Publication and non-publication of clinical trials: longitudinal study of applications submitted to a research ethics committee

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Summary

\textit{Background:} Not all clinical trials are published, which may distort the evidence that is available in the literature. We studied the publication rate of a cohort of clinical trials and identified factors associated with publication and non-publication of results.

\textit{Methods:} We analysed the protocols of randomized clinical trials of drug interventions submitted to the research ethics committee of University Hospital (Inselspital) Bern, Switzerland from 1988 to 1998. We identified full articles published up to 2006 by searching the Cochrane CENTRAL database (issue 02/2006) and by contacting investigators. We analyzed factors associated with the publication of trials using descriptive statistics and logistic regression models.

\textit{Results:} 451 study protocols and 375 corresponding articles were analyzed. 233 protocols resulted in at least one publication, a publication rate of 52%. A total of 366 (81%) trials were commercially funded, 47 (10%) had non-commercial funding. 346 trials (77%) were multi-centre studies and 272 of these (79%) were international collaborations. In the adjusted logistic regression model non-commercial funding (Odds Ratio [OR] 2.42, 95\% CI 1.14–5.17), multi-centre status (OR 2.09, 95\% CI 1.03–4.24), international collaboration (OR 1.87, 95\% CI 0.99–3.55) and a sample size above the median of 236 participants (OR 2.04, 95\% CI 1.23–3.39) were associated with full publication.

\textit{Conclusions:} In this cohort of applications to an ethics committee in Switzerland, only about half of clinical drug trials were published. Large multi-centre trials with non-commercial funding were more likely to be published than other trials, but most trials were funded by industry.

Key words: clinical trials; drug trials; full publication; study protocols; reporting biases; longitudinal study

Introduction

Patients, health professionals and policy makers need access to all the available evidence on the effects of health care interventions in order to make appropriate decisions. It has long been recognised that only a proportion of research projects ultimately reaches the stage of full publication in a peer-reviewed journal. In 1979, Rosenthal described the gloomy scenario where journals are filled with spurious results that happened to reach statistical significance, whilst researcher archives are filled with the many non-significant study results [1]. The selective publication of “positive”, statistically significant results, called the “file drawer problem” by Rosenthal, is better known as publication bias [2].

In practice, the dissemination of research findings follows a continuum from informal presentations, conference poster or oral presentation with or without a published abstract to letters, short reports and original articles in a journal indexed in the main bibliographic databases. Only original articles contain sufficient detailed information to allow critical appraisal and decision-making. Conference abstracts are difficult to locate as most appear in conference proceedings and these are typically not included in bibliographic databases.

The earliest stage of detailed study documentation is when study protocols are being submitted to research ethics committees or funding...
agencies. Such protocols are increasingly being recognised as a valuable source of information for research on the dissemination of research [3]. Several studies have followed research proposals approved by research ethics committees or institutional review boards [4–8].

We set out to investigate the publication or non-publication of clinical trials based on a cohort of protocols submitted to a research ethics committee of a university hospital in Switzerland.

Methods

Cohort of study protocols

We were granted access to the paper files of all study protocols submitted from 1988 to 1998 to the research ethics committee of University Hospital Bern (Inselspital), Switzerland. These files included submitted study protocols, amendments and related correspondence including committee decisions and communications on conduct and completion of studies. Our study was submitted to and approved by the Cantonal authorities responsible for data protection issues.

We classified all submitted studies by study design using predefined criteria. The present analysis was restricted to protocols of randomised trials of drug interventions (drug trials). A drug trial was defined as a study of one or more drugs in humans, independent of the route of administration. Studies that did not compare at least two different drugs or one drug with a placebo or no treatment were excluded. For example, we excluded studies comparing different doses or routes of administration of the same drug.

Identification of publications

Electronic searches

We systematically searched the CENTRAL database (Cochrane Library, issue 02/2006) to identify full publications with a potential link to the included protocols. CENTRAL is a comprehensive database of controlled trials maintained by the Cochrane Collaboration [9]. It includes trials published in journals not indexed in MEDLINE, EMBASE or other bibliographic databases and in languages other than English [10]. We defined a full publication as an article published in a medical journal providing detailed information on methods and results.

For each protocol, we developed a search strategy, based on information from the protocol, for example the study name or acronym, condition studied and the names of the investigator. Potentially eligible publications were retrieved and further examined. Publications were included if they reported results from an eligible study.

Survey of applicants

Between April and July 2006 we sent a standardized questionnaire to the investigators of all included protocols. The questionnaire asked about the current status of the project (ongoing or completed) and provided a list of publications identified. We asked the applicants to confirm that the publications corresponded to the study protocol in question and to provide references of any additional publications. We checked addresses of non-responders by electronic searches and attempted to contact them by letter, e-mail or telephone. For protocols submitted in the last two years of observation (1997 and 1998) with no publications and no response from investigators, we searched online trial registries and the internet to determine the status of the study. These searches identified no ongoing studies.

Data collection and definitions

We established two databases, one for data extracted from the protocols and another for data extracted from related publications. Databases were linked by unique identifier numbers. A standardised data abstraction form was used to extract data on study characteristics, including the experimental (and control) drug, study design, sample size, source of funding and pre-specified outcomes from all eligible protocols. Data were extracted by one investigator and cross-checked by a second; discrepancies were resolved by consensus.

Commercial funding was defined as any financial support or provision of study materials by industry. For commercially funded trials, we recorded if the sponsor was involved in the planning of the study, data management or analysis. We assumed such involvement if a co-author of the study protocol was affiliated with a company. Non-commercial funding included financial or other support by public funding agencies, public or private foundations (if not clearly linked to a private company) or research funds of hospital or university entities. A study with at least one collaborating centre outside Switzerland was classified as an international study. Some protocols indicated a range (rather than a single value) for the planned sample size and duration of follow-up. In these cases we used the smallest value.

Statistical analysis

We used standard descriptive statistics. The publication rate was calculated as the proportion of protocols with at least one related full article. We used multiple logistic regression models with full publication as the dependent variable and characteristics of protocols and publications as independent variables. We used STATA version 9.2 (STATA Corporation, Austin/Texas, USA) for all analyses. Results of regression models were expressed as odds ratios (ORs) with 95% CIs.

Results

Inclusions of protocols and publications

A total of 1698 protocols were submitted to the research ethics committee from 1988 to 1998 (fig. 1). We excluded 119 entries because the files could not be located or did not include a complete study protocol and a further 1048 protocols of studies other than randomized drug trials. We were left with 531 eligible protocols submitted by
of published and unpublished studies.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 451)</th>
<th>Published (n = 233)</th>
<th>Unpublished (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical specialty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>67 (15%)</td>
<td>45 (19%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>44 (10%)</td>
<td>32 (14%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>42 (9%)</td>
<td>20 (9%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>35 (8%)</td>
<td>12 (5%)</td>
<td>23 (11%)</td>
</tr>
<tr>
<td>Neurology</td>
<td>29 (6%)</td>
<td>18 (8%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>23 (5%)</td>
<td>10 (4%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Dentistry</td>
<td>20 (4%)</td>
<td>5 (2%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Dermatology</td>
<td>20 (4%)</td>
<td>5 (2%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>171 (39%)</td>
<td>86 (17%)</td>
<td>85 (38%)</td>
</tr>
<tr>
<td>Type of study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parallel group trial</td>
<td>418 (93%)</td>
<td>213 (91%)</td>
<td>205 (94%)</td>
</tr>
<tr>
<td>Cross over trial</td>
<td>33 (7%)</td>
<td>20 (9%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Planned sample size (median, range)</td>
<td>216 (4-15,000)</td>
<td>180 (6-15,000)</td>
<td>180 (4-8,000)</td>
</tr>
<tr>
<td>Number of centres</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>346 (77%)</td>
<td>182 (78%)</td>
<td>164 (75%)</td>
</tr>
<tr>
<td>≤1</td>
<td>105 (23%)</td>
<td>51 (22%)</td>
<td>54 (25%)</td>
</tr>
<tr>
<td>International collaboration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>272 (60%)</td>
<td>157 (67%)</td>
<td>115 (53%)</td>
</tr>
<tr>
<td>No</td>
<td>171 (38%)</td>
<td>75 (32%)</td>
<td>96 (44%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>8 (2%)</td>
<td>1 (≤1%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Source of funding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>346 (77%)</td>
<td>167 (72%)</td>
<td>179 (82%)</td>
</tr>
<tr>
<td>Non-commercial</td>
<td>27 (6%)</td>
<td>19 (8%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Both</td>
<td>20 (4%)</td>
<td>15 (6%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Unclear or not mentioned</td>
<td>58 (13%)</td>
<td>32 (14%)</td>
<td>26 (12%)</td>
</tr>
</tbody>
</table>

225 investigators. For 44 protocols the project status was documented as “stopped prematurely”. We contacted the applicants of the remaining 487 protocols. At the time of submission of the protocol most were affiliated with the University Hospital of Bern. We obtained responses for 348 of 487 protocols (response rate 71%). Eighty of 531 studies (15%) had not been completed at the time of the survey for various reasons (fig. 1): 57 trials (including the 44 trials mentioned above) were stopped prematurely, 16 trials never started, 5 trials were not approved by the ethics committee and two trials were ongoing. The reasons for stopping the 57 trials included insufficient enrolment of participants in 22, negative results or lack of efficacy in 9, adverse events in 7, loss of interest by investigators or sponsors in 7, other reasons in 10 and unknown reasons in two trials.

Our sample thus comprised 451 protocols of completed drug trials. We identified 126 publications through literature searches and 49 additional publications through our survey, for a total of 375 publications. These related to 233 study protocols. The publication rate was therefore 52% (233/451). The median number of publications per protocol was 1 (range 1 to 14). Sixty-three (14%) protocols had more than one related publication.

Characteristics of protocols

The characteristics of studies that resulted in a publication and of studies that remained unpublished are summarised in table 1. The 451 trials were conducted in various fields of academic medicine and dentistry; most commonly in oncology (n = 67, 15%), cardiology (n = 44, 10%) and infectious diseases (n = 42, 9%). The number of submitted protocols per year increased from 24 in 1989 (the first complete year included) to 69 in 1998.

Most trials were of a parallel design (n = 418, 93%). Among these 108 (26%) had three or more treatment arms and nine (2%) used a factorial design. Thirty-three trials (7%) were cross-over trials. The planned sample size was given in 447 (99%) protocols and ranged from 4 to 15,000 participants (median 236 participants). The planned duration of enrolment was specified in 220 (49%) protocols and ranged from 1 to 108 months (median 12 months).

One hundred and five (23%) studies were single-centre studies and 346 (77%) were multi-centre studies. Of the latter, 272 (79%) included international centres, 66 (19%) national collaborations and for eight (2%) the collaborating centres were not described in the protocol. Of the 272 international studies, seven (3%) were led by a Swiss study centre and 240 (88%) by a study centre abroad. The leading study centre was unclear in 25 (9%) protocols.

The source of funding was reported in 393 (87%) studies and was unclear in the remaining 58 (13%) studies. Commercial funding was reported in 366 (81%) protocols. In 42 of these studies (11%) the commercial sponsor provided study drugs or other material but was not involved in the conduct of the trial. Non-commercial funding was reported for 47 protocols (10%) and in 20 (4%) protocols
both commercial and non-commercial funding sources were mentioned. There was variation in the rate of commercial funding across specialities, ranging from 42 studies (63%) in oncology to 21 studies (91%) in psychiatry.

Factors associated with publication

In the unadjusted logistic regression models the probability of publication decreased if the study was commercially funded (OR 0.6) (table 2). It increased with non-commercial funding (OR 2.7), if the planned sample size was above the median (OR 2.1) and if the study was international (OR 1.7). In the adjusted model there were little changes in the point estimates except for multi-centre status, which was associated with the probability of publication in the adjusted model (OR 2.1) but not in the unadjusted analysis (OR 0.9).

Discussion

Summary of results

Only about half of the randomized drug trials approved by an ethics committee in Switzerland were published during a follow up period that ranged from seven to over 17 years after approval of the protocol. The publication of trials was associated with several study characteristics, including source of funding, study size, and international and multi-centre status. About four out of five studies were sponsored by industry and in most of these trials the company was directly involved in the conduct of the trial.

Findings in context with other studies

In a bibliographic study of 519 trials indexed in the PubMed database [11], about three quarters were of parallel group design, 72% were single-centre studies and 44% were partly or fully commercially funded. The median sample size was 52. In our study, more trials were of parallel-group design and commercially funded and fewer trials were single-centre studies. The median sample size in our study was larger. These differences may be explained by the different selection criteria: all of the PubMed-indexed trials were published (by definition), whereas only 52% of our trials reached publication. Also, we restricted our sample to drug trials, whereas only 76% of the PubMed-indexed trials examined drug interventions.

We found commercial funding in 81% of the studies included. In a high percentage (70%) the commercial sponsor was involved in the conduct of the study, for example in the design, data management or analysis. In other cohorts of study protocols submitted to ethic committees the percentage of commercial funding ranged from 1% to 89% [4–8]. This wide range may be due to differences in the studies examined, different definitions of “commercial funding” or different study periods. Clearly, commercial funding is more important for clinical trials than for other types of studies [6].

Table 2

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-commercial funding versus all other funding</td>
<td>2.7</td>
<td>2.4 (1.1-5.2)</td>
</tr>
<tr>
<td>Commercial funding versus all other funding</td>
<td>0.6</td>
<td>0.7 (0.4-1.3)</td>
</tr>
<tr>
<td>Large study versus small study**</td>
<td>2.1</td>
<td>2.0 (1.2-3.4)</td>
</tr>
<tr>
<td>Multi-centre study versus single-centre study</td>
<td>0.9</td>
<td>2.1 (1.0-4.2)</td>
</tr>
<tr>
<td>International versus national study</td>
<td>1.7</td>
<td>1.9 (1.0-3.6)</td>
</tr>
</tbody>
</table>

* Adjusted for all 5 listed variables
** Large studies have sample size above / small studies below the median sample size of all studies (n = 236).

Table 3

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Medical School</th>
<th>Public Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of REC approval</td>
<td>1980</td>
<td>1980</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>1988</td>
<td>1988</td>
</tr>
<tr>
<td>Number of proposals</td>
<td>342 (100%)</td>
<td>172 (100%)</td>
</tr>
<tr>
<td>Full publication</td>
<td>230 (67%)</td>
<td>104 (61%)</td>
</tr>
</tbody>
</table>

REC = research ethics committee
It is well known that many trials remain unpublished after completion of data collection and analysis. Only about half of abstracts of studies presented at conferences are later published in full [12]. Six studies of proposals submitted to ethics committees in Oxford [6], Sydney [8], the Johns Hopkins School of Medicine and School of Hygiene and Public Health in Baltimore [5] and to national ethics committees in France [4] and Spain [7] found rates of publication that ranged from 31% to 67%, with higher rates in the USA, England and Australia than in non-anglophone countries (table 3). In our study the publication rate was 52%. The previous studies did not combine surveys of applicants with electronic searches and included studies other than drug trials. Our results are therefore not directly comparable to those from the earlier studies.

Reasons for non-publication

We still lack a full understanding of the reasons for the non-publication of clinical trials. In a review of studies following scientific projects after meeting presentations, von Elm and colleagues found that lack of time was the most commonly mentioned barrier to publication, but researchers also mentioned negative results as an important reason [13]. Indeed, the selective publication of ‘positive’, statistically significant results is well documented. In studies of proposals submitted to ethics committees (table 3) of trials funded by the National Institutes of Health [14], trials submitted to licensing authorities [15], trials in HIV medicine [16] and analyses of trial registries [17], publication was more likely if effects were large and statistically significant. Figure 2 shows a meta-analytic summary of five ethics committee cohorts (the study done by Pich et al. [7] did not provide sufficient information on publication bias to be included). The probability of publication was 2.6 times greater if results were statistically significant (p < 0.05).

We did not examine publication bias. Ascertaining the results of unpublished studies that were completed many years ago is difficult and time-consuming and this was not feasible within the framework of this study. Clearly, this is a limitation of our study, also because the statistical significance of results may both be related to the probability of publication and other factors of interest, for example study size and the source of funding. The nature of the results may thus act as a confounding variable with respect to other factors of interest. Of note, previous studies of proposals approved by ethics committees or institutional review boards [5, 6] found only small effects for sample size in analyses adjusted for statistical significance – in contrast to the present analysis. In these studies external funding was associated with increased publication rates even after adjusting for statistical significance, although results were heterogeneous, possibly because no distinction was made between commercial and non-commercial sources of funding.

Strengths and limitations

We analyzed a large and unselected sample of trial protocols submitted to a University research ethics committee over a period of eleven years. Since most trials were international, our results are not only applicable to our local research environment but to similar settings of clinical research abroad. We used a comprehensive literature search and achieved a response rate of 71% in our survey of applicants. Nevertheless, we may have missed some publications. As mentioned above, we could not examine publication bias. Many of the studies date back more than 15 years and many were international collaborations with a co-ordinating centre outside of Switzerland. We found that in some cases the Swiss investigators participating in international studies did not know whether the study had been published. To obtain reliable information on the results of unpublished studies, it would be necessary not only to interview the Swiss investigators: sponsors, principal investigators or contract research organisations would probably also need to be contacted.

We restricted our study to drug trials. Consequently, some research fields will be underrepresented in our sample (for example surgery or interventional radiology). We did not use the phase I to III classification scheme for trials because it was not used consistently in the included protocols. Almost a decade has elapsed since submission of the most recent protocols included in our study. The rate of publication and quality and characteristics of protocols and publications may have changed since then, especially in the light of recent initiatives for the registration of clinical trials [18, 19]. This may limit the application of our findings to current practice and illustrates the dilemma faced by this and many other longitudinal studies: including more recent protocols would leave insufficient time for studies to be completed and results to be published [12]. In our sample, we had to exclude only two studies that were ongoing in 2006.

Implications

The high percentage of commercially funded trials must be a matter of concern. Associations between the source of funding and the conclusion of research articles have been reported repeatedly [20–23]. If funded by for-profit organisations, the
conclusions in randomised trials recommended the experimental drug as the drug of choice five times more often than with other funding, even after adjustment for the size of the treatment effect [24]. There is also evidence that the tobacco and telecommunication industries influence the results of research they funded [25–28]. Possible mechanisms include influence on the design of the study [29], choice of exposures [29, 30], outcomes [31–33], statistical methods [34] and investigators, as well as selective publication of outcomes [31–33] and studies [12].

In our study the probability of publication was higher if funding was from a non-commercial agency and tended to be reduced with commercial funding. In three cohorts of proposals submitted to ethics committees industry-independent funding by government agencies was significantly associated with publication [5, 6, 8] whereas in two cohorts, pharmaceutical industry sponsored studies were less likely to be published [5, 6]. A possible explanation is that the pharmaceutical industry tends to discourage the publication of negative studies that it has funded. At least one such example is well documented. A manuscript reporting on a trial comparing the bioequivalence of generic and brand levothyroxine products [35, 36], which had failed to produce the results the sponsor hoped for, was withdrawn because the company took legal action against the university and the investigators. This resulted in a delay in publication of about seven years. Twenty percent of life-sciences faculty members in the United States reported that they had experienced delays in publication of their work and reasons for not publishing included “to delay the dissemination of undesired results” [37]. Delays in publication were associated with involvement in commercialisation and academic-industry research relationships.

Independently of the source of funding, authors may often not submit studies with negative findings because they anticipate rejection by journal editors. Interestingly, empirical evidence indicates that selective submission of papers reporting statistically significant results is more important than acceptance or rejection of studies based on their results by journals [5, 6]. Studies of lower methodological quality are more likely to produce "positive" results [38] and may therefore be more likely to be published. We did not collect information on the possible submission (and rejection) of unpublished studies, nor did we attempt to assess the quality of studies.

The selective reporting of trials may introduce bias in reviews and meta-analyses of the available evidence [17, 34, 39–42], which again may affect conclusions and misguide policy and future research. The implication is that investigators and sponsors have the ethical obligation [43] to publish results independent of the nature of these results, or make them publicly available through other means [44], for example on the internet. The International Committee of Medical Journal Editors (ICMJE) argues that “patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health-care decisions” [18]. More than a decade ago, the underreporting of study results was called “a form of scientific misconduct” [45]. Considerable progress has been made, thanks to the initiative led by the World Health Organization, to register all clinical trials. However, the views of the different stakeholders concerning the content of these registries differ [46–48].

In conclusion, this large cohort of drug trials approved by an ethics committee in Switzerland showed that only about half of the trials were published. Among the factors influencing the probability of publication, the influence of the source of funding is of particular concern. Our findings support the need for compulsory trial registration as well as public funding streams for industry-independent clinical trials research.

We are grateful to the research ethics committee of the Canton of Bern, its former president Professor Jürg Hodler, Charles Senessie, Nicola Low, Claire Graber, Sheilagh Redmond, Marcel Zwahlen, Gerd Antes and Martin Schumacher for valuable contributions and support at the different stages of this study and to the investigators who responded to our survey.

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