UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCE


# PhD Thesis

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# When is a randomised trial justified?

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| Title: | When is a randomised trial justified – An analysis documents submitted to ethics committees |
| Dansk title: | Hvornår er et lodtrækningsforsøg retfærdiggjort – En analyse af forsøgsprotokoller indsendt til etiske komiteer. |
| Topic description: | This thesis investigates whether trials approved by ethics committees in Denmark are ethically justified by 1) examining the trial rationale and choice of comparator and assess whether these are supported by citing previous trials 2) assessing the quality of information of benefits and harms provided to participants 3) examining to what degree investigators' right to publish is restricted 4) compare the reporting of harms in different sources of clinical trial data |
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“Here is Edward Bear, coming downstairs now, bump, bump, bump, on the back of his head, behind Christopher Robin. It is, as far as he knows, the only way of coming downstairs, but sometimes he feels that there really is another way, if only he could stop bumping for a moment and think of it. And then he feels that perhaps there isn’t”

Alan Alexander Milne, Winnie-the-Pooh (1926)

# Contents

# Preface

The PhD project described in this thesis, and three of the supporting papers, were conducted at the Nordic Cochrane Centre from September 2017 to September 2020. The fourth paper is based on a projected conducted in cooperation with the Center for Epidemiology and Statistics Sorbonne Paris Cité at Hôpital Hotel-Dieu in Paris, where I stayed in March and April 2019.

This thesis is a synopsis based on four papers:

1) **Paludan-Müller AS**, Ogden MC, Marquardsen M, Vive J, Jørgensen KJ, Gøtzsche PC. Do protocols for new randomised trials take previous similar trials into account? Cohort study of contemporary trial protocols. *BMJ Open* 2019;9:e026661. doi: 10.1136/bmjopen-2018-026661

2) **Paludan-Müller AS**, Ogden MC, Marquardsen M, Jørgensen KJ, Gøtzsche PC. Are potential clinical trial participants adequately informed about benefits and harms? A comparison of informed consent materials and trial protocols. *Submitted* 2020.

3) **Paludan-Müller AS,** Ogden MC, Marquardsen M, Jørgensen KJ, Gøtzsche PC. Are investigators' access to trial data and rights to publish restricted and are trial participants informed about this? A comparison of trial protocols and informed consent materials. *Submitted* 2020.

4) **Paludan-Müller AS,** Crequit P, Boutron I. Reporting of harms in oncological clinical study reports compared to trial registries and publications. *Submitted* 2020.

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I also want to thank all my colleagues from the Nordic Cochrane Centre, who have been a part of my life for many years: Klaus Munkholm, I have truly appreciated our talks – both about science, football, and building PCs. I sincerely hope we will be able to continue them in the future; Jannie and Frihild, you've both helped me so many times and with so many different things that I have lost count but there is no doubt this thesis would not have been finished without your help; Dina and Anders, you are always friendly and we've had many great talks – although I have still not forgiven Anders for beating me in minigolf; Lastly, thank you to Kim Boesen, more than a colleague you have become a friend. I cannot count the laughs we have had in our office/room and your presence has truly made the last two years of my life so much better. I will miss you, but I am sure we'll see each other almost weekly in Berlin.

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## Conflicts of interest

None

# English summary

Research involving humans is necessary for the advancement of medical science. Principles to ensure that such research is ethical was set out by the World Medical Association in the Declaration of Helsinki. Amongst other things, it specifies that new trials must be based on a thorough knowledge of previous similar studies, participants must be informed about the potential benefits and harms of participating, and results on benefits and harms, both positive and negative, must be made publicly available.

In this thesis we examined to what extent the rationale and comparators of new randomised trials are justified by referencing previous similar trials (*Paper 1)*, to what extent the benefits and harms mentioned in documents available to ethics committees are also mentioned in documents provided to participants as part of the informed consent procedure (*Paper 2)*, to what extent investigators' right to publish their findings are constrained in trials with industry involvement and whether participants are informed about this (*Paper 3),* and finally we examined the quality of harms reporting in journal publications, clinical trial registries, and clinical study reports for recent oncological trials (*Paper 4)*.

*Paper 1*: In a sample of protocols and related documents for 67 trials approved by Danish ethics committees we found that 11 (16%) trials did not provide enough information to determine whether the rationale behind the trial was sound or the choice of comparator was justified. Two of the included protocols (3%) provided evidence of having conducted a systematic search and only one of these provided enough information to allow the search to be replicated. Finally, for eight protocols (12%) we found previous trials that would have been relevant to cite but were not.

*Paper 2:* In the same sample of 67 trials described above, we found that while research participants were generally adequately informed about benefits, for 28 trials (42%), harms mentioned in protocols or other documents were not mentioned in informed consent documents; in 22 of these trials the harms not mentioned were either common or serious.

Additionally, in 30 trials (45%) it was not mentioned that unforeseen harms might arise, although this is an explicit requirement.

*Paper 3:* We excluded 25 trials without industry involvement from the sample described above, which left us with 42 trials. We found that for 20 trials (48%) the industry sponsor owned all data accumulated during the trial and in 30 trials (71%) the investigators' right to publish was constrained in some manner. In none of these trials was publication constraints communicated to research participants in informed consent documents. We also found that in eight trials (19%) the industry sponsor could review unblinded data during the trial and in 23 trials (55%) the sponsor could stop the trial early for any reason.

*Paper 4:* In a sample of 42 trials in oncology, we found that harms were generally reported in much more detail in clinical study reports (CSRs) than in journal publications and clinical trial registries. We also identified marked discrepancies between different sources of data for the same trial, e.g. for the number of discontinuations due to adverse events, with discrepancies between CSRs and clinical trial registries in 23 out of 26 trials (88%) and between CSRs and publications in 18 out of 20 trials (90%).

In conclusion, we have documented several issues with the current system of ethical approval. While we cannot say for certain whether the trials included in our sample were in fact unethical, their ethical justification was poorly documented, and it is possible that a substantial amount of research participants have been exposed to unnecessary harm without their knowledge and acceptance, and to suboptimal treatment. We have also shown that selective reporting of harms and publication bias are still major problems, and it is possible that the constraints on publication rights that we identified contribute to this.

# Dansk resume / Danish summary

Forskning med forsøgspersoner er en forudsætning for ny medicinsk viden. I Helsinkideklarationen er der nedfældet principper, der skal sikre at sådan forskning foregår på etisk forsvarlig vis. Det fremgår blandt andet, at nye lodtrækningsforsøg skal bygge på detaljeret viden om tidligere studier, at deltagerne skal informeres om potentielle gavnlige og skadelige virkninger og at resultaterne, såvel positive som negative, skal gøres offentligt tilgængelige.

I denne afhandling har jeg undersøgt i hvilket omfang, rationalet bag nye lodtrækningsforsøg, samt valget af kontrolgrupper, er retfærdiggjort gennem systematiske søgninger med referencer til tidligere lignende studier (*Artikel 1);* i hvilket omfang gavnlige og skadelige virkninger nævnt i dokumenter tilgængelige for etiske komiteer også er nævnt i de dokumenter, som bliver udleveret til forsøgsdeltagere som en del af processen omkring at opnå informeret samtykke (*Artikel 2)*; i hvilket omfang de forsøgsansvarliges ret til at publicere er begrænset i studier med industrisamarbejde og hvorvidt forsøgsdeltagerne bliver informeret om dette (*Artikel 3);* og endeligt har vi undersøgt kvaliteten af rapportering af skadevirkninger i tidsskriftsartikler og registre over kliniske studier sammenlignet med kliniske studierapporter (*Artikel 4)*.

*Artikel 1:* I en stikprøve af protokoller og relaterede dokumenter for 67 lodtrækningsforsøg godkendt af danske etiske komiteer, fandt vi, at der for 16% af forsøgene ikke var nok information i protokollen til, at man kunne vurdere, hvorvidt rationalet bag studiets hypotese var legitimt eller, om valget af kontrolgruppen var retfærdiggjort på baggrund af tidligere studier. Kun to af de inkluderede protokoller (3%) indeholdt information om, at der var foretaget en systematisk søgning, og kun én af disse fremlagde dokumentation, der muliggjorde en gentagelse af søgningen. Endeligt fandt vi for otte protokoller (12%) tidligere studier gennem egne søgninger, som ville have været relevante at citere.

*Artikel 2:* I den samme stikprøve, som er beskrevet ovenfor, fandt vi, at mens forsøgsdeltagere generelt bliver tilstrækkeligt informeret om gavnlige virkninger, var der for 28 (42%) af de inkluderede forsøg skadevirkninger, som fremgik af protokollen eller andre

dokumenter til rådighed ved godkendelsen hos den etiske komité, men ikke i de dokumenter, som blev givet til deltagerne som en del af det informerede samtykke; i 22 af disse forsøg var der tale om bivirkninger som var enten alvorlige eller hyppige. Derudover fandt vi, at der for 30 forsøg (45%) ikke blev nævnt, at ukendte skadevirkninger kan opstå på trods af, at dette er et eksplicit krav i Helsinkideklarationen.

*Artikel 3:* Vi ekskluderede 25 forsøg uden industriinvolvering fra stikprøven beskrevet ovenfor, hvilket gav os en stikprøve på 42 industrisponsorerede forsøg. I 20 af disse forsøg (48%) fandt vi, at sponsoren havde ejerskab til al data, som blev akkumuleret i løbet af forsøget, og i 30 forsøg (71%) var de forsøgsansvarliges ret til at publicere eksplicit begrænset. I ingen af disse forsøg blev publikationsbegrænsninger nævnt i de dokumenter, som blev udleveret til deltagerne. I otte forsøg (19%) havde industrisponsoren adgang til ublindede data mens forsøget stod på, og i 23 forsøg (55%) kunne sponsoren stoppe forsøget af en hvilken som helst grund.

*Artikel 4:* For 42 nyere forsøg indenfor onkologi fandt vi, at skadevirkninger generelt blev rapporteret mere detaljeret i kliniske studierapporter ift. tidsskriftsartikler og registre over kliniske studier. Vi fandt også markante uoverensstemmelser mellem informationer i de forskellige kilder til data for de samme forsøg. F.eks. var der uoverensstemmelser angående antallet af deltagere, som stoppede pga. skadevirkninger mellem kliniske studierapporter og studieregistre for 23 ud af 26 forsøg (88%) og mellem kliniske studierapporter og tidskriftsartikler for 18 ud af 20 forsøg (90%).

Vi har altså dokumenteret adskillige potentielle problemer med det nuværende system for etisk godkendelse af lægemiddelforsøg. Vi kan ikke sige med sikkerhed, om nogle af forsøgene i vores stikprøve havde etiske problemer, men det er muligt, at et ikke uvæsentligt antal forsøgsdeltagere har været udsat for unødvendig skade, suboptimal behandling eller ikke er blevet informeret ordentligt om potentielle skadevirkninger ved deltagelse i forsøg. Vi har også vist, at selektiv rapportering og publikationsbias stadig er store problemer, og det er muligt, at publikationsbegrænsninger fra sponsors side bidrager til dette.

# Introduction

Research involving humans is an important tool for developing new treatments and for determining the benefits and harms of treatments. In 1948 the UK Medical Research Council's famous trial of streptomycin for pulmonary tuberculosis was published in the British Medical Journal.[1] This trial is generally considered to be the first properly conducted randomised controlled trial (RCT) and today randomised trials are the gold standard for establishing causal relationships in medicine.[2]

One of the most important documents outlining the ethical principles for medical research involving humans, and thus for randomised clinical trials, is the World Medical Association's Declaration of Helsinki.[3]

### Trial rationale and clinical equipoise

Some of the key principles outlined in the Declaration of Helsinki are that "*medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects*.", that "*all medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation*.", and that "*medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation.*"[3]

As risks and burdens of participating in research are not only balanced against the benefits to the participants, but also the benefits to future patients affected by the same condition, there is an inherent element of utilitarianism to such research, i.e. it can be justified to expose few people to harm in order to help many.[4] Thus, there seem to be a tension between

the physicians' duty to patients, which is to give the individual patient the best possible treatment, and the societal value of research, which might not benefit the individual participant.

Randomised trials are only justified when there is uncertainty about the effects of treatments, i.e. when it is not certain whether a given treatment is superior to alternative treatments or to no treatment. In this situation, participating in a well-performed randomised trial is not inferior to usual treatment as there is no certainty that being randomised to either arm will be preferable.[5]

This criterion, that there is genuine uncertainty about which treatment is best, is commonly referred to as *equipoise* and is generally recognised as an ethical requirement for performing RCTs.[6] There is, however, some disagreement about the so-called locus of uncertainty – i.e. whose uncertainty is most important. [7]

One locus of equipoise is reflected in the concept of "clinical equipoise". This term refers to a state where a group of experts disagree about which treatment is superior. This type of equipoise has great importance for the design of conduct of clinical trials, as it determines what intervention should be used in a control group.[8]

Two other types of equipoise of some importance are "theoretical equipoise" and "community equipoise". Theoretical equipoise reflects the belief of individual physicians that one treatment is not superior to another, while community equipoise describes equipoise among patients, advocate groups, and lay people. While both types of equipoise are important, they have little impact on trial design and justification and do not necessarily have implication for the ethics of a trial.[8]

Based on the above, it is clear that a RCT is only ethical when there is clinical equipoise. It follows that most RCTs must be based on a systematic review of previous trials, as this is the only way to establish whether clinical equipoise exists. This is not a new idea, e.g. it was proposed by Clarke and Chalmers in a 1998 study where they examined whether reports of RCTs discussed their findings in the light of all available evidence and found that this was not the case.[9] Since then the issue has been highlighted several times, and major journals such as the Lancet now formally requires all publication to put their findings into the context of previous

studies.[10–12] In 2013, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement, a guideline for the minimum content of protocols for clinical trials was published, along with an explanation and elaboration paper.[13,14] Item 6a of the SPIRIT statement underlines that a protocol should contain a "*description of [the] research question for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention."*[13] In the explanation and elaboration paper, this is expanded and it is made clear that a protocol must *"summarise the importance of the research question, justify the need of the trial in the context of available evidence, and present any available data regarding the potential effects of the interventions (benefits and harms)."*[14]

Cohort-studies have continuously shown that published reports of RCTs fail to mention previous similar studies or systematic reviews and discuss their results in relation to these.[15–20] In 2016, Pandis et al. published a study examining whether published trial protocols cited any randomised trial or systematic reviews and found that only 41% used a systematic review to inform trial design.[21]

When considering whether the requirement of clinical equipoise is met for a given RCT, the comparator treatment is of great importance. The Declaration of Helsinki addresses the issue of choice of comparator and it is stressed that, "*The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s)…".*[3] It is mentioned that if "for *compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention"* this can be acceptable, but only if no participants will be subject to additional risk or serious or irreversible harm.

Using an inferior comparator has both methodological and ethical implications. Ethical implications, because participants will receive inferior treatment and methodological implications because an intervention might seem more beneficial or less harmful when compared to an inferior comparator. For example, a 2019 study showed that out of 95

oncological drug approvals by the FDA, 17% were based on RCTs with suboptimal control arms, meaning that the approved drugs might not be superior to the current standard of care.[22]

**Informed consent**

Another fundamental ethical requirement of research involving human participants is that of informed consent. Principle 26 of the Declaration of Helsinki states that *"In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study."*[3] Similar sentiments are provided in other important documents outlining ethical and judicial requirements for research with human participants, such as the Belmont Report[23], The Council for International Organizations of Medical Sciences' (CIOMS) "International ethical guidelines for biomedical research"[24], and the "Guideline for good clinical practice" from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[25] One very important aspect of informed consent is information on potential benefits and harms. A questionnaire study of clinical trial participants with 122 respondents found that out of 11 categories of informed consent, "risks or discomforts" was the one respondents rated as most important.[26]

When informing patients about benefits of participating in clinical trials it is important to address what has been called the therapeutic misconception (TM), i.e. the failure to appreciate the difference between research and treatment. Hendersen et al. proposed the following definition of TM: "*Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial."*[27] As an example of TM, a study from 1982 found that participants enrolled in double-blind randomised trials with no-treatment control groups were not aware of the implications of the study design, e.g. many

believed they would receive a medication that had been judged superior for them, individually.[28] Thus, it is crucial to inform patient about what benefits they can expect from participating in a study, including an explanation that patients allocated to the experimental intervention may not necessarily benefit from such an allocation. The US Food and Drug Administration's (FDA) guidance on what to include in informed consent documents states, that: "*While research subjects may get personal treatment benefit from participating in a clinical trial, they must understand that they: may not benefit from the clinical trial, may be exposed to unknown risks, are entering into a study that may be very different from the standard medical practices that they currently know."*[29] In the United Kingdom (UK), The Health Research Authority's (HRA) guidance makes it clear that "*It is usually not possible to promise any direct benefits of taking part to potential participants, even though sometimes participants can end up benefitting directly. You need to ensure that potential participants are aware that you do not know what the outcome will be, and this is why you are conducting the research."*[30] In Denmark the rules do not explicitly address TM, but they mention that participants must be informed about whether they can expect any direct benefit.[31]

The exact requirements regarding information on harms also varies between different countries. In the United States of America the rules for informed consent are outlined in Title 21 of the Code of Federal Regulations, where it is stated that "*a description of any reasonably foreseeable risks or discomforts to the subject",* and *"a statement that the particular treatment or procedure may involve risks to the subject (or the embryo or foetus, if the subject is or may become pregnant) which are currently unforeseeable."* must be provided to participants in document form[32] and in the FDAs guidance it is made clear that such documents must include "*a description of any predictable risks."*[29] In the United Kingdom the Medical Research Council's (MRC) published guidance on informed consent states that informed consent documents must give "*a fair and honest evaluation of the consequences of research, including possible significant benefits and harms and their relative likelihoods must be described to potential participants."*[30] In Denmark the guidelines published by the Danish National Committee on Health Research Ethics explicitly state that informed consent documents must contain

information on all known or predictable harms associated with participating in the trial, regardless of their severity or frequency, and that it must be mentioned that unforeseen harms may arise.[31]

In 2009, a review examined how much research participants understood after informed consent. The review included seven studies that examined to what degree participants understood the potential benefits associated with participating in a clinical trial and found that in three studies (43%) less than 80% of the included participants 'highly understood' the benefits. Sixteen studies examined to what degree participants understood the potential harms; in eight of these studies (50%) less than 80% of participants 'highly understood' the potential harms.[33]

**Data ownership and reporting bias.**

In principle 36 of the Declaration of Helsinki it is made clear that *"researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available."*[3] Nonetheless, studies have shown that positive trials are more likely to be published than negative[34–36], a phenomenon referred to as publication bias[37]. For trials that are published, significant outcomes are more likely to be reported than non-significant outcomes[34,38], this is commonly referred to as outcome reporting bias.[39] The umbrella term reporting bias is used to cover these two types of bias, as well as additional types such as time-lag bias, citation bias, and language bias.[40]

There is no clear evidence that reporting bias is more prevalent in industry sponsored studies than in studies with other types of funding, although a review from 2013 concluded that type of funding is an important factor to be considered.[34] Nonetheless, cooperation between pharmaceutical companies and academics is a common way of organising randomised trials[41] and while this approach may have advantages, it is a type of business

transaction and thus holds the potential for conflicts of interest. In fact, it might be difficult for investigators in such trials to live up to principle 36 of the Declaration of Helsinki as their access to data and rights to publish may be restricted. A study published in 2006 found that out of 44 industry-initiated trials approved by an ethics committee in Denmark in 1994-1995, 40 trials (91%) had a description of publication restrictions in the study protocol; the same was true for 41 out of 44 trials (93%) approved in 2004.[42] In 2016, Kasenda et al. reported similar findings; They included 647 protocols for trials with an industry partner, 456 protocols mentioned publication agreements and in 393 (86%) of these the industry partner had the right to disapprove or at least review potential publications.[43]

**Reporting of harms and clinical study reports**

While reporting bias is a problem for all outcomes of clinical trials, harms data from RCTs is known to be particularly poorly reported in journal publications.[44–46] This has led to an increased focus on including unpublished data in systematic reviews of adverse events[47]; however, a study from 2016 found that most systematic reviews of harms did not include unpublished data[48] and it has been argued that including such data might not be worth the effort, because including such data might not alter conclusions.[49]

One possible source of unpublished data is clinical study reports, which are highly detailed and structured documents prepared by pharmaceutical companies and submitted to regulatory agencies as part of applications for marketing authorisation or extension of indications.[50] CSRs are lengthy, often thousands of pages, and their structure is specified in guidance from the ICH.[51]

Historically, it has been difficult to obtain access to clinical study reports but in 2010, after a lengthy process, the European Ombudsman declared that the EMA should grant researchers from the Nordic Cochrane Centre access to CSRs for the two anti-obesity drugs rimonabant and orlistat, which the EMA complied with.[52] This also led to the EMA changing their policy on access to data and now access to CSRs is possible for all drugs approved by the EMA under policy 0043.[53] In 2014, EMAs policy 0070 outlined that CSRs shall be made prospectively

available automatically once an application has been handled by the EMA.[54] In 2016 the EMA began making CSRs available, however as of August 1st 2018 the EMA temporarily suspended all clinical data publication, due to EMA's relocation to Amsterdam.[55] It is unclear if and when publication of clinical data will resume.

Numerous studies have compared the reporting of benefits and harms in CSRs with the reporting in journal publications. For example, using CSRs rather than only published sources of data in a systematic review of reboxetine for depression changed the direction of conclusions regarding both benefits and harms[56]. Wieseler et al. found that for studies included in 16 health technology assessments CSRs consistently reported more information than both journal publications and clinical trial registers[57,58], Fu et al. reviewed the benefits and harms of recombinant human bone morphogenetic protein-2 in spine fusion using CSRs and individual patient data and concluded that "*early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and underreporting*"[59], both Hodkinson et al. and Schroll et al. found that for the anti-obesity drug orlistat, harms were reported in more detail in CSRs than journal publications[60,61], and Maund et al. compared CSRs and publications for the anti-depressant Duloxetine and found that although there were internal inconsistencies in CSRs, harms were reported in more detail in CSRs.[62]

# Objectives

The objectives of this PhD were to assess the following:

1. Whether trial protocols approved by Danish ethics committees justified the rationale of conducting the trial and choice of comparator by referencing previous trials and systematic reviews when possible (Paper 1).
2. Whether harms associated with participating in trials described in protocols and other documents submitted to ethics committees matched the harms mentioned in informed consent documents provided to research participants (Paper 2).
3. To which extent investigators' access to trial data and their rights to publish were limited by the sponsor and to which extent this was reflected in informed consent documents (Paper 3).
4. To which extent data on harms available in journal publications and clinical trial registries matched the data available in clinical study reports submitted to the EMA for oncological trials (Paper 4).

# Description and methods of the research projects

### Cohort of clinical study protocols

Three of the papers included in this PhD (Paper 1-3) are based on a cohort of clinical study protocols approved by ethics committees in Denmark between October 2012 and March 2013.

We included parallel-group, randomised trials from all clinical fields. We included studies with a patient relevant primary outcome and excluded studies with only surrogate primary outcomes since it requires detailed content area knowledge from diverse fields to determine the relevance of such outcomes to patients.

The website of the Danish National Committee on Health Research Ethics[63] contains a list of all approved trials; we used information from list to identify eligible trials registered in the following clinical trial registers: clinicaltrials.gov, EU Clinical Trial Register (EUCTR), and the WHO International Clinical Trial Registry Platform (ICTRP).

Originally, we planned to include trials approved between January 2012 and March 2013, but as we identified substantially more trials than needed, and we limited the period to October 2012 to March 2013. For all potentially eligible trials, we requested access to clinical study protocols, informed consent documents, clinical trial agreements (CTAs) and other relevant documents through a Freedom of Information (FOI) request to the ethics committees. We then made a final eligibility check, based on the protocols.

For all eligible protocolss, we extracted trial characteristics such as planned sample size, whether the trial was single- or multi-centre, type of intervention, primary outcome, clinical speciality, and clinical phase of the study.

### Paper 1: Do protocols for new randomised trials take existing trials into account?

This paper examined the justification of trial rationale and choice of comparator in the sample of protocols described above. The paper was published in BMJ Open in 2019.[64]

For all eligible protocolss we extracted the following information: type of funding (whether the trial was fully, partially or non-industry sponsored), the type of comparator (active comparator, placebo, or nothing), whether any justification for the choice of comparator was provided, whether there was any indication that a systematic search had been carried out as part of planning the trial, and information on references to previous similar trials or systematic reviews.

For each protocol, we conducted our own searches to check if there were additional trials or systematic reviews that could have been relevant to cite. We used a very basic search strategy and limited all searches to one month before the first submission of the protocol to the ethics committee.

We analysed the extracted data and made assessments for the following four outcomes: whether the choice of comparator was justified, whether the rationale for conducting the study was justified, whether there any indication of a systematic search being done, and whether we identified additional trials or systematic reviews that would have been relevant to cite.

We did not categorise the trials described in the protocols as ethical or unethical, rather we examined whether enough information was presented to allow the ethics committees to evaluate whether the trials were justified.

**Paper 2: Are potential participants adequately informed about benefits and harms?**

This paper compared information on benefits and harms to the ethics committees provided in protocols and other documents with the information provided to potential participants in informed consent documents. The paper is based on the sample described above.

For each protocol we created a dedicated spreadsheet where we entered all benefits and harms mentioned in the protocol and related documents (e.g. the Investigator's Brochure, although this was rarely available to the ethics committees); for harms we also noted any estimates of frequency provided. We then checked whether all benefits and harms were also mentioned in the informed consent documents. We counted the total number of benefits

and harms respectively, and the number of these not mentioned in the informed consent document. We also examined whether it was explicitly mentioned in informed consent documents that unknown harms might arise.

For all trials we assessed to which degree the following domains were fulfilled: whether the benefits described in documents available to the ethics committees matched those described in informed consent documents; whether the harms described in documents available to the ethics committees matched those described in informed consent documents; whether harms mentioned in documents available to ethics committees and not mentioned in informed consent documents were either serious or common (defined as a frequency of more than one percent); and whether it was explicitly mentioned that unknown harms might arise.

For trials where all harms were not mentioned in informed consent documents we calculated the proportion of harms mentioned and presented the median and interquartile range (IQR).

**Paper 3: Are investigators' access to trial data and rights to publish restricted and are trial participants informed about this?**

This paper examined to what degree access to trial data and rights to publish is restricted in trials with industry involvement, and whether this is communicated to trial participants. We also examined whether sponsors could review unblinded data during the trial and/or stop the trial early.

We included all partially or fully industry sponsored trials from the sample described above. For all trials we extracted the following information from protocols and other relevant documents (e.g. CTAs or publication contracts): information on roles and responsibilities of sponsors and investigators, information on data ownership, information on publication restrictions, information on interim analyses and data monitoring committees (DMCs), information on early stopping of the trial, and finally whether there was any mention of potential publication constraints in informed consent documents.

For all trials, we assessed to which degree the following domains were met: whether the roles and responsibilities of sponsors and investigators were described, whether the sponsor or investigator owned the data accumulated during the study, whether investigators' rights to publish were restricted, whether such restrictions were mentioned in informed consent documents, whether the industry partner could accumulate unblinded data during the study, whether the industry partner could choose to stop the trial early, and if this was the case, whether specific reasons were required.

**Paper 4: Reporting of harms in oncological clinical study reports submitted to the European Medicines Agency compared to trial registries and publications**

This paper compared the quality of reporting of harms in CSRs, trial registries and journal publications. We included oncological trials submitted to the EMA for which CSRs were released under the EMAs policy 0070.

On the EMA clinical data website[65], we downloaded CSRs for all trials addressing targeted therapy and immunotherapy for cancer. We identified all randomised phase II, II/III, or III trials. We identified the corresponding trial records listed in clinicaltrials.gov and EUCTR, as well as journal publications reporting results from the trials.

For each trial, we assessed whether the following information was available from each source: number of patients randomised, number of patients in the safety population, number of patients with serious adverse events, total number of serious adverse events, number of patients with any adverse events, total number of adverse events, number of patients with Common Terminology Criteria for Adverse Events (CTCAE) grade 3-5 adverse events, total number of CTCAE grade 3-5 adverse events, the number of deaths due to adverse events and the number of discontinuations due to adverse events.

If an outcome was reported in more than one source, we checked whether there were discrepancies between sources.

For each of the outcomes described above and for each source we reported

the proportion of trials where outcome data was available and whether there were any discrepancies between the different sources.

# Summary of results and discussion

### Characteristics of trials in the cohort of protocols from Danish research ethics committees

We identified 1401 health research projects approved by any Danish research ethics committee between January 2012 and March 2013. Of these we excluded 1189, either because they did not fulfil our eligibility criteria (n = 395) or because we were unable to identify them in a trial registry (n = 794). This left 212 seemingly eligible protocols, but as this was more than we could realistically extract data we excluded 134 protocols approved before October 2012. Thus, we requested access to 78 protocols and related documents. Of these, 11 were ineligible for different reasons and the final sample consisted of 67 protocols, **Figure 1.**

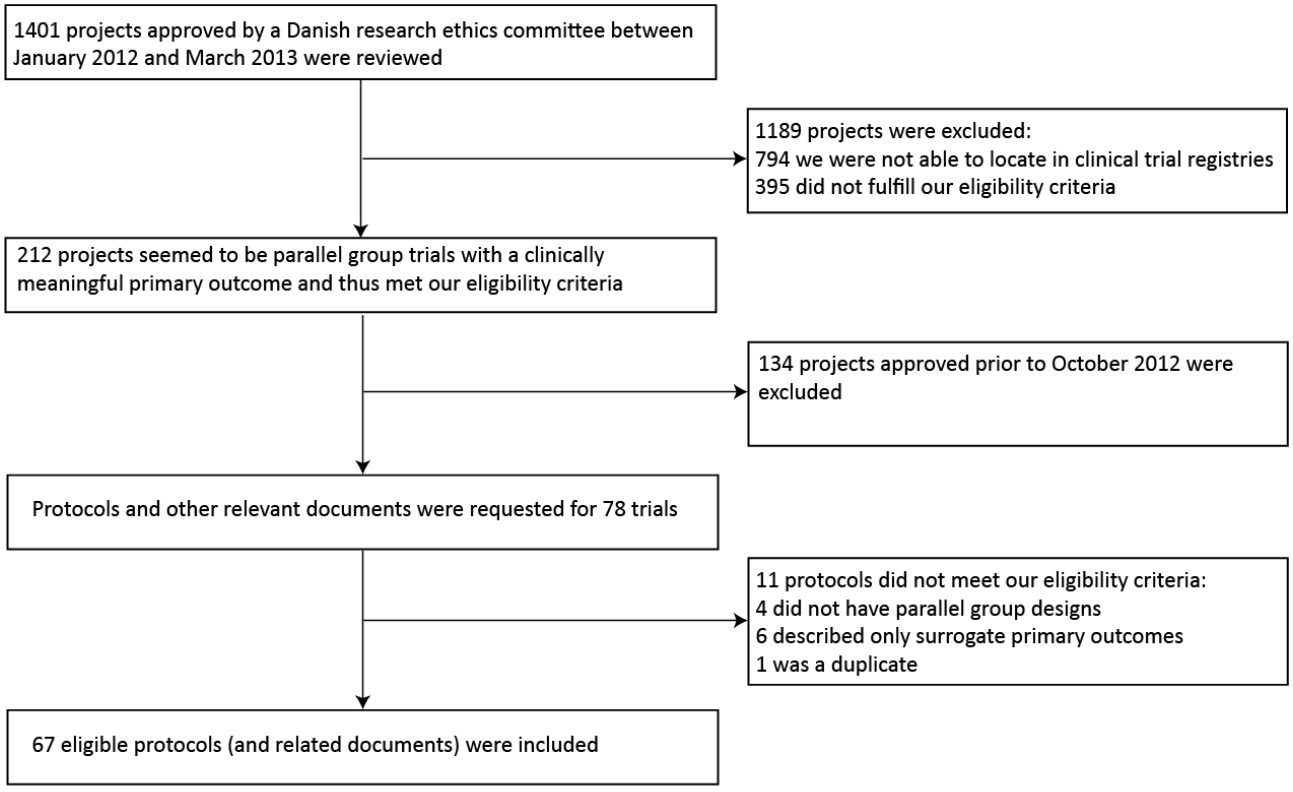



**Figure 1 - Flowchart of inclusion of protocols**

While access to the requested documents should be available under the Danish Freedom of Information act and we stressed that we would report our findings in a way so it would not be possible to identify individual trials, for 25 trials (37%) the request was initially either denied or the protocols were redacted. After a lengthy process we obtained access to all requested protocols. The process and the redactions are described in detail elsewhere.[66]

Of the 67 included protocols, 33 (49%) described industry sponsored trials, 10 (15%) described partially industry sponsored trials, and the remaining 24 (36%) were non-industry sponsored. Thirty-eight of the included protocols (57%) described multinational trials. Thirty out of 33 (91%) fully industry sponsored trials were multinational, versus five out of 10 (50%) partially industry sponsored trials and three out of 24 (13%) non-industry sponsored trials. The fully industry sponsored trials also had larger median planned sample sizes (620 participants) compared to partially industry sponsored trials (311) and non-industry sponsored trials (95). The medical specialities of the included planned trials can be seen in **Table 1**.

**Table 1 - Medical specialities of included protocols**

| Speciality | Protocols, n (%) |
|---|---|
| Oncology | 19 (28) |
| Surgery | 10 (15) |
| Obstetrics and gynaecology | 7 (10) |
| Rheumatology | 6 (9) |
| Anaesthesia | 5 (7) |
| Cardiology | 5 (7) |
| Endocrinology | 5 (7) |
| Dermatology | 2 (3) |
| Gastroenterology | 2 (3) |
| Psychiatry | 2 (3) |
| Pulmonary medicine | 2 (3) |
| Geriatrics | 1 (1) |

| | |
|---|---|
| Pediatrics | 1 (1) |

In 18 protocols (27%) placebo was the only comparator. Thirty-two protocols (48%) described only active comparators and 10 protocols (15%) described no treatment as the only comparator. In six protocols (9%) both a placebo arm and an active comparator arm was described, and one protocol (1%) described both an active comparator arm and an arm with no treatment.

**Paper 1: Do protocols for new randomised trials take existing trials into account?**

The characteristics of the included studies are described above.

#### Literature searches and referenced studies

We found that two of the included protocols (3%) contained a statement explicitly indicating that a literature search had been conducted. One of these provided information that allowed the search to be replicated, whereas the other protocol provided the date of the search and the databases searched but not the search strategy itself. Four additional protocols (6%) contained phrases that indicated that a search had been conducted.

We identified 12 protocols (18%) that cited a systematic review or RCT with clear, direct relevance for the planned trial. For 11 of these 12 protocols, our own searches did not find additional relevant studies that could have been cited. For the remaining protocols we identified a systematic review and two RCTs that would have been relevant to cite.

The remaining 55 protocols (82%) did not cite any systematic reviews or RCTs with clear, direct relevance. For 48 of these 55 protocols (87%) our own searches did not identify any studies that would have been relevant to cite. For the remaining seven protocols (13%) we identified a total of ten RCTs and one systematic review that could have been relevant to cite.

**Comparators and trial rationale**

O the 67 included protocols, 42 (63%) contained a justification for the choice of comparator. In 21 of the 42 protocols the justification was explicit, and in the remaining 21 the justification was implicit, e.g. mentioning that the control group would receive “standard care”.

In 11 protocols (16%) we assessed that the choice of treatment or comparator could be questioned based on the information provided in the protocols. Examples included three studies examining the effect of analgesic interventions that used placebo as a comparator although other treatments had been found effective for the conditions studied; a study that compared a special type of exercise with no intervention although regular exercise had been proven effective for the primary outcome studied; and a phase 3 study that was initiated before phase 2 studies of the same intervention were completed.

**Comparison with other studies**

A study published in 2016 examined protocols published in December 2015 and indexed in PubMed and found that 10.9% of included protocols did not cite any RCT or systematic review, and an additional 8.9% cited systematic reviews, but did not use them in trial design.[21] We found that only 18% cited a RCT or systematic review of clear, direct relevance; however, there are several key differences between our study and the one described above. First, we only looked at trials or systematic reviews that addressed a similar intervention in a similar population, whereas Pandis et al. counted all RCTs or systematic reviews, regardless of their relevance to the research question. Secondly, Pandis et al. included only published protocols, whereas we included any protocol that had been approved by an ethics committee, regardless of its public availability.

Multiple studies have examined whether previous trials were referenced in journal publications reporting new RCTs. A study published in 2011 examined references in 1523 trials and found that less than a quarter of relevant previous trials were cited.[15] Similarly, in 2010

Clarke et al. reported that most trials do not refer to updated systematic reviews in the discussion of results.[17]

**Strengths and limitations**

To our knowledge, this study is the first to study whether a sample of unpublished protocols approved by ethics committees live up to ethical requirements set out in the Declaration of Helsinki. Our results represent an optimistic scenario, as we chose to be conservative when judging whether trial rationale or choice of comparator was questionable. While our study only contains protocols approved in Denmark, more than half were multinational trials and we are not aware of any reason why trials approved in Denmark would be systematically different from trials performed in other similar countries, so we believe our findings are relevant outside Denmark.

The study has several limitations. The protocols in our sample are over five years old and it is possible that the quality of protocols has improved. However, as the legislations and guidelines have not changed, we believe our results are likely valid today. Additionally, we did not search for unpublished data, and since publication bias is known to be a significant problem[34], there might be relevant studies that we were not able to identify in our own searches. Likewise, we did not include observational studies, although these can be important for detecting rare or unexpected harms; thus, it is possible we would have assessed additional interventions or comparators as questionable if we had included such studies. Another limitation is the large amount of approved trials we were not able to identify in trial registries; if these trials are systematically different from the ones included it might limit the generalisability of our findings. Our relatively small sample size can also be considered a limitation, as this means we are not able to examine subgroup differences or perform inferential statistics.

Finally, as we had to sign confidentiality agreements to obtain documents from the ethics committees, we are not able to share our raw data which limits the transparency and reproducibility of the study.

**Paper 2: Are potential participants adequately informed about benefits and harms?**

The characteristics of the included studies are described above.

**Descriptions of benefit in clinical study protocols and informed consent documents**

Generally, we found that the benefits described in protocols matched those described in the informed consent documents. For two trials (3%) we found that benefits were understated in informed consent documents, as benefits mentioned in the protocol were not mentioned in the corresponding informed consent document.

We also found that for eight trials (12%) the informed consent documents contained explicit statements saying that participants would not gain any direct benefits, although the main hypothesis was superiority of an intervention for all the eight trials.

**Descriptions of harms in clinical study protocols and informed consent documents**

We identified 28 trials (42%) where all the harms mentioned in the protocols and related documents were not mentioned in the informed consent documents. In these trials the median percentage of harms mentioned in informed consent documents was 68% (IQR: 45% to 82%).

In 22 of the 28 trials (79%) were all the harms were not mentioned in informed consent documents, we assessed at least one of the harms not mentioned as being so common, or so serious, that it should have been mentioned. Examples of these harms can be seen in **Box 1**.

**Box 1 - Examples of serious or common harms not mentioned in informed consent documents**

Examples of harms that were not mentioned, but we considered important due to their prevalence:

- Fatigue (experienced by 56.4% of subjects receiving medication in a previous trial)
- Nausea (experienced by 43.6% of subjects receiving medication in a previous trial)
- Increased sweating (observed in 'almost all' that take medication)
- Irritability (observed in more than 1/100 that take medication)
- Disorientation (observed in more than 1/100 that take medication)

Examples of harms that were not mentioned, but were considered important due to their seriousness:

- Sudden death
- Stevens-Johnson's Syndrome
- Acute renal failure
- Respiratory failure
- Leukaemia
- Bleeding
- Aneurysms

For 30 trials (45%) the informed consent documents did not mention that unknown harms might arise, and for 6 trials (9%) there were statements in informed consent documents that insinuated that there were no harms associated with participating in the trials at all.

**Comparison with previous similar studies**

We are not aware of any previous studies that have compared information on benefits and harms in protocols with the information provided to participants in informed consent documents. Previous studies have, however, shown that trial participants do not always feel adequately informed about potential benefits and harms. Koh et al. conducted a survey of 122 participants in clinical trials conducted at Seoul National University Hospital and found that on average participants felt that they had received less information about “benefits to others”, “benefits to the subject”, and “risks or discomforts” than they wanted.[26] Similarly, a review by Falagas et al. examined studies assessing the quality of informed consent in clinical trials, and found that only eight out of 16 studies found that more than 80% of participants had adequately understood the risks from treatment, and only four out of seven studies found that more than 80% of participants had adequately understood the benefits of treatment.

**Strengths and limitations**

As mentioned above, we believe our study is the first to examine whether benefits and harms in protocols and informed consent documents match, and as we judged all domains conservatively our results likely represent a best-case scenario. Our sample consists of unpublished protocols, which we were able to obtain from ethics committees and thus give a fuller picture than if we had included published protocols only. Additionally, as more than half of the trials in our sample were multinational, we believe our findings are generalisable.

However, as we only compared harms mentioned in informed consent documents with harms mentioned in protocols and other documents available to ethics committees, it is possible that there are important harms associated with participating in the included trials that we have not identified and thus we might underestimate the number of harms that should have been mentioned. Additionally, at the time of approval of the trials in our sample, Danish ethics committees did not require submission of the Investigator’s Brochure, which might contain more detailed information of harms. As with Paper 1, the large number of trials we were unable to identify in trial registers and the relatively small sample size can be considered limitations.

Finally, the fact that we had to sign confidentiality agreements to obtain the included documents limits the transparency and reproducibility of our study.

**Paper 3: Are investigators' access to trial data and rights to publish restricted and are trial participants informed about this?**

This study was based on a subset of the sample described above. We excluded all non-industry sponsored studies which left us with a sample of 42 trials. Thirty-two (76%) of these were fully industry sponsored and the remaining 10 (24%) were partially industry sponsored. The median planned sample size was 576 participants and 39 trials (93%) were multi-centre trials.

#### Ownership of data and publication constraints

For 20 of the included trials (48%) it was clear that the sponsor owned all data accumulated during the trial, for six trials (14%) it was clear that the investigators owned data, and in the remaining 16 trials (38%) it was unclear who owned the data.

For 30 trials (71%) investigators' right to publish was constrained, in seven trials (17%) it was clear that rights to publish were unconstrained, and in the remaining five trials (12%) it was unclear. The types of constraints can be seen in **Table 2**.

**Table 2 - Types of publication constraints in included trials**

| Type of publication constraints | N = 42 |
|---|---|
| Publication not allowed for a pre-specified period | 22 trials (52%) |
| Sponsor can review potential publications or presentations | 30 trials (71%) |
| Sponsor can comment, but investigators must not comply with comments | 14 trials (33%) |

| | |
|---|---|
| Sponsor can comment, and investigators must comply with comments | 13 trials (31%) |
| Sponsor can delay publication after receiving for review | 21 trials (50%) |

In none of the included studies were data ownership or publication constraints mentioned in informed consent documents.

**Access to data during the trial and early stopping**

It was generally difficult to determine if the sponsor had the opportunity to review unblinded data during the trial, based on the documents available to us. Thus, for 20 of the 42 included trials (48%) we assessed this domain as unclear. In eight trials (19%) we were certain it was possible for the sponsor to review unblinded data while the trial was ongoing and in the remaining 14 (33%) we were confident it was not.

For 27 trials (64%) it was mentioned that the trial could be stopped early by the sponsor. For 23 of the trials (55%) the sponsor could stop the trial for any reason. For two trials (5%) specific reasons were needed, and in two trials (5%) it was unclear whether a specific reason was needed. For the remaining 15 trials (36%) there was no mention of early stopping

**Comparison with previous similar studies**

Our results are in concordance with results of previous studies examining investigators' right to publish in trials with industry involvement. In 2006, Gøtzsche et al. found that 41 out of 44 trials (93%) approved by ethics committees in Denmark in 2004 had publication constraints.[42] In 2016, Kasenda et al. showed that in a sample of 456 protocols approved between 2000 and 2003 and with a separate publication agreement, 393 (86%) described the industry partners right to review and in some cases disapprove potential manuscripts.[43] We found that at least 71% of included trials had any publication constraints. this is somewhat lower than the numbers described above, and could reflect a tendency towards less publication constraints, however as

12% of included trials in our sample were assessed as unclear with regards to publication constraints these numbers might in fact be quite similar.

Gøtzsche et al. also found that in 13 trials (30%) the sponsor owned the data accumulated during the study, whereas we found the same was true for at least 48% of the included trials.

We are not aware of any previous studies that have examined whether publication constraints are communicated to research participants in informed consent documents.

**Strengths and limitations**

Like the other studies based on the same sample, this study relies on unpublished protocols rather than published protocols, and as it is possible that published protocols are systematically different from unpublished, we consider our inclusion of non-published protocols a strength. Furthermore, the studies included in our sample are more recent than the ones included in the studies described above, which means that they might give a more accurate picture of the situation today. We were also able to compare the information provided in documents available to ethics committees with what was mentioned in informed consent documents, as we had access to these documents.

Our study also has important limitations. First, for several domains a substantial number of trials were assessed as unclear. The assessments of some domains were subjective and although all assessments have been checked by a second observer and we have generally tried to be conservative this should be considered.

Additionally, several years have passed since the protocols were approved, and the situation might have changed. Another potential limitation is the fact that all studies were approved by ethics committees in Denmark, although we believe this is mitigated by the fact that most included studies were multi-centre studies and we are not aware of any reason why trials approved in Denmark would differ systematically from other trials.

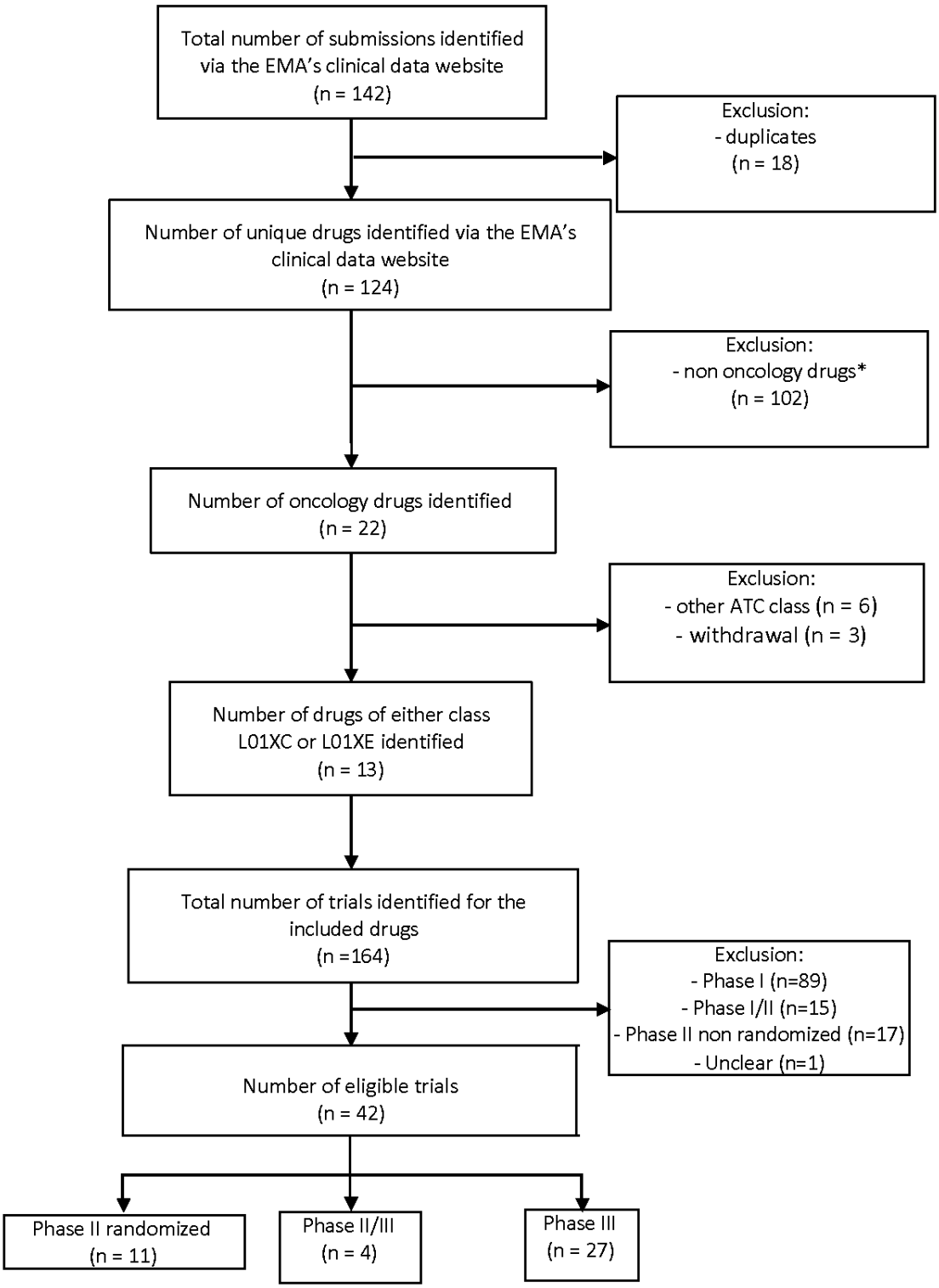
Lastly, like the other studies based on the same sample, the large number of unidentified trials and the small sample size are limitations and this study's reproducibility and

transparency is limited by the fact that we had to sign confidentiality agreements in order to obtain the included documents.

## Paper 4: Reporting of harms in oncological clinical study reports submitted to the European Medicines Agency compared to trial registries and publications

### Description of the sample

We included 42 oncological RCTs assessing targeted therapy and immunotherapy for cancer. These 42 trials had all been submitted to the EMA as part of an application for marketing authorisation or extension of an indication between October 2016 and June 2020, and thus were available from the EMA clinical data website.[65] The inclusion process is summarised in **Figure 2**.




*Number of drugs per therapeutic area: cardiology (10), dermatology (4), endocrinology (12), gastroenterology (4), hematology (20), hepatology (3), infectiology (18), internal medicine (3), neurology (9), ophthalmology (2), psychiatry (2), radiology (2), respiratory (3), rheumatology (10)

**Figure 2 - Flowchart of included studies in Paper 4**

We included trials assessing the benefits and harms of the following drugs: afatinib, bevacizumab, cabozantinib, cediranib, erlotinib, lenvatinib, nivolumab, olaratumab, palbociclib, and pembrolizumab.

The median number of randomised patients in the included trials was 364 (range: 142-666). Twenty-seven trials (64%) had progression-free survival as the primary outcome, eight trials (19%) had overall survival as the primary outcome, and in three trials (7%) both were primary outcomes. The remaining four trials (10%) had other primary outcomes.

For 37 of the 42 trials (88%) the EMA clinical data website contained a full CSR, for 36 trials (86%) results were posted on clinicaltrials.gov, for 20 trials (48%) results were posted in the EUCTR, and for 32 trials (76%) journal publications were available (**Figure 3**).

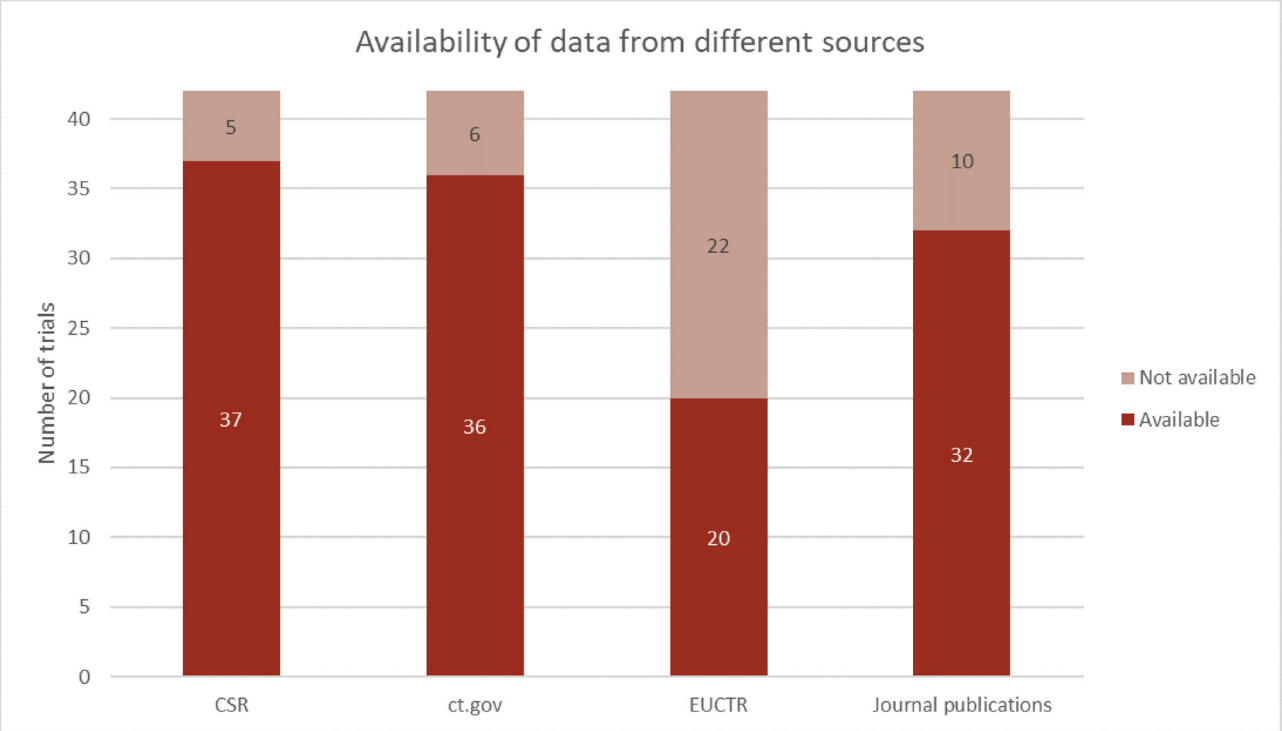



**Figure 3 - Availability of data from different sources**

**Reporting of harms**

We found that harms were generally reported in more detail in CSRs than in the other included sources. E.g. the total number of patients with at least one serious adverse event was available in all CSRs, in all clinicaltrials.gov entries, and in 19 out of 20 EUCTR entries (95%); but only in 16 of 32 trial publications (50%). The total number of patients with at least one adverse event

was available in all CSRs but not from any of the trial registries and only in publications for 13 out of 32 trials (41%) with any publication. Similarly, the number of patients with at least one CTCAE grade 3-5 adverse events was available in 36 out of 37 CSRs (97%) but not in any trial registries and only for 14 trials (44%) with publications. The number of deaths attributed to adverse events was available in 34 CSRs (92%) but not for any trials on clinicaltrials.gov. In EUCTR the number was available for 15 trials (75%) and in publications for 12 trials (38%).

While reporting was generally better in CSRs than in other sources, there were still problems, e.g. the total number of serious adverse events was only reported in nine out of 37 CSRs (24%), the total number of any adverse event in 12 CSRs (32%), and the total number of CTCAE grade 3-5 adverse events in six CSRs (16%).

Any information on how it was decided whether a death was due to an adverse event or progressive disease was only available in 10 CSRs (27%) and in none of the other sources.

**Discrepancies between sources of data**

We looked for discrepancies between different sources of data, for all trials were an outcome was reported in more than one source. We identified numerous discrepancies, e.g. in 15 out of 32 trials (47%) where the number of patients with at least one serious adverse event was available in both a CSR and a clinical trial register the numbers reported did not match. The same was true for five out of 13 trials (38%) where the number was available in both a CSR and a publication. Discrepancies were particularly common for the number of discontinuations due to adverse events, with discrepancies between CSRs and clinical trial registers for 23 out of 26 trials (88%) and between CSRs and publications for 18 out of 20 trials (90%).

**Delay in access to data**

The median delay from trial completion to availability of data was 4.34 (IQR: 3.09-7.22) years for CSRs, 2.94 (1.16–4.52) years for ClinicalTrials.gov, 5.39 (4.18–7.33) years for the EUCTR, and 2.15 (0.64–5.04) years for publications.

**Comparison with previous similar studies**

As mentioned in the introduction numerous studies have compared reporting of harms in CSRs with reporting in other sources and these have generally shown that harms are reported in more detail in CSRs.[58,60–62] Wieseler et al. found that in a sample of 86 trials where both a CSR and public source of data was available serious adverse events, adverse events, and withdrawals due to adverse events were reported more frequently in CSRs than in other sources.[58] Similarly, Maund et al. found that for nine antidepressant trials harms were generally poorly reported in journal publications and in more detail in CSRs.[62] Both Schroll et al. and Hodkinson et al. found that when comparing CSRs with other sources of data on harm, harms were reported in more detail in CSRs.[60,61] We have replicated these findings in a sample of newer CSRs published under the EMAs policy 0070 for oncological trials.

The studies mentioned above also examined whether there were discrepancies between CSRs and other sources of data.[58,61,62] E.g. Schroll et al. found that for four trials of orlistat only between 3% and 33% of the adverse events reported in CSRs were reported in journal publications.[61] Similarly, Munkholm et al. found that in a systematic review of antidepressants based primarily on published data, data on dropouts used in the review differed from data available in CSRs for 12 out of 19 trials (63%).[68]

**Strengths and limitations**

As mentioned above, our is the first study to compare the reporting of harms in CSRs released under policy 0070 with reporting in clinical trial registers and journal publications. We have systematically examined whether pre-specified outcomes were reported in a large sample of trials, and we have also compared whether there were discrepancies between different sources. However, our results should be interpreted in the light of important limitations. First, it is possible that our findings are not relevant in other areas of medicine. However, earlier studies have shown similar results in other clinical fields, so we consider it likely that harms are reported in more detail in CSRs across all specialities. It could also be considered a limitation that we did not synthesise data to show whether analyses based on CSRs would give different results than

analyses based on other sources of data; however, as the included trials assess different drugs for different indications we did not consider such analyses appropriate.

# Conclusions and perspectives for further research

### Overall conclusions

We have documented several potential issues with the current system of ethical approval of RCTs. First, we have shown that a substantial number of trials (16% in our sample) did not provide enough information to establish that they are indeed ethically acceptable. Either they failed to establish a rationale for conducting the trial based on previous research or they failed to provide convincing justification for the choice of comparator. This means that while we cannot say for sure whether the trials are unethical, a substantial amount of research participants may have been exposed to suboptimal treatment.

Secondly, we have shown that while benefits are generally adequately described in informed consent documents, harms were inadequately described for a substantial amount of trials. Twenty-two informed consent documents (33%) failed to mention harms described in protocols or other documents that were either so serious or so common that we consider it a clear mistake that they were not mentioned. In 30 informed consent documents (45%) it was not mentioned that unknown harms might arise, although this is an explicit requirement in most countries.

We have also shown that in trials with industry involvement, the investigators' right to publish was constrained in the majority of trials (71%), and we were confident that the industry sponsor owned all accumulated data in 48% of the included trials. This was not mentioned in informed consent documents for any of the included trials, which again might make true informed consent difficult to obtain.

Lastly, we have shown that while the problems of publication bias and selective outcome reporting have been known for decades, they continue to persist. In our sample of trials assessing immunotherapy and targeted therapy for cancer we have shown that harms

continue to be underreported in both journal publications and clinical trial registers. We have also shown marked discrepancies between different sources of data and we believe our findings, together with similar results from other studies, suggest that any systematic assessment of harms should rely on CSRs as the main source of data. This also means that it might be difficult for investigators planning new trials to make a reliable assessment of the benefits and harms of interventions, which again makes it difficult to provide information to participants that can facilitate informed consent.

**Implications for future research**

First, we have shown that an increased emphasis on the ethical approval of RCTs is warranted. Ethics committees and institutional review boards should prioritise confirming that the rationale behind a new trial is sound and that the choice of comparator is justified. One possible solution could be to formally require a systematic review before any new trial; this has previously been a formal requirement in Denmark, but unfortunately this requirement is no longer in force.[69] Another way to improve the quality of protocols would be for countries to formally require that protocols comply with the SPIRIT statement[13]. This would likely also make the work of ethics committees easier, as the protocols would follow a uniform format. Secondly, we have shown that the harms and benefits associated with participating in a trial are not always made sufficiently clear to participants, and we believe this should be a focus area for ethics committees. Similarly, publication constraints are common, and the research community should consider whether such constraints are acceptable, especially considering the known problems of publication bias and selective outcome reporting.

We have also documented that for recent oncological trials, harms are not reported in sufficient detail in journal publications and clinical trial registers to allow for an adequate assessment of the harms associated with treatment. Thus, we believe that such assessments should include CSRs as a primary source of data, however currently there is substantial problems associated with obtaining access to these documents and there is little clear guidance on how to implement them in systematic reviews. Therefore, we believe there is

a need for formalised procedures for obtaining access and using CSRs, and this should be an area of focus for future research and for concrete political action.

We also believe it would be relevant to replicate our findings in a larger sample of contemporary protocols to establish if the problems we have identified are still present. A larger sample size would allow for an exploration of subgroup differences, e.g. whether the source of funding has an influence on the problems described above.

Finally, there is a need for research examining effective ways of communicating benefits and harms to research participants.

# Abbreviations

| | |
|---|---|
| CSR | Clinical study report |
| CIOMS | Council for International Organisations of Medical Sciences |
| CTA | Clinical trial agreement |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data monitoring committee |
| EMA | European Medicines Agency |
| EUCTR | EU Clinical Trials Register |
| FDA | US Food and Drug Administration |
| FOI | Freedom of Information |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICTRP | International Clinical Trial Registry Platform |
| RCT | Randomised controlled trial |
| TM | Therapeutic Misconception |
| UK | United Kingdom |
| USA | United States of America |

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# Paper 1

Do protocols for new randomised trials take previous similar trials into account? Cohort study of contemporary trial protocols.

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GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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# PHD-THESIS
# DECLARATION OF CO-AUTHORSHIP

*The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.*

| **1. Declaration by** | |
|---|---|
| Name of PhD student | Asger Sand Paludan-Müller |
| E-mail | asp@cochrane.dk |
| Name of principal supervisor | John Brodersen |
| Title of the PhD thesis | The need for a new randomised trial |

| **2. The declaration applies to the following article** | |
|---|---|
| Title of article | Do protocols for new randomised trials take previous similar trials into account? Cohort study of contemporary trial protocols |
| **Article status** | |
| Published ☒<br>Date: November 10, 2019 | Accepted for publication ☐<br>Date: |
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| If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information). | BMJ Open,2019,9,e026661. doi: 10.1136/bmjopen-2018-026661 |

| **3. The PhD student's contribution to the article** ***(please use the scale A-F as benchmark)***<br>Benchmark scale of the PhD-student's contribution to the article<br>**A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant | **A, B, C, D, E, F** |
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| 1. Formulation/identification of the scientific problem | C |
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| 4. Conducting the experimental work/clinical studies/data collection/obtaining access to data | B |
| 5. Conducting the analysis of data | A |
| 6. Interpretation of the results | A |
| 7. Writing of the first draft of the manuscript | A |
| 8. Finalisation of the manuscript and submission | A |
| Provide a short description of the PhD student´s specific contribution to the article.[i]<br>ASPM helped with identifying the problem and developing methods. ASPM contributed to the data extraction, and carried out the data analysis and interpretation. ASPM wrote the first draft, finalised the manuscript, and submitted the manuscript. | |

| 4. Material from another thesis / dissertation[ii] | |
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**5. Signatures of the co-authors[iii]**

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| 9. | | | | |
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**6. Signature of the principal supervisor**

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
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[i] This can be supplemented with an additional letter if needed.

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*"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."*

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# Do protocols for new randomised trials take previous similar trials into account? Cohort study of contemporary trial protocols

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## ABSTRACT

**Objective** To investigate to what extent evidence from previous similar trials or systematic reviews was considered before conducting new trials.

**Design** Cohort study of contemporary protocols for trials with ethical approval.

**Methods** All protocols for randomised trials approved by the five ethical committees in Denmark between January 2012 and March 2013 were screened for eligibility. Included protocols were read in full to determine whether a systematic search had been conducted and references were checked to evaluate whether trial rationale and design could be challenged for not adequately considering previous evidence. To investigate whether protocols cited relevant trials, we used simple search strategies that could easily be conducted by researchers without experience with literature searches.

**Results** Sixty-seven protocols were included. Only two (3%) of the protocols explicitly stated to have conducted a literature search and only one (1%) provided information that allowed the search to be replicated. Eleven (16%) of the protocols described trials where we found the information insufficient to judge if the trial was ethically justified, either due to a comparator that was not supported by the presented evidence (six protocols), because they did not present a rationale for conducting the trial (two protocols), or for both reasons (three protocols). For eight (12%) of the protocols, our search identified trials that could have been relevant to cite as justification.

**Conclusions** While most protocols seem to adequately consider existing evidence, a substantial minority of trials might lack a sufficient evidence base. Very few trials seemed to have been based on a literature search which makes it impossible to know whether all relevant previous trials had been considered. Rules for ethical approval should include requirements for systematic literature searches to ensure that research participants are not exposed to sub-optimal treatments or unnecessary harms as well as to reduce research waste.

## Strengths and limitations of this study

- For the first time, we have examined to what extent contemporary protocols describe systematic literature searches and use the results to inform trial design.
- We performed our own searches to identify any relevant trials that could have been cited.
- Our sample only contain trials approved in Denmark and the sample size was not large enough to perform inferential statistics.
- The legal regulation has changed since the protocols in our sample were approved, meaning that the ethical committees now have access to the investigator's brochure (a document containing clinical information on the studied intervention) which could be important for our conclusions.

## INTRODUCTION

Medical research involving humans must meet high ethical standards. The Declaration of Helsinki specifies that a research project should only be carried out 'if the importance of the objective outweighs the risks and burdens to the research subjects'.[1] As a prerequisite, the Declaration underlines that trial participants are properly informed about the harms and benefits of the studied interventions. Similar requirements are found in the European Clinical Trials Directive[2] and in the Good Clinical Practice guidelines published by the European Medicines Agency.[3] It follows that before a new trial is undertaken, knowledge gained from previous similar trials needs to be considered for trial planning and must also be communicated to the participants.

In 2013, the Standard Protocol Items: Recommendations for Interventional Trials statement was published. It outlines 33 items (with sub-items) that should be adequately reported in clinical trial protocols. Item six is 'Background and Rationale' which describes the importance of justifying a new trial in the context of the available evidence. It is 'strongly recommended that an up-to-date systematic review of relevant studies be summarised and cited in the protocol'.[4]

In Denmark, a systematic literature review is not required in protocols for randomised trials although the Danish Medicines Agency state in their guidelines for applications for clinical trials that relevant results from previous clinical and non-clinical studies must be reported in trial protocols.[5–7] For decades, researchers have argued that in order for a study to be scientifically and ethically justifiable its design should take previous research into consideration based on a systematic review.[8 9] We obtained a cohort of trial protocols approved by one of the five regional research ethics committees in Denmark and used this cohort to study whether the ethical approval system ensures that trials justify their scientific rationale and use of comparators based on previous trials and take their results, whether positive or negative, into account.

## METHODS

Access to trial protocols is possible through the Danish Freedom of Information Act. Between 1 October 2013 and 28 February 2014, we screened the titles of all research projects approved by either one of the five regional ethics committees in Denmark between January 2012 and March 2013. The research projects could be found on the website of the Danish National Committee on Health Research Ethics which functions as a common web-page for all five regional committees. Eligible protocols were then requested from the ethics committees.

### Inclusion and exclusion criteria

A protocol was eligible if it described a randomised, parallel group trial and had prespecified non-surrogate primary outcomes. We excluded trials with only surrogate outcomes as determining the relevance of such outcomes to patients require detailed content area knowledge from diverse fields. We also excluded trials that could not be identified via trial registries as our initial assessment of eligibility was based on information from these registries.

As we identified substantially more eligible trials than we could realistically extract data from, we limited our predefined period of inclusion to 1 October 2012 to 31 March 2013.

The website of the ethics committees only contained information on the date of approval, the project title, the Danish region where the trial would take place and the name of the coordinating investigator. We sought additional information (described below) about the research projects through clinicaltrials.gov, the EU Clinical Trials Register (EudraCT) and the WHO International Clinical Trial Registry Platform using information from the website of the ethics committee (for example, intervention or a trial identifier found in the project title). If we were unable to identify the eligible studies in trial registries, we attempted to identify a trial ID through Google searches using the information from the committee's website. Trial characteristics from these registries were extracted, and eligibility was assessed by one observer. We extracted information on the following characteristics: study type, design, population, interventions, inclusion and exclusion criteria of the trial, primary outcomes and desired sample size. When there was uncertainty about eligibility, a second observer was consulted.

For trials that we considered potentially eligible based on information from trial registries, we contacted the relevant regional ethics committee and requested copies of the protocols, informed consent forms, financial and publication agreements between the study sponsors and the investigators, and any other relevant information about the trials, for example, the investigators' brochure. We emphasised that the results would be published in a manner that would not allow identification of individual trials.

Based on the protocols, we made a final assessment of eligibility and assigned each trial a unique, anonymised identifier.

### Data extraction

As the protocols were long and contained much information irrelevant to our project, one observer entered applicable text into a Word document. The introduction or background section as well as any sections of the protocol addressing ethical issues or clinical information on the used interventions were extracted this way. All subjective judgements based on the extracted texts were performed by two observers independently and all ambiguities or disagreements were discussed, if necessary involving a third observer.

Additionally, all trials where the choice of treatment and comparator could be questioned were discussed with a senior researcher. Our assessments were entered into a standardised data extraction sheet.

Any information in the protocols about the source of funding and the type of comparator used were also extracted from the protocol and entered into the data extraction sheet.

#### Funding issues

A trial was considered fully industry sponsored when a commercial company was listed as the primary or only sponsor; partially industry sponsored when the primary sponsor was a non-commercial entity but a commercial company provided either funding, devices, medications, manpower or similar to the project; and non-industry funded when the sponsor was a non-commercial entity and no commercial funding, devices, medications, manpower or similar was received.

#### Type of comparator

The type of comparator used in the control arm was classified as either an active comparator, placebo or 'nothing'. In trials that used a comparator classified as 'nothing' participants received either no treatment or were put on a waiting list. Trials with more than two arms could use more than one type of comparator; in this case we classified a trial as using a combination of the above, for example, a trial could be classified as

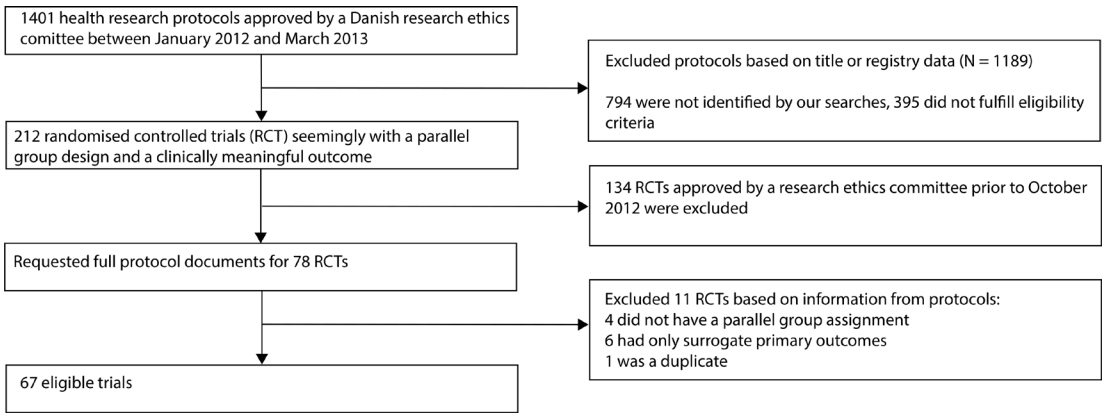


**Figure 1** Flow chart of included studies.

having a placebo arm as well as an active comparator arm. Comparators described in the protocol as 'usual/standard care' could be either 'active treatment' or 'no treatment' and was classified according to the description in the protocol.

### Justification for choice of comparator

We noted whether the choice of comparator in the individual protocol was justified as recommended in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines.[4 10] We distinguished between an explicit and an implicit justification.

We defined that a protocol explicitly justified the choice of comparator when a specific reason for the choice was given, for example, a section such as 'Rationale for choice of comparator' or statements such as 'Regarding justification of placebo: "Placebo is the appropriate comparator, since the approved therapies available in some countries are not routinely used for treatment of lower-risk disease."'

The justification for choice of comparator was considered implicit when, for example, the control group was stated to simply receive the usual standard of care or when there was documented uncertainty about which of two active interventions was superior.

### Literature search

We noted whether it was stated or implied in protocols and related documents whether a systematic literature search had been performed and if search strings, restrictions, filters, dates for searches and names of databases were described.

### Citations of relevant trials or systematic reviews

We read the included protocols in full and checked their references to identify trials of similar interventions, for similar indications and in similar populations. We also checked all references in any systematic reviews that were cited in the protocol to see if these identified relevant trials. When we checked the existing trials and systematic reviews, we looked for both evidence on benefits and harms.

### Our searches for relevant trials

For each protocol, we conducted systematic searches to identify additional randomised trials or systematic reviews that could have been relevant to cite in the protocols. We restricted the study design to randomised trials when searching and we used simple and broad search strategies that could have been performed by researchers without experience with systematic literature searches. We searched PubMed and EMBASE and the search strings followed a general template:

- [Indication] AND [intervention]

For example, the following search string was used for a study of the use of surgical mesh in inguinal hernia operations: *inguinal hernia AND mesh AND fixation*.

All searches were restricted to publications entered into the databases at least one month before the first submission of the protocol to the research ethics committee. We screened titles and abstracts from our searches and potentially eligible trials were read in full text to assess their relevance.

### Analysis

We compared the references in the protocols with the results of our own systematic search.

We deemed a comparator questionable if:

- One or more previous randomised trials conducted with the same intervention, for the same condition and using the same outcome had found that the intervention was superior to the proposed comparator and the choice was not further justified in the protocol.

We deemed the rationale for conducting a study questionable if a protocol did not provide any evidence of clinical equipoise to justify a randomised controlled trial. We based this judgement on the principles outlined in item 6A of the SPIRIT statement[4] and in the SPIRIT explanation and elaboration paper[10] where it is explained that a protocol should 'summarise the importance of the research question, justify the need of the trial in the context of available evidence, and present any available data regarding the potential effects of the interventions (benefits and harms)'.[4 10] Thus we examined if protocols:

- Identified a lack of studies of direct relevance.

Table 1 Prespecified sample size by type of funding

| Patients included | Fully industry sponsored (n=33) | Partially industry sponsored (n=10) | Non-industry sponsored (n=24) |
|---|---|---|---|
| Range | 91–18 000 | 80–2314 | 30–2844 |
| Median | 620 | 311 | 95 |
| Mean | 1799 | 612 | 414 |

- Established that results of previous studies were inconclusive.

We also considered whether the choice of outcomes and methodology (for example, timing of treatment) was appropriate for the scientific question posed, based on the available evidence.

For both the justification of comparators and the scientific rationale for the research question, we did not judge whether a trial was unethical but examined whether the information presented would enable ethics committees to evaluate if the trials were justified.

For studies where we found insufficient information, we summarised the reasons in a tabular format.

### Patient and public involvement

Patients were not involved in this study.

## RESULTS

### Screening and retrieval of protocols

The regional ethics committees approved a total of 1401 protocols between 1 January 2012 and 31 March 2013. We excluded 1189 protocols either because the trials could not be identified in trial registries or via Google searches (n=794) or because they did not fulfil our eligibility criteria (n=395). This is summarised in figure 1.

The remaining 212 protocols all seemed to describe trials with a randomised parallel group design and patient relevant outcomes, based on the available information. As our desired sample size was 60 protocols we excluded all trials approved prior to October 2012 which limited our sample to 78 protocols. We applied to the committees for full access to the protocols and any related documents.

Even though we stressed in our application that results of this project would be published in a way that would not allow identification of individual trials access was initially denied or the protocols were redacted for 25 trials (37%). Details of the redactions in protocols for trials that were industry sponsored are published elsewhere.[11] We gained access to the full unredacted protocols after an appeal to the Danish National Committee on Health Research Ethics, a process which took several years and involved lawyers. This process is also described elsewhere.[11]

After reading the documents we had received, we excluded 11 trials because it turned out they either did not use a parallel group design (n=4), only used surrogate primary outcomes (n=6) or was a duplicate (n=1). This led to our final sample of 67 eligible protocols.

### Study characteristics

Of the 67 included protocols, 33 (49%) were for fully industry sponsored trials, 10 (15%) were partially industry sponsored, and 24 (36%) were non-industry sponsored. Thirty of the fully industry sponsored trials (91%) were multinational, in contrast to five partially industry sponsored trials (50%) and three non-industry sponsored trials (13%).

The prespecified sample sizes in the protocols ranged from 30 to 18 000 patients (mean 1124, median 400). Industry sponsored trials generally had considerably larger sample sizes than trials with no or partial industry funding (see table 1).

Nineteen protocols (28%) described trials in oncology and 10 protocols (15%) surgical interventions. The specialities of the remaining 38 protocols can be seen in table 2.

### Comparators

Placebo was the only comparator in 18 (27%) of the trials. Thirty-two trials (48%) used active comparators only and 10 trials (15%) used no treatment as the only comparator. Six trials (9%) used both a placebo-arm and an arm with an active comparator. One trial (1%) used both an active comparator arm and an arm with no treatment.

Twenty protocols (30%) described the comparator as 'usual care' which in 18 cases was an active comparator and in two was no treatment.

The protocol authors justified their choice of comparator in 42 protocols (63%). The justification was explicit in 21 protocols and implicit in 21, for example, by mentioning that participants in the control group would receive 'standard care'.

We identified 11 protocols (16%) where the choice of treatment or comparator could be questioned given the evidence available at the time and the information provided in the protocols. The reasons for our judgements are described in box 1.

### Literature searches described in protocols and comparison with our search results.

Only 2 (3%) of the 67 protocols explicitly stated to have conducted a literature search and only one of these provided full information that allowed the search to be replicated. The other protocol disclosed only when the search was performed and the databases searched; there were no search strings or information on any restrictions used. Four additional protocols used phrases indicating that a literature search may have been done, for example, 'Review of literature… suggest', 'According to searches on the PubMed database', 'Unfortunately only a few studies examine the effect of MP on acute pain… (PubMed search Feb. 2012)' and 'A review of the literature thus indicates…'.

Table 2 Medical specialities of included protocols

| Speciality | Protocols, n (%) |
|---|---|
| Oncology | 19 (28) |
| Surgery | 10 (15) |
| Obstetrics and gynaecology | 7 (10) |
| Rheumatology | 6 (9) |
| Anaesthesia | 5 (7) |
| Cardiology | 5 (7) |
| Endocrinology | 5 (7) |
| Dermatology | 2 (3) |
| Gastroenterology | 2 (3) |
| Psychiatry | 2 (3) |
| Pulmonary medicine | 2 (3) |
| Geriatrics | 1 (1) |
| Paediatrics | 1 (1) |

Thus, if very broad criteria are applied, the protocol authors did a literature search in six cases (9%).

Twelve protocols (18%) cited either a systematic review or a randomised trial with clear, direct relevance for the intervention, population and/or indication studied. Two protocols (3%) cited one or more systematic reviews, eight protocols (12%) cited one or more randomised trials and two protocols (3%) cited both systematic reviews and randomised trials. For 11 of these 12 protocols (92%), we did not find additional relevant trials through our own systematic search. For the remaining one protocol (8%), we identified one systematic review and two randomised trials (819 included trial participants) that could have been relevant to cite.

The remaining 55 protocols (82%) cited no relevant systematic reviews or randomised trials. However, for 48 of these 55 protocols (87%), we did not identify any studies that could have been cited. For the remaining seven protocols (13%), we identified 10 randomised trials and one systematic review (with a total of 2080 included trial participants) that could have been cited. These results are summarised in table 3.

**Box 1 Examples of studies where the justification could be challenged, based on the information available in the protocols.**

- A study examined the effect of a procedure on the fertility rate. The control group did not get a procedure that the protocol authors described as the gold standard.
- A phase 3 study was initiated before phase 2 studies were completed although the studied drug belonged to a class known to be quite toxic.
- A study examining treatment for serious cardiovascular disease used a bare metal stent as comparator, even though a systematic review found that a drug-coated stent was more effective regarding the primary outcome of the study.
- A study examining the effect of a special form of exercise used a control group that received no intervention even though the effects of exercise on the primary outcome (quality of life) were well established.
- A study compared 'liberal' and 'restrictive' red blood cell transfusion practices despite citing a systematic review which found that, 'According to the results of the largest RCT, maintaining a higher haemoglobin level… seems to confer little clinical benefit.' Furthermore, it has been shown that blood transfusions carry important harms.
- A study compared a training programme that started in the hospital and continued at home with usual practice (ie, very little rehabilitation) in elderly patients. The benefits of training were well established.
- A study convincingly established that a special diet is effective in reducing postoperative infections but the most effective timing of intervention had yet to be established; however, preoperative administration of the diet was compared with usual diet rather than a different timing of the diet.
- A study examining relapse free survival for a type of cancer compared an investigational drug with observation only although other treatments had shown effects on the primary outcome when compared with observation only.
- Three studies examined the efficacy of analgesic drugs or techniques and used placebo as comparator, although other treatments had been proven effective. All the studies allowed for the use of rescue medication in some form, but it was clear that patients in the placebo groups received sub-optimal treatment.

## DISCUSSION

### Principal findings

We found that only one (1%) of the 67 included protocols described a reproducible systematic search for previous randomised trials of the same intervention. Even when applying very broad criteria, only six (9%) protocols indicated that a search may have been carried out, whether systematic or not. We found 12 (18%) protocols that cited relevant systematic reviews or randomised trials. The remaining 55 (82%) protocols cited no such evidence but our own searches did not identify any relevant systematic reviews or randomised trials for 48 of them.

Sixteen percent of included trial protocols either did not present a rationale for conducting the study or used comparators that could be questioned based on the evidence available at the time and did not provide information to explain these choices. While these trials may be ethically acceptable, we were unable to confirm this based on the information available in the protocols. Thus, a considerable number of research participants could potentially have been exposed to sub-optimal treatment or unnecessary inconvenience, discomfort or risk of harm.

A systematic search for previous trials is not an explicit requirement for ethical approval in Denmark but it is difficult to see how researchers can know whether relevant previous trials exist without performing a systematic search, especially considering the high number of new publications today. In 2010, a study found that 75 reports of trials and 11 systematic reviews were published every day and these numbers had been rising.[12]

Table 3 Citations of trials and reviews of direct relevance

| | |
|---|---|
| Cited trials or reviews of direct relevance and no additional studies were identified | 11 protocols (16%) |
| Cited no trials or reviews of direct relevance and no relevant studies were identified | 48 protocols (72%) |
| **Protocols where no additional relevant trials or reviews were identified through our searches** | **59 protocols (88%)** |
| Cited trials or reviews of direct relevance, but additional relevant studies were identified | 1 protocol (1%) |
| Cited no trials or reviews of direct relevance, but relevant studies were identified | 7 protocols (11%) |
| **Protocols where additional relevant trials or reviews were identified through our searches** | **8 protocols (12%)** |
| **Total** | **67 protocols (100%)** |

Although conducting trials on topics where previous trials exists can be warranted (eg, to replicate findings or when a previous trial could not answer the research question due to either size or quality), there is evidence that superfluous trials represent a considerable waste of resources, both in terms of financial and intellectual resources.[13] A formal requirement for systematic searches in trial protocols may reduce this waste.

## Comparisons with other studies

There are historical cases of superfluous trials, for example, of intravenous streptokinase as thrombolytic treatment. In 1992, a cumulative meta-analysis showed that in 1973, after just eight trials of 33 total performed since the late 1950s, a consistent and statistically significant reduction in total mortality was shown. The remaining 25 trials (with a total of 34 542 participants enrolled) had little effect on the OR and only narrowed the CI.[14] Still, new trials of the intervention were performed until the late 1980s. As meta-analyses were not routinely used at this point in time, we should not judge this by modern standards. However, it highlights the importance of examining existing evidence before conducting a new trial.

Several previous studies have examined published protocols to assess if they live up to ethical requirements. In 2016, a study found that 41% of 101 trial protocols cited any randomised trial or a systematic review, whether the trials addressed a similar question or not.[15] We found that only 18% of protocols cited a randomised trial, which may be because we only included trials that we found to be of direct relevance for the protocol. Additionally, the 2016 study included only published protocols whereas we included any protocol given ethical approval.

Several studies have investigated whether publications of randomised trials reference previous trials, and it has repeatedly been shown that this is often not the case. In 2011, a study of 1523 trials found that less than a quarter of the relevant previous trials were cited, and that for the 1101 RCTs where five or more previous trials could have been cited, 23% cited no trials and another 23% cited only one.[16] In 2010, Clarke *et al.* reproduced their previous findings from 1997, 2001 and 2005 that most reports of trials fail to cite updated systematic reviews when discussing their results.[9]

## Strengths and limitations

To our knowledge, this is the first cohort of contemporary protocols approved by an ethics committee that have studied whether they live up to the ethical standards expressed in the Declaration of Helsinki.[1] We chose to be conservative when judging whether the choice of comparator was reasonable given existing evidence for potentially effective treatments and whether an evidence base supporting the rationale for the investigated treatment was provided, because such assessments are inevitably subjective.

Our included protocols are over five years old but as systematic literature searches are still not mandatory for approval of protocols in Denmark, our results are likely valid today. Ethics committees in Denmark now have access to the investigators' brochure which might contain some of the information we looked for but did not find.

Some of the protocols in our sample described trials involving medications or devices at an early stage of development and for such trials systematic reviews are unlikely to exist. However, a systematic search could still be relevant as similar interventions may have been tested. In 2006, six participants developed multiple organ failure after a phase 1 trial in the UK, and it has been suggested that a systematic review of preclinical and clinical data could have predicted the life-threatening adverse effects.[17 18]

We did not search for unpublished trials in our own systematic searches. Publication bias is a significant problem in medical research,[19] and trials with positive results are more likely to be published. Thus, there could be relevant studies that we did not identify. However, expecting protocol authors to find these may be unreasonable.

We did not search for observational studies, although they can be important for detecting rare or unexpected harms. It is therefore possible that we would have found additional interventions or comparators to be problematic, had we included such studies

Finally, the reporting and reproducibility of our study is limited by the confidentiality agreements signed in order to obtain access to protocols.

## Implications for practice and research

Other researchers have highlighted problems with the current system of ethical approval and shown examples of cases where unethical studies were granted ethical approval.[15 20] Our review supports the need for policy changes.

We suggest that protocols and other documents should be made publicly available as soon as the protocol has received ethical approval. These documents are currently very difficult to get access to, especially for trials with commercial sponsors.[10] Access to such documents is of vital public interest as it is the public that participate in trials, and the safety and rights of research participants should be weighted higher than commercial interests. Indeed, commercial interests are likely not at stake as trial protocols rarely contain commercially sensitive information.[21]

We also propose a requirement to conduct a systematic literature search prior to applications for ethical approval. In 2005, The *Lancet* made it a requirement for authors of clinical trials to include a clear summary of previous research and explain how their trial results affect the summary.[22] In 2010, the executive editor and editor-in-chief of the *Lancet* commented on the disappointing implementation of this policy and made the policy more specific by requiring that authors either conduct their own systematic review or cite a recent systematic review and put their own trial results into this context.[23] Almost no other journals have a similar policy and the responsibility to safeguard the rights of participants should be shared with ethics committees.

Lastly, we recommend that ethics committees formally endorse and apply the SPIRIT statement[4 10] which is an evidence-based set of items that should be addressed in a protocol. We believe all protocols for randomised trials submitted to ethics committees should follow the format and report on the items presented in the SPIRIT statement.

**Contributors** PCG came up with the idea for the study and wrote the protocol. MCO, MM and ASPM collected data. MCO, ASPM and JV analysed the data. ASPM, JV, KJJ and PCG interpreted the data. ASPM wrote the first draft manuscript. All authors read and commented on the final manuscript.

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# Paper 2

Are potential clinical trial participants adequately informed about benefits and harms? A comparison of informed consent materials and trial protocols

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*Submitted for publication*

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

# PHD-THESIS
# DECLARATION OF CO-AUTHORSHIP

*The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.*

| **1. Declaration by** | |
|---|---|
| Name of PhD student | Asger Sand Paludan-Müller |
| E-mail | asp@cochrane.dk |
| Name of principal supervisor | John Brodersen |
| Title of the PhD thesis | The need for a new randomised trial |

| **2. The declaration applies to the following article** | |
|---|---|
| Title of article | Are potential clinical trial participants adequately informed about benefits and harms? A comparison of informed consent materials and trial protocols |
| **Article status** | |
| Published ☐<br>Date: | Accepted for publication ☐<br>Date: |
| Manuscript submitted ☒<br>Date: 19-08-2020 | Manuscript not submitted ☐ |
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| **3. The PhD student's contribution to the article** ***(please use the scale A-F as benchmark)***<br>Benchmark scale of the PhD-student's contribution to the article<br>**A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant | **A, B, C, D, E, F** |
|---|---|
| 1. Formulation/identification of the scientific problem | B |
| 2. Development of the key methods | B |
| 3. Planning of the experiments and methodology design and development | B |
| 4. Conducting the experimental work/clinical studies/data collection/obtaining access to data | B |
| 5. Conducting the analysis of data | A |
| 6. Interpretation of the results | B |
| 7. Writing of the first draft of the manuscript | A |
| 8. Finalisation of the manuscript and submission | B |
| Provide a short description of the PhD student´s specific contribution to the article.[i]<br>ASPM helped with identifying the problem and developing methods. ASPM contributed to the data extraction, and carried out the data analysis and interpretation. ASPM wrote the first draft, finalised the manuscript, and submitted the manuscript. | |

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**5. Signatures of the co-authors[iii]**

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| 10. | | | | |

**6. Signature of the principal supervisor**

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
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Principal supervisor:

**7. Signature of the PhD student**

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Date: 24/09/20
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[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):
*"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."*
[iii] If more signatures are needed please add an extra sheet.

# Are potential clinical trial participants adequately informed about benefits and harms? A comparison of informed consent materials and trial protocols

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**Abstract**

*Background: We sought to* examine if information on benefits and harms in planned randomised trials described in documents available to ethics committees are also available in the information in Informed Consent Documents (ICDs).

*Methods:* Cohort study of trial protocols compared with informed consent documents, obtained through Freedom of Information requests, for 67 trials approved by ethics committees in Denmark. All data was extracted by one researcher and checked by another.

*Main outcome measures:* Proportion of trials where information on benefits and harms in ICDs does not match information available to ethics committees; proportion of trials where the harms that were not mentioned in ICDs are either serious or common.

*Results:* The information in ICDs did not overstate the benefits for any of the included trials. For two of 67 trials (3%) we found that benefits were understated in the ICDs. For 28 of 67 trials (42%), harms mentioned in documents submitted to the ethics committees were not mentioned in the ICDs. For 22 of these 28 trials (76%), we considered that at least one harm was either so common or serious that this may conflict with the Helsinki Declaration section on informed consent. Thirty of the 67 trials (45%) did not inform patients that unforeseen harms might occur, which also conflicts with the Helsinki Declaration.

*Conclusions:* Almost half of the included trials did not mention harms described in material available to ethics committees in the information available to potential trial participants. We assessed most of these unmentioned harms to be either serious or common.

*Keywords: Research ethics, informed consent, harms, clinical study protocols*

## Background

A fundamental ethical principle underlying clinical research involving humans is expressed in the 26th principle of the Declaration of Helsinki, under the subsection "Informed consent". It states that potential trial participants must be informed about "*the anticipated benefits and potential risks of the study and the discomfort it may entail*" and that "*ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing.*"[1] Thus, if the participants are not adequately informed about the benefits and harms, an informed decision whether or not to participate in the trial is not possible.[1–3]

According to the guidelines published by the Danish National Committee on Health Research Ethics, the Informed Consent Documents (ICD) must contain information about all known or predictable harms of participating in the trial and must also explicitly mention that unforeseen harms or inconveniences might occur; harms must be mentioned without regard to their frequency or severity, i.e. it is not sufficient to mention only the most severe or the most common harms.[4] In the United Kingdom, the Medical Research Council has published guidance on informed consent that appear less specific. It mentions that ICDs must contain *"A fair and honest evaluation of the consequences of research, including possible significant benefits and harms and their relative likelihoods must be described to potential participants."* [5] In the United States, the Food and Drug Administration requires the ICD to contain "*a description of any predictable risks*" as well as information on any possible discomfort and any possible benefits.[6]

Thus, while the exact requirements vary between countries, a description of known or predictable benefits and harms is universally accepted as a requirement for informed consent and the conduct of clinical research. Nonetheless, research has shown that trial participants sometimes feel inadequately informed [7, 8], indicating that true informed consent is not always obtained.

We examined to what degree descriptions of benefits and harms in a sample of unpublished clinical study protocols (CSPs), obtained from the Danish regional ethics committees through a Freedom of Information Act request, match information provided to potential participants in informed consent documents (ICDs). This sample of protocols has previously been used to study whether the choice of comparator treatments was justified.[9]

## Methods

### *Retrieval of clinical study protocols*

Access to CSPs and related materials was possible through Freedom of Information requests to the five regional ethics committees, which handle all applications for ethical approval of clinical trials that take place in Denmark, partially or fully.

We included CSPs from any parallel group randomised clinical trial within all clinical fields and excluded trials with only surrogate primary outcomes because determining whether such outcomes were relevant and adequately described to patients requires detailed content area expertise from diverse clinical fields.

*Identification and retrieval of trials.*

On the website of the Danish National Committee on Health Research Ethics, we identified all clinical trials approved between January 2012 and March 2013. We used information from the website to locate these trials in trial registers (clinicaltrials.gov, the EU Clinical Trials Register, and the WHO International Clinical Trial Registry Platform.)[10–12] We used the information in the trial registers to determine which trials met our eligibility criteria.

As we identified substantially more relevant trials than we needed for our analysis, we limited the period of inclusion to October 2012 to March 2013. We requested requesting the following documents from the relevant regional committees: CSPs, Informed Consent Documents, financial agreements between study sponsors and investigators, publication agreements between study sponsors and investigators, and any

other relevant documents, e.g. the Investigator's Brochure. Based on the CSPs we made a final eligibility assessment. The process of obtaining the documents is described in more detail elsewhere.[9]

***Data extraction***

*Trial characteristics*

One observer extracted trial characteristics from the CSPs, and if necessary, from other documents, for all included trials. We extracted the following information:

- Title
- Medical speciality
- Experimental intervention and comparator(s) used, including dosing schedules
- Number of arms
- Single-site or multi-centre study
- Planned sample size
- Funding sources
- Trial duration
- Primary outcomes
- Trial phase (not relevant for trials studying procedures or non-medicinal products).

The trial characteristics were entered into a Microsoft Excel spreadsheet.[13]

*Information on benefits and harms*

One observer extracted all information on the known possible benefits and harms of the active intervention from the CSPs and other relevant documents (e.g. the Investigator's Brochure if available).

From the ICD, one observer extracted the same information, i.e. all information on known possible benefits and harms of the active intervention. We also checked whether participants were informed that unknown harms might arise.

All extracted data were checked by a second observer.

The available information on benefits and harms was copied from the CSPs (and other documents, such as Investigators' Brochure or summaries in Danish) and ICDs into a separate Excel spreadsheet for each trial to allow a comparison of the information available for investigators and trial participants.

We noted which benefits and harms were mentioned, as well as any estimates of their likelihoods and counted the number of benefits and harms mentioned in the CSPs and other documents and noted how many of these that were mentioned in the ICD.

***Analysis***

One observer compared the information on specific benefits and harms provided in CSPs with that in the ICDs. We assessed to which degree the included trials fulfilled our four pre-specified domains described below. All judgements were checked by another observer. Any cases of doubt were discussed with a senior researcher.

1. *Do the benefits of the active intervention(s) described in the ICD match those described in the documents available to the ethics committees?*

In case of disagreement, we conservatively assumed this domain was fulfilled.

2. *Do the harms of the active intervention(s) described in the ICD match those described in the other materials available to the ethics committees?*

As benefits and harms were not always described in the same way in CSPs and ICD's, there is some degree of subjectivity in making this judgement. In cases where there was still doubt after discussion with a senior researcher, we conservatively assumed that this domain was fulfilled.

3. *If harms are not described, are these either serious or common?*

We defined an event as common if it was expected to occur in more than 1% of participants. Regarding the criteria of seriousness, as this is a subjective judgement, a third researcher was involved in cases of disagreement and we conservatively assumed that this domain was fulfilled in cases were agreement could not be reached.

4. *Is it explicitly mentioned in the ICD that unknown harms might arise during the study?*

We only noted this criterion as being met if it was mentioned explicitly in the ICD.

*Statistical analyses*

We present descriptive statistics for the trial characteristics and our pre-specified criteria.

For ICDs that did not mention all known possible benefits and harms, we calculated the proportion of benefits and harms mentioned and present the median and interquartile range for all studies.

We planned to explore differences between trials with different types of funding, but our sample size was too small for such analyses.

## Results

### *Screening and retrieval of documents*

We identified 1,401 CSPs approved by the regional ethics committees between 1 January 2012 and 31 March 2013. We excluded 1,189 CSPs because we were not able to identify the trials in trial registries (n=794) or because they did not meet our eligibility criteria (n=395). The remaining 212 CSPs all seemed to be eligible based on the information available, but as our pre-specified target sample size was 60 CSPs we

excluded all trials approved prior to October 2012; this limited the initial sample to 78 CSPs for which we applied for full access to CSPs and related documents.

After reading the CSPs, we excluded a further 11 trials as they did not meet our eligibility criteria. Thus, our final sample consisted of 67 CSPs. The process is summarised in **Figure 1.**

***Characteristics of included trials***

Of the 67 included trials, 33 (49%) were fully industry sponsored, 10 (15%) were partially industry sponsored, and the remaining 24 (36%) were non-industry sponsored. Thirty-eight of the included trials (57%) were multi-national trials. Industry sponsored trials were much more likely to be multinational (30 (91%) versus five (50%) and three (13%) for partially and non-industry sponsored trials, respectively).

Planned sample sizes ranged from 30 to 18,000 participants (mean 1125, median 400). Fully industry sponsored trials were generally larger than partially and non-industry sponsored trials with a median planned size of 620 versus 311 and 95, respectively.

The included trials are described in more detail elsewhere[9] and characteristics are summarised in the **Appendix**.

***Description of benefits and harms in Informed Consent Documents***

Overall, the ICD adequately described the benefits of participating in the trials. Two of 67 included trials (3%) understated the benefits in the ICD by not describing benefits mentioned in the CSPs. Eight trial ICDs (12%) explicitly stated that participants would not gain direct benefits, although the hypothesis of the trial was superiority of one intervention.

For 28 trials (42%), the ICDs did not contain information on all harms that were explicitly mentioned in the documents submitted to the ethics committees.

For the trials where ICDs did not contain information on all the known possible harms, the median percentage of harms mentioned was 68% (IQR: 45% to 82%).

In 22 of the 28 trials (79%) where ICDs did not mention all the known possible harms, at least one of the unmentioned harms was assessed to be either serious or common (See **Table 1** for examples). Thus, for 22 trials (33%), the ICDs likely did not present the important known harms in a manner sufficiently allowing for informed consent. Whether harms were common was difficult to judge in some cases, as several CSPs did not describe their expected frequency. Twelve of the 28 trials (42%) where all harms were not mentioned in the ICDs did not present expected frequency; we conservatively classified the harms in these trials as being so uncommon that they need not be mentioned.

For 30 trials (45%), it was not mentioned in the ICD that unknown harms could arise during the study. The ICD for 6 trials (9%) claimed or insinuated that there were no risks or harms associated with participating in the trial. Excerpts from these trials are available in **Table 2.**

## Discussion

In this study, we explored whether recent trials lived up to the requirements for informed consent as stipulated in Principle 26 of the Declaration of Helsinki.[1] While patients were generally adequately told about the possible benefits of participating in the Informed Consent Documents for the included trials, ICDs for eight trials (12%) explicitly said that participants would not get any direct benefit even though the experimental treatment were hypothesised to be superior. We also found that almost two-thirds of ICDs (64%) did not inform participants adequately about potential harms; either by not informing of all serious and common harms (9%), by not explicitly mentioning that unknown harms can arise during a trial (31%), or both (24%).

Our previous study, based on the same sample, assessed whether Principles 17 and 21 were met. These state that "*All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with*

*foreseeable benefits to them to other individuals or groups affected by condition under investigation"* and *"Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation."*[1] We found that 11 of the 67 trials (16%) did either not present a rationale for conducting the trial or a justification for the choice of comparator.[9]

Together, this suggests several possible breaches in the current system of ethical approval of clinical trials.

Additionally, we have shown that access to essential documents such as trial CSPs is difficult to obtain; although we stressed in our request that we would report results in a way that would not allow for identification of individual trials, we were initially not granted full access to 25 trials (37%) as individual local committees did not interpreted the rules differently. We were either denied access to any documents or the documents where redacted. After a lengthy appeal process involving the Danish National Committee on Health Research Ethics, we were granted full access to unredacted CSPs for all trials. This process, and the details of the redactions, is described elsewhere.[14]

*Strengths and limitations*

Our study has several strengths. To our knowledge, this is the first study to compare information about benefits and harms available to ethical committees with the information provided to research participants. This is likely because the possibility to obtain access to these documents through the Ethics Committee system is quite unique to Denmark. Our sample could therefore include unpublished CSPs describing relatively recent trials. More than half of the included trials were multi-national trials, so we consider it likely that our results may be generalisable. Finally, as we judged all domains conservatively, our results likely represent a best-case scenario.

However, our study also has important limitations. Firstly, we only compared the harms described in the ICDs with those mentioned in the CSP and other submitted documents. As all important harms may not

have been mentioned in the submitted documents, it is possible that there are important harms that were not considered. Additionally, at the time of our request the Danish Ethics Committees did not require access to the Investigators Brochure where a more detailed account of possible harms is given. It could be considered a limitation that we only included trials approved by Danish Ethics Committees; however, as more than half of the included trials were multi-national, and since we are not aware of any reason why the situation in Denmark would be substantially different from other countries, we believe our findings are also relevant in other countries. Finally, an important limitation is that we had to sign confidentiality agreements to obtain the CSPs and related documents. Thus, we are unable to provide details that would allow for identification of individual trials which precludes data sharing and limits the transparency and reproducibility of our study.

*Relation to previous research*

We are not aware of any previous studies that have compared information on benefits and harms provided to research participants with the information available to ethics committees. A 2012 study found that participants in two trials did not feel adequately informed about benefits and harms.[8] A 2009 review identified 16 studies that examined trial participants' understanding of complications and risk of participating in clinical trials and concluded that "*risks and benefits of participation as well as alternatives to treatment appeared to have been comprehended by a relatively small number of participants in clinical trials."*[15] Thus, our findings are in concordance with previous studies showing that a substantial proportion of trial participants are likely not adequately informed, and less so for the harms than the benefits of participating in clinical research.

*Implications for practice and research*

The current system of ethical approval of clinical trials may not adequately ensure that true informed consent is possible. An explicit requirement that ethical approval of future trials include an assessment of the adequacy of information provided to potential trial participants seems necessary. The information on

harms in ICDs for approved trials is not always adequate but we have not examined to what degree the harms mentioned in the documents submitted to ethics committees match harms described in the medical literature for the relevant interventions; this should be examined in future research. Future research should also elucidate how information on potential harms are best communicated to patients.

*Conclusion*

In our sample of 67 relatively recent trials, information material for potential participants generally described benefits adequately. However, serious and common harms were not mentioned in such materials for 22 of the trials (33%), whereas 30 trials (45%) failed to inform that unknown harms might arise, despite explicit requirements to do so. Thus, the current system of ethical approval might not ensure informed consent.

*List of abbreviations*

ICD: Informed Consent Documents

CSP: Clinical Study Protocol

**Declarations**

*Ethics approval and consent to participate*

Not applicable.

*Consent for publication*

Not applicable

*Availability of data and materials*

The datasets generated and/or analysed during the current study are not publicly available due as we had to sign confidentiality statements in order to obtain access to the documents.

*Competing interests*

None declared.

*Funding*

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*Authors' contributions*

PCG came up with the idea for the study. ASPM, PCG, and KJJ wrote the protocol. MCO, MM, and ASPM collected data. ASPM analysed the data. ASPM, KJJ, and PCG interpreted the data. ASPM wrote the first draft manuscript. All authors read and commented on the final manuscript.

*Transparency declaration*

Asger Sand Paludan-Müller, the study's guarantor, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

*Acknowledgements*

We wish to thank David T. Laursen for his help assessing which harms were either serious or common enough that they should have been mentioned.

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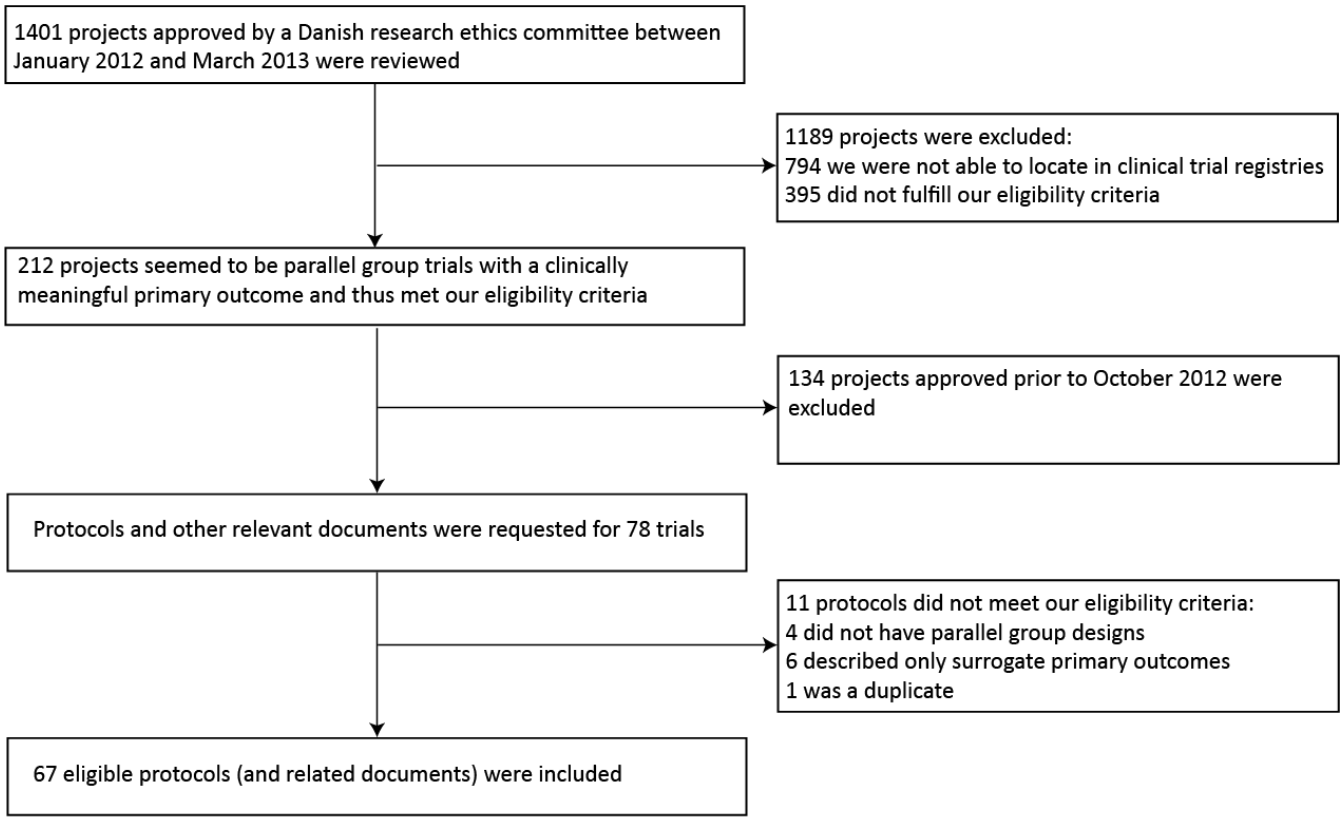
***Table 1 - Examples of serious or common harms not mentioned in informed consent documents***

| |
|---|
| Examples of harms that were not mentioned, but we considered important due to their prevalence:<br><br>- Fatigue (experienced by 56.4% of subjects receiving medication in a previous trial)<br>- Nausea (experienced by 43.6% of subjects receiving medication in a previous trial)<br>- Increased sweating (observed in 'almost all' that take medication)<br>- Irritability (observed in more than 1/100 that take medication)<br>- Disorientation (observed in more than 1/100 that take medication) |
| Examples of harms that were not mentioned, but were considered important due to their seriousness:<br><br>- Sudden death<br>- Stevens-Johnson's Syndrome<br>- Acute renal failure<br>- Respiratory failure<br>- Leukaemia<br>- Bleeding<br>- Aneurysms<br>- Polymyalgia rheumatica |

***Table 2 - Excerpts from ICDs claiming or insinuating no risks or harms***

| Excerpts from ICDs claiming or insinuating that there were no risks or harms associated with participating in trials: |
| --- |
| • "There is not estimated to be any risks associated with your participation the trial."<br>• "There are no disadvantages associated with your participation."<br>• "The trial poses no specific risk for you, as the treatments you are offered are treatments that are already used broadly."<br>• "We don't expect you to have any advantages or disadvantages from participating in the study."<br>• "There are no expected adverse effects, discomfort, or risks associated with participating in the study."<br>• "There are no risks or adverse effects associated with participating in the trial." |

**Figure 1**


1401 projects approved by a Danish research ethics committee between January 2012 and March 2013 were reviewed
1189 projects were excluded:
794 we were not able to locate in clinical trial registries
395 did not fulfill our eligibility criteria
212 projects seemed to be parallel group trials with a clinically meaningful primary outcome and thus met our eligibility criteria
134 projects approved prior to October 2012 were excluded
Protocols and other relevant documents were requested for 78 trials
11 protocols did not meet our eligibility criteria:
4 did not have parallel group designs
6 described only surrogate primary outcomes
1 was a duplicate
67 eligible protocols (and related documents) were included

# Paper 3

Are investigators' access to trial data and rights to publish restricted and are potential trial participants informed about this? A comparison of trial protocols and informed consent materials

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*Submitted for publication*

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

# PHD-THESIS
# DECLARATION OF CO-AUTHORSHIP

*The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.*

| **1. Declaration by** | |
|---|---|
| Name of PhD student | Asger Sand Paludan-Müller |
| E-mail | asp@cochrane.dk |
| Name of principal supervisor | John Brodersen |
| Title of the PhD thesis | The need for a new randomised trial |

| **2. The declaration applies to the following article** | |
|---|---|
| Title of article | Are investigators' access to trial data and rights to publish restricted and are potential trial participants informed about this? A comparison of trial protocols and informed consent materials |
| **Article status** | |
| Published ☐<br>Date: | Accepted for publication ☐<br>Date: |
| Manuscript submitted ☒<br>Date: 30-09-2020 | Manuscript not submitted ☐ |
| If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information). | |

| **3. The PhD student's contribution to the article** ***(please use the scale A-F as benchmark)***<br>Benchmark scale of the PhD-student's contribution to the article<br>**A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant | **A, B, C, D, E, F** |
|---|---|
| 1. Formulation/identification of the scientific problem | B |
| 2. Development of the key methods | B |
| 3. Planning of the experiments and methodology design and development | B |
| 4. Conducting the experimental work/clinical studies/data collection/obtaining access to data | B |
| 5. Conducting the analysis of data | A |
| 6. Interpretation of the results | B |
| 7. Writing of the first draft of the manuscript | A |
| 8. Finalisation of the manuscript and submission | B |
| Provide a short description of the PhD student´s specific contribution to the article.[i]<br>ASPM helped with identifying the problem and developing methods. ASPM contributed to the data extraction, and carried out the data analysis and interpretation. ASPM wrote the first draft, finalised the manuscript, and submitted the manuscript. | |

| 4. Material from another thesis / dissertation[ii] | |
|---|---|
| Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)? | Yes: ☐ No: ☒ |
| If yes, please state name of the author and title of thesis / dissertation. | |
| If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another. | |

**5. Signatures of the co-authors[iii]**

| | Date | Name | Title | Signature |
|---|---|---|---|---|
| 1. | 21-09-2020 | Michelle C. Ogden | MSc | |
| 2. | 24/09/20 | Mikkel Marquardsen | MD | |
| 3. | 21-09-2020 | Karsten J. Jørgensen | MD, DMSc | |
| 4. | 22-09-2020 | Peter C. Gøtzsche | MD, DMSc, MSc | |
| 5. | | | | |
| 6. | | | | |
| 7. | | | | |
| 8. | | | | |
| 9. | | | | |
| 10. | | | | |

**6. Signature of the principal supervisor**

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 28/09/20
Principal supervisor:

**7. Signature of the PhD student**

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 24/09/20
PhD student:

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

*"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."*

[iii] If more signatures are needed please add an extra sheet.

# Are investigators' access to trial data and rights to publish restricted and are potential trial participants informed about this? A comparison of trial protocols and informed consent materials

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**Abstract**

*Objectives:* To determine to which degree industry partners in randomised clinical trials own the data and can constrain publication rights of academic investigators.

*Methods:* Cohort study of trial protocols, publication agreements and other documents obtained through Freedom of Information requests, for a sample of 42 trials with industry involvement approved by ethics committees in Denmark.

*Main outcome measures:* Proportion of trials where data was owned by the industry partner, where the investigators right to publish were constrained and if this was mentioned in informed consent documents, and where the industry partner could review data while the trial was ongoing and stop the trial early.

*Results:* The industry partner owned all data in 20 trials (48%) and in 16 trials (38%) it was unclear. Publication constraints were described for 30 trials (71%) and this was not communicated to trial participants in informed consent documents in any of the trials. In eight trials (19%) the industry partner could review data during the trial, for 20 trials (48%) it was unclear. The industry partner could stop the trial early without any specific reason in 23 trials (55%).

*Conclusions:* Publication constraints are common, and data is often owned by industry partners. This is rarely communicated to trial participants. Such constraints might contribute to problems with selective outcome reporting. Patients should be fully informed about these aspects of trial conduct.

*Keywords: Research ethics, informed consent, publication rights, publication bias, clinical study protocols*

## Background

Cooperation between pharmaceutical companies and academic investigators is common for randomised clinical trials (RCTs).[1, 2] While this has advantages, it is essentially a business transaction and conflicts of interest abound. There is convincing empirical evidence of selective reporting of results in industry funded trials [1, 3], and industry trials are less likely to be published than non-industry trials.[4, 5]

The World Medical Association's Declaration of Helsinki states that "*researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects"* and that "*Negative and inconclusive as well as positive results must be published or otherwise made publicly available."*[6]

However, it may be difficult for investigators in industry-sponsored trials to adhere to these requirements, as their rights to publish may be constrained. Previous studies have examined constraints on publication rights in industry-initiated trials. In 2006, a study found that 40 of 44 (91 %) trials approved by ethics committees in Denmark between 1994 and 1995 described constraints on publication for participating clinicians in the trial protocol and the same was true for 41 of 44 trials (93%) approved in 2004.[7] In 2016, a study examined whether there were constraints on publication in 647 protocols approved by ethics committees in Switzerland and Germany between 2000 and 2003. Four-hundred-fifty-six (70%) trial protocols mentioned publication agreements and in 393 of those (86%) the industry partner had the right to either disapprove or at the least review publications.[8]

Both studies used relatively old samples. To our knowledge, no study has examined publication constraints in a recent sample of randomised clinical trials (RCTs) approved by ethics committees. Additionally, none of the previous studies have compared information on publication restraints available to ethics committees with the information provided to research participants, who should be informed about key conditions of the trial prior to making an informed decision according to the Helsinki Declaration. As altruism is generally

considered an important reason for participating in clinical trials [9, 10], it is important that patients are informed of potential publication constraints.

Another potentially problematic issue in clinical trials is early stopping. A 2010 review found that for trials stopping prematurely for benefit, effects were exaggerated by 29% compared to trials of the same intervention that had not stopped early and this bias persisted regardless of whether stopping rules were pre-defined.[11] In the 2006 study, the industry sponsor had access to accumulating data in 16 out of 44 trials (36%) and the sponsor could stop the trial at any time, for any reason, in an additional 16 trials (36%).[7]

In this study we examined to which degree access to data and the right to publish is restricted, whether this is communicated to patients, and whether the industry partner has the opportunity to accumulate data and stop the trial prematurely. We used a sample of relatively recent RCTs approved by ethics committees in Denmark. This sample was also used to examine to which degree trial rationale and choice of comparator was justified through prior literature reviews [12] and whether potential trial participants were adequately informed of benefits and harms associated with participating in the trial.[13]

## Methods

### *Access to clinical trial protocols*

As described elsewhere[12, 13] we gained access to clinical study protocols and other documents submitted to Danish ethics committees through Freedom of Information requests.

We included protocols from parallel group RCTs with industry involvement from all clinical fields. We excluded trials with only surrogate primary outcomes, as it requires detailed content area expertise from diverse clinical fields to determine the clinical relevance of such outcomes.

*Identification and retrieval of trial documents*

We used the website of the Danish National Committee on Health Research Ethics[14] to identify all clinical trials approved by them between January 2012 and March 2013. We then used information from the website to identify the trials in trial registries (clinicaltrials.gov, the EU Clinical Trials Register, and the WHO International Clinical Trial Registry Platform).[15–17] We used this information to identify potentially eligible trials but limited the period of inclusion to October 1 2012 to March 31 2013, as we identified substantially more trials than we needed for our analysis.

For eligible trials, we submitted Freedom of Information requests to the regional ethics committees in Denmark to obtain the following documents: Clinical study protocols , informed consent documents, publication agreements between study sponsors and investigators, financial agreements between study sponsors and investigators, and any other relevant documents. We used the protocols to make a final assessment of eligibility.

The process of identifying and retrieving relevant trial documents is described in detail elsewhere.[12]

***Data extraction***

All data were extracted by one researcher and checked by another researcher. Any discrepancies were solved through discussion, potentially involving a third researcher.

*Characteristics of included trials*

For all trials, we extracted the following characteristics from the protocols: medical specialty, experimental intervention and comparator(s), number of arms, single-site or multi-centre study, planned sample size, funding source, trial duration, primary outcomes, and trial phase.

We determined whether trials were partially or fully industry sponsored. We considered a trial fully industry sponsored when a commercial entity was the primary or only sponsor and partially industry sponsored when the primary sponsor was a non-commercial entity but a commercial entity provided either medication, devices, manpower, funding or similar to the trial.

*Information on rights to data and publication constraints*

We extracted information on the roles and responsibilities of sponsors, ownership of data and rights to access data, as well as whether publication constraints existed and the nature of such constraints. The information was extracted from the protocols and other relevant documents (e.g. publication agreements or layperson summaries in Danish).

*Information on sponsor's ability to accumulate data during the trial and early stopping rules*

We extracted information on the sponsor's ability to review data while the study was ongoing, e.g. through interim analyses or through participation in data monitoring committees (DMCs), and information on the sponsor's ability to stop the trial early, including pre-defined stopping rules.

***Analysis***

The extracted information was assessed according to our six pre-specified questions. All assessments were checked by a second researcher. Disagreements were discussed with a senior researcher. In cases of doubt, we conservatively assumed that the reply was affirmative

1. *Were the roles and responsibilities of the trial funders and sponsors described?*
2. *Who owned the data accumulated during the trial?*
3. *Were the investigators' rights to publish restricted?*

We particularly assessed whether there were restrictions to the time-period for which investigators could publish; if the sponsor had the right to review and comment on potential publications; if investigators were obliged to take the comments from sponsors into consideration; and whether sponsors could delay or prevent publication.

4. *Was information about potential publication constraints described in the informed consent document?*
5. *Did the industry partner have the opportunity to review data during the study?*

6. *Could the industry partner stop the trial early?*

If yes, we determined whether this could be done for any reason, or whether there were pre-defined stopping rules.

We present descriptive statistics for trial characteristics and for these assessments.

**Results**

We identified 1,401 trials approved by ethics committees in Denmark between January 2012 and March 2013. Of those, we excluded 1,189 trials because we were not able to identify them in trial registries (n = 794) or because they did not meet our eligibility criteria (n = 395). The remaining 212 trials appeared eligible, but we could not realistically extract data from so many trials, so we limited the timeframe to October 2012 to March 2013. The resulting sample was 78 trials for which we applied for access to CSPs and other documents through a Freedom of Information request. Of these, we excluded 36 trials; 10 because they did not meet our eligibility criteria; one because it was a duplicate; and 25 because they did not have any industry involvement. Thus, our final sample was 42 trials. The process is summarised in Figure 1.

***Characteristics of included trials***

Thirty-nine of the 42 included trials (93%) were multi-centre trials. The median planned sample size was 576 participants (IQR: 361-1130 participants). Twenty-nine of the included trials (69%) were drug trials, 6 (14%) tested devices, one (3%) a type of surgery, and six (14%) were classified as 'other'. Trial characteristics for partially and fully industry sponsored trials are shown in Table 1.

***Access to data and publication constraints***

The roles and responsibilities of the sponsor and investigators were described in some detail in 20 of 42 trials (48%). Thus, for more than half of trials (n=22, 52%) it was not clear which role the sponsor had in the project, apart from providing the funding.

*Accumulation of data and early stopping*

In 8 trials (19%) we were certain that the sponsor had the opportunity to review data during the study and in 14 trials (33%) we were confident it was not possible. In the remaining 20 trials (48%) it was unclear. In 27 trials (64%) it was mentioned that the sponsor could stop the trial early and in 15 trials (36%) early stopping was not mentioned in any of the documents. In 23 of the trials (55%) the sponsor could stop the trial for any reason, in two trials (5%) specific reasons for stopping were mentioned, and in two trials (5%) it was unclear whether specific reasons were needed. The specific reasons mentioned were, for example, "*reasonable medical or administrative reasons", "futility"* and *"benefit".*

*Ownership of data and rights to publish*

In 20 trials (48%) it was clear that the sponsor owned all data accumulated during the trial and in six trials (14%) the investigators owned the data. In the remaining 16 trials (38%) it was unclear who owned the data. Of the 32 fully industry sponsored trials, the sponsor owned the data in 19 trials (59%).For the remaining 13 trials (41%), ownership of data was unclear, whereas the investigator did not have ownership of data for any of the fully industry sponsored trials. Ownership of data was not mentioned in the ICDs for any of the included trials.

Investigators' right to publish was explicitly constrained in 30 trials (71%), explicitly unconstrained in 7 trials (17%), and unclear in the remaining 5 trials (12%). In fully-industry sponsored trials there were explicit publication constraints for 29 out of 32 trials (91%) while for partially-industry sponsored trials only 1 of 10 (10%) had explicit publication constraints. The constraints on publication rights were not mentioned in the ICDs for any of the 30 trials with publication constraints. The types of publication constraints are described in Table 3.

All results can be seen for partially and fully industry sponsored trials, respectively, in Table 2.

**Discussion**

We found that in almost all fully industry sponsored trials (91%) in our sample, the investigators' right to publish was explicitly constrained in some way. The most common types of constraints were that the sponsor had the right to review potential publications; that investigators could not publish results for a period of time; and that the sponsor could delay potential publication. In one third (31%) of the included trials, the sponsor could comment on potential publications and the investigators needed to comply with the comments. In all fully industry-sponsored trials where determination of data ownership was possible, the sponsor explicitly owned the data. In none of the included trials were ownership of data or publication constraints mentioned in the ICDs.

We also found that in 19% of trials the sponsor could review data during the trial, and as the sponsor could stop the trial for any reason in 55% of trials, this meant that the sponsor had the opportunity to stop the trial based on interim results and potentially without using pre-defined criteria. In 2011, Eli Lilly voluntarily withdrew drotrecogin alfa from the US market. The drug was approved based on a trial that was stopped early due to apparent benefit. However, a subsequent post-marketing trial found no significant benefit.[18]

*Relation to previous research*

In 2006, Gøtzsche et al. showed that out of 44 industry-initiated trials approved in Denmark in 2004, 41 (93%) had publication constraints. Similarly, Kasenda et al. have shown that out of 456 protocols approved by ethics committees in Switzerland, Germany, and Canada between January 2000 and November 2003, 393 (86%) described an industry partner's right to disapprove or review the manuscript. Our study replicates these findings in a recent sample of trials. Additionally, to the best of our knowledge, this study is the first study to examine whether publication constraints are communicated to research participants, which was never the case.

*Limitations*

Our study has important limitations. First, for a relatively high number of trials we did not have sufficient information to assess all criteria, e.g. it was unclear whether the sponsor could accumulate data in 48% of

included trials. Additionally, some of the assessments were subjective and while all assessments have been checked by a second author and we tried to be conservative, this should be taken into consideration.

Second, while our sample is relatively recent, standards for core documents to be evaluated by ethics committees for a clinical trial application might have changed. All included trials were approved by ethics committees in Denmark, which might also limit the generalisability of our results, although almost all trials were multi-centre, multi-national studies. We are not aware of any reason that trials approved in Denmark should be systematically different from trial approved elsewhere. Another issue that might limit the generalisability of our results, is the fact that we had to exclude a large number of trials because we were not able to identify them in trial registries based on the information available from the website of the Danish National Committee on Health Research Ethics.

Lastly, we had to sign confidentiality agreements to obtain access to CSPs and related documents, which means we are not able to share our more detailed data or provide in depth examples. This limits the transparency and reproducibility of our study.

*Implications for future research*

Our study has several implications for research practice. As publication constraints are widespread, the research community must consider whether this is an acceptable practice. Dissemination bias has been documented to be a widespread problem and publication constraints can contribute to this.[3] Additionally, early stopping of trials when the sponsor has access to data can lead to overestimation of the benefits. Ethics committees should ensure that interim analyses and DMCs are independent of industry sponsors. Finally, research participants should be fully informed about key aspects of trials, including data ownership and publication constraints in informed consent documents. As one of the primary motivations for participating in research is altruism[9, 10], this is important information that is necessary for true informed consent.

**Conclusions**

Publication constraints are common in industry sponsored trials, and data is almost always owned by the sponsor. Additionally, the sponsor can often stop the trial for any reason and can sometimes review unblinded data while the trial is ongoing whereas explicit pre-defined stopping rules were not mentioned. The circumstances described above were not communicated to potential trial participants.

## List of abbreviations

RCT Randomised controlled trial

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Availability of data and materials*

The datasets generated and/or analysed during the current study are not publicly available as we needed to sign confidentiality statements in order to obtain access to the documents.

### *Competing interests*

None declared.

### *Funding*

This study was funded by the Laura and John Arnold Foundation, the Nordic Cochrane Centre, and Helsefonden. The funders had no role in the design or conduct of the study.

### *Authors' contributions*

PCG came up with the idea for the study. ASPM, PCG, KJJ wrote the protocol. MCO, MM, and ASPM collected data. ASPM analysed the data. ASPM, KJJ, and PCG interpreted the data. ASPM wrote the first draft. All authors read and commented on the final manuscript.

*Transparency declaration*

Asger Sand Paludan-Müller, the study's guarantor, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained

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1 **Table 1: Characteristics of included trials**

| | Total (n = 42) | Partially industry sponsored (n = 10) | Fully industry sponsored (n = 32) |
|---|---|---|---|
| ***Type of trial*** | | | |
| Multi-centre | 39 trials (93%) | 9 trials (90%) | 30 trials (94%) |
| Single centre | 3 trials (7%) | 1 trial (10%) | 2 trials (6%) |
| ***Planned sample size*** | | | |
| Median | 576 participants | 275 participants | 641 participants |
| Interquartile range | 361-1130 participants | 172-781 participants | 407-1217 participants |
| ***Type of intervention examined*** | | | |
| Drug | 29 trials (69%) | 2 trials (20%) | 27 trials (84%) |
| Device | 6 trials (14%) | 2 trials (20%) | 4 trials (13%) |
| Surgery | 1 trial (2%) | 0 trials (0%) | 1 trial (3%) |
| Other | 6 trials (14%) | 6 trials (60%) | 0 trials (0%) |

2

1 **Table 2: Results from included trials**

| | Total (n = 42) | Partially industry sponsored (n = 10) | Fully industry sponsored (n = 32) |
|---|---|---|---|
| ***Roles and responsibilities of sponsor described*** | | | |
| Yes | 20 trials (48%) | 6 trials (60%) | 45 trials (44%) |
| No | 22 trials (52%) | 4 trials (40%) | 18 trials (56%) |
| ***Owner of data accumulated during the trial*** | | | |
| Sponsor | 20 trials (48%) | 1 trial (10%) | 19 trials (59%) |
| Investigator | 6 trials (14%) | 6 trials (60%) | 0 trials (0%) |
| Unclear | 16 trials (38%) | 3 trials (30%) | 13 trials (41%) |
| ***Sponsor had the opportunity to review data during trial*** | | | |
| Yes | 8 trials (19%) | 0 trials (0%) | 8 trials (25%) |
| No | 14 trials (33%) | 7 trials (70%) | 7 trials (22%) |
| Unclear | 20 trials (48%) | 3 trials (30%) | 17 trials (53%) |
| ***Sponsor had the opportunity to stop the trial early*** | | | |
| Yes, for any reason | 23 trials (55%) | 0 trials (0%) | 23 trials (72%) |
| Yes, but only for specific reasons | 4 trials (9%) | 0 trials (0%) | 4 trials (13%) |
| No | 7 trials (17%) | 6 trials (60%) | 1 trial (3%) |
| Unclear | 8 trials (19%) | 4 trials (40%) | 4 trials (12%) |
| ***Rights to publish were constricted*** | | | |
| Yes | 30 trials (71%) | 1 trial (10%) | 29 trials (91%) |
| No | 7 trials (17%) | 7 trials (70%) | 0 trials (0%) |

| | | | |
|---|---|---|---|
| Unclear | 5 trials (12%) | 2 trials (20%) | 3 trials (9%) |
| ***Publication constraints mentioned in ICDs ( n =30)*** | | | |
| Yes | 0/30 trials (0%) | 0/1 trial (0%) | 0/29 trials (0%) |
| No | 30/30 trials (100%) | 1/1 trial (100%) | 29/29 trials (100%) |

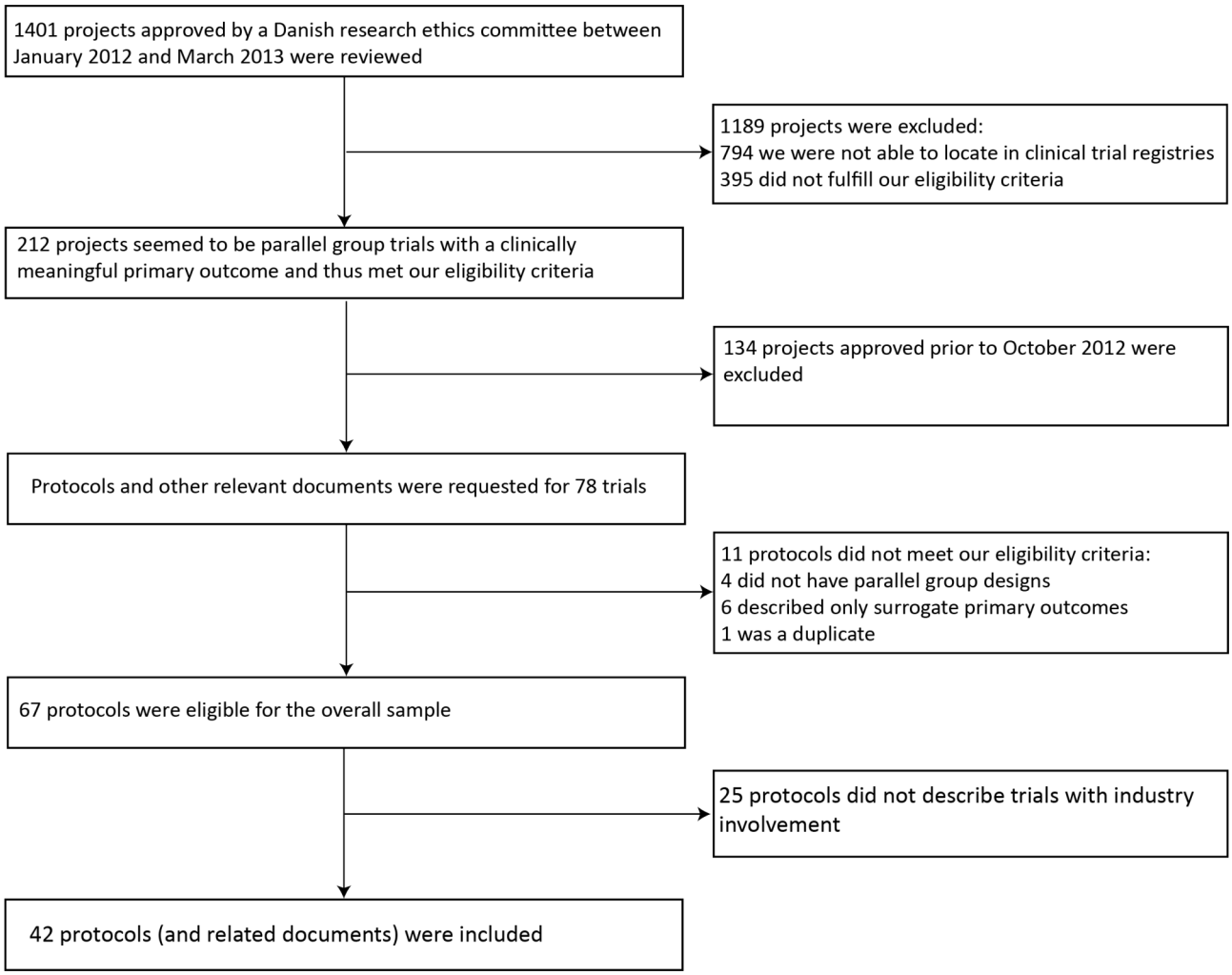
1

2

**Table 3: Types of publication constraints described for included trials**

| *Type of publication constraints* | **N = 42** |
|---|---|
| *Publication not allowed for a pre-specified time period* | 22 trials (52%) |
| *Sponsor can review potential publications or presentations* | 30 trials (71%) |
| *Sponsor can comment, but investigators must not comply with comments* | 14 trials (33%) |
| *Sponsor can comment, and investigators must comply with comments* | 13 trials (31%) |
| *Sponsor can delay publication* | 21 trials (50%) |

**Figure 1**


1401 projects approved by a Danish research ethics committee between January 2012 and March 2013 were reviewed
1189 projects were excluded:
794 we were not able to locate in clinical trial registries
395 did not fulfill our eligibility criteria
212 projects seemed to be parallel group trials with a clinically meaningful primary outcome and thus met our eligibility criteria
134 projects approved prior to October 2012 were excluded
Protocols and other relevant documents were requested for 78 trials
11 protocols did not meet our eligibility criteria:
4 did not have parallel group designs
6 described only surrogate primary outcomes
1 was a duplicate
67 protocols were eligible for the overall sample
25 protocols did not describe trials with industry involvement
42 protocols (and related documents) were included

# Paper 4

Reporting of harms in oncological clinical study reports submitted to the European Medicines Agency compared to trial registries and publications – A methodological review

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*Submitted for publication*

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

# PHD-THESIS
# DECLARATION OF CO-AUTHORSHIP

*The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.*

| **1. Declaration by** | |
|---|---|
| Name of PhD student | Asger Sand Paludan-Müller |
| E-mail | asp@cochrane.dk |
| Name of principal supervisor | John Brodersen |
| Title of the PhD thesis | The need for a new randomised trial |

| **2. The declaration applies to the following article** | |
|---|---|
| Title of article | Reporting of harms in oncological clinical study reports submitted to the European Medicines Agency compared to trial registries and publications – A methodological review |
| **Article status** | |
| Published ☐<br>Date: | Accepted for publication ☐<br>Date: |
| Manuscript submitted ☒<br>Date: 14-09-2020 | Manuscript not submitted ☐ |
| If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information). | |

| **3. The PhD student's contribution to the article** ***(please use the scale A-F as benchmark)***<br>Benchmark scale of the PhD-student's contribution to the article<br>**A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant | **A, B, C, D, E, F** |
|---|---|
| 1. Formulation/identification of the scientific problem | C |
| 2. Development of the key methods | B |
| 3. Planning of the experiments and methodology design and development | C |
| 4. Conducting the experimental work/clinical studies/data collection/obtaining access to data | B |
| 5. Conducting the analysis of data | A |
| 6. Interpretation of the results | B |
| 7. Writing of the first draft of the manuscript | A |
| 8. Finalisation of the manuscript and submission | B |
| Provide a short description of the PhD student´s specific contribution to the article.[i]<br>ASPM helped with identifying the problem and developing methods. ASPM contributed to the data extraction, and carried out the data analysis and interpretation. ASPM wrote the first draft, finalised the manuscript, and submitted the manuscript. | |

| 4. Material from another thesis / dissertation[ii] | |
|---|---|
| Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)? | Yes: ☐ No: ☒ |
| If yes, please state name of the author and title of thesis / dissertation. | |
| If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another. | |

**5. Signatures of the co-authors[iii]**

| | Date | Name | Title | Signature |
|---|---|---|---|---|
| 1. | 21-09-2020 | Perrine Crequit | MD, PhD |  |
| 2. | 28/09/20 | Isabelle Boutron | MD, PhD, Professor |  |
| 3. | | | | |
| 4. | | | | |
| 5. | | | | |
| 6. | | | | |
| 7. | | | | |
| 8. | | | | |
| 9. | | | | |
| 10. | | | | |

**6. Signature of the principal supervisor**

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 28/09/20
Principal supervisor: 

**7. Signature of the PhD student**

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 21-09-2020
PhD student: 

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

*"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."*

[iii] If more signatures are needed please add an extra sheet.

# Reporting of harms in oncological clinical study reports submitted to the European Medicines Agency compared to trial registries and publications – A methodological review

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Abstract: 286 words

Manuscript: 2988 words

Tables: 4

Figures: 3

References: 20

## ABSTRACT

**Background:** An accurate assessment of harms is a fundamental part of true informed consent; however, harms are known to be underreported in journal publications. Therefore, we sought to compare the completeness of reporting of harm data, discrepancies in harm data reported, and the delay to access results of oncological clinical trials between three sources: clinical study reports (CSRs), clinical trial registries and journal publications.

**Materials and methods**: We identified all trials evaluating targeted therapy and immunotherapy for cancer listed on the EMA clinical data website. We retrieved all CSRs, then identified related records in clinical trial registries and journals. We included all Phase II, II/III or III randomised controlled trials (RCTs) assessing targeted therapy and immunotherapy for cancer. We determined the completeness of reporting of harm data and extracted harm data available in each of the three sources.

**Results:** We identified 42 RCTs evaluating 13 different drugs. Results were available on the EMA website in CSRs for 36 (86%) RCTs, ClinicalTrials.gov for 36 (86%), the European Clinical Trials Register (EUCTR) for 20 (48%), and in journal publications for 32. Harms reporting was more complete in CSRs than other sources. We identified marked discrepancies in harms data between sources. The median (interquartile range) delay between the primary trial completion date and access to results was 4.34 (3.09–7.22) years for CSRs, 2.94 (1.16–4.52) years for ClinicalTrials.gov, 5.39 (4.18–7.33) years for EUCTR, and 2.15 (0.64–5.04) days for publications.

**Conclusions:** Harms of recently approved oncological drugs were reported more frequently and in more detail in CSRs available on the EMA website than in trial registries and journal publications. Systematic reviews seeking to address harms of oncological treatments should use CSRs as the primary source of data.

**Keywords:** systematic reviews, reporting bias, clinical study reports, adverse events

## Introduction

Systematic reviews of randomised controlled trials (RCTs) are considered the gold standard for evaluating the effectiveness and harms of interventions[1]. However, results of many completed RCTs are not published, which leads to reduced power and potential publication bias in reviews[2–4]. Moreover, peer-reviewed publications are not always an accurate reflection of how trials were planned, conducted and analysed. A lack of transparency or missing information on harms is common[3, 5].

One potential source of unpublished data is clinical study reports (CSRs): extensive reports prepared by pharmaceutical companies and submitted to regulatory authorities as a part of an application for marketing authorisation. The structure of CSRs is outlined in a guideline from the International Conference on Harmonisations[6]. Access to CSRs has historically been difficult [7], but since 2015, the European Medicines Agency (EMA) has launched an initiative (policy 0700) to increase transparency of information on medicinal drugs by providing access to CSRs submitted to the agency. However, the EMA has not published any CSRs since December 4, 2018, when the initiative was paused indefinitely during the EMA's move to Amsterdam [8]. Although several systematic reviews have included CSRs [9–12] and a questionnaire study found that respondents consider CSRs valuable for systematic reviews [13], a 2014 study found that most systematic reviews continue to rely on publications as the primary source of data [14].

Several studies have compared reporting in publications, trial registries and CSRs; for example, a study found that CSRs had higher reporting quality than did registry reports and publications [15], a finding that was confirmed in several other studies [16–19]. However, no study has systematically compared reporting of harms in trial registries and publications with a large sample of recent CSRs from oncological trials.

Targeted therapy and immunotherapy for cancer have revolutionised the care of most patients with cancer. Several of these specific oncologic drugs have recently been approved by the US Food and Drug Administration and EMA. Evaluating the harms of these new drugs is essential. Thus, we aimed to compare the delay to access results of oncological RCTs, the completeness of reporting harm data and discrepancies in harm data reported between the three sources: CSRs available on the EMA Website, clinical trial registries and journal publications.

**Methods**

We identified all trials evaluating targeted therapy and immunotherapy for cancer available on the EMAs clinical data Website and retrieved the related CSRs. Then, we systematically searched for the related records in clinical trial registries and related publications. Finally, we compared the delay to access results, the completeness of reporting of harm data and discrepancies in harm data reported between the three sources.

*Identification of trials*

In November 2019, we used the EMA's clinical data Website (https://clinicaldata.ema.europa.eu) to identify all submissions for marketing authorisation or extension of indication under the EMA policy 0070. We updated the search in June 2020 and identified no new submissions. For all submissions, we extracted the product name, active substance, marketing authorisation holder and Anatomical Therapeutic Chemical (ATC) code. We selected the ATC codes for monoclonal antibodies (L01XC) and protein kinase inhibitors (L01XE) corresponding to targeted therapy and immunotherapy.

Once we had identified all eligible active substances, we downloaded all documents from the EMA website (i.e., CSR and related documents) and used these to create a list of all trials submitted to the EMA. We included phase II, II/III or III RCTs that were part of a submission for a targeted therapy and immunotherapy. We excluded trials that compared only different dosages of the same treatment.

Two reviewers (ASPM and PC) independently identified trials from the documents for one-quarter of the eligible active substances. Because of no discrepancies in this identification, the remaining identifications involved one reviewer (ASPM).

*Identification of related clinical-trial registry records for the identified RCTs*

One reviewer (ASPM) systematically searched ClinicalTrials.gov and the European Clinical Trials Register (EUCTR) by using 1) the trial registry identifier or ID number if mentioned in the CSR or 2) the name of the experimental drug (or its international non-proprietary name). If we were still unable to identify the corresponding trial, we used other keywords (e.g., treatment comparator and indication). The records identified were systematically checked by a second reviewer (PC). Then we checked whether results were posted on the trial registries identified. If the study was registered in both registries, we extracted data from both.

*Identification of results publications for identified RCTs*

We first searched for citations listed in trial registries. For ClinicalTrials.gov, the only registry to give access to citations, we used the citations listed under "publication of results" and "publications automatically indexed to this study by ClinicalTrials.gov identifier (NCT Number)". We included all publications reporting results for the trial identified. We did not include publications of reviews or publications that presented pooled analyses of several trials and did not include data from the individual trial. If no publications were indexed in the registry record, we searched MEDLINE and EMBASE by using the name of the experimental drug, treatment comparator, indication, and name of the principal investigator.

*Data extraction*

For each trial, we extracted information from the CSR available on the EMA Website, the clinical trial registry records (both ClinicalTrials.gov and EUCTR) and all related publications. The extracted

information was entered in a data extraction spreadsheet. Two reviewers (ASP and PC) independently extracted data for 10% of trials. Because of only minor disagreements, one reviewer (ASP) extracted the data for the remaining trials. All extractions were then checked by a second reviewer (ASP and PC). All discrepancies were resolved by discussion.

We extracted the following information for each trial:

*1) General characteristics*: name of trial, name of studied drug, clinical development phase, condition; number of centres, number of arms, number of participants randomised, whether the trial was a non-inferiority trial, the primary outcome, funding, and whether the trial was blinded.

*2) Delay in access to trial results:* The CSRs included in this project are released under the EMA policy 0070[20], which dictates that clinical data submitted to the EMA as part of a marketing authorisation application or a post-authorisation procedure shall be released once the concerned procedure (hereafter EMA procedure) has been finalised. We recorded the date of finalization of the procedure for all included submissions by using the European Commission's register[21] and determined the delay between the finalisation of the procedure and publication of CSRs on the EMA website.

To determine the time between completion of the study and release of results in each source, we recorded the primary trial completion date (i.e., the date of the last participant's final follow-up visit for measurement of the primary outcome) from ClinicalTrials.gov. If this was not available, we checked the other sources (CSRs, publications, and EUCTR) for a primary completion date. We also recorded for each source the date when the results were released and available. For trials with multiple publications, we used the earliest publication date.

*3) Completeness of reporting harm data and discrepancies in harm data:* We extracted the following information from all three sources of data for each trial: number of patients randomized, whether a

definition of safety population was provided, number of patients in the safety population, threshold for reporting adverse events (e.g., 10%, 5% or none), number of patients experiencing at least one adverse event, total number of adverse events, number of patients experiencing at least one serious adverse event, total number of serious adverse events, number of patients experiencing at least one adverse event judged to be grade 3-5 according to the Common Terminology Criteria for Adverse Events (CTCAE), total number of adverse events judged to be grade 3-5 according to the CTCAE, number of patients discontinuing the trial due to adverse events, number of deaths due to adverse events, and whether a description of the process of determining whether a death was due to adverse events, including whether the person(s) making the judgement were blinded, was provided. For all variables, we recorded the numbers per arm. Some sources reported CTCAE grade 3-4 events rather than grade 3-5 events. If the number of grade 5 events was reported separately, we added the numbers. If the number of grade 5 events was not reported, we still gave the trial a "yes" for the question, extracted the number of grade 3-4 events and noted this.

*Analysis*

We compared reporting of the different variables defined above in CSRs with that in clinical trial registries and publications, separately. We performed Kaplan-Meier analysis on the delay from primary trial completion date to publication of the CSR, the first publication of results in trial registries, and a publication in a medical journal. If a trial had not been published in a source, we calculated the delay between the primary completion date and June 29, 2020 and considered the trial right censored. For numerical variables reported in at least two of the data sources, we examined whether the numbers reported were the same. For this analysis, we pooled results from ClinicalTrials.gov and EUCTR. If results were available from both registries, we used the data from ClinicalTrials.gov for the analysis of discrepancies.

*Patient involvement*

No patients were involved in the planning or conduct of this study.

**Results**

*Selection of trials*

We identified 142 submissions through the EMA clinical data Website. These submissions corresponded to 124 unique substances: 22 concerned oncology drugs and 13 of these corresponded to targeted therapy and immunotherapy (Appendix). For these 13 drugs included in the study, we identified 164 unique trials, of which 42 met our eligibility criteria (phase II, II/III or III RCTs). The inclusion process is shown in **Figure 1**.

The drugs included and number of trials for each drug are in **Table 1**. The median number of randomised patients in the included trials was 364 (range 142-666) (**Table 2**). The primary outcome was progression-free survival for 27 of the 42 (64%) included trials, overall survival for eight (19%) and both for three (7%). The remaining four trials (7%) had other primary outcomes. Additional characteristics of included studies are in the **Appendix.**

*Availability of sources*

The EMA's Website had complete CSRs for 37 of the 42 (86 %) included trials. For the remaining five (12%) trials, the EMA Website did not contain full CSRs and only documents such as summaries, pharmacokinetic data or periodic safety reports were available; the EMA Website did not explain why full CSRs are not available for these trials, but the trial may have been ongoing at the time of the application for marketing authorisation. Among the 42 included trials, trial results were posted on ClinicalTrials.gov for 36 (86%) and on the EUCTR for 20 (48%). We were able to identify publications with results for 32 of the 42 (76%) included trials (all included publications are in the

**Appendix**). Trial results were available in the three sources for 25 (60%) trials and in two sources for 13 (31%) (i.e., CSR and clinical trial registry for six trials, in CSR and publication for three trials, in clinical trial registry and publications for four trials). Results were available in only one source for three (7%) trials (two in CSRs and one in a clinical trial registry), and one (2%) trial had no results available.

*Delay in access to trial results*

The median delay between finalisation of the EMA procedure and availability of CSRs was 1.21 years (range 0.91-1.78). **Figure 2** shows Kaplan-Meier curves for the delay between primary trial completion dates and publication of the different sources. The median (interquartile range) delay was 4.34 (3.09–7.22) years for CSRs, 2.94 (1.16–4.52) years for ClinicalTrials.gov, 5.39 (4.18–7.33) years for the EUCTR, and 2.15 (0.64–5.04) years for publications.

*Reports of harms in each source*

**Table 3** shows the proportion of trials for which we could obtain data on our pre-specified variables from each of the four sources of data. For most variables, results were more frequently reported in CSRs than both trial registries and publications. The number of patients with at least one serious adverse event was reported for all trials in both CSRs and ClinicalTrials.gov and in 19/20 (95%) trials in the EUCTR but only 16/32 (50%) trials with publications. The number of patients with any adverse events was reported in all CSRs but was not available for any trials or registries because the number of patients with serious and non-serious adverse events are reported separately. The number of patients with any adverse events was available for only 13/32 (41%) trials with publications. The number of patients with CTCAE grade 3-5 events was available in 36/37 (97%) CSRs but only 14/32 (44%) publications. The CTCAE grade was not reported in either of the trial registries.

The total number of serious adverse events, any adverse events, and CTCAE grade 3-5 events was available in 9/37 (24%), 12/37 (32%), and 6/37 (16%) CSRs, respectively; 10/36 (28%), 10/36 (28%), and 0/36 (0%) records at ClinicalTrials.gov; and 17/20 (85%), 17/20 (85%), and 0/20 (0%) records at the EUCTR. For publications, only 1/32 (3%) reports gave the total number of serious adverse events. The number of total adverse events and grade 3-5 adverse events was not available in publications for any trial.

The number of deaths due to adverse events was available in CSRs for 34/37 (92%) trials, from ClinicalTrials.gov for no trials, from EUCTR for 15/20 trials (75%) and from publications for 12/32 (38%) trials. Only 10/37 (27%) trials in CSRs and no trials in other sources had a detailed explanation of how it was decided whether a death was due to an adverse event or progressive disease.

*Discrepancies between sources*

For trials for which results were available for a variable in a minimum of two sources of data, we compared the data and noted any discrepancies. The proportion of trials with discrepancies are in **Table 4. Figure 3** shows discrepancies for each variable in each included trial.

We found marked discrepancies in harms data between CSRs, trial registry entries and publications. The number of patients who discontinued the treatment due to adverse events was particularly problematic, with discrepancies in 88% and 90% of trials for CSRs as compared with registries and publications, respectively.

**Discussion**

Our study shows that data on harms in RCTs evaluating targeted therapy and immunotherapy for cancer are reported more frequently and in more detail in CSRs than in registries and publications. However, reporting is not perfect. CSRs were missing for five (12%) trials and the reason was unclear, but the trials may have been ongoing at the time of submission. Furthermore, important data were

incompletely reported; for example, the total number of serious adverse events and all adverse events was available in only 9/37 (24%) and 12/37 (32%) CSRs. Also, although data should be available at the date the EMA procedure is completed, we showed a median of 1.21 years between the finalisation of the procedure and publication of CSRs on the Website. Overall, access to data from a CSR required a much longer delay than that from other sources. We also demonstrated discrepancies in harms data between CSRs and other sources.

Our results are consistent with other findings. In 2013, Wieseler et al. examined a sample of 86 trials with both a CSR and a publicly available source of data and found that serious adverse events, adverse events and withdrawals due to adverse events were more frequently reported in CSRs than another source[16]. In 2014, Maund et al. found that for nine antidepressant trials, CSRs were a more reliable source of information on harms than were journal articles[17]. In 2016, two reports described the reporting of harms of orlistat in CSRs and journal publications: both concluded that reporting of harms was more extensive in CSRs than in journal publications[18, 19].

Our study is the first to compare reporting of harms in CSRs released under EMA policy 0070 with publications and trial registries for oncological trials. The automatic release of the CSRs might have led to better reporting of harms in other sources of data, but this does not seem to be the case. Additionally, we systematically examined predefined variables in a relatively large sample of trials.

Our study has some limitations. First, we focused on oncology trials, and our findings might not be applicable to other fields of medicine. However, our results, together with results from previous studies, suggest that the reporting of harms is better in CSRs than trial registries and journal publications across all specialities. Second, we examined only two clinical trial registries, and more information might be available from other registries; however, ClinicalTrials.gov and EUCTR are

two of the most-used registries, and information available elsewhere is unlikely to substantially alter our conclusions.

Our study has important implications for both research and practice. Our results suggest that any systematic review or other assessment of harms associated with oncological treatments must rely on CSRs for making sound conclusions. If such an assessment relies on data from only publications and trial registries, it will only be able to include a subset of the available data. This is problematic for several reasons, namely reduced power to detect differences between groups and the fact that the data reported in registries and publications might vary systematically from data not reported. Additionally, we have shown marked discrepancies in data reported in CSRs and other sources, especially for withdrawals due to adverse events; therefore, we consider results based on CSRs more reliable.

In addition, current estimates of the harms of oncological treatments based on published data might not be accurate and not able to inform clinical practice. Because oncological treatments are generally toxic, the harms profile is an important piece of information for assessing the benefit/harm balance, and true informed consent is only possible if the estimate of harms is accurate.

**Conclusions**

Harms in trials evaluating targeted therapy and immunotherapy for cancer are reported in more detail and more reliably in CSRs than in trial registries and journal publications. This finding confirms previous results and suggests that any systematic assessment of harms of oncological treatments and likely other treatments in other fields of medicine should rely on CSRs.

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**Contributors**: All authors had complete access to the data in the study. ASP, PC and IB contributed to the study concept and design and wrote the protocol. ASP and PC acquired and extracted the data for the study; ASP, PC and IB contributed to the analysis. ASP, PC and IB contributed to the interpretation of the data. ASP developed the first draft of the manuscript and the other authors critically revised it and approved the final version.

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**Competing interests**: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:
no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval**: Not required.

**Transparency**: The lead author (ASP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspect of the study has been omitted. No discrepancies are withheld.

**Data sharing**: The CSRs used for this study are available at the EMA's clinical data Website. All data files and the code for the statistical analysis are available from the Open Science Framework database (link).

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**Table 1: Included drugs and trials**

| Drug name | Number of trials | Pharmaceutical company | Type of cancer | Trial name available |
|---|---|---|---|---|
| Afatinib | 6 | Boehringer Ingelheim | Head and neck squamous cell carcinoma, non-small cell lung cancer | LUX-Head & Neck 1, LUX-Lung 5, LUX-Lung 6, LUX-Lung 8, LUX-LUNG 1 |
| Bevacizumab | 6 | Roche | Non-small cell lung cancer | ATLAS, EURTAC, BeTa |
| Cabozantinib | 4 | Exelixis | Medullary thyroid cancer, renal cell carcinoma, prostate cancer | EXAM, METEOR, COMET-1, COMET-2 |
| Cediranib | 5 | AstraZeneca | Ovarian cancer, colorectal cancer, renal cell carcinoma, glioblastoma | ICON6, HORIZON III, HORIZON II, REGAL |
| Cediranib | 2 | NCIC Clinical Trials Group | Non-small cell lung cancer | |
| Erlotinib | 1 | Roche | Non-small cell lung cancer | |
| Everolimus | 1 | Novartis | Neuro-endocrine tumor (gastro-intestinal or lung origin) | RADIANT-4 |
| Lenvatinib | 4 | Eisai | Non-small cell lung cancer, glioma, differentiated thyroid cancer, hepatocellular carcinoma | SELECT |
| Nivolumab | 4 | Bristol-Myers Squibb | Renal cell carcinoma, non-small cell lung cancer, melanoma | CheckMate 025, CheckMate 057, CheckMate 067, Checkmate 069 |

| | | | | |
|---|---|---|---|---|
| Olaratumab | 3 | ImClone Systems | Ovarian Cancer, Non-small cell lung cancer, Prostate Cancer | |
| Palbociclib | 3 | Pfizer | Breast cancer | PALOMA-2, PALOMA-3, PALOMA-4 |
| Pembrolizumab | 3 | Merck | Melanoma, non-small cell lung cancer | Keynote-006, Keynote-010, Keynote-024 |

**Table 2: Characteristics of included trials**

| **Clinical development phase** | **N (%)** |
|---|---|
| Phase II | 12 (29) |
| Phase II/III | 4 (10) |
| Phase III | 26 (61) |
| **Blinding** | **N (%)** |
| Open label | 22 (52) |
| Double blind | 20 (48) |
| **Primary outcome** | **N (%)** |
| Progression-free survival | 27 (64) |
| Overall survival | 8 (19) |
| Progression-free survival and overall survival | 3 (7) |
| Other | 4 (7) |
| | **Median (IQR)** |
| Number of participants randomised | 364 (142-666) |
| Number of centers | 99 (42-142) |

IQR, interquartile range

**Table 3: Proportion of trials for which data, including harms data, could be obtained from the sources examined (n=42).**

| | CSR | ClincalTrials.gov | EU Clinical Trials Register | Publications |
|---|---|---|---|---|
| *Source of data identified* | 37 (88%) | 36 (86%) | 20 (48%) | 32 (76%) |
| **Reporting of** | | | | |
| *Included participants* | | | | |
| - Number of participants randomised | 37 (100%) | 36 (100%) | 19 (95%) | 32 (100%) |
| - Number of participants in safety population | 37 (100%) | 36 (100%) | 19 (95%) | 32 (100%) |
| *Serious adverse events (SAEs)* | | | | |
| - Number of patients with at least one SAE | 37 (100%) | 36 (100%) | 19 (95%) | 16 (50%) |
| - Total number of SAEs | 9 (24%) | 10 (28%) | 17 (85%) | 1 (3%) |
| *Any adverse events (AEs)* | | | | |
| - Number of patients with at least one AE | 37 (100%) | 0 (0%) | 0 (0%) | 13 (41%) |
| - Total number of AEs | 12 (32%) | 10 (28%) | 17 (85%) | 0 (0%) |
| *CTCAE grade 3-5 AEs* | | | | |
| - Number of patients with at least one Grade 3-5 AE | 36 (97%) | 0 (0%) | 0 (0%) | 14 (44%) |
| - Total number of Grade 3-5 AEs | 6 (16%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *Deaths due to AEs* | | | | |
| - Number of deaths due to AEs | 34 (92%) | 0 (0%) | 15 (75%) | 12 (38%) |
| - Information on how it was decided whether | 10 (27%) | 0 (0%) | 0 (0%) | 0 (0%) |

| | | | | | |
|---|---|---|---|---|---|
| | a death was considered due to an AE | | | | |
| *Discontinuations due to AEs* | | | | | |
| - | Number of patients who discontinued trial due to AEs | 32 (86%) | 28 (78%) | 17 (85%) | 25 (78%) |

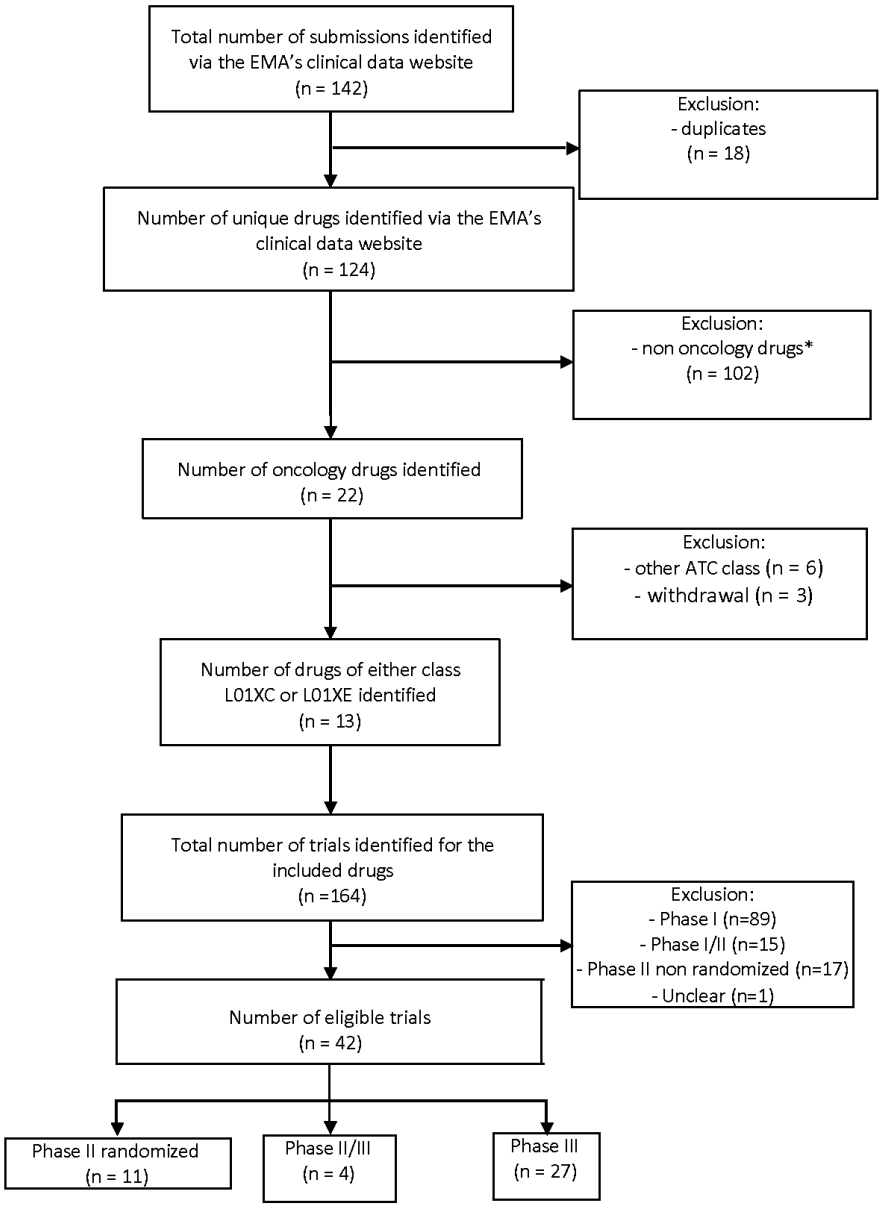
CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events

**Table 4: Discrepancies in harms data between CSRs, trial registries, and publications for variables that were reported in two sources**

| | CSR and trial registries | CSR and publications | Publications and trial registries |
|---|---|---|---|
| *Discrepancies* | | | |
| - Number of patients with at least one SAE | 15/32 trials (47%) | 5/13 trials (38%) | 8/14 trials (57%) |
| - Total number of SAEs | 5/5 trials (100%) | 0/1 trial (0%) | No trials with data from both sources |
| - Number of patients with at least one AE | No trials with data from both sources | 2/11 trials (18%) | No trials with data from both sources |
| - Total number of AEs | 5/5 trials (100%) | No trials with data from both sources | No trials with data from both sources |
| - Number of patients with at least one Grade 3-5 AE | No trials with data from both sources | 7/12 trials (58%) | No trials with data from both sources |
| - Total number of Grade 3-5 AEs | No trials with data from both sources | No trials with data from both sources | No trials with data from both sources |
| - Number of deaths due to AEs | 12/13 trials (92%) | 4/10 trials (40%) | 4/4 trials (100%) |
| - Number of patients who discontinued trial due to AEs | 23/26 trials (88%) | 18/20 trials (90%) | 11/18 trials (61%) |

CSR, clinical study report; AE, adverse event; SAE, serious adverse event

Figure 1: Flow chart




*Number of drugs per therapeutic area: cardiology (10), dermatology (4), endocrinology (12), gastroenterology (4), hematology (20), hepatology (3), infectiology (18), internal medicine (3), neurology (9), ophthalmology (2), psychiatry (2), radiology (2), respiratory (3), rheumatology (10)

Figure 2

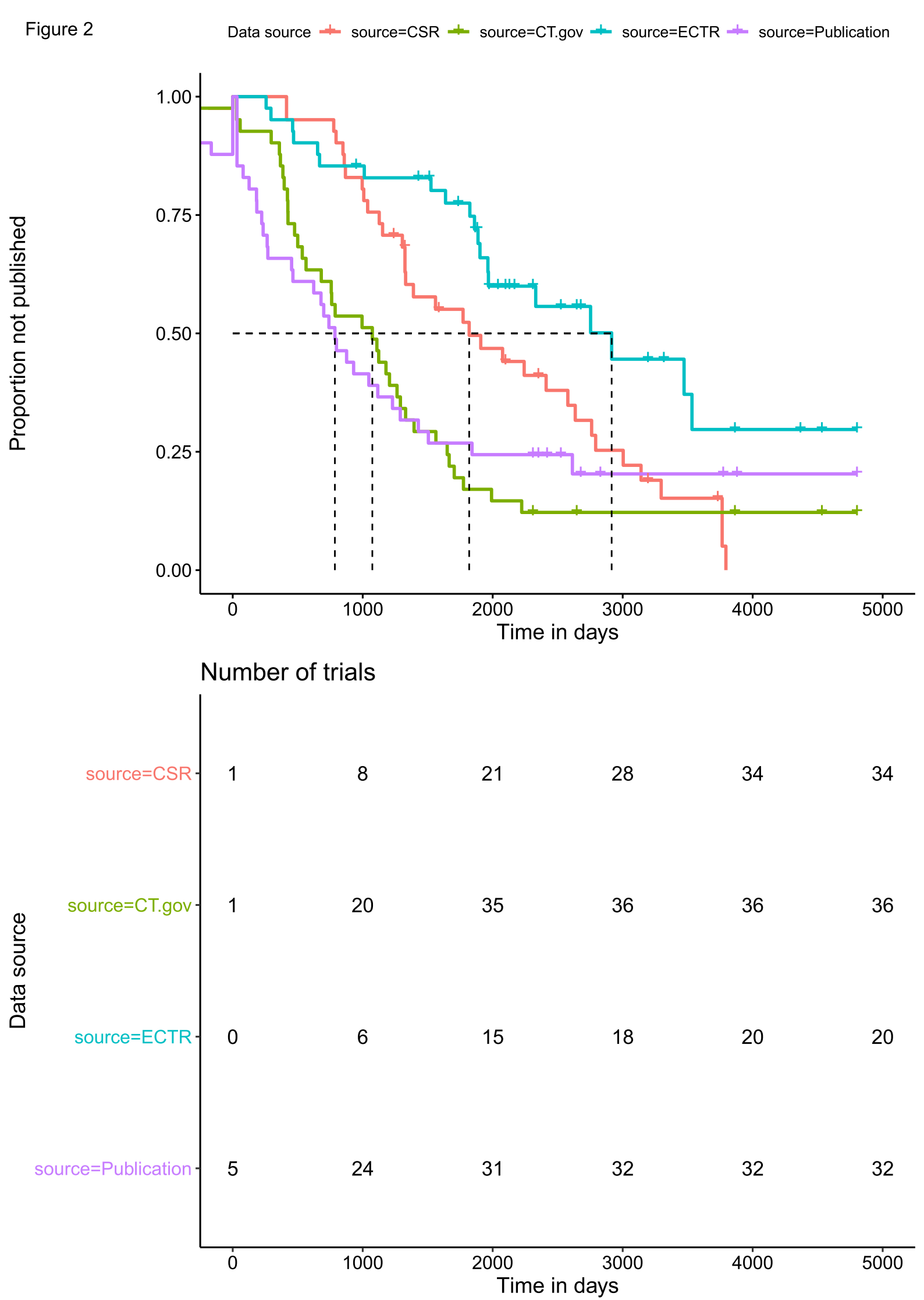
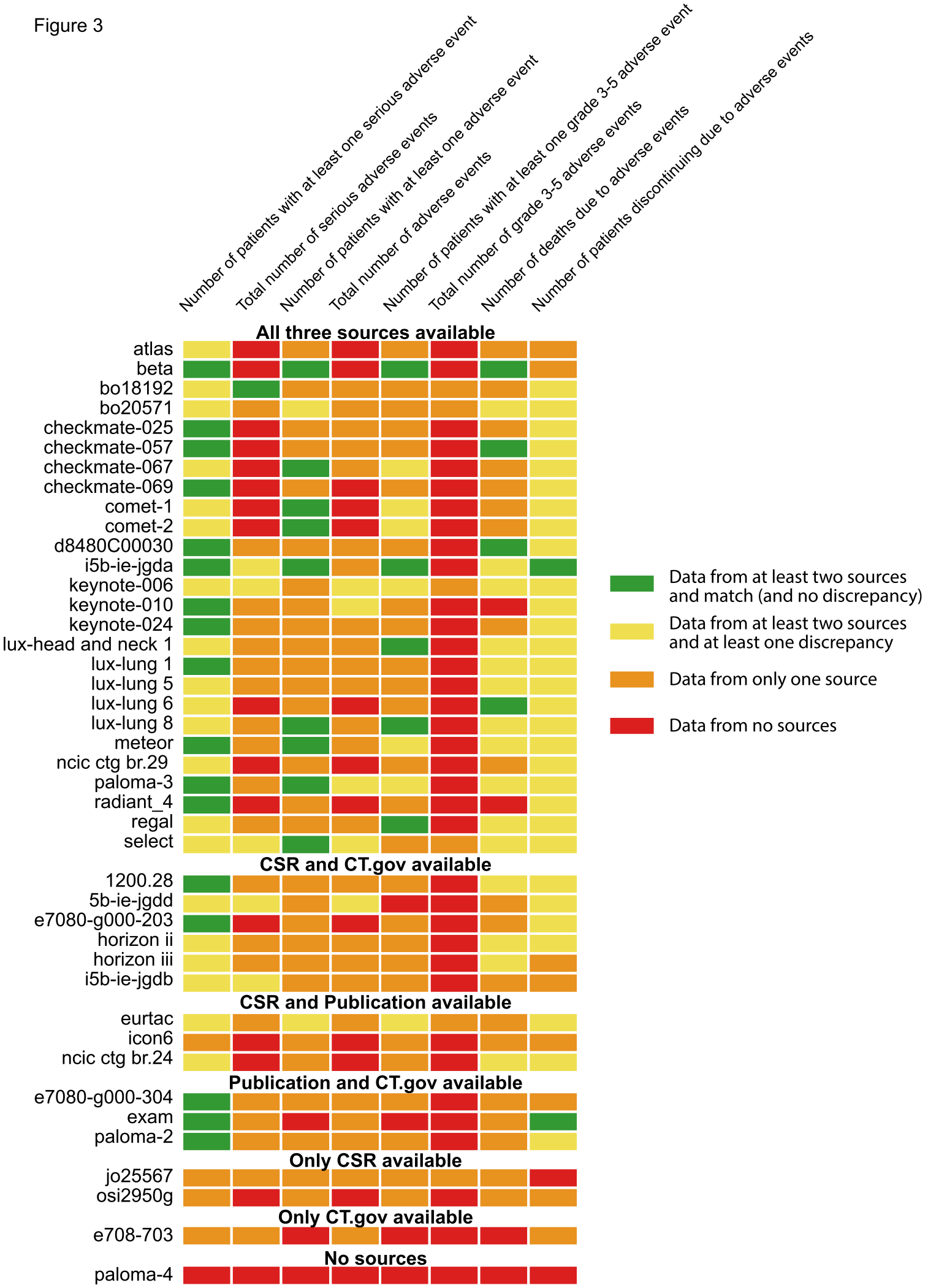

Data source
source=CSR
source=CT.gov
source=ECTR
source=Publication
Proportion not published
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
4000
5000
Time in days
Number of trials
source=CSR
1
8
21
28
34
34
source=CT.gov
1
20
35
36
36
36
source=ECTR
0
6
15
18
20
20
source=Publication
5
24
31
32
32
32
Data source
0
1000
2000
3000
4000
5000
Time in days

Figure 3


Number of patients with at least one serious adverse event
Total number of serious adverse events
Number of patients with at least one adverse event
Total number of adverse events
Number of patients with at least one grade 3-5 adverse event
Total number of grade 3-5 adverse events
Number of deaths due to adverse events
Number of patients discontinuing due to adverse events
All three sources available
atlas
beta
bo18192
bo20571
checkmate-025
checkmate-057
checkmate-067
checkmate-069
comet-1
comet-2
d8480C00030
i5b-ie-jgda
keynote-006
keynote-010
keynote-024
lux-head and neck 1
lux-lung 1
lux-lung 5
lux-lung 6
lux-lung 8
meteor
ncic ctg br.29
paloma-3
radiant_4
regal
select
CSR and CT.gov available
1200.28
5b-ie-jgdd
e7080-g000-203
horizon ii
horizon iii
i5b-ie-jgdb
CSR and Publication available
eurtac
icon6
ncic ctg br.24
Publication and CT.gov available
e7080-g000-304
exam
paloma-2
Only CSR available
jo25567
osi2950g
Only CT.gov available
e708-703
No sources
paloma-4
Data from at least two sources and match (and no discrepancy)
Data from at least two sources and at least one discrepancy
Data from only one source
Data from no sources

**Appendix**

**Information about included trials**

| Trial name | Registration number | Drug name | Phase | Pharmaceutical company | Type of cancer |
|---|---|---|---|---|---|
| LUX-Head & Neck 1 | NCT01345682 | Afatinib | 3 | Boehringer Ingelheim | Head and Neck Squamous Cell carcinoma |
| LUX-Lung 5 | NCT01085136 | Afatinib | 3 | Boehringer Ingelheim | Non-small cell lung cancer |
| LUX-Lung 6 | NCT01121393 | Afatinib | 3 | Boehringer Ingelheim | Non-small cell lung cancer (non-squamous with an EGFR-activating mutation) |
| LUX-Lung 8 | NCT01523587 | Afatinib | 3 | Boehringer Ingelheim | Non-small cell lung cancer (squamous cell carcinoma) |
| LUX-LUNG 1 | NCT00656136 | Afatinib | 2/3 | Boehringer Ingelheim | Non-small cell lung cancer |
| | NCT00514943 | Afatinib | 2 | Boehringer Ingelheim | Head and Neck Squamous Cell carcinoma |
| ATLAS | NCT00257608 | Bevacizumab | 3 | Roche | Non-small cell lung cancer |
| EURTAC | NCT00446225 | Bevacizumab | 3 | Roche | Non-small cell lung cancer with an EGFR-activating mutation |
| | JapicCTI-111390 | Bevacizumab | 2 | Roche | Non-small cell lung cancer |
| | NCT00531960 | Bevacizumab | 2 | Roche | Non-small cell lung cancer |
| | NCT00095225 | Bevacizumab | 2 | Roche | Non-small cell lung cancer |
| BeTa | NCT00130728 | Bevacizumab | 3 | Roche | Non-small cell lung cancer |
| EXAM | NCT00704730 | Cabozantinib | 3 | Exelixis | Medullary Thyroid Cancer |
| METEOR | NCT01865747 | Cabozantinib | 3 | Exelixis | Renal Cell Carcinoma |
| COMET-2 | NCT01522443 | Cabozantinib | 3 | Exelixis | Prostate Cancer |
| COMET-1 | NCT01605227 | Cabozantinib | 3 | Exelixis | Prostate Cancer |
| ICON6 | NCT00532194 | Cediranib | 3 | AstraZeneca | Ovarian Cancer |
| HORIZON III | NCT00384176 | Cediranib | 2/3 | AstraZeneca | Colorectal Cancer |
| | NCT00423332 | Cediranib | 2 | AstraZeneca | Renal Cell Carcinoma |
| HORIZON II | NCT00399035 | Cediranib | 3 | AstraZeneca | Colorectal Cancer |
| | NCT00795340 | Cediranib | 3 | NCIC Clinical Trials Group | Non-small cell lung cancer |
| | NCT00245154 | Cediranib | 2/3 | NCIC Clinical Trials Group | Non-small cell lung cancer |
| REGAL | NCT00777153 | Cediranib | 3 | AstraZeneca | Glioblastoma |
| | NCT00556712 | Erlotinib | 3 | Roche | Non-small cell lung cancer |
| RADIANT-4 | NCT01524783 | Everolimus | 3 | Novartis | Neuro-Endocrin Tumor (gastro-intestinal or lung origin) |
| | NCT01529112 | Lenvatinib | 2 | Eisai | Non-small cell lung cancer (non-squamous) |
| | NCT01137604 | Lenvatinib | 2 | Eisai | Glioma |
| SELECT | NCT01321554 | Lenvatinib | 3 | Eisai | Differentiated Thyroid Cancer |

**Appendix**

| | | | | | |
|---|---|---|---|---|---|
| | NCT01761266 | Lenvatinib | 3 | Eisai | Hepatocellular Carcinoma |
| CheckMate 025 | NCT01668784 | Nivolumab | 3 | Bristol-Myers Squibb | Renal Cell Carcinoma (Clear-cell) |
| CheckMate 057 | NCT01673867 | Nivolumab | 3 | Bristol-Myers Squibb | Non-small cell lung cancer (non-squamous) |
| CheckMate 067 | NCT01844505 | Nivolumab | 3 | Bristol-Myers Squibb | Melanoma |
| Checkmate 069 | NCT01927419 | Nivolumab | 2 | Bristol-Myers Squibb | Melanoma |
| | NCT00913835 | Olaratumab | 2 | ImClone Systems | Ovarian Cancer |
| | NCT00918203 | Olaratumab | 2 | ImClone Systems | Non-small cell lung cancer |
| | NCT01204710 | Olaratumab | 2 | ImClone Systems | Prostate Cancer |
| PALOMA-2 | NCT01740427 | Palbociclib | 3 | Pfizer | Breast Cancer |
| PALOMA-3 | NCT01942135 | Palbociclib | 3 | Pfizer | Breast Cancer |
| PALOMA-4 | NCT02297438 | Palbociclib | 3 | Pfizer | Breast Cancer |
| Keynote-006 | NCT01866319 | Pembrolizumab | 3 | Merck | Melanoma |
| Keynote-010 | NCT01905657 | Pembrolizumab | 2/3 | Merck | Non-small cell lung cancer |
| Keynote-024 | NCT02142738 | Pembrolizumab | 3 | Merck | Non-small cell lung cancer |

**Appendix**

## List of publications used for extraction of data on harms

**1200.28**

No publications identified

**LUX-Head&Neck 1**


1. Machiels J-PH, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol 2015;16:583–94. doi:10.1016/S1470-2045(15)70124-5
2. Clement PM, Gauler T, Machiels JP, et al. Afatinib versus methotrexate in older patients with second-line recurrent and/or metastatic head and neck squamous cell carcinoma: subgroup analysis of the LUX-Head & Neck 1 trial. Ann Oncol 2016;27:1585–93. doi:10.1093/annonc/mdw151
3. Cohen EEW, Licitra LF, Burtness B, et al. Biomarkers predict enhanced clinical outcomes with afatinib versus methotrexate in patients with second-line recurrent and/or metastatic head and neck cancer. Ann Oncol 2017;28:2526–32. doi:10.1093/annonc/mdx344


**LUX-LUNG 1**


4. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528–38. doi:10.1016/S1470-2045(12)70087-6


**LUX-LUNG 5**


5. Schuler M, Yang JC-H, Park K, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. Ann Oncol 2016;27:417–23. doi:10.1093/annonc/mdv597


**LUX-LUNG 6**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**PALOMA-4**

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