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Title page

Occurrence and determinants of selective reporting of clinical drug trials: design of an inception cohort study

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Keywords

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Abstract

Introduction

Responsible conduct of research implies that results of clinical trials should be completely and adequately reported. This article describes the design of a cohort study that aims to investigate the occurrence and the determinants of selective reporting in an inception cohort of all clinical drug trials that were reviewed by the Dutch Institutional Review Boards (IRBs) in 2007. It also describes the characteristics of the study cohort.

Methods and analysis

In 2007, Dutch MRECs reviewed 622 clinical drug trials. For each trial, we assessed the stages of progress. We discriminated five intermediate stages and five definite stages. Intermediate stages of progress are: approved by an IRB; started inclusion; completed as planned; prematurely terminated; published as article. The definite stages of progress are: rejected by an IRB; never started inclusion; not published as article; completely reported; selectively reported.

We will investigate whether trial characteristics are associated with non-publication using bivariate and multivariable models. Furthermore, we will use Cox regression models to identify trial characteristics associated with the time to publication.

We will identify seven trial-specific discrepancy items including the objectives, inclusion and exclusion criteria, outcomes, sample size, additional analyses, type of population analysis, and sponsor acknowledgement. The percentage of trials with discrepancies between the protocol and the publication will be scored. We will investigate the association between trial characteristics and the occurrence of discrepancies.

Ethics and dissemination

No IRB-approval is required for this study. Access to confidential research protocols was provided by the Central Committee on Research Involving Human Subjects. We plan to finish data collection in June 2015, and expect to complete data cleaning, analysis and manuscript preparation within the next 3 months. Hence, a first draft of an article containing the results is expected before the end of October 2015.

Strengths of this study

- The major strength of our study is that we investigate the occurrence of both the non-publication rate and selective publication in the same cohort. By addressing both issues, our analyses will likely offer more insight than most of the previous publications on this topic.
- We use original protocol data, which enables us to assess discrepancies more completely and objectively than if we would have used trial registry data only. We will not have to depend on voluntary provision of access to the original protocols in our assessment of selective reporting, which is an important limitation of most other studies.

Limitation of this study

- The most important limitation of our study is that we have to rely on the response to the questionnaire of the investigators and sponsors for verification whether the study was published. Hence, non-response may introduce bias in our study. To assess the potential impact of non-response bias, we will compare characteristics between responders and non-responders.

Introduction

Responsible conduct of clinical research implies that results of clinical trials should be completely and adequately reported[1 2]. However, a significant part of clinical trial results is never reported: on average, only 50 percent of clinical trials that are started are published in the scientific literature[3-20]. When reporting depends on the nature or direction of the trial conclusions, incomplete reporting may result in publication bias[8 9 19 21-24]. For example, if negative findings are more often not published than positive findings, the overall evidence synthesis will be biased, which can harm patients[25-27].

Publishing negative results is sometimes judged irrelevant or uninteresting by the investigator, the journal editor or the sponsor of the trial[28]. Negative trials, however, add valuable information to the body of evidence on the effects of the interventions studied. Moreover, publishing negative findings can prevent the start of unnecessary new clinical trials. This may make the use of resources for investigators and sponsors more efficient[29 30].

Selective reporting of trial results comes in two forms. Firstly, selective reporting can mean that the trial at issue is never published in the scientific literature (non-publication). This can be judged by searching for publications on trials included in an inception cohort, e.g. using information from a trial register[6 12 16 31]. Secondly, selective reporting may indicate that a trial is published in the scientific literature with changes, additions, or omissions of study aspects or findings (selective publication)[32-34]. This second meaning is more subtle and can only be judged by comparing published reports to the full original study protocol.

Non-publication rates of 10 to 88 percent have been reported in the literature[3 5 7-12 14-19]. Selective publication was identified by studying discrepancies between the protocol and publication in reporting outcomes, sample size, statistical methods and subgroup analysis[33 35-37].

That non-publication and selective publication can lead to patient harm was also shown for clinical trials with drugs intended for marketing authorization[15 38 39]. Some new drugs had to be withdrawn from the market after additional data was revealed, showing harmful effects. For example, clinical data on the new anti-inflammatory drug rofecoxib were neither published in the literature, nor revealed to the regulators[39]. Other examples of non-publication and selective publication resulting in patient harm include the antihypertensive drug reboxetine [38], and the antiarrhythmic drug lorcainide[22]. The negative media attention about these and other drug trials has caused a decrease of the public's trust in the pharmaceutical industry and medical research[40 41]. Since then, various codes and guidelines aiming at reducing selective reporting[42-44] were developed. However, recent research showed that these guidelines have only reduced selective reporting marginally[45 46].

Most studies that investigate selective reporting use data from a public registry, like clinicaltrial.gov. However, not all clinical trials are registered in public registries, and details of the original trial protocol are often unclear or lacking because these registers often do not include full study protocols. Also, information published in public registries may be subject to selective reporting as well. The availability of the full and original trial protocol submitted to an Institutional Review Board (IRB) enables to track the stages of progress of a study from the start. Therefore, to our opinion, starting with a series of consecutive full trial protocols submitted to an IRB in a defined time window and in a defined area is the best approach to examine non-publication and selective publication. Currently, few studies have been done using this approach[47].

We report the design of a study that aims to evaluate reporting practices in an inception cohort of clinical drug trials in the Netherlands. The primary objectives of the study is to investigate non-publication and selective publication in an inception cohort of clinical drug trials. With regard to non-publication, we will identify factors associated with non-publication. With regard to selective publication, we will evaluate factors associated with discrepancies between the protocol and the

publications of the trials. The secondary objective of this study is to investigate whether selective publication is associated with the direction of trial conclusions. Furthermore, we describe the characteristics of the study cohort.

Methods and analysis

Characteristics and data sources

We identified all clinical drug trials reviewed by the Dutch accredited IRBs [48] between 1 January 2007 and 31 December 2007 (n = 622). These trials define the inception cohort. According to previous studies, a seven year time window is sufficient for most trials to recruit participants, collect data, prepare a manuscript and publish the manuscript[5 8 16].

Also, we identified the characteristics of these trials (supplementary file, table 1). The used source was the General Assessment and Registration (GAR) form. This is a standard obligatory form that investigators submit to the IRB. For 194 trials, multiple therapeutic area were indicated. Two investigators (CAB and CTMB) independently examined whether these trials could be reclassified to a single therapeutic area and reclassified the combination trials as one therapeutic area. Differences were solved by consensus after involving a third investigator (GHK). To reduce the large number of different therapeutic areas, we reclassified the variable to the International Classification of Diseases, version 10[49]. This reclassification retained 11 therapeutic areas and 1 'other' category.

From the trials included, we will extract data on the stages of progress, non-publication and selective publication. In addition to the public data sources and original trial protocols, we plan to send out a questionnaire to the investigators. An overview of the variables we plan to extract is presented in the data extraction form (supplementary file, table 2).

Stages of progress

For the 622 trials in the inception cohort, we will determine the various stages of progress (figure 1). For each clinical drug trial, we will discriminate ten stages of progress. Of these, five are intermediate (meaning that further action is observed or possible), and five are definite (meaning that no further action is observed or possible). We named the stages of progress according to the flow of the cohort, shown in figure 1. The intermediate stages of progress are: B1. approved by IRB; C1. started inclusion; D1. completed as planned; D2. prematurely terminated; E1. published as article. The definite stages of progress are: B2. rejected by IRB; C2. Never started inclusion; E2. Not published as article; F1. completely reported; F2. selectively reported. We primarily aim to investigate the publication-related stages of progress E1, E2, F1, and F2. However, to understand why these stages of progress are not reached, we also determine the other stages of progress.

Non-publication

We search for publications on the trial results in the scientific literature using a standardized algorithm (figure 2). A publication is defined as a full article in a peer-reviewed scientific journal. If we identify more than one publication of trial results, we classify the publication as either primary (i.e., containing the overall results and conclusions) or secondary (i.e., interim, post hoc, subgroup or other analysis). In general, we assume that this will be clearly stated in the publications[42]. Other information collected includes the full-text of the article, the journal, and the first date of publication (e.g., advance online publication). We plan to complete the publication search in March 2015.

We will also collect the end of trial date and information about (premature) termination of the trial. We define the end of trial date as the date of the last visit of the last patient undergoing the trial[50]. Because premature termination is an intermediate endpoint of a trial, we include premature termination as a potential determinant for the outcomes studied (table 1).

Table 1 Planned analyses, outcomes and determinants

	Determinants	Outcome
Analysis of non-publication	Trial characteristics + premature termination	Time to publication
Analysis of selective publication*	Trial factors	Discrepancies between protocol and publication
	Discrepancies between protocol and publication†	Direction of publication conclusions*

* Only among published trials; † Only among comparative trials

To validate the used publication search algorithm, two investigators independently searched for publications using the algorithm, using a random selection of 30 trials of the cohort. The two searches identified no differences. We checked the external validity of the algorithm by comparing the results to a search algorithm used for another study[33], kindly provided by the investigators. This comparison showed no differences, which suggested that the construct validity of our algorithm was adequate.

In addition, we will send questionnaires to the main investigators of the research divisions or hospital departments that conducted the trials. We will specifically ask the investigators to confirm or rectify our information about which endpoint the trial reached according to our findings. In addition, for the non-published trials we ask for the reasons that the trial was not published (table 2). When the investigator does not respond to the mailed questionnaire, we will try to engage the investigator by telephone contact. In case we are unable to contact the investigator, we will contact the sponsor of the trial.

Table 2 Reasons for not publishing results, to be obtained from the questionnaire (for unpublished protocols of completed trials in cohort)

Manuscript is in preparation / under review
Results were not interesting enough to publish
Journal rejected the manuscript
Sponsor decided not to publish without providing a reason
Other

The various stages of progress of the trial in the flowchart will be updated according to the results of the questionnaire. In case neither the investigator nor the sponsor could be reached, the stages of progress remain unchanged. We assume that if a trial was incorrectly placed in the endpoint boxes C2, D2, or E2, the investigator or sponsor would have responded.

Selective publication

Among the trial protocols that resulted in a publication, we will further investigate selective publication. Selective publication can be measured by identifying discrepancies between protocol and publication. Discrepancies between protocol and publication are indications of selective publication, which may lead to reporting bias. The degree of the risk of reporting bias depends on the association of discrepancies with the direction of trial conclusions. Therefore, among the trials with a comparative design, we will also assess the direction of publication conclusions and investigate whether the direction of publication conclusions is associated with discrepancies between protocol and publication.

We define discrepancies between protocol and primary publication as additions, omissions, or changes in pre-specified discrepancy-items. To identify discrepancies systematically, we developed an extraction form containing relevant items. We used items from common protocol and publication guidelines like SIRIT and CONSORT to compel a list with trial items that should be reported. From that list, we selected seven items in which we expected selective reporting (supplementary file, table

2)[33 36 37]. The seven discrepancy items include: (1) objectives, (2) inclusion and exclusion criteria, (3) outcomes, (4) sample size, (5) additional analyses, (6) type of population analysis, and (7) sponsor acknowledgement. We will extract these items both from the protocols and the publications. Subsequently, we will compare the extracted data of the protocol to the publications. With regard to discrepancies in the objectives and outcomes, we will distinguish between discrepancies in the primary and in the secondary objectives and outcomes. With regard to discrepancies in the inclusion and exclusion criteria, we will only consider an objective change as discrepancy because inclusion and exclusion criteria are often not fully reported in publications due to the limited availability of space. We will operationalize discrepancies in the planned vs. included sample size as the ratio of sample size achieved divided by sample size planned. With regard to discrepancies in the publication analysis, we will assess whether an intention to treat or per protocol analysis was planned and used accordingly. We will also indicate when there was a lack of information in the protocol and/or in the publication to assess a discrepancy.

In case we identify multiple publications of one trial protocol, we will include the primary publication in the discrepancy assessment. In addition, if a secondary publication contains any analyses that were not described in the study protocol and this was not stated in the publication, we classify that as an additional discrepancy.

Among the trials with a comparative design, we will classify the direction of publication conclusions as either positive or negative. For example, if a non-inferiority trial shows no difference in treatment effect between the drug and its comparator, and therefore concludes that the treatment showed non-inferiority, the direction of publication conclusion is positive. On the other hand, if a superiority trial shows no difference in treatment effect between the drug and its comparator, the direction of trial conclusions is negative. For this classification, we will use the set of rules developed by Van Lent

et al. (supplementary file, table 3,[51]). Two independent investigators (CAB and PCS) will independently classify the trials, and solve differences by consensus.

Data analysis

According to the objectives of the study, we will analyze three outcomes (table 1): non-publication, discrepancies between the protocol and the publication as a proxy for selective publication, and the direction of publication conclusions. Trial factors consist of the trial characteristics and premature termination.

Non-publication

In a survival analysis of the non-publication rate, only trials that started inclusion were analyzed (box C1 of figure 1). The trial end date marks the start of follow-up. We chose this date instead of the date of IRB approval, because the trials in the cohort might differ in time span. This time span may depend, for example, on the phase of the trial and the number of participants to be recruited. In case of multiple publications of one trial protocol, we use the publication date of the primary publication.

We assume that all trials that started including patients are eligible for publication. Thus, to calculate the non-publication rate, we used the number in box C1 (figure 1) as the denominator and the number in box E1 as the numerator. To avoid duplicates, we counted trials with multiple publications as one in box E1.

To identify characteristics that are associated with (non-)publication, we conduct bivariate analysis (Chi-square test) to test for differences between published and non-published trials and perform Cox regression analysis to estimate the strength of the association between characteristics and publication status, expressed as hazard ratios and 95% confidence intervals. Because trials of oncolytic drugs are different with respect to the disease severity compared to most trials in other therapeutic areas (which may affect publication), a stratified analysis will be conducted as well.

Selective publication

For each of the seven discrepancy-items, we calculate the proportion of trials with the discrepancy. We investigate the association between characteristics and discrepancies for each item (chi-square test) and for the total discrepancy summary score (paired t-test). We will use multivariate logistic (individual discrepancies) and linear (total discrepancy score) regression models to estimate the strength of the association of characteristics and publication status, expressed as odds ratios and 95% confidence intervals. Among the trials with a comparative design, we investigate whether the discrepancies are associated with the direction of the publication conclusions using identical bivariate and multivariate analyses.

By measuring non-publication and selective publication, the study will identify the extent of research underreporting waste in a cohort of clinical trials in the Netherlands[52 53]. To increase the value derived from clinical trials, transparency from protocol to the public is needed[54]. Our study will provide this on a national level and may elucidate areas for improvement. Ultimately, this study may contribute to evidence-based medicine by improving the unbiased reporting rates of clinical drug trials. This may increase the overall trust in research on drugs and the willingness of participants to enroll in clinical drug trials.

Ethics and dissemination

Because our study involves no human subjects, no IRB-approval is required. Access to confidential research protocols was provided by the Central Committee on Research Involving Human Subjects. We plan to finish data collection in June 2015, and expect to complete data cleaning, analysis and manuscript preparation within the next 3 months. Hence, a first draft of an article containing the results is expected before the end of October 2015.

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Competing interests

The author(s) declare that they have no competing interests.

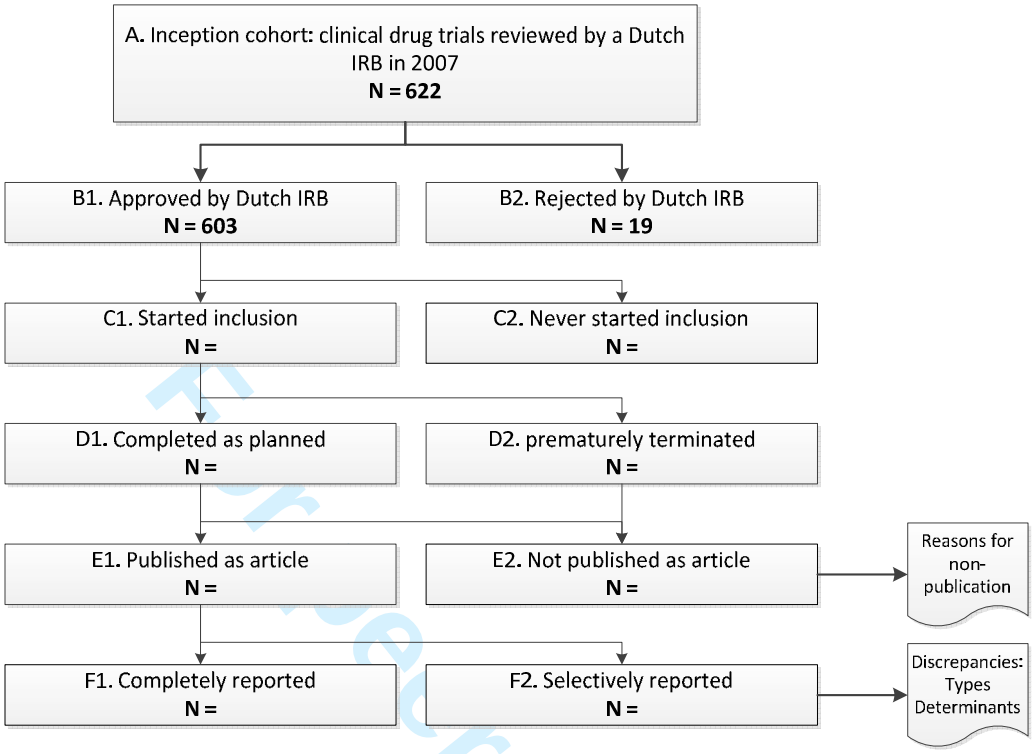
Contributorship Statement

CAB, PCS, CTMB, SWJ, GHK, HGML, and LMB engaged from the start of the project in discussing and structuring the methodology. MH is involved as a visiting scientist in performing the pilot data collection project from August 2014 until January 2015. CAB, PCS, CTMB and GHK were involved in analyzing the baseline trial characteristics of the cohort. CAB was as first author responsible for drafting the manuscript. PCS, CTMB, SWJ, MH, GHK, HGML, and LMB provided feedback on the full text, on all tables and figures, and on the abstract.

Figure legends

Figure 1 Overview of stages of progress of the 2007 inception cohort of clinical drug trials in the Netherlands. The numbers in the boxes indicate the numbers of trials that succeeded to the specific stages of progress. From B1, C1, D1, E1 to F1 is the 'perfect' flow of a trial in the cohort, meaning that all aspects took place according to the application. The sum of the boxes B2, C2, E2 F1 and F2, which are the five final stages of progress, will be 622.

Figure 2 Publication search algorithm. EudraCT = European Union Drug Regulating Authorities Clinical Trials: obligatory registration database for clinical drug trials carried out in the European Union.



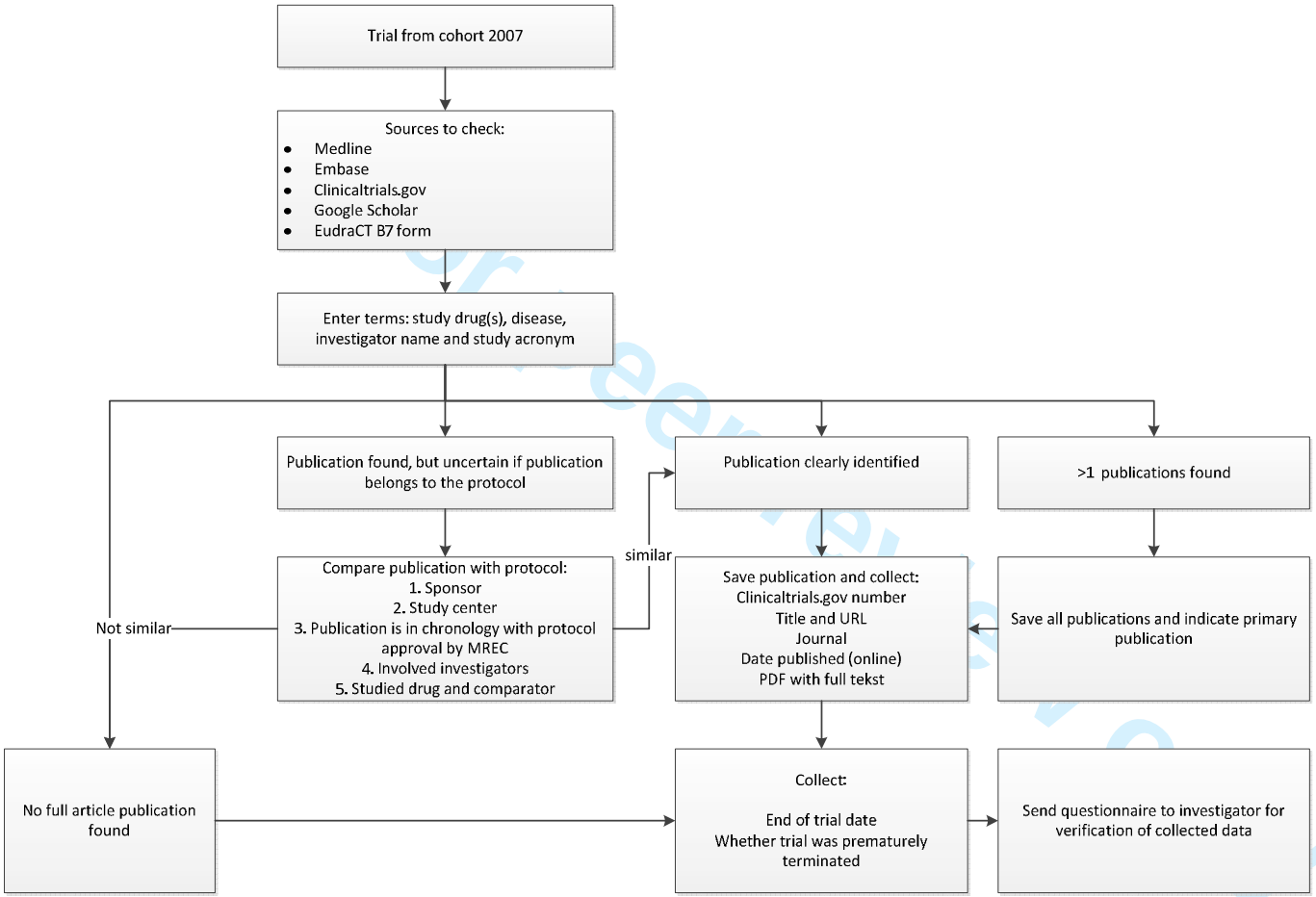


Table 1 Cohort 2007 characteristics retrieved from the General Review and Registration-forms

Characteristic	N	%
Total clinical trials in cohort	622	100.0%
Sponsor		
Pharmaceutical industry	372	59.8%
Investigator (industry (co-)funded)	74	11.9%
Investigator (no industry funding involved)	176	28.3%
Applicant		
CRO	220	35.4%
Investigator	402	64.6%
Centers involved		
Single center	274	44.1%
Multi center, only in Netherlands	61	9.8%
Multi center, Netherlands and EU	87	14.0%
Multi center, Netherlands and rest of the world	200	32.2%
Phase of study		
Phase 1	125	20.1%
Phase 2	137	22.0%
Phase 3	185	29.7%
Phase 4	66	10.6%
Other/not applicable	109	17.5%
Therapeutic/non therapeutic		
Therapeutic	386	62.1%
Non-therapeutic	236	37.9%

Table 1 continued

Characteristic	N	%
Intervention/observational		
Intervention	556	89.4%
Observational, invasive	51	8.2%
Observational, non-invasive	15	2.4%
Participant category		
≥18 years old and mentally capacitated	571	91.8%
<18 years old and/or mentally incapacitated	51	8.2%
Registration status of product		
Unregistered product	297	47.7%
Registered, studied outside indication	159	25.6%
Registered, studied within indication	128	20.6%
No registration status indicated	38	6.1%
Product category		
Regular medicinal product	590	94.9%
Complex product involved: vaccine, radiopharmaceutical, somatic cell therapy, antisense oligonucleotide	32	5.1%
Therapeutic area		
Neoplasms	117	47.9%
Neurological diseases (including analgesia and anesthesia trials)	74	39.2%
Endocrine diseases	70	35.7%
Cardiovascular diseases	68	48.6%
Mental and behavioral disorders	45	40.0%
Infectious diseases (including vaccine trials)	44	56.8%
Hematological and immunological diseases	38	44.7%
Respiratory diseases	36	52.8%
Musculoskeletal diseases	34	55.9%
Digestive system diseases	26	30.7%
Genitourinary system diseases	25	28.0%
Other	45	35.6%

Table 2 Data extraction form. GAR = General Assessment and Registration

Extract:	**Source**	**Use**	**If categorical, options**
Approved or rejected by Dutch medical research ethics committee	GAR-form	Stage of progress B1/B2	Approved / rejected
Started inclusion/never started inclusion	Questionnaire	Stage of progress C1/C2	Started / never started
Completed as planned/preliminary terminated	EudraCT B7-form and questionnaire	Stage of progress D1/D2; determinant	Completed as planned / preliminary terminated
End of trial date	EudraCT B7-form and questionnaire	Time to publication calculation	
Publication date	Pubmed and questionnaire	Time to publication calculation	Published (yes/no); if yes, date of online publication
Complely reported / selectively reported	Protocol and publication	Stage of progress F1/F2; outcome	Completely reported / selectiverly reported
If not published: reason for non-publication	Questionnaire	Reasons for non-publication	
Randomized/non-randomized	Protocol	Characteristic	Randomized / non-randomized
Trial framework	Protocol	Characteristic	Single-arm / parallel group / crossover/adaptive; superiority / non-inferiority / exploratory / no information*
Primary, secondary, and other/exploratory objectives	Protocol; publication	Discrepancy-item 1	No discrepancies / primary objectives added / primary objectives omitted / primary objectives changed / other additions, omissions or changes / no information
Inclusion and exclusion criteria for participants	GAR-form; publication	Discrepancy-item 2	No discrepancies / criteria changed / no information
Primary, secondary, and other outcomes	Protocol; publication	Discrepancy-item 3	No discrepancies / primary outcomes added / primary outcomes omitted / primary outcomes changed / other additions, omissions or changes / no information

Table 2 Continued

Estimated and included number of participants needed	GAR-form; publication	Discrepancy-item 4	No discrepancies / sample size smaller / sample size larger / no information
Methods for any additional analyses (e.g. subgroup)	Protocol; publication	Discrepancy-item 5	No discrepancies / analysis added / analyses omitted / analyses changed / no information
Intention to treat (ITT) or per protocol (PP) analysis	Protocol; publication	Discrepancy-item 6	No discrepancies / changed / no information
Sponsor acknowledgement	Publication	Discrepancy-item 7	Yes (specific sponsor) / no
Secondary publications: planned in protocol and mentioned in publication	Protocol; publication	Multiple publications	Planned / not planned and not mentioned / not planned and mentioned / no information
Direction of publication conclusion	Publication	Direction of publication conclusion	Positive / negative

*No information means that no clear information was available in the protocol or in the publication on the item

Table 3 Classification of outcomes of clinical trials based on results reported for primary endpoint [50]

	Positive outcome	Negative outcome
Results for primary endpoint statistically significant and supporting the efficacy of test drug	x	
Results for primary endpoint do not reach statistical significance		x
Results for primary endpoint statistically significant in direction of control treatment being more efficacious		x
Treatments equivalent regarding primary endpoint in non-inferiority or equivalence trials	x	
Treatments equally effective regarding primary endpoint in trials not explicitly described as superiority or non-inferiority study	x	
Test drug as safe or safer than control treatment in trials with safety parameter as primary endpoint	x	
Treatments equally harmful in trials with safety parameter as primary endpoint, when hypothesized that test drug is expected to be safer than control		x
Results for >50% of (primary) endpoints statistically significant in favor of test drug, when no/multiple primary endpoints are reported	x	
Results for one primary endpoint statistically significant in favor of test drug, when two co-primary endpoints are reported		x
Treatment effects not compared between groups but against baseline in each arm; results for primary endpoint statistically significant in favor of test drug	x	
Exploratory, descriptive and/or observational research, no hypothesis stated		

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Occurrence and determinants of selective reporting of clinical drug trials: design of an inception cohort study

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Keywords:	Selective reporting, Non-publication, Selective publication, Responsible conduct of research, Publication bias

Title page

Occurrence and determinants of selective reporting of clinical drug trials: design of an inception cohort study

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Abstract

Introduction

Responsible conduct of research implies that results of clinical trials should be completely and adequately reported. This article describes the design of a cohort study that aims to investigate the occurrence and the determinants of selective reporting in an inception cohort of all clinical drug trials that were reviewed by the Dutch Institutional Review Boards (IRBs) in 2007. It also describes the characteristics of the study cohort.

Methods and analysis

In 2007, Dutch MRECs reviewed 622 clinical drug trials. For each trial, we assessed the stages of progress. We discriminated five intermediate stages and five definite stages. Intermediate stages of progress are: approved by an IRB; started inclusion; completed as planned; terminated early; published as article. The definite stages of progress are: rejected by an IRB; never started inclusion; not published as article; completely reported; selectively reported.

We will use univariate and multivariate Cox regression models to identify trial characteristics associated with non- publication.

We will identify seven trial-specific discrepancy items including the objectives, inclusion and exclusion criteria, endpoints, sample size, additional analyses, type of population analysis, and sponsor acknowledgement. The percentage of trials with discrepancies between the protocol and the publication will be scored. We will investigate the association between trial characteristics and the occurrence of discrepancies.

Ethics and dissemination

No IRB-approval is required for this study. Access to confidential research protocols was provided by the Central Committee on Research Involving Human Subjects. We plan to finish data collection in

June 2015, and expect to complete data cleaning, analysis and manuscript preparation within the next 3 months. Hence, a first draft of an article containing the results is expected before the end of October 2015.

Strengths of this study

- The major strength of our study is that we investigate the occurrence of both the non-publication rate and selective publication in the same cohort. By addressing both issues, our analyses will likely offer more insight than most of the previous publications on this topic.
- We use original protocol data, which enables us to assess discrepancies more completely and objectively than if we would have used trial registry data only. We will not have to depend on voluntary provision of access to the original protocols in our assessment of selective reporting, which is an important limitation of most other studies.

Limitation of this study

- The most important limitation of our study is that we have to rely on the response to the questionnaire of the investigators and sponsors for verification whether the study was published. Hence, non-response may introduce bias in our study. To assess the potential impact of non-response bias, we will compare characteristics between responders and non-responders.

Introduction

Responsible conduct of clinical research implies that results of clinical trials should be completely and adequately reported[1 2]. However, a significant part of clinical trial results is never reported: on average, only 50 percent of clinical trials that are started are published in the scientific literature[3-20]. When reporting depends on the nature or direction of the trial conclusions, incomplete reporting may result in publication bias[8 9 19 21-24]. For example, if negative findings are more often not published than positive findings, the overall evidence synthesis will be biased, which can harm patients[25-27].

Publishing negative results is sometimes judged irrelevant or uninteresting by the investigator, the journal editor or the sponsor of the trial[28]. Negative trials, however, add valuable information to the body of evidence on the effects of the interventions studied. Moreover, publishing negative findings can prevent the start of unnecessary new clinical trials. This may make the use of resources for investigators and sponsors more efficient[29 30].

Selective reporting of trial results comes in two forms. Firstly, selective reporting can mean that the trial at issue is never published in the scientific literature (non-publication). This can be judged by searching for publications on trials included in an inception cohort, e.g. using information from a trial register[6 12 16 31]. Secondly, selective reporting may indicate that a trial is published in the scientific literature with changes, additions, or omissions of study aspects or findings (selective publication)[32-34]. This second meaning is more subtle and can only be judged by comparing published reports to the full original study protocol.

Non-publication rates of 10 to 88 percent have been reported in the literature[3 5 7-12 14-19]. Selective publication was identified by studying discrepancies between the protocol and publication in reporting endpoints, sample size, statistical methods and subgroup analysis[33 35-37].

That non-publication and selective publication can lead to patient harm was also shown for clinical trials with drugs intended for marketing authorization[15 38 39]. Some new drugs had to be withdrawn from the market after additional data was revealed, showing harmful effects. For example, clinical data on the new anti-inflammatory drug rofecoxib were neither published in the literature, nor revealed to the regulators[39]. Other examples of non-publication and selective publication potentially resulting in patient harm include the antihypertensive drug reboxetine [38], and the antiarrhythmic drug lorcainide[22]. The negative media attention about these and other drug trials has caused a decrease of the public's trust in the pharmaceutical industry and medical research[40 41]. Since then, various codes and guidelines aiming at reducing selective reporting[42-44] were developed. However, recent research showed that these guidelines have only reduced selective reporting marginally[45 46].

Most studies that investigate selective reporting use data from a public registry, like clinicaltrials.gov. However, not all clinical trials are registered in public registries, and details of the original trial protocol are often unclear or lacking because these registers often do not include full study protocols. Also, information published in public registries may be subject to selective reporting as well. The availability of the full and original trial protocol submitted to an Institutional Review Board (IRB) enables to track the stages of progress of a study from the start. Therefore, to our opinion, starting with a series of consecutive full trial protocols submitted to an IRB in a defined time window and in a defined area is the best approach to examine non-publication and selective publication. To date, few studies have been done using this approach[47].

We report the design of a study that aims to evaluate reporting practices in an inception cohort of clinical drug trials in the Netherlands. The primary objective of the study is to investigate non-publication and selective publication in an inception cohort of clinical drug trials. With regard to non-publication, we will identify factors associated with non-publication. With regard to selective publication, we will evaluate factors associated with discrepancies between the protocol and the

publications of the trials. The secondary objective of this study is to investigate whether selective publication is associated with the direction of trial conclusions. Furthermore, we describe the characteristics of the study cohort.

Methods and analysis

Characteristics and data sources

We identified all clinical drug trials reviewed by the Dutch accredited IRBs [48] between 1 January 2007 and 31 December 2007 (n = 622). These trials define the inception cohort. According to previous studies, a seven year time window is sufficient for most trials to recruit participants, collect data, prepare a manuscript and publish the manuscript[5 8 16].

Also, we identified the characteristics of these trials (supplementary file, table 1). The used source was the General Assessment and Registration (GAR) form. This is a standard obligatory form that investigators submit to the IRB. For 194 trials, multiple therapeutic areas were indicated. Two investigators (CAB and CTMB) independently examined whether these trials could be reclassified to a single therapeutic area and reclassified the combination trials as one therapeutic area. Differences were solved by consensus after involving a third investigator (GHK). To reduce the large number of different therapeutic areas, we reclassified the variable to the International Classification of Diseases, version 10[49]. This reclassification retained 11 therapeutic areas and 1 'other' category.

From the trials included, we will extract data on the stages of progress, non-publication and selective publication. In addition to the public data sources and original trial protocols, we plan to send out a questionnaire to the investigators. An overview of the variables we plan to extract is presented in the data extraction form (supplementary file, table 2).

Stages of progress

For the 622 trials in the inception cohort, we will determine the various stages of progress (figure 1). For each clinical drug trial, we will discriminate ten stages of progress. Of these, five are intermediate (meaning that further action is observed or possible), and five are definite (meaning that no further action is observed or possible). We named the stages of progress according to the flow of the cohort, shown in figure 1. The intermediate stages of progress are: B1. approved by IRB; C1. started inclusion; D1. completed as planned; D2. terminated early; E1. published as article. The definite stages of progress are: B2. rejected by IRB; C2. Never started inclusion; E2. Not published as article; F1. completely reported; F2. selectively reported. We primarily aim to investigate the publication-related stages of progress E1, E2, F1, and F2. However, to understand why these stages of progress are not reached, we also determine the other stages of progress. The stage of progress F2 (selectively reported) is definite for the end of our data collection; later publications can still fill remaining gaps, moving trials to F1 (completely reported).

Non-publication

We search for publications on the trial results in the scientific literature using a standardized algorithm (figure 2). A publication is defined as a peer-reviewed article containing at least methods and results . All reports not fulfilling this publication (e.g. results reported in registries, conference abstracts containing results, trial summaries on sponsor websites containing methods and results) will be also collected. Peer-reviewed publication is in our opinion the golden standard for reporting clinical research, but trial results can be reported by other means (e.g. registries, sponsor websites, conference abstracts). Using only peer-reviewed articles as endpoint for non-publication is in line with the majority of other research[47]. If we identify more than one publication of trial results, we classify the publication as either primary (i.e., containing the overall results and conclusions) or secondary (i.e., interim, post hoc, subgroup or other analysis). In general, we assume that this will be clearly stated in the publications[42]. Other information collected includes the full-text of the article,

the journal, and the first date of publication (e.g., advance online publication). We have completed this part of the publication search in March 2015.

We will also collect the end of trial date and information about (early) termination of the trial. We define the end of trial date as the date of the last visit of the last patient undergoing the trial[50]. A trial is terminated early if either the inclusion or the follow-up is terminated earlier than foreseen in the research protocol. Because early termination is an intermediate stage of progress of a trial, we include early termination as a potential determinant for the endpoints studied. In addition, prospective registration on clinicaltrials.gov will be examined as a potential determinant (table 1). We define prospective registration as registration of the trial before the first patient is recruited[1]. The data field 'first received' on clinicaltrials.gov will be used as the date of registration.

Table 1 Planned analyses, endpoints and determinants

	Determinants	Endpoint
Analysis of non-publication	Trial characteristics + early termination + prostpective registration on clinicaltrials.gov	Publication as peer-reviewed article
Analysis of selective publication*	Trial characteristics + early termination + prospective registration on clinicaltrials.gov	Discrepancies between protocol and publication
	Discrepancies between protocol and publication†	Direction of publication conclusions*

* Only among published trials; † Only among randomized trials

To validate the used publication search algorithm, two investigators independently searched for publications using the algorithm, using a random selection of 30 trials of the cohort. The two searches identified no differences. We checked the external validity of the algorithm by comparing

the results to a search algorithm used for another study[33], kindly provided by the investigators. This comparison showed no differences, which suggested that the construct validity of our algorithm was adequate.

In addition, we will send questionnaires to the main investigators of the research divisions or hospital departments that conducted the trials. We will specifically ask the investigators to confirm or rectify our information about which stage of progress the trial reached according to our findings.For the non-published trials we ask for the reasons that the trial was not published (table 2), and whether the results of the trial were reported in alternative ways, such as on clinicaltrials.gov. When the investigator does not respond to the mailed questionnaire, we will try to engage the investigator by telephone contact. In case we are unable to contact the investigator, we will contact the sponsor of the trial.

Table 2 Reasons for not publishing results, to be obtained from the questionnaire (for unpublished completed trials in cohort)

Manuscript is in preparation / under review
Results were not interesting enough to publish
Journal rejected the manuscript
Sponsor decided not to publish without providing a reason
Other

The various stages of progress of the trial in the flowchart will be updated according to the results of the questionnaire. In case neither the investigator nor the sponsor could be reached, the stages of progress remain unchanged. We assume that if a trial was incorrectly placed in the stage of progress boxes C2, D2, or E2, the investigator or sponsor would have responded. If we are unable to find any information on whether a trial started inclusion, ended, or was published, we will exclude the trial for subsequent analysis. After showing construct validity, the publication search was performed by two

authors (CAB and MH), double-checked by the questionnaire to the investigators. To assess the likelihood of bias, we will investigate whether the characteristics of included cases differ from excluded cases.

Selective publication

Among the trial protocols that resulted in a publication, we will further investigate selective publication. We include only peer-reviewed articles for the discrepancy analysis because other reports contain too little detail to investigate discrepancies with the trial protocol. Selective publication can be measured by identifying discrepancies between protocol and publication. Discrepancies between protocol and publication are indications of selective publication, which may lead to reporting bias. The degree of the risk of reporting bias depends on the association of discrepancies with the direction of trial conclusions. Therefore, among the trials with a randomized design, we will also assess the direction of publication conclusions and investigate whether the direction of publication conclusions is associated with discrepancies between protocol and publication.

We define discrepancies between protocol and primary publication as additions, omissions, or changes in pre-specified discrepancy-items. To identify discrepancies systematically, we developed an extraction form containing relevant items. We used items from common protocol and publication guidelines like SIRIT and CONSORT to compel a list with trial items that should be reported. From that list, we selected seven items in which we expected selective reporting (supplementary file, table 2)[33 36 37]. The seven discrepancy items include: (1) objectives, (2) inclusion and exclusion criteria, (3) endpoints, (4) sample size, (5) additional analyses, (6) type of population analysis, and (7) sponsor acknowledgement. We will extract these items both from the protocols and the publications. Subsequently, we will compare the extracted data of the protocol to the publications. With regard to discrepancies in the objectives and endpoints, we will distinguish between discrepancies in the primary and in the secondary objectives and endpoints. With regard to discrepancies in the inclusion

and exclusion criteria, we will only consider an objective change as discrepancy because inclusion and exclusion criteria are often not fully reported in publications due to the limited availability of space. We will operationalize discrepancies in the planned vs. included sample size as the ratio of sample size achieved divided by sample size planned. With regard to discrepancies in the type of population analysis, we will assess whether an intention to treat or per protocol analysis was planned and used accordingly. We will also indicate when there was a lack of information in the protocol and/or in the publication to assess a discrepancy.

In case we identify multiple publications of one trial protocol, we will include the primary publication in the discrepancy assessment. In addition, if a secondary publication contains any analyses that were not described in the study protocol and this was not stated in the publication, we classify that as an additional discrepancy.

The discrepancy assessment was developed by one author (CAB), and will be tested for construct validity by a second author (PCS), by performing an independent discrepancy assessment of a random selection of 10% of the published trials. Remaining differences will be solved by discussing them with two other authors (CTMB and SWJ). The remaining trials will then be assessed by one author (CAB), with a randomly selected double-check of 20 of the published trials by a second author (PCS). Uncertainties will be solved by a discussion involving two other authors (CTMB and SWJJ).

Among the trials with a randomized design, we will classify the direction of publication conclusions as either positive or negative. This classification is included to investigate whether discrepancies are associated with the direction of the conclusions (and the interpretation) that the authors draw in the discussion sections of the publications. If trials with a positive conclusion have more discrepancies than trials with a negative conclusion, this may mean that discrepancies are used to spin trial conclusions towards a positive direction. . Two independent investigators (CAB and PCS) will independently classify the trials, and solve differences by consensus.

Data analysis

According to the objectives of the study, we will analyze three endpoints (table 1): non-publication, discrepancies between the protocol and the publication as a proxy for selective publication, and the direction of publication conclusions.

Non-publication

In a survival analysis of the non-publication rate, only trials that started inclusion will be analyzed (box C1 of figure 1). The endpoint used is non-publication as peer-reviewed article, according to the definition provided above. The trial end date marks the start of follow-up (i.e. the date the trial transits to the stage of progress D1 or D2, figure 1). We chose this date instead of the date of IRB approval, because the trials in the cohort might differ in time span. This time span may depend, for example, on the phase of the trial and the number of participants to be recruited. In case of multiple publications of one trial protocol, we use the publication date of the primary publication.

We assume that all trials that started including patients are eligible for publication. Thus, the population of the non-publication survival analysis includes all trials that started inclusion (box C1, figure 1). Trials that never started inclusion are excluded from this analysis.

To identify characteristics that are associated with (non-)publication, we perform Cox regression analysis to estimate the strength of the association between characteristics and publication status, expressed as hazard ratios and 95% confidence intervals. Because trials of oncolytic drugs are different with respect to the disease severity compared to most trials in other therapeutic areas (which may affect publication), a stratified analysis will be conducted as well. In addition, we will tabulate reasons for non-publication. Finally, we will describe the means of publication by other means than by the definition of publication. By doing so, we will identify the subset of trials with no results reported at all (not as peer-reviewed article and not by other means).

Selective publication

For each of the seven discrepancy-items, we calculate the proportion of trials with the discrepancy. We investigate the association between characteristics and discrepancies for each item (chi-square test) and for the total discrepancy summary score (paired t-test). We will use multivariate logistic (individual discrepancies) and linear (total discrepancy score) regression models to estimate the strength of the association of characteristics and publication status, expressed as odds ratios and 95% confidence intervals. Among the trials with a randomized design, we investigate whether the discrepancies are associated with the direction of the publication conclusions using identical bivariate and multivariate analyses. Data analysis will be performed by two authors (CAB and PCS), and double-checked by all other authors.

By measuring non-publication and selective publication, the study will identify the extent of research underreporting waste in a cohort of clinical trials in the Netherlands[51 52]. To increase the value derived from clinical trials, transparency from protocol to the public is needed[53]. Our study will provide this on a national level and may elucidate areas for improvement. Ultimately, this study may contribute to evidence-based medicine by improving the unbiased reporting rates of clinical drug trials. This may increase the overall trust in research on drugs and the willingness of participants to enroll in clinical drug trials.

Ethics and dissemination

Because our study involves no human subjects, no IRB-approval is required. Access to confidential research protocols was provided by the Central Committee on Research Involving Human Subjects. We plan to finish data collection in June 2015, and expect to complete data cleaning, analysis and manuscript preparation within the next 3 months. Hence, a first draft of an article containing the results is expected before the end of October 2015.

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Competing interests

The author(s) declare that they have no competing interests.

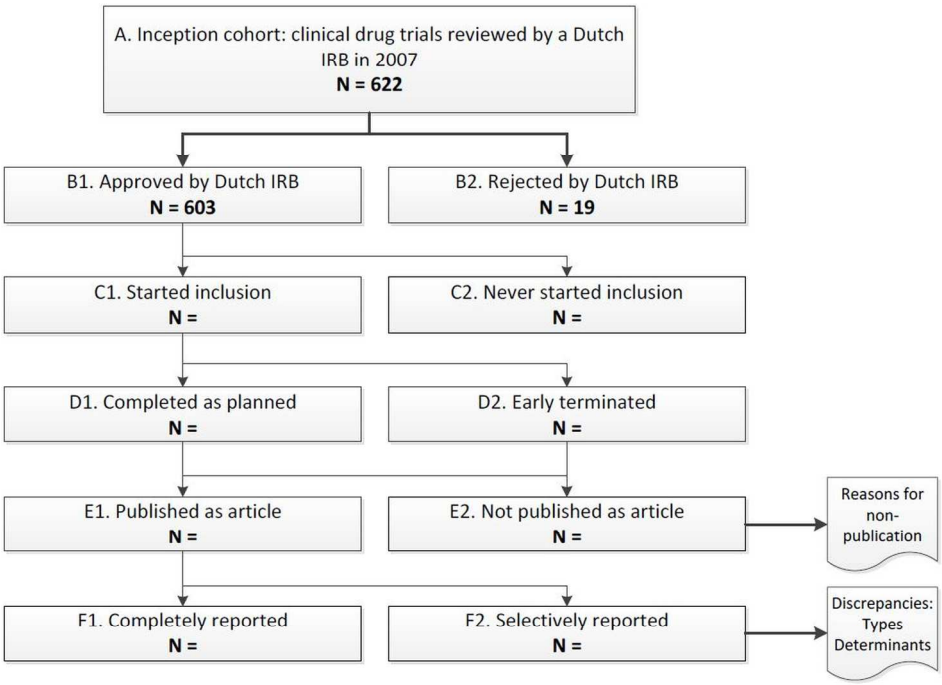
Authors' contributions

All authors except MH engaged from the start of the project in discussing and structuring the methodology. MH is involved as a visiting scientist in data collection and analysis from August 2014 until January 2015. CAB, PCS, CTMB and GHK were involved in analyzing the baseline trial characteristics of the cohort. CAB was as first author responsible for drafting the manuscript. All other authors provided feedback on the full text, on all tables and figures, and on the abstract.

Figure legends

Figure 1 Overview of stages of progress of the 2007 inception cohort of clinical drug trials in the Netherlands. The numbers in the boxes indicate the numbers of trials that succeeded to the specific stages of progress. From B1, C1, D1, E1 to F1 is the 'perfect' flow of a trial in the cohort, meaning that all aspects took place according to the application. The sum of the boxes B2, C2, E2 F1 and F2, which are the five final stages of progress, will be 622.

Figure 2 Publication search algorithm. EudraCT = European Union Drug Regulating Authorities Clinical Trials: obligatory registration database for clinical drug trials carried out in the European Union.



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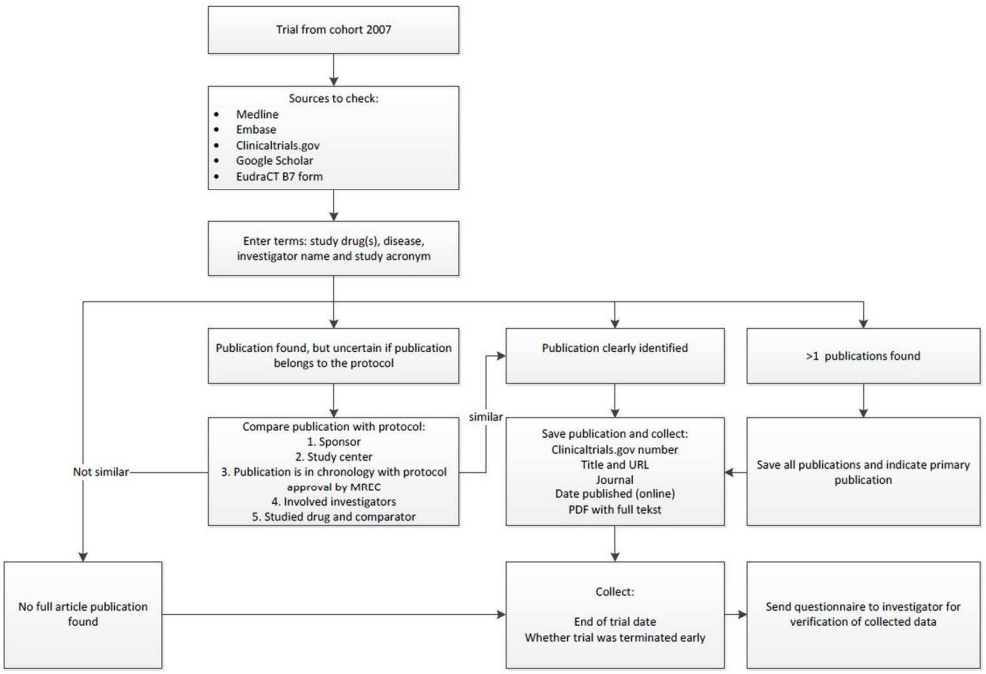

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Table 1 Cohort 2007 characteristics retrieved from the General Review and Registration-forms

Characteristic		N	%
Total clinical trials in cohort		622	100.0%
Sponsor			
	Pharmaceutical industry	372	59.8%
	Investigator (industry (co-)funded)	74	11.9%
	Investigator (no industry funding involved)	176	28.3%
Applicant			
	CRO	220	35.4%
	Investigator	402	64.6%
Centers involved			
	Single center	274	44.1%
	Multi center, only in Netherlands	61	9.8%
	Multi center, Netherlands and EU	87	14.0%
	Multi center, Netherlands and rest of the world	200	32.2%
Phase of study			
	Phase 1	125	20.1%
	Phase 2	137	22.0%
	Phase 3	185	29.7%
	Phase 4	66	10.6%
	Other/Not applicable	109	17.5%
Therapeutic/non therapeutic			
	Therapeutic	386	62.1%
	Non-therapeutic	236	37.9%

Table 1 continued

Characteristic	N	%
Intervention/observational		
Intervention	556	89.4%
Observational, invasive	51	8.2%
Observational, non-invasive	15	2.4%
Participant category		
≥18 years old and mentally capacitated	571	91.8%
<18 years old and/or mentally incapacitated	51	8.2%
Registration status of product		
Unregistered product	297	47.7%
Registered, studied outside indication	159	25.6%
Registered, studied within indication	128	20.6%
No registration status indicated	38	6.1%
Product category		
Regular medicinal product	590	94.9%
Complex product involved: vaccine, radiopharmaceutical, somatic cell therapy, antisense oligonucleotide	32	5.1%
Therapeutic area		
Neoplasms	117	47.9%
Neurological diseases (including analgesia and anesthesia trials)	74	39.2%
Endocrine diseases	70	35.7%
Cardiovascular diseases	68	48.6%
Mental and behavioral disorders	45	40.0%
Infectious diseases (including vaccine trials)	44	56.8%
Hematological and immunological diseases	38	44.7%
Respiratory diseases	36	52.8%
Musculoskeletal diseases	34	55.9%
Digestive system diseases	26	30.7%
Genitourinary system diseases	25	28.0%
Other	45	35.6%

Table 2 Data extraction form. GAR = General Assessment and Registration

Extract:	Source	Use	If categorical, options
Approved or rejected by Dutch medical research ethics committee	GAR-form	Stage of progress B1/B2	Approved / rejected
Started inclusion/never started inclusion	Questionnaire	Stage of progress C1/C2	Started / never started
Completed as planned/preliminary terminated	EudraCT B7-form and questionnaire	Stage of progress D1/D2; determinant	Completed as planned / preliminary terminated
End of trial date	EudraCT B7-form and questionnaire	Time to publication calculation	
Publication date	Pubmed and questionnaire	Time to publication calculation	Published (yes/no); if yes, date of online publication
Complely reported / selectively reported	Protocol and publication	Stage of progress F1/F2; endpoint	Completely reported / selectiverly reported
If not published: reason for non-publication	Questionnaire	Reasons for non-publication	
Randomized/non-randomized	Protocol	Characteristic	Randomized / non-randomized
Trial framework	Protocol	Characteristic	Single-arm / parallel group / crossover/adaptive; superiority / non-inferiority / exploratory / no information*
Primary, secondary, and other/exploratory objectives	Protocol; publication	Discrepancy-item 1	No discrepancies / primary objectives added / primary objectives omitted / primary objectives changed / other additions, omissions or changes / no information
Inclusion and exclusion criteria for participants	GAR-form; publication	Discrepancy-item 2	No discrepancies / criteria changed / no information
Primary, secondary, and other endpoints	Protocol; publication	Discrepancy-item 3	No discrepancies / primary endpoints added / primary endpoints omitted / primary endpoints changed / other additions, omissions or changes / no information

Table 2 Continued

Planned and actual number of participants	GAR-form; publication	Discrepancy-item 4	No discrepancies / sample size smaller / sample size larger / no information
Methods for any additional analyses (e.g. subgroup)	Protocol; publication	Discrepancy-item 5	No discrepancies / analysis added / analyses omitted / analyses changed / no information
Intention to treat (ITT) or per protocol (PP) analysis	Protocol; publication	Discrepancy-item 6	No discrepancies / changed / no information
Sponsor acknowledgement	Publication	Discrepancy-item 7	Yes (specific sponsor) / no
Secondary publications: planned in protocol and mentioned in publication	Protocol; publication	Multiple publications	Planned / not planned and not mentioned / not planned and mentioned / no information
Direction of publication conclusion	Publication	Direction of publication conclusion	Positive / negative
Prospective registration on clinicaltrials.gov	www.clinicaltrials.gov	Determinant	Yes / no

*No information means that no clear information was available in the protocol or in the publication on the item

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.