included trials had independent analysis. However, it is possible for academics to demand control over design, data storage, full data ownership, analysis and reporting, thereby improving independence and greater reliability of trial results.

Conclusion

Academic authors are involved in the design and reporting of most industry trials in high impact journals, but to a lesser degree in data analysis. Academics view the collaboration as beneficial, but some report loss of academic freedom.

Ethics

We contacted the Regional Committee on Health Research Ethics and the Danish Data Protection Agency and both confirmed that this survey does not require any form of approval according to Danish law.

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FIGURE 1 STUDY FLOW DIAGRAM

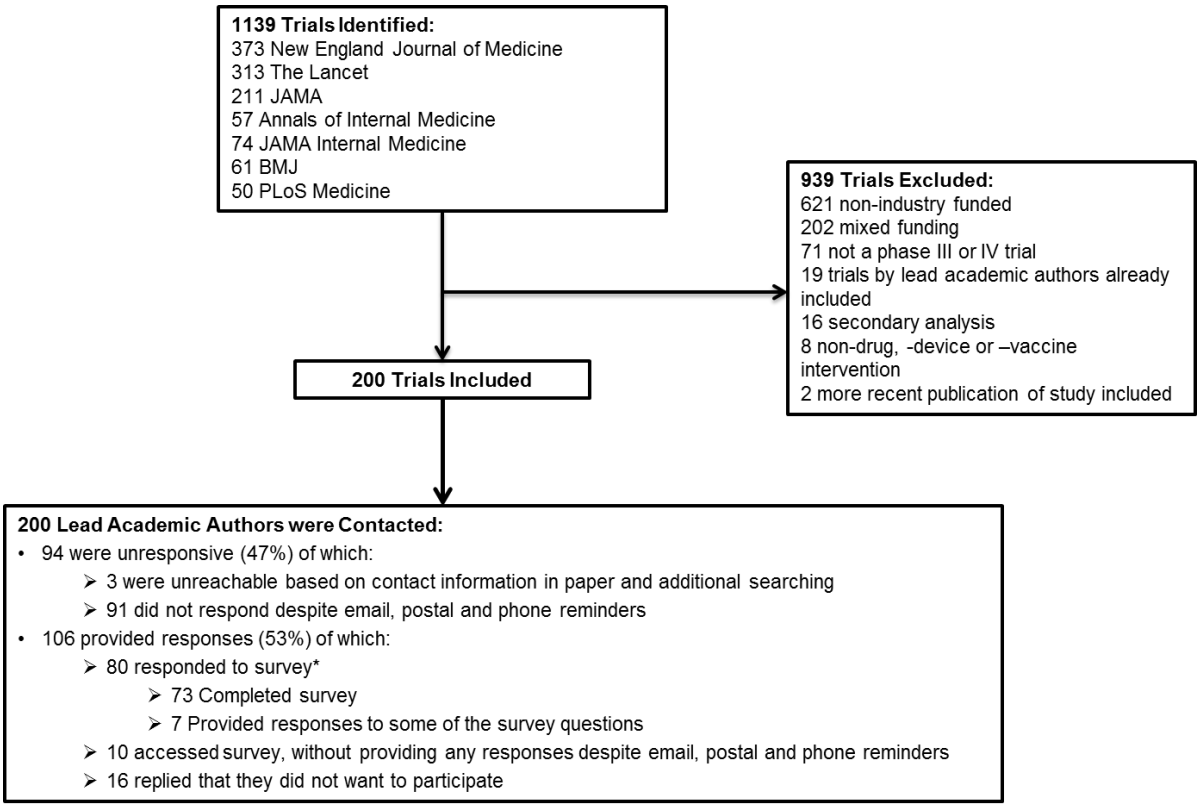

Figure 1: *A response was included by one of the authors who later replied that he did not have time to complete the survey.

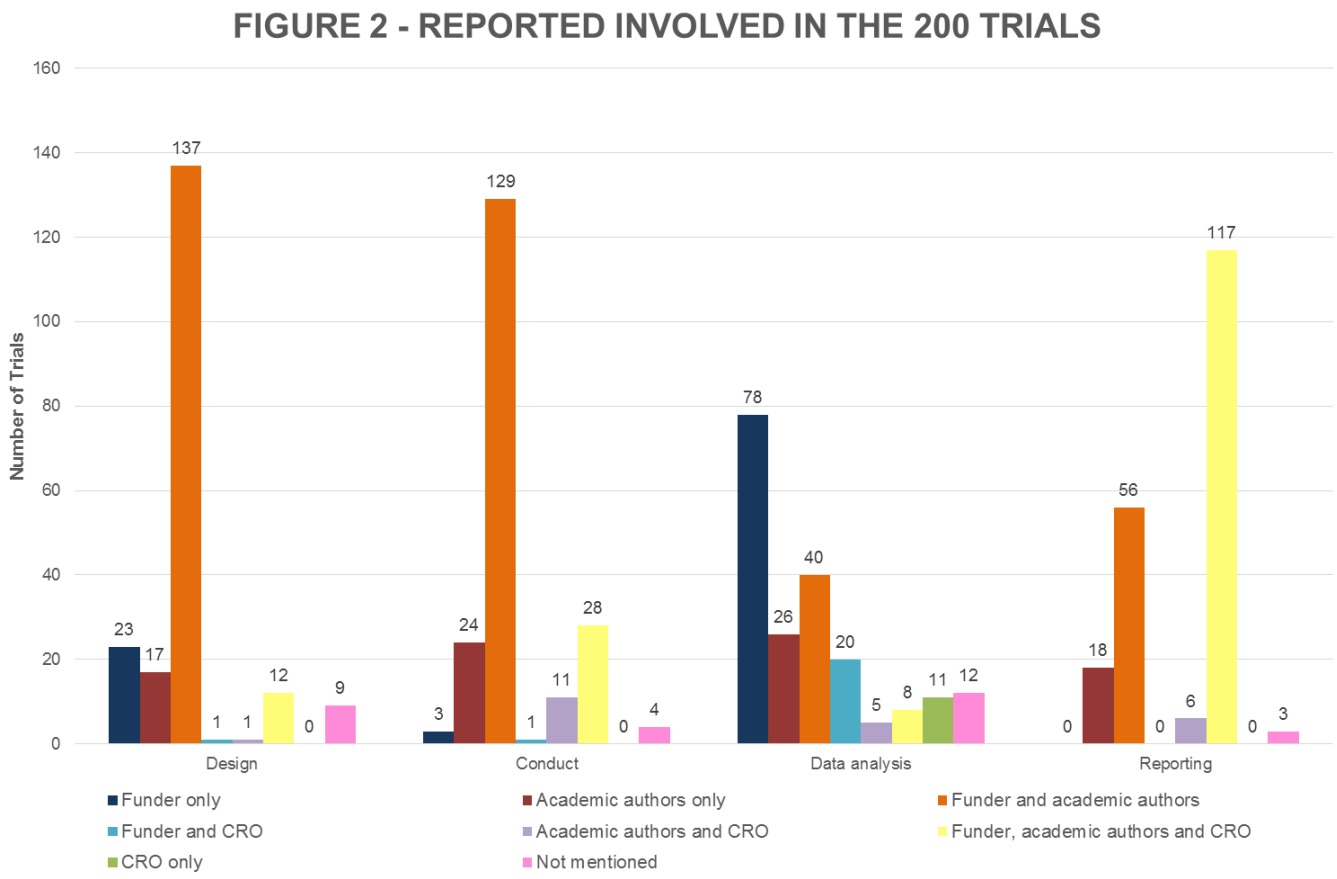

Figure 2: CRO –contract research organisation.

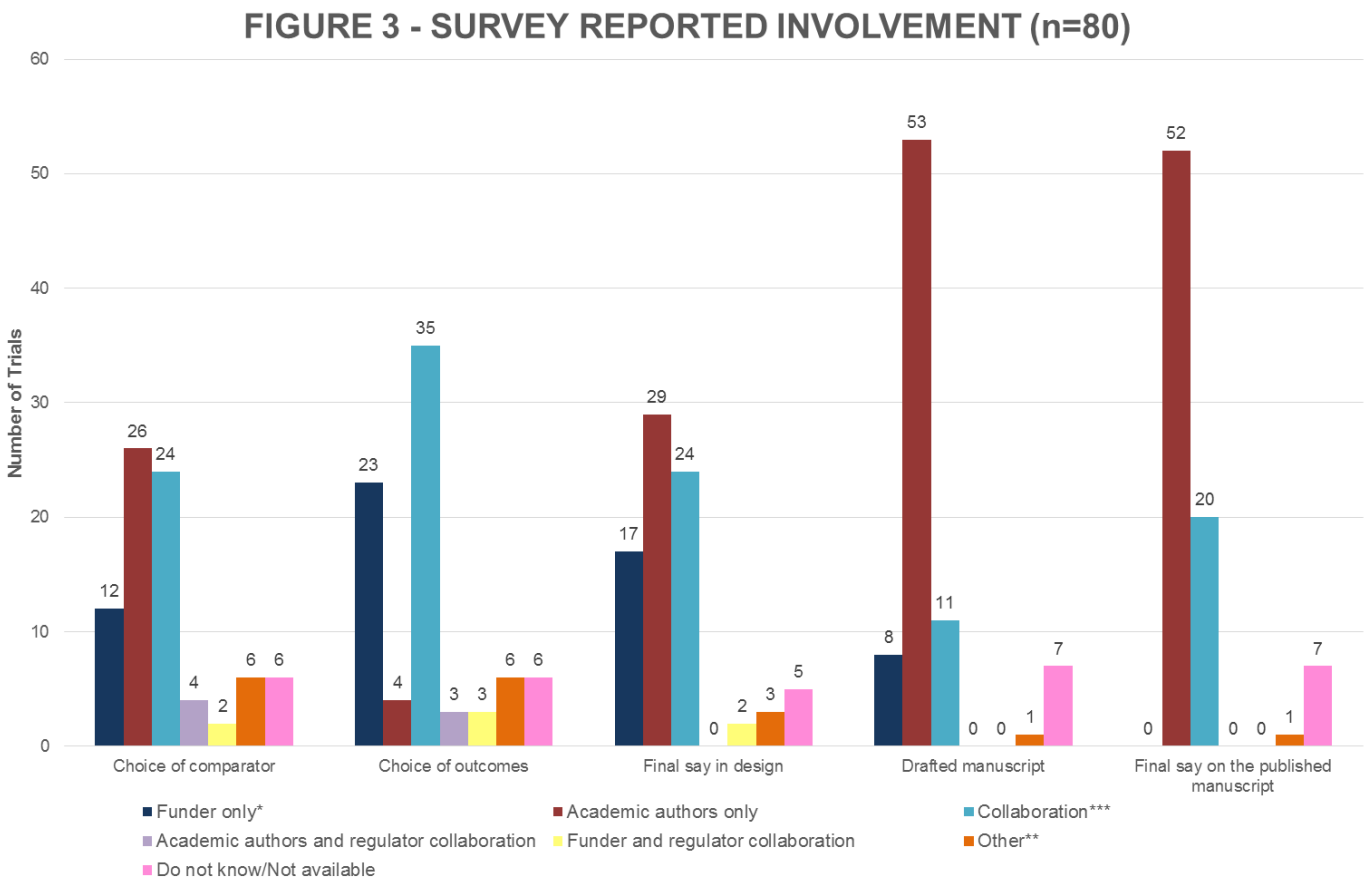

Figure 3: CRO –contract research organisation
*Funder and CRO also includes unacknowledged persons for the conducted statistical analysis and drafting of manuscript.
**Other can include trials classified as regulator, journal, unknown or unclear.
***Collaboration includes academic, funder, and/or CRO; academic, funder and/or regulator; academic and CRO; funder and CRO.
No responders reported CRO as the only actor for any of the categories above.

Figure 4 Selected comments to the survey questions

Selected comments from Benefits of collaborating with the trial industry funder
Funding: "Study would not have been possible without funding which came as a donation. No strings attached."
*Publication: "*The *Journal X* paper! And more to come." "Opportunity to author papers of important study results in high impact journals"
*Personal benefits: "*Being PI of a positive trial is always a benefit in CV and recognition"; "…That being said, I would not object to all industry-sponsored studies being listed as 'the *Trial X* Investigators' or something similar - ultimately, despite our input, these are studies done by the company"
Selected comments for confidentiality agreement
Confidential until publication: "No for results which are already in the public domain, obviously, but yes for all other unpublished data"
Miscellaneous: "The agreement stated that sponsor could request up to 30 days confidentiality if necessary for patent protection."
Selected comments for choice of comparator
*Collaboration: "*The company has to obviously agree with the study design. They fund the trial."
*Miscellaneous: "*The sponsor did not want a placebo arm in the trial. We insisted upon it for safety evaluation and they ultimately agreed to a placebo arm with deferred treatment."
Selected comments for final say in study design
*Funder: "*We advised the sponsor study team (extensively) and I would generally say that they listened, but they did not 'require' sign-off from the steering committee before finalizing the protocol so in that sense, they had final say."
Selected comments for statistical analysis
Miscellaneous: "We analyse with independent academic and with the funder statisticians. Sometimes we have to rely on only the funder statisticians which is less satisfactory. However SAPs and protocols are submitted to regulatory and editors before analysis and publication."; "Stats team employed by company. Monitored by independent data monitoring committee, not named, not part of sponsor or investigators."
Selected comments for access to data
Miscellaneous: "Not the ENTIRE dataset, but much of it and we were encouraged to ask for specific analyses."; "I had access to all the data but did not have access to the database. E.g., all analyses conducted in sponsor's dataset. Any analysis that we wanted was done."
Selected comments for using data access
Miscellaneous: "I anticipate some 30 high-quality papers will be published using this data set. 12 already published, 4 submitted and 10 currently in preparation"
Selected comments for drafting the manuscript
*Academics writing intro and discussion: "*I drafted the introduction and discussion sections, while the company scientific writers drafted the methodology and results sections."
Selected comments for how disagreements with funder were handled by the funder
Miscellaneous: "Want to postpone and change the wording"
Selected comments from additional comments
Miscellaneous: "Further report not approvable or not approved by the sponsor"

Figure 4 legend: Typos have been corrected. Comments from different authors are separated by ";". Words have been replaced *by pseudonyms* to ensure the anonymity of the author.

TABLE 1
CHARACTERISTICS OF THE 200 INDUSTRY-FUNDED TRIALS

Journal	n	%
New England Journal of Medicine	106	53%
The Lancet	62	31%
JAMA	25	13%
Annals of Internal Medicine	4	2%
JAMA Internal Medicine	2	1%
BMJ	1	1%
Intervention		
Drug	165	83%
Device	26	13%
Vaccine	9	5%
Comparator		
Active treatment	79	40%
Multiple arms (active treatment and placebo)	27	14%
Placebo or no additional treatment	94	47%
Authorship		
Academic and industry funder authors*	173	87%
Academic and CRO authors	5	3%
Solely academic authors	22	11%
1st author academic	196	98%
1st author funder	4	2%
Last author academic	154	77%
Last author funder	42	21%
Last author CRO	2	1%
Last author other**	2	1%
Corresponding author academic	192	96%
Corresponding author funder	8	4%
Lead academic author's reported conflicts of interest		
Conflict(s) of interest with funder***	165	83%
Conflict(s) of interest with other company	14	7%
No conflict of interest	21	11%

Table 1: CRO –contract research organisation.
Due to rounding the percentages may not add up to 100%
*Some trials also had CRO co-authors
**Other refers to an author employed by an industry company other than the industry funder and one author where it was unclear if the affiliation was a CRO or private clinic.
***Those who had conflicts of interest with the funder could also have conflicts of interest with another industry company.

TABLE 2
SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS n=80*

	Yes		No		Do not know or Not Available	
Trial agreement	**n**	**%**	**n**	**%**	**n**	**%**
Signed trial agreement with industry funder	63	79%	16	20%	1	1%
Signed trial agreement included a publication agreement**	46	73%	12	19%	5	8%
Signed trial agreement included presentation agreement**	33	52%	21	33%	9	14%
Signed trial agreement included confidentiality agreement**	39	62%	19	30%	5	8%
Data access						
Had access to the entire trial data set	63	79%	9	11%	8	10%
Access used by those with access to entire data***	56	89%	6	10%	1	2%
Problems						
Delay in publication due to funder	3	4%	70	88%	7	9%
Disagreements with funder	9	11%	64	80%	7	9%
Collaboration						
Already collaborating with funder/would in the future	67	84%	1	1%	12	15%

Table 2: *7 authors only provided responses to some of the questions
**n=63 Question was only available to those who answered yes to signing an agreement with industry funder
***n=63 Question was only available to those who answered yes to data access
Due to rounding the percentages may not add up to 100%.

Appendices

Supplementary material for paper 1: Citations of scientific results and conflicts of interest: the case of mammography screening

Appendix 1: Not applicable articles

Not applicable in all of the outcomes **Topic of paragraph**	**% (n)**
Controversy	47%(15)
A trial not including one of the Cochrane reviews	3% (1)
Ubiquitous literature	3% (1)
Informed choice	3% (1)
Lung cancer screening	3% (1)
Numbers needed to treat	3% (1)
Incidence and survival	3% (1)
Screening <50 year olds	6% (2)
Critique of mammography screening	3% (1)
Mammography screening RCTs	3% (1)
Uncertainty of estimates from RCTs	3% (1)
Table on trial selection	3% (1)
Benefits of Breast cancer screening	6% (2)
False positives	3% (1)
Inclusion of trials in different studies	3% (1)
Screening frequency	3% (1)

Appendix 1: The topic of the 32 paragraphs classified as 'not applicable' in all of the 5 outcomes (*overdiagnosis, overtreatment, breast cancer mortality, total mortality and*

Appendix 2: Reference list of included articles.

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Appendix 3: Comparison of European vs North American journals

	Overdiagnosis			Overtreatment					
	Europe	North America	P-value	Europe	North America	P-value			
Accept	4 (5%)	6 (7%)	0,75	4 (5%)	4 (4%)	1,00			
Neutral	1 (1%)	0	0,47	2 (3%)	0	0,22			
Reject	0	0	1,00	3 (4%)	2 (2%)	0,67			
Unclear	8 (10%)	4 (4%)	0,24	9 (11%)	6 (7%)	0,42			
Not applicable	67 (83%)	81 (89%)	0,82	62 (78%)	79 (87%)	0,65			
	Breast cancer mortality			**Total mortality**			**Methods**		
	Europe	North America	P-value	Europe	North America	P-value	Europe	North America	P-value
Accept	1 (1%)	5 (5%)	0,22	4 (5%)	2 (2%)	0,71	5 (6%)	5 (5%)	1,00
Neutral	5 (6%)	2 (2%)	0,47	1 (1%)	0 (0%)	0,47	2 (3%)	2 (2%)	1,00
Reject	15 (19%)	18 (20%)	0,85	4 (5%)	5 (5%)	1,00	14 (18%)	15 (16%)	1,00
Unclear	18 (23%)	16 (17%)	0,46	11 (14%)	17 (18%)	0,54	9 (11%)	14 (15%)	0,66
Not applicable	41 (51%)	50 (54%)	0,90	60 (75%)	67 (73%)	0,91	50 (63%)	55 (60%)	1,00

Appendix 3. Comparison of European vs North American journals. Two-tailed p-values are shown.

Supporting Information for paper 2: Under-reporting of conflicts of interest among trialists: a cross-sectional study

Table S1. Sensitivity analysis (exclusion of investigator conflicts of interest) and overview of disclosed, undisclosed and no conflicts of interest for all Danish non-industry physician authors

	All conflicts of interest disclosed n (%)	**Some conflicts of interest undisclosed n (%)**	**All conflicts of interest undisclosed n (%)**	**No conflicts of interest identified[a] n (%)**	**Total (%)**
COI related to trial sponsor or manufacturer	44 (14%)	28 (9%)	12 (4%)	234 (74%)	318 (100%)
COI related to competing manufacturer	12 (4%)	28 (9%)	37 (12%)	241 (76%)	318 (100%)
COI related to any drug manufacturer	19 (6%)	67 (21%)	55 (17%)	177 (56%)	318 (100%)

a No conflicts of interest identified either in publication or in Danish Health Authority's list

Table S2. Sensitivity analysis (exclusion of authors with multiple publications) and overview of disclosed, undisclosed and no conflicts of interest for all Danish non-industry physician authors

	All conflicts of interest disclosed n (%)	**Some conflicts of interest undisclosed n (%)**	**All conflicts of interest undisclosed n (%)**	**No conflicts of interest identified[a] n (%)**	**Total (%)**
COI related to trial sponsor or manufacturer	25 (13%)	4 (2%)	6 (3%)	159 (82%)	194 (100%)
COI related to competing manufacturer	5 (3%)	12 (6%)	13 (7%)	164 (85%)	194 (100%)
COI related to any drug manufacturer	10 (5%)	26 (13%)	34 (18%)	124 (64%)	194 (100%)

a No conflicts of interest identified either in publication or in Danish Health Authority's list

Appendix for Paper 3: Collaboration Between Academics and Industry in Clinical Trials: cross-sectional study of publications and survey of lead academic authors

Contents

Appendix 1 Data extraction categories and their classification

- Name of first author
- Name of lead academic author
- Institutional address and email of lead academic author
- Categorisation of first, last and corresponding author as academic, funder or CRO
- Name of trial(s)
- Journal name
- Number of authors
- Number of authors involved in the statistical analysis
- Drug(s) and device(s) used in trial
- Publication date
- Trial registration in a WHO approved registry (e.g. clinicaltrials.gov)
- Name(s) of trial industry funder(s)
- Contributions statement
- Whether there is a “role of the funder statement”?
- Whether funder is listed as a co-author?
- Funder’s disclosed role in trial in relation to:
- - study design
- - study conduct
- - study analysis
- - study reporting
- Academic author’s role in trial in relation to:
- - study design
- - recruitment of patients
- - study conduct
- - study analysis
- - study reporting
- Any use of a contract research organisation and their role in relation to:
- - study design
- - study conduct
- - study analysis
- - study reporting
- Lead academic author’s disclosed conflicts of interest
- Lead academic author’s access to data

- Type of data accessible
- Whether a confidentiality agreement was signed

Categorisation and classification

We classified the role of the funder, lead academic and CRO according to the following criteria:

Yes: Clearly mentioned that the person participated and had a role.

Yes other academic: Used when it is clearly mentioned that the category has been done by an academic, but it was done by someone other than the lead academic or it is an unnamed academic e.g. “the manuscript was drafted by the academic authors”.

No: Clearly mentioned that the person had no role, or the role had been listed for another person e.g. the funder did the statistical analysis and there is no mention of the lead academic being involved.

Unclear likely: When the category has been mentioned, but not clearly enough for a sound judgement as yes or when e.g. the funder has claimed no role in the design, but an academic has not been described as designing the trial either. Also used when it is stated that the person in question interpreted data and no one else is reported to have analysed the data. Unclear likely was also used to categorise co-authors’ role in the manuscript preparation when their role was not clearly described.

Unclear unlikely: Used when the category has been mentioned, but not clearly enough for a sound judgement as no e.g. when the lead academic has drafted the manuscript and done revisions, but the funders role in reporting has only been described as funded a CRO.

Not mentioned: Used when the category has not been mentioned at all. For CROs this is also used when the category has been mentioned for the funder or academic, but no CRO is acknowledged in any role or is listed as a co-author.

We extracted the information on who conducted the statistical analysis. If a person was listed as conducted statistical analysis it was a clear yes. However, if the paper stated that one or more persons did the data analysis without mentioning statistical analysis this would also be classified as yes. Yet, if the paper did not specify and reported that all authors did the data analysis then the category would be classified as unclear likely, since it is unlikely that all authors run statistical analyses on all the data.

Data access was classified as all authors had access to the data, as some authors (including the lead academic) had access to the data, authors vouched for the data or no description of data access. We classified the accessed data as data unspecified, raw data, processed data (e.g. analyses), clinical study reports (CSRs), case report forms (CRFs) and other data (e.g. access to the data used in this manuscript or access to data upon request).

Appendix 2 Survey questions

1. Contract

a. Was any contract(s) or agreement(s) signed between you or other academic investigators and the trial funder (e.g. an investigator or publication agreement)?
(If yes these questions appeared):
    i. Did it include a publication agreement (e.g. any trial publication needs approval from the funder prior to submission)?
    ii. Did it include a presentation agreement (e.g. any trial presentation needs approval from the funder before presentation)?
    iii. Did it include a confidentiality agreement (e.g. study results or protocol information may only be shared with third party after approval from the funder)?
    iv. Did it include other types of agreements, please describe (blank text box)?

2. Benefits of collaboration with the trial funder
    a. Please describe any benefits to your collaboration?
    b. Would you collaborate with this funder again?

3. Trial design
    a. Who decided what the comparator treatment should be (e.g. choice of active versus placebo comparator, type and dose of comparator drug or comparator device used)?
    b. Who decided which outcomes to measure in the trial?
    c. Who had the final say with regard to trial design?

4. Data analysis
    a. Who performed the actual statistical analysis of the trial data i.e. using statistical analysis software?
    b. Did you personally have access to the entire dataset?
    (If yes this question appeared)
        i. Did you actively use this access?

5. Manuscript
    a. Who wrote the draft manuscript?
    b. Who made the final decision on the content in the published manuscript (For example, which outcomes to report or how data should be interpreted)?

6. Collaboration with funder
    a. Was there any delay of publications due to funder?
    b. Were there any disagreements between you as academic investigator(s) and the funder concerning design, analysis, reporting of outcomes and/or writing the publication
    (If yes this question appeared)
        i. Please describe how these disagreements were managed by the funder?

7. If you have any additional comments you find relevant for this survey, please describe them here.

Appendix 3 Reasons for declining to participate

APPENDIX 3 TABLE 1 REASONS PROVIDED VIA EMAIL FOR NOT PARTICIPATING IN THE SURVEY	n
Not interested in participating	5
Lack of time	4
Do not wish to collaborate with the Cochrane Collaboration/The Nordic Cochrane Centre	2
Do not have the information requested/unable to help	2
Concerns with objectivity of the survey	1
Contact funder instead	1
Impossible I have joined industry	1

Appendix 4 Characteristics of the trials stratified by response type

APPENDIX 4 TABLE 1
CHARACTERISTICS OF THE TRIALS STRATIFIED BY RESPONSE TYPE

	Responders*		Accessed survey without responding		Declined participation		Non-responders**	
Authorship	**n=80**	**%**	**n=10**	**%**	**n=16**	**%**	**n=91**	**%**
Median number of authors (range)	18	(1-48)	19	(10-36)	16	(5-35)	19	(6-40)
Academic and industry funder authors	68	85%	8	80%	15	94%	80	88%
Solely academic authors	12	15%	2	20%	1	6%	11	12%
Corresponding author academic	77	96%	10	100%	16	100%	86	95%
Corresponding author funder	3	4%	0	0%	0	0%	5	5%
Comparator								
Active treatment	33	41%	5	50%	6	38%	34	37%
Multiple arms (active treatment and placebo)	9	11%	1	10%	1	6%	16	18%
Placebo or no additional treatment	38	48%	4	40%	9	56%	41	45%
Role of funder								
Funder involved in design	66	83%	6	60%	16	100%	79	87%
Funder involved in conduct	58	73%	7	70%	13	81%	66	73%
Funder involved in data analysis	53	66%	8	80%	14	88%	70	77%
Funder involved in reporting	68	85%	8	80%	16	100%	74	81%
CRO involved in reporting	43	54%	7	70%	14	88%	55	60%
Lead academic author's reported conflicts of interest								
Conflict(s) of interest with funder***	58	73%	10	100%	14	88%	78	86%
Conflict(s) of interest with other company	11	14%	0	0%	1	6%	4	4%
No conflict of interest	11	14%	0	0%	1	6%	9	10%

Appendix 4 Table 1: CRO –contract research organisation.
Due to rounding the percentages may not add up to 100%
*7 authors only provided responses to some of the questions, 1 of them later emailed to say he did not have time to complete the survey, and he has been counted under Responders in this table
**3 unreachable authors' trials were not included in the non-responders.
***Those who had conflicts of interest with the funder could also have conflicts of interest with another industry company.

Appendix 5 Survey responses

APPENDIX 5 TABLE 1

SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

n=80*	Academic		Funder**		CRO**		Regulator		Other***	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	26	33%	12	15%	0	0%	6	8%	0	0%
Choice of outcomes	4	5%	23	29%	0	0%	5	6%	1	1%
Final say in design	29	36%	17	21%	0	0%	3	4%	0	0%
Conducted statistical analysis	21	26%	28	35%	7	9%	0	0%	1	1%
Drafted manuscript	53	66%	8	10%	0	0%	0	0%	1	1%
Final say on the published manuscript	52	65%	0	0%	0	0%	0	0%	1	1%

n=80*	Academic, funder and/or CRO collaboration		Academic and CRO collaboration		Funder and CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%	n	%	n	%
Choice of comparator	23	29%	1	1%	0	0%	4	5%	2	3%	6	8%
Choice of outcomes	35	44%	0	0%	0	0%	3	4%	3	4%	6	8%
Final say in design	24	30%	0	0%	0	0%	0	0%	2	3%	5	6%
Conducted statistical analysis	11	14%	0	0%	5	6%	0	0%	0	0%	7	9%
Drafted manuscript	8	10%	3	4%	0	0%	0	0%	0	0%	7	9%
Final say on the published manuscript	19	24%	1	1%	0	0%	0	0%	0	0%	7	9%

APPENDIX 5 TABLE 1: *7 authors only provided responses to some of the questions

**Funder and CRO also includes unacknowledged persons for the conducted statistical analysis and drafting of manuscript. In 7 trials the statistical analysis was conducted by a funder or CRO employee who was not a named author or contributor (3 of the 7 trials had unacknowledged funder employees, 3 trials had unacknowledged CRO employees and 1 trial had both an unacknowledged funder and unacknowledged CRO employee conduct the statistical analysis). In 5 trials the manuscript was drafted by a funder or CRO employee who was not a named author or contributor (4 of the 5 trials had an unacknowledged funder employee and 1 trial had an academic and an unacknowledged CRO draft the manuscript). Two trials had both an unacknowledged funder or CRO employee conduct the statistical analysis and an unacknowledged funder or CRO employee draft the manuscript. Thus, lead academic authors of 10 trials reported contributions to statistical analysis and/or drafting of the manuscript from unacknowledged persons.

***Other refers to one trial where it was unclear who had chosen outcomes and conducted statistical analysis and one where the academic did not know who drafted the manuscript and one where the academic found that the journal had the final say on the published manuscript.

Due to rounding the percentages may not add up to 100%.

Appendix 6 Selected comments to the survey questions

Different author comments have been separated by ";". Words have been replaced by "*pseudonyms"* to anonymise the author. Typos have been corrected.

Selected comments from Benefits of collaborating with the trial industry funder
Generating new research: "They were willing to do a global trial of an orphan disease that no other source would have EVER funded."; "Chance to move the field forward and to develop medicine based on prior lab discoveries"
Infrastructure and management: "Efficient operational management of multi-center trial"; "Much faster at helping address quality concerns and organizing than government"
*Funding: "*funding (much better than with governmental funding)"; "Fully funded trial with additional funding for translational research to be done by co-operative group"; "Study would not have been possible without funding which came as a donation, no strings attached."; "Funding (in this case, there would have been no funding to conduct the trial otherwise)"
*Publication: "*The *Journal X* paper! And more to come."; "Opportunity to author papers of important study results in high impact journals"
*Personal benefits: "*Being PI of a positive trial is always a benefit in CV and recognition"; "I was able to work closely with the study team to write and revise the protocol. We had a lot of discussions and I generally found that they listened to the advice offered by the trial steering committee. I was able to review the data prior to drafting the manuscript and we had a few calls to discuss the implications of the data and how to focus the paper. I found their statistical team generally helpful - at times they pushed back because I asked for a lot of additional analyses but they were generally accommodating. After the first draft was written, we definitely had some back and forth on messaging but ultimately, I was very comfortable with the final product and found that they listened to my point of view. Aside from the process itself, there are 'academic' benefits in the sense that this type of study is highly regarded by our institution and brings some notoriety to our institution. That being said, I would not object to all industry-sponsored studies being listed as 'the *Trial X* Investigators' or something similar - ultimately, despite our input, these are studies done by the company."; "consulting fee, publication of research"
*Miscellaneous: "*very fruitful and pragmatic collaboration with funder, allowing to transparently enrol patients in our country, and very transparent discussions of results, that is what I call "benefits""; "Not really any other than data analysis help"; "Industry funded the trial at substantial cost. They organized the sites. They created most of the study materials. Contractors did most of the work, contributed to design, analysis and reporting. Industry could do it themselves I assume. I do think the partnership brings value to both parties and patients."; "Input into protocol, input to data interpretation, development of scientific expertise in clinical trials and in the subject are of research, working with other key international leaders in the field, scientific excellence of the study sponsor, well-resourced study."; "The major benefits of industry collaboration for this investigator designed, led and run study were the provision of funding, labelled IMP and placebo, and logistical support."; "Transparency, faster results and execution, excellent funding."; "You can answer questions that academic or government funders cannot do. This mainly due to the scale of research funding needed and the risks taken. / There is better oversight of industry funded research. Much stricter auditing, monitoring and reporting of events etc."; "funding provided. Help in data analysis and publication provided"
*No benefits: "*No real benefits...."; "Nothing"

Selected comments from trial agreement between academics and funder
Miscellaneous: “Very thorough, well prepared With mutual respect”; “Non-disclosure Agreement / Clinical Trial Agreement w/ Payment schedule”
Selected comments from publication agreement
*Review and comment: “*the trial publication can be reviewed and comments provided. / but they do not get "approval" rights.”; “2-week period to allow for input, which the executive committee (independent of sponsor) could choose to ignore.”; “Not “approval” but rather an opportunity for them to make comments (which we could either take or reject)”
*Miscellaneous: “*Yes and aimed at journals With high impact factor”; “the contract explicitly stated that sponsor approval was NOT required for publication.”
Selected comments for presentation agreement
*Review and comment: “*Stipulated right of review by sponsor”; “they would be sent for review by sponsor but we have final say”; “I underline that there was an agreement, but in no way some kind of censorship.”
Selected comments for confidentiality agreement
Confidential until publication: “Until approval or public disclosure of the information.”; “No for results which are already in the public domain, obviously, but yes for all other unpublished data”; “Prior to presentation & simultaneous publication, the data was 100% embargoed for all parties”
Miscellaneous: “At some point I did sign confidentiality agreement. At beginning of trial and then before reviewing final data.“; “after publication.....”; “non-public information could not be shared with a 3rd party - for obvious reasons”; “the agreement stated that sponsor could request up to 30 days confidentiality if necessary for patent protection.”
Selected comments for other types of agreement
*Miscellaneous: “*The contract required the trial database to be transferred to the academic lead author's institution for statistical analysis and publication”; “adhere to good practices”; “Intellectual property clauses. Scope of work. Indemnification. Termination conditions. Many additional aspects...”
Selected comments for future collaboration with the funder
*Miscellaneous: “*I have done so for over 30 years”; “Such collaborations are essential (provided independent data analysis, publication and presentation is guaranteed) as trials of this size are rarely supported by charities or governmental institutions.”
Selected comments for choice of comparator
*Academics: “*The entire trial design was not influenced by the funder or any other party”
*Funder: “*As mentioned, this is a substudy of *Drug X* in the context of a RCT. The funder designed the study.
*Collaboration: “*The company has to obviously agree with the study design. They fund the trial.”; “There was a discussion between the pharma key people and the clinical investigator team about the best study design.”; “Funder, FDA, academic steering committee”; “Me and academic steering committee in discussions with industry partner. Industry partner has final say”; “Arduous, iterative process with input from FDA, academic steering committee, funder, and site investigators.”; “Research and development team of the sponsor. Input was obtained from study investigators.”
*Regulatory body: “*In accordance with FDA and EMA”;

“Having a placebo control in a double blinded trial design was recommended by the FDA”
*Miscellaneous: “*The sponsor did not want a placebo arm in the trial. We insisted upon it for safety evaluation and they ultimately agreed to a placebo arm with deferred treatment.”; “The Steering committee specifically designed the trial - and we had an active comparator and the trial was neutral compared to the comparator. If we would have chosen *Drug X* (one might assume with industry or even guidelines that would be reasonable - maybe different finding) - but the SC chose the comparator”
Selected comments for choice of outcomes
Academic: “A steering committee of academic advisors, including me.“; “Again, the funder had no influence on our primary and secondary outcomes.”
Regulatory body: “FDA”
Collaboration: “Collaboration between funder, academics and of course the funder incorporated suggestions from regulatory bodies”; “Funder did primarily but they gathered many opinions including investigators and FDA/EMA”; “This was collaboration between academic investigators, regulators (Phase IV commitment) and industry sponsor”
Miscellaneous: “Entire trial was designed by the steering committee - this is actually less involvement than government sources often have in designing trials where they are hyper-focussed on cost”
Selected comments for final say in study design
*Academics: “*The principal investigator, which was the head of the research team.”
*Funder: “*We advised the sponsor study team (extensively) and I would generally say that they listened, but they did not 'require' sign-off from the steering committee before finalizing the protocol so in that sense, they had final say.”; “Again there was discussion but final saying by industry”
*Regulatory body: “*FDA of course- it was a regulatory study so they had to approve any study design”
*Collaboration: “*Again, making use of the funder's experience together”; “Funder and FDA”; “It was a combined decision of investigators, sponsor and finally FDA.”
Miscellaneous: “On most aspects, academic steering committee members and funder were in agreement, so question of final say did not arise. On several aspects, FDA had final say, placing requirements that would not have been selected by the academic steering committee members or the funder. On other aspects, the community had say by having specialty societies issue guidances. These were sometimes poorly selected directives, but the funder felt it important to comply with international specialty society recommendations.”
Selected comments for statistical analysis
*Academics: “*A statistician and I performed the analysis. No influence or contact with the funder in the whole process.”
*Funder: “*Biostatistical team of the funder”; “Lots of analyses by a number of funder statisticians”
*CRO: “*Independent statistical bureau”; “The CRO agency was hired for this purpose.”
*Collaboration: “*Jointly between Funder and Academic Investigators”; “Statistical consultant, along with study team and appropriate funder personnel”
Miscellaneous: “Independent biostatistician contracted by study sponsor and in-house industry biostatisticians.”; “We analysed with independent academic and with the funder statisticians. Sometimes we have to rely on only the funder statisticians, which is less satisfactory. However SAPs and protocols are submitted to regulatory and editors before analysis and publication”; “Most of the analysis was done by the sponsor statistician who is listed as an author but the aggregated data were available to us (steering committee) and individual patient-level data was

available upon request. We were able to do additional analyses using these data - some of which ultimately ended up in the paper."; "Stats team employed by company. Monitored by independent data monitoring committee, not named, not part of sponsor or investigators."
Selected comments for access to data
Miscellaneous: "It varies from study to study"; "Although for person-level data, access was provided in response to questions. I had an aggregated data set, not person-level data."; "Not the ENTIRE dataset, but much of it and we were encouraged to ask for specific analyses."; "I had access to all the data but did not have access to the database. E.g., all analyses conducted in sponsor's dataset. Any analysis that we wanted was done."; "...in theory yes, but I didn't review all data"; "If I ask."
Selected comments for using data access
Miscellaneous: "The dataset was open for the research team and locked or the rest of the members"; "I anticipate some 30 high-quality papers will be published using this data set. 12 already published, 4 submitted and 10 currently in preparation"; "Not yet, but it is available to me for secondary analyses"; "Huge database housed at our institution. Could not possibly review every page, but all of the key outcomes reviewed carefully"; "I personally requested the independent statistician perform many analyses of the entire dataset, using shell tables that I designed. Every analysis I requested was performed."
Selected comments for drafting the manuscript
*Intro and discussion by academics methods and results by funder: "*I drafted the introduction and discussion sections, while the company scientific writers drafted the methodology and results sections."; "It was really a collaboration. The methods and initial draft of the results was written by a medical writer who works for the sponsor (and is acknowledged) but the intro and discussion were written by me and the last author on the paper. We then provided comment and revisions to the sections written by the sponsor and with back and forth iterations, we came to a final draft that was circulated to the other authors."
*Miscellaneous: "*I did and it was reviewed by the funder's scientific collaborators. Disagreements regarding data interpretation were hotly discussed but the academic point of view prevailed"; "In collaboration with the co-authors of the funder"; "This was an unusually coherent scientific partnership"; "Myself and an academic colleague"; "I wrote the first draft together with one funding representative and one other academic collaborator. The other authors commented on that and subsequent drafts."
Selected comments for final say on published manuscript
*Journal: "*Often also unfortunately - the journal has a larger and larger role"; "The journal!"; "In part, these decisions were also impacted upon by *Journal X* whose editorial policies regarding manuscript length and number of figures and tables forced us to consolidate. Ultimately, it was my responsibility to do this along with my academic colleagues and the statistician"
*Academics: "*Absolute no influence of the funder. We kept them out during the process."
Miscellaneous: "Company had review privilege but investigators had final say"; "There is input from the sponsors but the final decisions is with all authors, some who may work for funders"; "Primarily the Investigators/authors. Some guidance from funder."; "The funder and the authors did together...."; "Investigator in agreement with sponsor"

Selected comments for delay in publication
Miscellaneous: "There was a delay in publication, which was related to internal data check."; "Actually, less delay"; "It varies from trial to trial"; "Despite the stipulations in the contract, the manuscript was not sent to the funder prior to submission. This was considered unnecessary by both sides (despite the negative result, i.e. the medication is completely ineffective)"
Selected comments for disagreements with funder
Miscellaneous: "The sponsors were originally reluctant to run the study, but we won over by the academic advisors"; "The interpretation criteria stated in the protocol were partially contradicted by the data forcing to present data according to protocol and new criteria. This was actually requested by the publisher."; "When an external trial resulted positive, we needed to decide whether to place enrolment in the current trial on hold until a slightly earlier than planned interim analysis could be performed, or to continue enrolling. The funder would have preferred to continue enrolling. The academic steering committee voted 4 to 2 place the study on hold. The funder respected this decision and enrolment was placed on hold."
*Minor disagreements: "*Spirited discussion but agreement usually prevails"; "Small differences between PI/statistician and funder. The final version was exactly the version as proposed by PI/Statistician"; "The 'disagreements' were minor. Mostly on the points to emphasize in the discussion. Ultimately they accepted very close to our original version."; "Minimal. There were some analyses some investigators wanted to do but truly were beyond the scope of the primary goals of the trial."
Selected comments for how disagreements with funder were handled by the funder
Miscellaneous: "Want to postpone and change the wording"; "Back and forth emails and teleconferences. As noted, ultimately, they agreed on very close to our original version."; "We initially communicated about the disagreements via email, but with continued analysis and discussion, specific teleconferences were set up to improve communication efforts."; "The journal and I ended up determining the outcome"; "Other than the funder author, who gave appropriate scientific input, they were handled at arm's length."
Selected comments from additional comments
Miscellaneous: "For this research, academic independence was of importance for the academic staff. That is what was agreed with the funder, whether they liked it or not. We could provide the funder an academic setting, with highly skilled personnel to conduct the study. And that was what they wanted too. So for both groups it was a win-win."; "The study was somewhat unusual for pharma phase III studies, with greater input from the academic investigators, including study design, manuscript preparation, analyses etc."; "It is incredibly important that you distinguish between academically-led and performed trials, such as those conducted by my unit, and industry-led, conducted and analysed trials that may well have a degree of academic oversight but with most of not all of the rights remaining with the company"; "We had to manage possible conflicts of interest at our sites carefully."; "Discussions with the funder had a high intellectual and scientific level"; "The study and its publication brought prestige to *Society X*. Investigators are very keen to join hands for more studies now."; "Would have preferred to have the whole dataset. Got quite a lot but not everything"; "I found participating in this project to be a quite positive experience. I did not feel any pressure from the funder, believe I functioned in a totally independent manner, was able to obtain constructive feedback from my two primary academic colleagues as well as the other academic authors, and received no payment or grant for this project other than travel expenses for one

planning meeting.";
"In principle this type of partnership is vital to move the field forward. Rules for collaboration need to be set in advance, ideally on a contractual basis taking academic freedom as well as the needs of the industry into account, which can be tough, especially in the light of patent rights.";
"Further report not approvable or not approved by the sponsor"

Appendix 7 Subgroup analyses

Funder Problems stratified by Lead Academic's Conflicts of Interest

The nine academic authors with disclosed conflicts of interest (COIs) with an industry company other than the funder were not included in this subgroup analysis.

No COIs

Eleven lead academic authors disclosed no COIs and responded to the survey. One reported there was a delay in publication due to the funder doing an internal data check. Eight reported no delays in publication and two did not provide a response.

Similarly only one author reported to have had minor disagreements about wording with the industry funder. Eight reported no disagreements but one added that the funder was more interested in the secondary outcome. Two did not provide a response.

COIs with the funder

Sixty lead academic authors disclosed COIs with the industry funder. Two reported there was a delay in publication due to the funder with one reporting that this was due to internal approval and one author responding that delay in publication varies from trial to trial. Fifty-four reported no delays and 4 did not provide a response.

Seven reported they had disagreements with the industry funder. Most of the authors added that the disagreements were minor. One reported that the funder was reluctant to run the study and one reported disagreements between the PI/statistician and the funder. Forty-nine reported no disagreements, but one added they had spirited discussions, but agreement usually prevailed. Four did not provide a response.

APPENDIX 7 TABLE 1A
CHARACTERISTICS OF THE 200 INDUSTRY-FUNDED TRIALS BY INTERVENTION TYPE

	Drug		Device		Vaccine	
Journal	**n**	**%**	**n**	**%**	**n**	**%**
New England Journal of Medicine	92	56%	9	35%	5	56%
The Lancet	49	30%	10	38%	3	33%
JAMA	17	10%	7	27%	1	11%
Annals of Internal Medicine	4	2%	0	0%	0	0%
JAMA Internal Medicine	2	1%	0	0%	0	0%
BMJ	1	1%	0	0%	0	0%
Comparator						
Active treatment	55	33%	20	77%	4	44%
Multiple arms (active treatment and placebo)	27	16%	0	0%	0	0%
Placebo or no additional treatment	83	50%	6	23%	5	56%
Authorship						
Median (range)	18	(1-48)	17	(6-35)	27	(17-31)
Academic and industry funder authors	151	92%	13	50%	9	100%
Solely academic authors	14	8%	13	50%	0	0%
1st author academic	162	98%	26	100%	8	89%
1st author funder	3	2%	0	0%	1	11%
Last author academic	127	77%	23	88%	4	44%
Last author funder	35	21%	2	8%	5	56%
Last author CRO	1	1%	1	4%	0	0%
Last author other*	2	1%	0	0%	0	0%
Corresponding author academic	160	97%	26	100%	6	67%
Corresponding author funder	5	3%	0	0%	3	33%
Lead academic author's reported conflicts of interest						
Conflict(s) of interest with funder**	139	84%	19	73%	7	78%
Conflict(s) of interest with other company	12	7%	2	8%	0	0%
No conflict of interest	14	8%	5	19%	2	22%

APPENDIX 7 TABLE 1A: CRO –contract research organisation.
Due to rounding the percentages may not add up to 100%
*Other refers to an author employed by an industry company other than the industry funder and one author where it was unclear if the affiliation was a CRO or private clinic.
**Those who had conflicts of interest with the funder could also have conflicts of interest with another industry company.

APPENDIX 7 TABLE 1B
CHARACTERISTICS OF INDEPENDENT ACADEMIC TRIALS AND TRIALS WITH FUNDER INVOLVEMENT

	Independent* n=8		Funder Involved n=192	
Journal	**n**	**%**	**n**	**%**
New England Journal of Medicine	1	13%	105	55%
The Lancet	2	25%	60	31%
JAMA	3	38%	22	11%
Annals of Internal Medicine	1	13%	3	2%
JAMA Internal Medicine	1	13%	1	1%
BMJ	0	0%	1	1%
Comparator				
Active treatment	4	50%	75	39%
Multiple arms (active treatment and placebo)	0	0%	27	14%
Placebo or no additional treatment	4	50%	90	47%
Authorship				
Median (range)	13	(6-21)	19	(1-48)
Academic and industry funder authors	0	0%	173	90%
Solely academic authors	8	100%	19	10%
1st author academic	8	100%	188	98%
1st author funder	0	0%	4	2%
Last author academic	8	100%	146	76%
Last author funder	0	0%	42	22%
Last author CRO	0	0%	2	1%
Last author other**	0	0%	2	1%
Corresponding author academic	8	100%	184	96%
Corresponding author funder	0	0%	8	4%
Lead academic author's reported conflicts of interest				
Conflict(s) of interest with funder***	4	50%	161	84%
Conflict(s) of interest with other company	0	0%	14	7%
No conflict of interest	4	50%	17	9%

APPENDIX 7 TABLE 1B: CRO –contract research organisation.
Due to rounding the percentages may not add up to 100%
*Independent trials defined as trials with no funder or CRO co-authors and no funder or CRO involvement in the design, conduct, analysis and reporting of the trial.
**Other refers to an author employed by an industry company other than the industry funder and one author where it was unclear if the affiliation was a CRO or private clinic.
***Those who had conflicts of interest with the funder could also have conflicts of interest with another industry company.

APPENDIX 7 TABLE 2A

SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

Drug n=61	Academic		Funder*		CRO*		Regulator		Other**	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	20	33%	11	18%	0	0%	5	8%	0	0%
Choice of outcomes	17	28%	3	5%	0	0%	3	5%	1	2%
Final say in design	23	38%	14	23%	0	0%	1	2%	0	0%
Conducted statistical analysis	18	30%	25	41%	3	5%	0	0%	1	2%
Drafted manuscript	41	67%	7	11%	0	0%	0	0%	1	2%
Final say on the published manuscript	39	64%	0	0%	0	0%	0	0%	1	2%

Drug n=61	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	18	30%	4	7%	0	0%	3	5%
Choice of outcomes	29	48%	3	5%	2	3%	3	5%
Final say in design	18	30%	0	0%	2	3%	3	5%
Conducted statistical analysis	10	16%	0	0%	0	0%	4	7%
Drafted manuscript	8	13%	0	0%	0	0%	4	7%
Final say on the published manuscript	17	28%	0	0%	0	0%	4	7%

Device n=13	Academic		Funder*		CRO*		Regulator		Other**	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	4	31%	0	0%	0	0%	1	8%	0	0%
Choice of outcomes	5	38%	0	0%	0	0%	1	8%	0	0%
Final say in design	5	38%	1	8%	0	0%	2	15%	0	0%
Conducted statistical analysis	3	23%	2	15%	3	23%	0	0%	0	0%
Drafted manuscript	10	77%	0	0%	0	0%	0	0%	0	0%
Final say on the published manuscript	10	77%	0	0%	0	0%	0	0%	0	0%

Device n=13	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	5	38%	0	0%	1	8%	2	15%
Choice of outcomes	5	38%	0	0%	0	0%	2	15%
Final say in design	3	23%	0	0%	0	0%	2	15%
Conducted statistical analysis	3	23%	0	0%	0	0%	2	15%
Drafted manuscript	1	8%	0	0%	0	0%	2	15%
Final say on the published manuscript	1	8%	0	0%	0	0%	2	15%

Vaccine n=6	Academic		Funder*		CRO*		Regulator		Other**	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	2	33%	1	17%	0	0%	0	0%	0	0%
Choice of outcomes	1	17%	1	17%	0	0%	1	17%	0	0%
Final say in design	1	17%	2	33%	0	0%	0	0%	0	0%

Conducted statistical analysis	0	0%	1	17%	1	17%	0	0%	0	0%
Drafted manuscript	2	33%	1	17%	1	17%	0	0%	0	0%
Final say on the published manuscript	3	50%	0	0%	0	0%	0	0%	0	0%

Vaccine n=6	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	1	17%	0	0%	1	17%	1	17%
Choice of outcomes	1	17%	0	0%	1	17%	1	17%
Final say in design	3	50%	0	0%	0	0%	0	0%
Conducted statistical analysis	3	50%	0	0%	0	0%	1	17%
Drafted manuscript	1	17%	0	0%	0	0%	1	17%
Final say on the published manuscript	2	33%	0	0%	0	0%	1	17%

APPENDIX 7 TABLE 2A: *Funder and CRO also includes unacknowledged persons for the conducted statistical analysis and drafting of manuscript

**Other refers to one trial where it was unclear who had chosen outcomes and conducted statistical analysis and one where the academic did not know who drafted the manuscript and one where the academic found that the journal had the final say on the published manuscript.

Due to rounding the percentages may not add up to 100%.

APPENDIX 7 TABLE 2B

SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

Independent n=4	Academic		Funder*		CRO*		Regulator		Other**	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	4	100%	0	0%	0	0%	0	0%	0	0%
Choice of outcomes	4	100%	0	0%	0	0%	0	0%	0	0%
Final say in design	4	100%	0	0%	0	0%	0	0%	0	0%
Conducted statistical analysis	4	100%	0	0%	0	0%	0	0%	0	0%
Drafted manuscript	4	100%	0	0%	0	0%	0	0%	0	0%
Final say on the published manuscript	4	100%	0	0%	0	0%	0	0%	0	0%

Independent n=4	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	0	0%	0	0%	0	0%	0	0%
Choice of outcomes	0	0%	0	0%	0	0%	0	0%
Final say in design	0	0%	0	0%	0	0%	0	0%
Conducted statistical analysis	0	0%	0	0%	0	0%	0	0%
Drafted manuscript	0	0%	0	0%	0	0%	0	0%
Final say on the published manuscript	0	0%	0	0%	0	0%	0	0%

Funder involved n=76	Academic		Funder*		CRO*		Regulator		Other**	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	22	29%	12	16%	0	0%	6	8%	0	0%
Choice of outcomes	19	25%	4	5%	0	0%	5	7%	1	1%
Final say in design	25	33%	17	22%	0	0%	3	4%	0	0%
Conducted statistical analysis	17	22%	28	37%	7	9%	0	0%	1	1%
Drafted manuscript	49	64%	8	11%	0	0%	0	0%	1	1%
Final say on the published manuscript	48	63%	0	0%	0	0%	0	0%	1	1%

Funder involved n=76	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	24	32%	4	5%	2	3%	6	8%
Choice of outcomes	35	46%	3	4%	3	4%	6	8%
Final say in design	24	32%	0	0%	2	3%	5	7%
Conducted statistical analysis	16	21%	0	0%	0	0%	7	9%
Drafted manuscript	11	14%	0	0%	0	0%	7	9%
Final say on the published manuscript	20	26%	0	0%	0	0%	7	9%

APPENDIX 7 TABLE 2B: *Funder and CRO also includes unacknowledged persons for the conducted statistical analysis and drafting of manuscript

**Other refers to one trial where it was unclear who had chosen outcomes and conducted statistical analysis and one where the academic did not know who drafted the manuscript and one where the academic found that the journal had the final say on the published manuscript.
Due to rounding the percentages may not add up to 100%.

APPENDIX 7 TABLE 2C

SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

Collaborating with funder/ would in the future n=67	Academic		Funder**		CRO**		Regulator		Other***	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	23	34%	10	15%	0	0%	6	9%	0	0%
Choice of outcomes	19	28%	3	4%	0	0%	5	7%	1	1%
Final say in design	25	37%	15	22%	0	0%	3	4%	0	0%
Conducted statistical analysis	19	28%	26	39%	4	6%	0	0%	1	1%
Drafted manuscript	48	72%	6	9%	0	0%	0	0%	1	1%
Final say on the published manuscript	47	70%	0	0%	0	0%	0	0%	1	1%

Collaborating with funder/ would in the future n=67	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	23	34%	4	6%	1	1%	0	0%
Choice of outcomes	33	49%	3	4%	3	4%	0	0%
Final say in design	22	33%	0	0%	2	3%	0	0%
Conducted statistical analysis	16	24%	0	0%	0	0%	1	1%
Drafted manuscript	11	16%	0	0%	0	0%	1	1%
Final say on the published manuscript	18	27%	0	0%	0	0%	1	1%

Would not collaborate with funder again or does not know n=8*	Academic		Funder**		CRO**		Regulator		Other***	
	n	%	n	%	n	%	n	%	n	%
Choice of comparator	3	38%	2	25%	0	0%	0	0%	0	0%
Choice of outcomes	4	50%	1	13%	0	0%	0	0%	0	0%
Final say in design	4	50%	2	25%	0	0%	0	0%	0	0%
Conducted statistical analysis	2	25%	2	25%	3	38%	0	0%	0	0%
Drafted manuscript	5	63%	2	25%	0	0%	0	0%	0	0%
Final say on the published manuscript	5	63%	0	0%	0	0%	0	0%	0	0%

Would not collaborate with funder again or does not know n=8*	Academic, funder and/or CRO collaboration		Academic and regulator collaboration		Funder and regulator collaboration		Do not know/Not available	
	n	%	n	%	n	%	n	%
Choice of comparator	1	13%	0	0%	1	13%	1	13%
Choice of outcomes	2	25%	0	0%	0	0%	1	13%
Final say in design	1	13%	0	0%	0	0%	1	13%
Conducted statistical analysis	0	0%	0	0%	0	0%	1	13%
Drafted manuscript	0	0%	0	0%	0	0%	1	13%
Final say on the published manuscript	2	25%	0	0%	0	0%	1	13%

APPENDIX 7 TABLE 2C: *1 of the 8 authors would not collaborate with funder again, the remaining 7 did not know.
**Funder and CRO also includes unacknowledged persons for the conducted statistical analysis and drafting of manuscript

***Other refers to one trial where it was unclear who had chosen outcomes and conducted statistical analysis and one where the academic did not know who drafted the manuscript and one where the academic found that the journal had the final say on the published manuscript.
Due to rounding the percentages may not add up to 100%.

APPENDIX 7 TABLE 3A

SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

	Drug n=61					
	Yes		No		Do not know or Not Available	
	n	%	n	%	n	%
Signed trial agreement with industry funder	50	82%	11	18%	0	0%
Signed trial agreement included a publication agreement*	36	72%	10	20%	3	6%
Signed trial agreement included presentation agreement*	26	52%	18	36%	5	10%
Signed trial agreement included confidentiality agreement*	28	56%	17	34%	4	8%
Had access to the entire trial data set	47	77%	9	15%	5	8%
Access used by those with access to entire data*	42	89%	4	9%	1	2%
Delay in publication due to funder	2	3%	55	90%	4	7%
Disagreements with funder	4	7%	53	87%	4	7%
	Device n=13					
	Yes		No		Do not know or Not Available	
	n	%	n	%	n	%
Signed trial agreement with industry funder	8	62%	5	38%	0	0%
Signed trial agreement included a publication agreement*	5	63%	2	25%	1	13%
Signed trial agreement included presentation agreement*	3	38%	2	25%	3	38%
Signed trial agreement included confidentiality agreement*	7	88%	1	13%	0	0%
Had access to the entire trial data set	11	85%	0	0%	2	15%
Access used by those with access to entire data*	9	82%	2	18%	0	0%
Delay in publication due to funder	1	8%	10	77%	2	15%
Disagreements with funder	4	31%	6	46%	2	15%
	Vaccine n=6					
	Yes		No		Do not know or Not Available	
	n	%	n	%	n	%
Signed trial agreement with industry funder	5	83%	0	0%	1	17%

Signed trial agreement included a publication agreement*	5	100%	0	0%	0	0%
Signed trial agreement included presentation agreement*	4	80%	1	20%	0	0%
Signed trial agreement included confidentiality agreement*	4	80%	1	20%	0	0%
Had access to the entire trial data set	5	83%	0	0%	1	17%
Access used by those with access to entire data*	5	100%	0	0%	0	0%
Delay in publication due to funder	0	0%	5	83%	1	17%
Disagreements with funder	0	0%	5	83%	1	17%

APPENDIX 7 TABLE 3A: Due to rounding the percentages may not add up to 100%
*n=50, n=8 and n=5 for drug, device and vaccine trials, respectively. Question was only available to those who answered yes to signing an agreement with industry funder
**n=47, n=11 and n=5 for drug, device and vaccine trials, respectively. Question was only available to those who answered yes to data access.

APPENDIX 7 TABLE 3B
SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

	Independent n=4						Funder involved n=76					
	Yes		No		Do not know or Not Available		Yes		No		Do not know or Not Available	
	n	%	n	%	n	%	n	%	n	%	n	%
Signed trial agreement with industry funder	2	50%	2	50%	0	0%	61	80%	14	18%	1	1%
Signed trial agreement included a publication agreement*	1	50%	1	50%	0	0%	45	74%	11	18%	5	8%
Signed trial agreement included presentation agreement*	0	0%	2	100%	0	0%	33	54%	19	31%	9	15%
Signed trial agreement included confidentiality agreement*	0	0%	2	100%	0	0%	39	64%	17	28%	5	8%
Had access to the entire trial data set	3	75%	1	25%	0	0%	60	79%	8	11%	8	11%
Access used by those with access to entire data**	3	100%	0	0%	0	0%	53	88%	6	10%	1	2%
Delay in publication due to funder	1	25%	3	75%	0	0%	2	3%	67	88%	7	9%
Disagreements with funder	0	0%	4	100%	0	0%	9	12%	60	79%	7	9%

APPENDIX 7 TABLE 3B: Due to rounding the percentages may not add up to 100%
*n=2 and n=61 for independent and funder involved trials, respectively. Question was only available to those who answered yes to signing an agreement with industry funder
**n=3 and n=60 for independent and funder involved trials, respectively. Question was only available to those who answered yes to data access.

APPENDIX 7 TABLE 3C
SURVEY REPORTED EXPERIENCE AMONG THE LEAD ACADEMIC AUTHORS

	Collaborating with funder/ would in the future n=67						Would not collaborate with funder again or does not know n=8*					
	Yes		No		Do not know or Not Available		Yes		No		Do not know or Not Available	
	n	%	n	%	n	%	n	%	n	%	n	%
Signed trial agreement with industry funder	56	84%	11	16%	0	0%	4	50%	4	50%	0	0%
Signed trial agreement included a publication agreement**	40	71%	12	21%	3	5%	3	75%	0	0%	1	25%
Signed trial agreement included presentation agreement**	29	52%	20	36%	6	11%	3	75%	0	0%	1	25%
Signed trial agreement included confidentiality agreement**	34	61%	18	32%	3	5%	2	50%	1	25%	1	25%
Had access to the entire trial data set	57	85%	8	12%	2	3%	6	75%	1	13%	1	13%
Access used by those with access to entire data***	49	86%	7	12%	1	2%	6	100%	0	0%	0	0%
Delay in publication due to funder	2	3%	64	96%	1	1%	1	13%	6	75%	1	13%
Disagreements with funder	8	12%	58	87%	1	1%	1	13%	6	75%	1	13%

APPENDIX 7 TABLE 3C: *1 of the 8 authors would not collaborate with funder again the remaining 7 did not know.
**n=56 and n=4 for collaborating with funder and would not collaborate with funder, respectively. Question was only available to those who answered yes to signing an agreement with industry funder
***n=56 and n=4 for collaborating with funder and would not collaborate with funder, respectively. Question was only available to those who answered yes to data access
Due to rounding the percentages may not add up to 100%.

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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DECLARATION OF CO-AUTHORSHIP

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Principal supervisor	Peter C. Gøtzsche

Title of PhD thesis:
Conflicts of interest in scientific articles

This declaration concerns the following article:
Citations of Scientific Results and Conflicts of Interest: The Case of Mammography Screening

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	c
2. Planning of the experiments and methodology design, including selection of methods and method development	c
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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8/2-18	Peter C Gøtzsche	Professor	

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Date: 6/2/18 PhD student:	Date: 8/2-18 Principal supervisor:

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Conflicts of interest in scientific articles

This declaration concerns the following article:
Collaboration between academics and industry in clinical trials: cross-sectional study of publications and survey of academic authors

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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Title of PhD thesis:
Conflicts of interest in scientific articles

This declaration concerns the following article:
Under-reporting of conflicts of interest among trialists: a cross sectional study

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	B
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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