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SHORT REPORT

Non-commercial *vs.* commercial clinical trials: a retrospective study of the applications submitted to a research ethics committee

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There are many difficulties in undertaking independent clinical research without support from the pharmaceutical industry. In this retrospective observational study, some design characteristics, the clinical trial public register and the publication rate of noncommercial clinical trials were compared to those of commercial clinical trials. A total of 809 applications of drug-evaluation clinical trials were submitted from May 2004 to May 2009 to the research ethics committee of a tertiary hospital, and 16.3% of trials were noncommercial. They were mainly phase IV, multicentre national, and unmasked controlled trials, compared to the commercial trials that were mainly phase II or III, multicentre international, and double-blind masked trials. The commercial trials were registered and published more often than noncommercial trials. More funding for noncommercial research is still needed. The results of the research, commercial or noncommercial, should be disseminated in order not to compromise either its scientific or its social value.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- There is a need to support independent clinical research addressed to relevant questions about public health and clinical decisions.
- There are many difficulties in undertaking clinical research without the support of the pharmaceutical industry.

WHAT THIS STUDY ADDS

- The proportion of noncommercial clinical trials submitted to research ethics committees is still low compared to commercial trials.
- Results of clinical trials with a commercial sponsor are published in peer-review scientific journals and registered in public registers, such as http://clinicaltrials.gov, at a higher percentage in comparison with noncommercial clinical trials.
- Clinical researchers, especially those of noncommercial studies, must make a greater effort to disseminate results of their research and not to compromise the social value of clinical trials.

Introduction

The information generated by clinical trials is essential, not only to have the necessary data that lead to the commercialization of a new drug, but also to establish its role in the treatment of a specific disease, as well as in health policy decisions [1, 2]. Sometimes the current needs of clinical practice do not align with the interests of the pharmaceutical industry when new drugs are developed [3]. For this reason, there is a need to support independent clinical research addressing some relevant clinical questions. Nevertheless, there are many difficulties in undertaking clinical research without support from the pharmaceutical industry [1–3]. In Europe, between 10 and 30% of clinical trials are conducted by academic or noncommercial sponsors [4].

The European Directive (ED) on Clinical Trials (EU 2001/20 / EC), published in 2001, came into force in Europe in 2004 to harmonize and simplify multicentre clinical trials throughout the European Union [5].

It is essential that, with the independence of the sponsor, the results of clinical trials, either positive or negative, are available. It is also important that ongoing clinical research is available. In this sense, in 2004, the International Committee of Medical Journal Editors established the requirement to register all clinical trials before the onset of patient enrolment. This is a condition to publish clinical trials in biomedical journals [6]. The US http://clinicatrials.gov website is considered the main public register of clinical trials and it was launched in 2000 [7]. Also, in Spain, the publication of results of authorized clinical trials in scientific journals, either positive or negative, was included as a compulsory condition [8] even though this was not a requirement of the ED [4].

The purpose of this study was to analyse some design characteristics, the public register of clinical trials and the publication rate of noncommercial clinical trials from 2004 to 2009, and these facts were compared with those of clinical trials sponsored by the pharmaceutical industry.

Methods

A retrospective observational study of the applications of clinical trials submitted from May 2004 to May 2009 to the research ethics committee (REC) of our tertiary hospital (University Hospital Vall d'Hebron, Barcelona, Spain) was performed. This study period was chosen because 2004 was when the new ED came into force in Spain. The analysis was restricted to drug-evaluation clinical trials. Commercial clinical trials were defined as when a pharmaceutical industry was the trial sponsor, and noncommercial clinical trials when the sponsor was an academic or hospital institution, a scientific group or society, or a clinical investigator. For each clinical trial, information on the following characteristics was obtained from the REC database: sponsor, participating sites, design, masking and phase of drug development, REC's final opinion and the date of their final opinion and the start-up date of clinical trials.

Collected data from public registers – the http://clinicaltrials.gov site and the European Union Clinical Trials Register (EU-CTR) – included the date of approval from the Spanish Regulatory Agency and the status of trials.

The Medline Library and the http://clinicaltrials.gov site were checked for publications in peer review journals of the active, completed and prematurely terminated clinical trials. When more than one publication of a clinical trial was found, only the main publication of clinical trial results was taken into consideration. The following search strategy was used to identify the publications: the EudraCT number, http://clinicaltrials.gov identification number and the sponsor code protocol were initially considered. If no publication was found, the evaluated medical condition and medicine, the name of the sponsor and the name of the principal investigator were subsequently considered to complement the search. The last date of the search was 15 July 2015.

This study was submitted to and approved by the REC of the University Hospital Vall d'Hebron (Institutional Review Board - IRB00002850) because most data were collected from the REC database.

Standard descriptive statistics were used for the statistical analysis. Continuous variables have been described with the usual parameters of central tendency and dispersion (mean and standard deviation for variables that follow a normal distribution, or median and interquartile range for those following a non-normal distribution). Categorical variables have been described with absolute and relative frequency distributions. To compare the continuous variables, the Student *t* test was applied if a normal distribution was followed, or the Mann–Whitney *U* test otherwise; and the chi-square test or the Fisher exact test to compare the categorical variables,

respectively. The statistical package SPSS Version 18 was used, and a significance level of 0.05 was established for all analyses.

Results

A total of 809 clinical trials with drugs were submitted to and evaluated by the REC of the Hospital. The clinical trials with an unfavourable opinion were 31 (3.8%), without statistical differences depending on the sponsor.

The median time from the submission of the application to the REC opinion, (favourable and unfavourable), was within the average time established by the ED (<60 days), without differences depending on the sponsor.

Table 1 lists the main characteristics of the 778 approved trials. The percentage of commercial *vs*. noncommercial clinical trials in the study period was 83.7% vs 16.3%. Noncommercial studies were mainly phase IV, multicentre national and unmasked controlled clinical trials, compared with the commercial clinical trials that were mainly phase II and III, multicentre international, and double-blind masked studies. Information on the start-up of only 541 clinical trials was available on the REC database. The period from the approval by the Spanish Medicine Agency to the start-up was longer for noncommercial clinical trials than for the commercial ones (Table 2).

Commercial clinical trials were registered more often in the public registry http://clinicaltrials.gov. Information on the follow-up and the status of clinical trials was less frequently updated for noncommercial clinical trials than for commercial ones (Table 3). The categories of the status are defined in http://clinicaltrials.gov (https://clinicaltrials.gov/ct2/about-studies/glossary#closed-studies). The results of 297 (44.5%) studies were reported in the public register, and only one was a noncommercial clinical trial.

Sixty percent of the approved clinical trials were published in peer-review scientific journals: 63.8% (404) of commercial clinical trials and 39.4% (43) of noncommercial clinical trials ($P < 0.001$).

Discussion

The proportion of noncommercial clinical trials was only 16.3% compared to commercial trials, and they were mainly multicentre national and unmasked controlled. In addition, in our study the percentage of noncommercial clinical trials recorded in http://clinicaltrials.gov register and the publication rate in scientific journals was lower than for trials with a commercial sponsor.

The proportion of noncommercial clinical trials found in our study (16%) was similar to that reported on previously in Spain [4, 9] and Germany [4, 10]. However, this percentage is still lower compared to that reported on in other countries such as UK, Netherlands, Denmark, Italy and France, where the described percentage is higher than 25% [4].

In our study, which began at the same time as the implementation of the ED in Spain, time from the submission of clinical trials to the REC's authorization depended on the ED requirement. However, results from other studies have shown a longer assessment period [11–13], especially for noncommercial research [13].

In our study, noncommercial clinical trials were mainly multicentre national and unmasked controlled. The organization and development of multicentre international and double-blind masked studies could be affected by logistical and financial difficulties.

In addition, our results show that phase I/II clinical trials have increased compared to the results reported on in another study performed before this period in our centre, but most of them were sponsored by the pharmaceutical industry [9]. This trend has been described both in Spain and in Italy [4].

We considered the http://clinicaltrials.gov as the main public register because the EU-CTR was not recognized as a

Table 1

Characteristics of approved clinical trials with drugs

		Commercial sponsored clinical trials (n = 651)	Noncommercial sponsored clinical trials (n = 127)	P	Total (n = 778)
Participating sites	Multicentre international	599 (92.0%)	33 (26.0%)		632 (81.2%)
	Multicentre national	37 (5.7%)	76 (59.8%)	$P < 0.001$	113 (14.5%)
	Single-centre study	15 (2.3%)	18 (14.2%)		33 (4.3%)
Design	Controlled	493 (75.7%)	92 (72.4%)	$P = 0.501$	585 (75.2%)
	Uncontrolled	158 (24.3%)	35 (27.6%)		193 (24.8%)
Masking of controlled clinical trials	Unmasked	122 (24.7%)	51 (55.4%)		173 (29.6%)
	Double blind	359 (72.8%)	35 (38.0%)	$P < 0.001$	394 (67.4%)
	Simple blind	5 (1.0%)	1 (1.1%)		6 (1.0%)
	Observer blind	7 (1.4%)	5 (5.4%)		12 (2.1%)
Phase of clinical trials	Phase I	56 (8.6%)	6 (4.7%)		62 (8.0%)
	Phase II	196 (30.1%)	24 (18.9%)	$P < 0.001$	220 (28.3%)
	Phase III	307 (47.2%)	17 (13.4%)		324 (41.6%)
	Phase IV	92 (14.1%)	80 (63.0%)		172 (22.1%)

Table 2

Time from the approval of the Spanish Medicine agency to the start-up of clinical trials

		Commercial sponsored clinical trials	Noncommercial sponsored clinical trials	Total
Median (days)*		126.5	206.0	144.0
Percentiles	25	75.8	137.0	81.0
	75	238.0	388.0	254.0
Minimum		0	44	0
Maximum		893	989	989
Total clinical trials		466 (100%)	75 (100%)	541 (100%)

*$P < 0.001$

Table 3

Registry to the http://clinicaltrials.gov register and status of the research ethics committee-approved clinical trials

	Commercial sponsored clinical trials (651)	Non-commercial sponsored clinical trials (127)	Total(778)
http://clinicaltrials.gov*	597 (91.7%)	71 (55.9%)	668 (85.9%)
Completed	433 (72.5%)	41 (57.7%)	474 (71.0%)
Terminated	98 (16.4%)	5 (7.0%)	103 (15.4%)
Active, not recruiting	42 (7.0%)	7 (9.9%)	49 (7.3%)
Recruiting	8 (1.3%)	4 (5.6%)	12 (1.8%)
Withdrawn prior to enrolment	4 (0.7%)	1 (1.4%)	5 (0.7%)
Approved for marketing	3 (0.5%)	0 (0.0%)	3 (0.4%)
Suspended	1 (0.2%)	1 (1.4%)	2 (0.3%)
Others	2 (0.3%)	0 (0.0%)	2 (0.3%)
Unknown	6 (1.0%)	12 (16.9%)	18 (2.7%)

*$P < 0.001$

public register by the Word Health Organization until September 2011. A total of 85.9% of clinical trials were recorded in http://clinicaltrials.gov. However, the percentage was higher for trials with a commercial sponsor. Altogether, this percentage has increased compared with the results described in a previous study (27.4%) [9]. This rise may be because the initiative to register clinical trials in the public register started in 2004. In addition, in our study, the percentage of clinical trials with the results reported on in the register was low. In other studies, this percentage has been variable, but, as in our study, in most of them a higher percentage of the reporting results for the commercial clinical trials has been reported on [14, 15].

Furthermore, the publication rate described in this study has been higher than that reported on in others [9, 10, 14, 16]. However, unlike in some of them [9, 10], a lower rate of publication of noncommercial clinical trials was found. The publication of results in biomedical journals may entail some difficulties. However, authors should not ignore the need to make the results of their research public. The ethical justification for conducting clinical trials is its scientific and also its social values [17]. If the sponsors do not disseminate the results of the research, both the social and the scientific values are compromised. In this sense the public registers http://clinicaltrials.gov and EU-CTR offer them the opportunity to make the results accessible to the scientific community. In addition, new European legislation requires the publication of results in public databases and this initiative could also help to make the results of the research public [18].

In contrast, noncommercial clinical trials with drugs are often limited by the scarcity of economic resources and of professionalization of clinical research activities [3]. To partially solve this problem, new European Regulation on clinical trials has defined the low-interventional clinical trials, subjecting them to less stringent rules than standard clinical trials [18]. Moreover, initiatives such as the European Clinical Research Network [19] and the funding of European funds such as Horizon2020 could be good opportunities for noncommercial research.

Some limitations of this study have to do with the fact that the publication data were only reviewed on a limited number of databases and only in English peer-review

journals. As well as this, the study was done in a single centre. However, our hospital is one of the largest tertiary hospitals in Spain, both at the level of healthcare and research.

In conclusion, in our study, a low percentage of published results of trials was observed, especially for noncommercial trials and this is a major issue to be solved. Future studies should analyse whether some European initiatives such as the new European legislation on clinical trials, some clinical research support networks and public funding calls help to improve the situation.

Competing Interests

All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and none of the authors have financial or nonfinancial competing interests.

Contributors

I.F. and A.G. conceived and designed the experiments; I.F. extracted the data and I.F. and A.G. analysed the data; I.F., A.R. and A.G. wrote the paper and gave the final approval.

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