Outcome reporting bias in publishing of clinical trials: A report of basic data collection from Helsinki area in 2000s

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Tiivistelmä - Referat – Abstract

Outcome reporting bias (ORB) and publication bias are prevalent problems in medical research and cause a threat to reliability of evidence based medicine.

In this work I will 1) present the basic data collection conducted for an ORB and publication bias study, 2) illustrate the usefulness and difficulties in using REC submissions for research, and 3) review the preliminary results of the study by Chan et al.

My data collection included all trial protocols in HUS area in 2002 and 2007. There were in total 265 (2002: 139, 2007: 126) trial protocols. Protocols had a lot of variation in their manner and completeness of reporting.

The data collection was somewhat cumbersome and included a lot of bureaucracy. However, these kind of studies are important in order to accurately determine ORB and publication bias. Moreover, the forthcoming publication by Chan et al. is, to my knowledge, the first to compare all three sources: protocols, trial registries and publications.

Avainsanat – Nyckelord – Keywords

clinical protocols, publication bias, treatment outcome, research ethics committees

Säilytyspaikka – Förvaringställe – Where deposited

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1 INTRODUCTION

Reporting of unmodified study results is one of the main standards in research ethics. It is, however, common in clinical trials not to publish undesired study results (1-3) as well as leave certain outcomes out of the publication or report them inadequately while unspecified outcomes can be reported as primary (4-5). This phenomenon is called reporting bias and it can occur in study level or in outcome level. The latter is called outcome reporting bias (ORB), which is defined as the selection for publication of a subset of the original recorded outcome variables on the basis of the result. It means that the study endpoints, which investigators choose prior to initiating the trial and pre-specify in the trial protocol, are changed or incompletely reported in the final publication, causing biased study results.

The latest revision of World Medical Association's (WMA) Declaration of Helsinki (6), a consensus document in research ethics originally adopted in 1964, says the following about research publication and dissemination of results: "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. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."

ORB includes both omitting and introducing outcomes as well as changing the order of their importance (7). Accordingly, outcome reporting bias either limits the efficacy or harm data of an intervention or emphasizes certain results over others, which may lead to unsound conclusions about a treatment. In order to reliably

assess ORB one needs to compare published articles to original trial protocols. However, full trial protocols are not currently available for public, but they are controlled by national research authorities, which creates a challenge in interpretation of clinical trial results. (8) Hence, a serious problem in ORB resides in applying research results in practice. Even though selective reporting of outcomes, as such, is an ethical problem, the actual threat is that it can distort the interpretation of efficacy or harm outcomes of an individual treatment and consequently may risk the patient safety.

2 REVIEW OF THE LITERATURE

2.1 Publication bias

Publication bias has got a lot of attention during the last few years. It seems to be more widely recognized and understood than its “little sister” outcome reporting bias. Publication bias in clinical trials has been studied quite a lot in different areas of medical research (1-5) and there is rather much recent evidence of the frequency of publication bias (9-11). A systematic review by Dwan et al. (9) shows that publication bias is prevalent. In the review the publication rate of randomized controlled trials (RCTs) had, however, a great variation from 21% to 93%. But when this range was divided into positive and negative results it was seen that trials with positive results had less variation (60% - 98%) than those with negative results (19% - 85%). The review suggests that trials with positive and statistically significant results are more likely to be published.

Efforts have been made to reduce publication bias. These include, for instance, prospective trial registration, peer review process and open-access publishing. However, none of these have been shown to be very effective (12). Publication rate in clinical trials still remains low (10, 11).

2.2 Outcome reporting bias

Selective reporting of outcomes has not been as much discussed as publication bias, but it is only quite recently more widely recognized. It is important to understand these biases as they both create a potential threat to reliability of medical research. Even though it is not very meaningful to separate publication bias and ORB too much from each other, I will now concentrate more on the latter.

It has been shown in many studies that outcome reporting bias in clinical trials is common (1-5, 13-22). ORB includes omitting outcomes from publication that were mentioned in the protocol, introducing new outcomes in published article that were not listed in the protocol and changing primary outcomes to non-primary or vice versa. Studies have been shown that all of these forms of ORB are prevalent (4, 14). In one of the first large studies on ORB Chan et al. (4) found that of the inconsistently reported outcomes 46% were changed (primary to non-primary or vice versa), 26% omitted and 17% introduced. In a quite recent study by Fleming et al. (16) 39% of non-primary outcomes were omitted and 44% introduced.

There is still rather few studies that have actually determined reporting of the outcomes by comparing publications to full original protocols. Chan et al. had the access of full trial protocols in two separate studies (4, 5) and found that a third or more of trial outcomes were incompletely reported. Al-Marzouki et al. (13) also compared protocols to published reports and found that 29% of trials had major differences in primary outcome. Other studies show similar findings. Hahn et al. (17) found that only 40% of trials had pre-specified primary outcomes and 33% of these reported the outcomes inconsistently in the final publication. In another study, two thirds of the included trials had discrepancies between the protocol and the published article in primary outcome and up to 92% of trials in secondary outcomes (21).

Yet, there are ways to assess the existence of ORB in clinical trials without having access to the original trial protocols. These include comparing trial registry entries to final publications. This has been more extensively possible after 2005 when

the International Committee of Medical Journal Editors (ICMJE) stated that all its member journals start to require registration of all clinical trials prior to recruiting first subject as a precondition for publication (23), which, as expected, led to a remarkable increase in trial registration rates (24). In studies comparing trial registry entries to published articles consistent numbers with those discussed above are shown. A study that looked clinical trials of surgical interventions found that 49% of included trials had some inconsistency between registered and published outcomes (18). In two other studies, including RCTs from a broader area of medicine, discrepancies between registered and published outcomes were found in 31% of all outcomes (19), in 31% of primary outcomes and 70% of secondary outcomes (15). Nevertheless, a quite recently published study found discrepancies in only 18% of primary outcomes but 64% of non-primary outcomes (16) suggesting that reporting of primary outcomes in trial registries and publications might be improving, yet the rate of overall discrepancies remains high.

Apart from the two already presented ways of studying ORB, there is a number of studies where a multiple point classification system has been introduced in order to detect missing or incompletely reported outcome data (25, 26). Even though only presenting an estimate of the frequency of ORB, the results of these works are also consistent with the ones comparing publications with original protocols. To my knowledge, a study that compares publications to both trial protocols and registry entries has not been conducted before, making our ongoing study (27) to be presented in chapter 3 the first one of that kind.

There is clear evidence that statistically significant outcomes have higher odds for being completely reported than statistically insignificant ones (4, 5, 14, 18, 19). According to Chan et al. (5) the difference is remarkable, statistically significant outcomes having more than two times higher probability for being fully reported. Studies in which the reasons for omitting outcomes have been asked by contacting the authors of the publication, the most common answers included need for brevity or space constraints imposed by journals, lack of statistical significance, lack of clinical importance, lack of understanding about the

importance of reporting “negative” results and there being too few events worth reporting (14, 20). In one study 86% of contacted trialists denied the existence of unreported outcomes (4). These findings suggest that researchers do not recognize the problem lying in ORB and that it should be openly discussed more. The influence of source of funding in ORB in clinical trials have also been discussed, however, there is conflicting results concerning the question. Bourgeois et al. (28) found that industry funded trials more often report positive findings compared to non-industry funded trials; the proportion of publications reporting positive results were 85% for industry funded, 50% for government funded and 72% for nonprofit or nonfederal organization funded trials. Yet, no association between change of primary or non-primary outcome and source of funding were found in the study by Fleming et al. (16).

An interesting question is, how ORB effects on treatment decisions. Clinical decision-making is largely leaning on research evidence from RCTs (29-31). Systematic reviews and meta-analyses represent the best available evidence as they gather and analyse results of all relevant RCTs investigating a certain healthcare intervention in order to provide a summary of the results and to reduce possible biases in individual trials. Many national guidelines and recommendations for treatment are made based on high-quality systematic reviews, such as Cochrane reviews. (32) However, if the pool of analysed outcomes in individual RCTs is distorted favouring positive and scientifically significant results, the results of reviews and meta-analysis are likely to overestimate the efficacy of health care interventions (9).

Moreover, the selective reporting of negative study results creates a possibility to perhaps an even more serious threat: underestimation of treatment harm. It has been shown that harm outcomes more often are inadequately reported than other outcomes (5) and that non-published trials include more information about adverse events than published reports (33). Recent research evidence suggests that ORB for benefit outcomes is prevalent in over a third of reviews (25) and ORB for harm in more than 80% of systematic reviews (26). According to Kicinski et al. (10) outcomes favouring treatment are on average 27% more likely to be

included in meta-analysis than those not favouring treatment and results with no evidence of adverse effects are up to 78% more likely to be included than those showing that adverse effects exist. Hence, study evidence shows that ORB is also prevalent in systematic reviews and meta-analyses, which is a serious threat to the whole evidence based medicine, and, moreover, ORB seems to involve harm outcomes even more than other outcomes.

2.3 Clinical trial protocols

Trial protocol is a study plan where investigators describe how the trial will be conducted and report essential information about the trial (rationale, design, objective, study population, outcomes, statistical methods, time frame, sponsor etc.). Clinical trial protocol should be done prior to initiation of the trial and submitted to national ethics committee for approval. (6) Clinical trial protocols have been found to have a large amount of variation in completeness of reporting. Therefore, international guidelines for reporting in protocols have been made to improve the quality of trial protocols. (36) While The CONSORT (CONsolidated Standards of Reporting Trials) (34) and The PRISMA (Transparent Reporting of Systematic Reviews and Meta-analyses) (35) Statements guide with reporting RCTs and systematic reviews, The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement 2013 (36) provides a 30 point checklist of minimum information that should be described in clinical trial protocols, including administrative information, introduction, participants, interventions, outcomes, assignment of interventions (for controlled trials), data collection, management, analysis, monitoring, ethics and dissemination and appendixes.

Full trial protocols that are submitted to the research authorities are confidential and not currently available for public. Work has been done to make protocols publicly available and thus increase transparency of medical research: medical journals have started to require study protocol when submitting a trial for

publication (37-39) and trial registries provide public with the basic information from protocols (23, 40) but none of these gives access to full original trial protocols leaving a lot information still unavailable. This makes the complete assessing of ORB challenging.

2.4 Trial registration

The Declaration of Helsinki 2013 (6) gives a clear statement for trial registration: “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.” Moreover, WHOs Statement on Public Disclosure of Clinical Trial Results (41) says: “Before any clinical trial is initiated (at any Phase) its details are to be registered in a publicly available, free to access, searchable clinical trial registry complying with WHOs international agreed standards. The clinical trial registry entry should be made before the first subject receives the first medical intervention in the trial.” However 39% of all RCTs published in 2010 had not been registered, yet the range is wide between different research areas and journals, registration rate of published articles varying from 21% to 87% (42). Furthermore, there is quite a remarkable discrepancy between the outcome information in trial registries and publications. Norris et al. (43) found that only 50% of index outcomes were mentioned in registries and for 90% of included RCTs there were some evidence of selective outcome reporting or selective analysis reporting. Regardless of the wide range in registration rates, these numbers question the benefit of trial registration in reducing reporting biases.

In addition to trial registration, other efforts have been made to reduce ORB in clinical trials. In October 2015 Compare Project (The Center of Evidence Based Medicine Outcome Monitoring Project) was initiated in order to detect switching of outcomes and to provide a full open access to the outcome discrepancy data. The Compare Project Team compares every trial report published in top five medical journals (NEJM, JAMA, The Lancet, Annals of Internal Medicine, BMJ)

to its most original protocol found in trial registry and records the changes in outcome data. In the Compare website all this up-to-date data is collected and visible to anybody. (44)

2.5 Research ethics committees

All medical research is regulated and supervised by national research ethics committees (RECs), but the REC system varies a lot from country to country. In Finland there are five regionally operating RECs handling clinical research, one in each university clinic. HUS (The Hospital District of Helsinki and Uusimaa) research ethics committee is the biggest committee in Finland and works in cooperation with the University of Helsinki. HUS REC is divided into 4 subcommittees that together are in charge of all clinical trials in HUS area and in the university hospital district of Helsinki. In addition to the regional committees there is a central REC called TUKIJA (the National Committee on Medical Research Ethics) that operates nationally and is mostly concentrated on multicenter drug trials. (45, 46)

Compared to other countries there is a very small number of RECs operating in Finland and unlike in many other countries, there are no private RECs. The number of RECs in Finland has been reduced from 22 to 6 in 2010, presumably in order to rationalize their work. What is surprising, though, even alarming, is that although existence of these six RECs in Finland is defined by the law, their function is not supervised by anyone but the committees themselves. (45, 46).

According to the Finnish medical research law, all trials involving human subjects have to apply a research permit from one of the six operating RECs in Finland. The correct REC is determined by the working place of the principal investigator. Applications with their many appendixes are submitted to the given REC by the principal investigator of the trial.

During the data collection, which will be described in detail in chapter 5, I had the opportunity to follow the work of the HUS research ethics committees from a distance as the data collection was conducted in their facilities. From my perspective, the work in the HUS committees seemed to be well organized and people I encountered (mainly assistants) seemed to be dedicated to their jobs. The work in HUS REC seemed to be quite regulated and to include a lot of bureaucracy, but the main idea still seemed to be to help researchers instead of hindering their work. However, I did not have a chance to follow an official meeting of the HUS REC, so my observations of the operation of the committee is quite superficial.

3 BACKGROUND OF THE REPORT

My data collection was a part of a Canadian-Finnish study (27), where we compared original trial protocols approved in Helsinki in 2002 and 2007 to trial registries and final publications. The paper by Chan et al. (27) is soon to be submitted for publication. The objectives of this inception cohort study were to determine 1) completeness of protocols and registry records, 2) registration and publication rates, 3) consistency in primary outcomes and 4) impact of registration on publication and outcome reporting. The study cohort included A) all clinical trial protocols and amendments approved by HUS REC in 2002 and 2007 and TUKIJA National Committee on Medical Research Ethics in 2007 as well as B) corresponding registry records from trial registers and C) corresponding publications searched from various publication files, such as Medline. To my knowledge this study is the first comparing all these three sources for researching reporting bias.

4 AIM OF THE REPORT

Purpose of this report is to 1) present the basic data collection, 2) illustrate the usefulness and difficulties in using REC submissions to study publication and outcome reporting bias, and 3) review the preliminary results of the above mentioned study (27) as reported by An-Wen Chan in REWARD EQUATOR Conference on September 29th 2015.

5 MY DATA COLLECTION AND OBSERVATIONS

As a part of the above mentioned study I collected a large data from trial protocols in Helsinki. The purpose of the data collection was to record the original protocol data for the inception cohort study (27), in which completeness and consistency of reporting in protocols vs. trial registries and published reports were determined.

I reviewed under seven months in 2011 all clinical trial protocols submitted to the HUS research ethics committees in 2002 and 2007 and all HUS area trials submitted to TUKIJA National Committee on Medical Research Ethics in 2007. TUKIJAs 2002 submissions were not included for logistic reasons. These research ethics committees were chosen for collecting the inception cohort because together they (HUS and TUKIJA) compose the biggest RECs in Finland handling a lot of multicenter RCTs. Also, HUS and TUKIJA RECs are located in Helsinki, which was convenient for us.

Our definition of a trial was: a prospective study, where healthcare interventions are actively assigned to participants to test their effects and outcomes are measured to evaluate the effects of the interventions. We excluded all extensions to earlier than 2002 or 2007 initiated studies (secondary reports), pharmacokinetics and diagnostic test properties.

Clinical trial submissions to RECs were rather extensive. In addition to the application page the submission included the protocol, investigators' guide, multiple ethical and other reports by the principal investigator and documents to be given to the subjects. I collected data only from the trial protocols. However, contact information of the investigators could be taken from other parts of the submission, since contact information was collected only for locating corresponding trial publications in the later phase.

In HUS REC all the submission material was located in paper files in HUS ethics boards archive. There were some challenges in finding and collecting all the files. Firstly, the archive was located quite far from my desk and all the files from 2002

and 2007 had to be moved from the archive to the office. Secondly, some of the files were not in the correct place in the archive and had to be searched for. Two of the files were never found and obviously these trials had to be excluded from the study. In TUKIJA the submission material was also located in an archive, but the files were moved from the archive and back by TUKIJAs own employees. It seemed that there were no difficulties in locating the correct files and all of the included submissions were found. Yet, in TUKIJA there were much less submissions than in HUS REC.

The submission material was well organized in the files in both HUS and TUKIJA, and thus the protocols were easily found with one exception in HUS REC, when the file did not include any protocol. However, information from the protocols was sometimes hard to find. In some cases the information we were looking for was not mentioned in the protocol, but was found or could be concluded from other parts of the submission.

5.1 Permissions for data extraction

Submissions for RECs, including protocols, are confidential documents. In order to be able to extract the data from trial protocols we had to apply research permission from the Ministry of social affairs and health for the whole study and moreover from HUS REC and TUKIJA separately for extracting their submissions. Getting the permission for reviewing trial protocols was not a simple process. There was a lot of bureaucracy in the process, especially with TUKIJA. It had strict regulation and very precise procedures for sharing their submission data. In order to ensure the protection of the confidential trial data, both HUS and TUKIJA demanded that the data collection had to be conducted in their own facilities under supervision. Collected data files had to be well protected and paper copies of the protocol sections (HUS) had to be preserved carefully to make sure that any third party could not get access to the documents.

In HUS REC we were granted permission for extracting information from trial protocols and applications and also for copying the sections ‘outcomes’, ‘statistical analyses’ and ‘sample size calculation’ for later reviewing. Information from the photocopied sections was later extracted and analyzed by An-Wen Chan with his study group in Canada.

TUKIJA did not grant us a permission to take any photocopies. Accordingly, I had to type all the information needed for the study, also the outcome, statistical analyses and sample size calculation data, which meant a lot of writing. It was quite hard for me to decide which information inside these sections would be relevant for the study, since I was not the one to review and analyze these sections. Thus, I transliterated almost all text from the sections 'outcomes', 'statistical analyses' and 'sample size' to ensure that any relevant data would not be left out. This made the data collection in TUKIJA slow, even though there were much less trial submissions compered to HUS REC.

Furthermore, we translated all the Finnish data (trial titles and photocopies from Finnish protocols) to English in order to enable the study group in Canada to review and analyze the data. Translation work was conducted during the year 2012. There were in total 100 trial protocols in Finnish. Trial titles were translated by me with the help of NETMOT dictionary by Kielikone Ltd on the intranet of Helsinki University, whereas the material from the photocopies (outcomes, statistical analysis and sample size calculation) was translated by the principal investigator of the study Elina Hemminki. The latter was quite substantial work and much more time-consuming than translation of the trial titles.

5.2 Collecting the data from the protocols

There were 265 protocols in total, out of which 139 was from 2002 (83 in English, 56 in Finnish) and 126 was from 2007 (82 in English, 44 in Finnish). 9 of the 2007 protocols were submitted to TUKIJA and the rest were submitted to HUS REC. Table 1 illustrates the data characteristics listing the number of protocols

submitted to HUS and TUKIJA and the number of single-center/ multicenter trials as well as academic/ industry funded trials. From the total number of the protocols 38% was in Finnish. Trials that had protocols written in Finnish were usually single-center studies and they were more often academically funded than trials with English protocols. Table 2 shows the percentage of industry vs. academically funded and single-center vs. multicenter trials in Finnish and English protocols in 2002 and 2007.

Table 1. Data characteristics. Protocols submitted to HUS and TUKIJA, numbers.

	HUS 2002	**HUS 2007**	**TUKIJA 2007**
single-center	51	27	1
multicenter	86	90	8
industry funded	70	57	9
academic	20	19	0
protocols in Finnish	56	44	0
protocols in English	83	73	9
total	139	117	9

Table 2. Proportions (numbers) by language of the application and trial characteristics.

	Finnish protocols 2002	English protocols 2002	Finnish protocols 2007	English protocols 2007
single-center	73% (n=41)	12% (n=10)	55% (n=24)	5% (n=4)
multicenter	25% (n=14)	87% (n=72)	45% (n=20)	95% (n=78)
industry funded	8% (n=5)	78% (n=65)	2% (n=1)	79% (n=65)
academic	30% (n=17)	4% (n=3)	36% (n=16)	4% (n=3)

Variables to be collected were agreed with the principal author of the forthcoming publication (An-Wen Chan). These variables are listed in Appendix. Some of the information (contact information) was collected for finding the final reports, but most of the data was collected to determine the completeness of reporting in protocols and for later comparison to publications and registry entries in order to study discrepancies between protocols, trial registries and final reports.

In addition to the variables listed in the Appendix, in HUS REC we took photocopies of the ‘outcomes’, ‘statistical analyses’ and ‘sample size calculation’ sections of the protocols for later reviewing. We decided to copy these sections rather than extract the relevant data, because the amount of information under these titles was very large and the nature of this information was very specific. Also, we considered it to be a difficult and time-consuming task for a person who do not have a lot of experience in this area to summarize the relevant information from all of these three sections (outcomes, statistical analyses and sample size calculation). However, from TUKIJA submissions we were not allowed to take any photocopies, hence, in TUKIJA I had to transliterate the information under these subheadings.

Office Exel was used for data collection. The Exel sheet was created according to the variables that we planned to collect. For protocol sections ‘outcomes’, ‘statistical analyses’ and ‘sample size calculation’ in TUKIJA’s submissions we used Office Word for transliterating. The photocopies from HUS protocols were collected and organized in folders according to the year (2002 or 2007) and protocol number. The folders (one for each year) were kept in the HUS REC’s office during the data collection. During the later study period they were kept locked in Elina Hemminki’s office at THL.

Data collection was time-consuming. Finding information from the protocols sometimes required reading the whole protocol or large parts of it. Some of the study protocols, especially protocols of international drug trials, were very extensive and long making the data extracting laborious. Almost all the English protocols were multicenter trials with industry sponsor and these protocols usually followed a certain pattern in reporting. These protocols were often well structured and usually contained most of the information we were collecting, but on the other hand they were usually very long, sometimes containing more than 100 pages, and exhausting to read. Furthermore, they contained a lot of difficult terminology, which made it sometimes hard to extract the data. Smaller, academic trials, often having the protocols written in Finnish, sometimes had protocols with only a single page, being very easy to read and to find information from, but on the other hand, often lacked relevant data. In some cases, however, they succeeded to have a lot of relevant information summarized in one page whereas many industry funded trials still had deficiencies in reporting, even though the protocols seemed extensive. Nevertheless, it is noteworthy that for me Finnish protocols were easier to read and understand as Finnish is my mother tongue.

When generalizing, it could be said that Finnish protocols of national, academically funded trials were compact and reader-friendly, but had quite many deficiencies in reporting. On the contrary, English protocols of international, multicenter, industry funded trials were long, structured and complete, yet quite

opaque. Nevertheless, the obvious conclusion of the quality of the trial protocols was that they had a lot of variation.

The best way of reporting in protocols probably lies somewhere in the middle. In my opinion short and compact protocols would be more convenient, but the importance of complete reporting cannot be overlooked. However, from my perspective, it is equally important that the protocols are understandably written. The SPIRIT Checklist (36) provides a practical tool for improving the completeness of reporting in protocols, whereas protocol authors should pay attention to clearness and compactness of the protocols, so that anyone could understand them.

5.2.1 Limitations of the data collection

Using this kind of multiphase method for researching selective reporting involves a risk for reporting errors itself. The fact that protocols we were reviewing were on paper and every single protocol had to be picked up from the archive, makes mixing up the trial protocols unlikely. However, data collection and filling up information in Exel sheet required meticulousness and there were no systematic double checking of the collected information, hence the possibility for human errors exists.

5.3 Processing of the data

As a result of my data collection two 46-variable Exel sheets were formed, one for 2002 and one for 2007 trials. This data included in total 265 trials. Some of the unambiguous information (i.e. reported/ not reported) was coded for analyzing. The finalized data included also photocopies/ transcribed documents of ‘outcomes’, ‘statistical analyses’ and ‘sample size calculation’ sections of the trial protocols. The photocopies were scanned to computer and all the data was sent as protected files to An-Wen Chan. The photocopies and the Word files from TUKIJA protocols were reviewed by him and his study group in Canada.

Our study group in Finland helped to search the Finnish publications form Finnish national research databases, but otherwise all the later phases of the study were conducted in Canada. Processing of the data had many phases and, unlike the data collection, multiple people executing it. People working both in Finland and in Canada and cooperating in data processing added its own challenges, but did not cause any bigger problems.

The whole process of data collection was time-consuming and somewhat cumbersome, but in my opinion, it was worth the hard work for many reasons. First of all, there are not many studies like this one, where final reports of clinical trials have been compared to original protocols, which is the most reliable method for determining ORB. Secondly, the data collected from the protocols was extensive and thus has given a unique possibility to research the completeness of reporting in wide spectre. Finally, this study is, to my knowledge, the first to compare all three sources: protocols, trial registries and final publications.

6 PRELIMINARY RESULTS ON REPORTING BIAS

Below I will summarize the preliminary results of the study as presented by An-Wen Chan in REWARD EQUATOR Conference on September 29th 2015 (27). This cohort differs slightly from my data presented earlier in this dissertation, because six of the trials (three from 2002 and three from 2007) were excluded from the study after the data collection was finalized.

6.1 Cohort characteristics and completeness of reporting in protocols

The inception cohort consisted of 259 trial protocols out of which 123 were submitted in 2007 and 136 in 2002. The cohorts in 2002 and 2007 were quite similar to each other both in characteristic and in completeness of reporting. The only clear differences between the years were that there were less multicenter trials in 2002 (2002: 63%, 2007: 78%) and the median sample size was bigger in 2007. In 2002 the median sample size was 140 (range 40-420) and in 2007 200 (72-732). Most of the trials were randomized (2002: 86%, 2007: 88%) and parallel group (2002: 77%, 2007: 81%), more than two-thirds were drug trials (2002: 69%, 2007: 67%) and a half of the trials were industry funded (2002: 51%, 2007: 53%).

Most of the trial protocols reported protocol date and eligibility criteria completely, Table 3. Also primary outcome and blinding were reported well (only RCTs included), Table 4. However, role of sponsor and interim analysis as well as sequence generation and allocation concealment (only RCTs taken) were completely reported in only half of the trial protocols (Tables 3 and 4).

Table 3. Completeness of reporting in protocols.

	2002 (n=136)	2007 (n=123)
Protocol date	116 (85%)	108 (88%)
Protocol version	79 (58%)	85 (69%)
Eligibility criteria	133 (98%)	116 (94%)
Interim analysis	51 (37%)	58 (47%)
Role of sponsor	68 (50%)	56 (55%)

Table 4. Completeness of reporting in protocols, only RCTs included.

	2002 (n=117)	2007 (n=108)
Primary outcome	95 (81%)	89 (82%)
Blinding	91 (78%)	90 (83%)
Sequence generation	49 (42%)	61 (56%)
Allocation concealment	66 (56%)	61 (56%)

6.2 Completeness of registration

Since clinical trial registries were not in a wide use in 2002, completeness of registration was only determined for the 2007 cohort. 63% of all 2007 trials and 64% of all 2007 randomized trials were registered. From WHO Trial Registration Data Set criteria, countries (100%), health condition (100%) and sample size (100%) were completely documented in the registries. Also outcomes (95%),

eligibility criteria (94%) and funder (84%) were documented in most cases. On the contrary only 51% of registered trials documented information about the intervention and only 6% documented a scientific contact.

6.3 Completeness of publishing and reporting of outcomes

During the time of 2002-2015, 49% of both cohort trials were published (in 2002 the number was 66 and in 2007 60). The publication rate was about the same for randomized trials (2002: 49%, 2007: 51%) as for all trials. The median publication year was 2007 (range: 2003-2014) for the 2002 initiated trials and 2011 (range: 2008-2015) for the 2007 initiated trials. Results on ORB, as well as all the final results from the study (27) will be presented in final report soon to be published.

7 DISCUSSION

Publication bias and selective reporting of outcomes are prevalent problems, which distort the results of healthcare interventions, mainly by overestimating their efficacy or underestimating their harm. This may lead to using ineffective treatments and, at its worse, may jeopardize patient safety. Furthermore, not publishing trial results or omitting outcomes from the published article can be considered as limiting availability of scientific knowledge and wasting the overall resources for medical research.

It is quite difficult and time-consuming to research publication bias and ORB. There are multiple ways of assessing the existing of selective reporting but our method (comparing original protocols to publications) is so far the only accurate one. This method is, however, quite cumbersome, multiphase and requires a lot of permissions and other bureaucracy. These studies are, however, important in order to illustrate the frequency and extent of the problem.

Work has been done to improve the situation. Trial registries, The SPIRIT (36), The CONSORT (34) and The PRISMA (35) Statements, ethical statements by WHO and WMA, requirements of medical journals, COMPARE project (44) and several other efforts have given the problem of selective publishing and reporting more publicity and are guiding research community to the right path. Still, no sufficient improvement or adequate solution for the problem have been found.

Next step in this path might be releasing full trial protocols and increasing transparency in the work of RECs. Making trial protocols available for public would help detecting selective reporting and reduce its existence, resulting in enhancing reliability of clinical trial results. Open access to full trial protocols would also simplify researching of ORB. However, it is also necessary that reporting in protocols is complete as well as compact and clear to make sure everyone can read them.

Furthermore, independent researchers have a great responsibility in reporting trial outcomes completely and publishing all trial results, even non-significant and negative ones. In Finland, the medical research law doesn't say anything about publishing the trial results, so for now, the onus is on the trialists. Also, peer reviewers and medical journals has an opportunity and thus responsibility to intervene when noticing selective reporting in clinical trial reports. Better knowledge and more extensive discussion among researchers about the matter, especially about less widely recognized ORB, would presumably help reducing selective reporting. Much has been done, but there is still need to actively search for solutions for reducing publication bias and ORB. This is crucial for remaining the good level of evidence based medicine, on which all clinical decision-making is leaning.

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APPENDIX

List of variables for data collection.

Variable	Alternatives/ Explanation	Source
1. Protocol number	number	REC's arciving system
2. Study number	number	application
3. Trial	yes/ no/ unclear	own judgement
4. Study title		protocol
5. Speciality		protocol
	anesthesiology	
	cardiology	
	dermatology	
	endocrinology	
	general practise	
	gynegology	
	hemathology	
	infectious diseases	
	internal medicine	
	neurology	
	oncology	
	ophtalmology	
	orthopedics	
	otorhinolaryngology	
	pediatrics	
	pharmacology	
	physiology	
	psychiatry	
	radiology	
	rheumatology	
	surgery	
	urology	
	other	

Variable	Alternatives/ Explanation	Source
6. Funding		protocol
	industry	
	partial industry	
	academic	
	government	
	private	
	health services	
	other	
	none	
	not reported	
7. Investigators	names	application or protocol
-principal inverstigator		
-other investigators in Finland		
-other international investigators		
8. Contact information (PI)		application
-phone	number	
-e-mail	address	
9. Protocol information	reported/ not reported/ unclear	protocol
-protocol version		
-protocol date		
-protocol authors		
10. Sites		protocol
	single-center	
	multicenter	
11. Phase		protocol
	pilot	
	1	
	2	
	3	
	4	

Variable	Alternatives/ Explanation	Source
12. Design		protocol
	parallel	
	cross-over	
	split	
	cluster	
	non-controlled	
13. Framework		protocol
	superiority	
	non-inferiority	
	equvivalence	
	non-controlled	
14. Intervention		protocol
	drug	
	surgery	
	procedure	
	other substance	
	other therapy	
	device	
	lifestyle	
	counselling	
	education	
	managemet strategy	
	diagnose test	
15. Name of the intervention	name of the drug/surgical technique etc.	protocol
16. Intervention group	intervention more detailed: dose, administation etc.	protocol
17. Control groups:	name of the control intervention(s)	protocol
-control group 1		
-control group 2 etc.		
18. Overall sample size	number	protocol
19. Number of groups	number	protocol

Variable	Alternatives/ Explanation	Source
20. Allocation ratio	ratio (eg. 1:1)	protocol
21. Randomization:		protocol
-allocation		
	full individual randomization	
	cluster randomization	
	split-body	
	other	
-sequence generation		
	computer generated	
	random tables	
	lottery	
	other	
-allocation concealment mechanism		
	sealed envelopes	
	calling to a person	
	calling to a computer	
	other	
22. Blinding label		protocol
	single	
	double	
	triple	
	open-label	
	blinded	
	no blinding	
	not reported	
23. Blinding:		protocol
-patient	yes/ no/ not reported/ unclear	
-caregiver	yes/ no/ not reported/ unclear	
-investigator	yes/ no/ not reported/ unclear	
-outcome assessor	yes/ no/ not reported/ unclear	
-data analyst	yes/ no/ not reported/ unclear	

Variable	Alternatives/ Explanation	Source
24. Eligibility criteria	reported/ not reported/ unclear	protocol
25. Duration of the trial	time	protocol
-duration of the intervetion		
-duration of the follow-up		
26. Interim analysis:		protocol
	yes → how often	
	no	
	not reported	
	unclear	
-statistical anlysis plan	yes/ no	
-data monitoring committee	yes/ no/ not reported/ unclear	
27. Role of sponsor in:		protocol
-study design	reported/ not reported/ unclear	
-data collection	reported/ not reported/ unclear	
-management	reported/ not reported/ unclear	
-analysis	reported/ not reported/ unclear	
-interpretation	reported/ not reported/ unclear	
-writing manuscript	reported/ not reported/ unclear	
28. Amendments	yes/no if yes: how many, relevant changes, date of the amendements	protocol amendments