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EDITORIAL

Disclosing negative trial results – procedure

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1. Introduction

In order to identify and reduce biases in clinical research, during the last years, several rigorous methodological methods were applied to clinical trial management. Nevertheless, to date, too many biases still affect clinical studies. Since 1986, when the first data demonstrating publication bias was published, several biases related to clinical trial management were identified [1]. One of misconduct clinical research is also identified in reporting results. The so-called 'file-drawer effect' refers to the non-reporting of clinical trial results, which are often negative or neutral [2]. During the last 15 years, several Big Pharmas withheld negative trial results, such as the cases of the cardiovascular toxicity associated with rofecoxib and suicide-related behavior associated with paroxetine [3]. Unpublished negative trial results are not the only problem. Sometimes, also positive trial results are fake or exaggerated [4]. An example of withholding negative information is represented by the case of a celecoxib CLASS trial. Author's trial reported a better safety for celecoxib compared to ibuprofen and diclofenac at 6 months of follow-up, but they did not show results at week 65, which demonstrated that the drugs were associated to a similar number of ulcer complications [5,6].

In the light of these considerations, the main risk factors for the omission on negative trial results and/or the publication of the false ones, such as the clinical trial characteristics, conflicts of interest, blinded-treatment, and definition of high quality endpoints, have to be changed. Among these factors, the conflict of interest, a set of conditions in which the judgment on a professional interest tends to be disproportionately influenced by secondary interest, has to be strictly controlled. Since conflict of interest could influence the management of a clinical trial and lead to several publication biases, especially those related to the reporting of efficacy and safety results, it would be desirable that the investigators had not any conflicts of interest or at least they had to declare it [7].

In order to minimize the risk associated to clinical trial unpublished negative results and/or exaggerated positive ones, avoiding the distortion of clinical evidence deriving from such activities, different approaches can be adopted. Many projects have been recently started (i.e. the European Medicine Agency proactive publication of clinical trial data [8] and the Ben Goldacre AllTrial initiative [9]), but a great help for the management and the publications of clinical studies performed in European Union (EU) countries was given by the adoption of the new Clinical Trials Regulation (CTR) No. 536/2014, which will be effective from 2018. One of the main aims of the new Regulation is to guarantee that EU Member States authorize and supervise the management of clinical trials on identical rules. Since transparency is undoubtedly the key value that promises the better access to all clinical trial data, a great importance is given to this aspect. According to CTR No. 536/2014, all the data regarding clinical trials application will be submitted in the EU database and will be publically accessible (except for commercially, personal, and communication confidential data). According to the new Regulation, the sponsor has to submit a summary of trial results within 1 year by the end of the trial. Moreover, 30 days after the marketing authorization, a Clinical Summary Report shall be submitted [10]. Although the undeniable usefulness of changes introduced by the new Regulation, we will have to wait years before all these will be real. Thus, other approaches, such as the potentiation of registration sites of clinical studies, the publication of Development Safety Update Report (DSUR) and Investigator's Brochure (IB), the promotion of independent clinical research, and the establishment for each negative trial of a section dedicated to an external expert, can be adopted.

2. Registration of clinical studies

In July 2005 the International Committee of Medical Journal Editors required the registration of all clinical trial before the publication of their results. However, a recent analysis of Harriman et al. revealed that out of 108 clinical studies published in 2013 on BMC journal, 33 and 72 were registered prospectively and retrospectively before the publication of their results, respectively, while 6 were registered after the publication on BMC [11]. Even though two public big databases are today available for the registration of clinical trial

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(ClinicalTrial.gov, instituted by Food and Drug Administration – FDA, and European union Drug Regulating Authorities Clinical Trials – EudraCT by EMA), researchers are still not prone to register prospectively their trial. The prospective registration of clinical trial data could potentially represent the way to avoid the omission of negative trial results and to improve clinical trial transparency and reduce publication biases.

3. Promoting the publication of DSUR

Given the limitation of premarketing studies, such as the short-term drug exposure, the selection of patient populations, and the clinical trial duration, missing efficacy and safety data on medicines are frequently detected during the postmarketing phase. The main aim of the DSUR is to share with regulatory agencies,ethic committees, clinicians and, patients new safety data and findings from both premarketing and postmarketing studies of drugs under investigation. According to EMA ICH guideline E2F, DSUR is an annual report that should be submitted to regulatory authorities for as long as the sponsor manages clinical trials with the investigational drug. Considering that DSUR contains both cumulative and periodic safety information relating to the investigational drug, it will be more useful if this document could be accessible to anyone interested. In that way, new drug informations will be available for clinicians and patients and safer use of drugs will be allowed. Given the importance of data listed in the IB, this document should be available for everyone. However, since IB very frequently includes confidential information, according to Good Clinical Practice, the protection of rights, integrity, and confidentiality of trial subjects must be guaranteed [12].

4. Promoting the potentiation of independent clinical research

The results of a survey on 324 cardiovascular trials published between 2000 and 2005 revealed that clinical studies funded by profit organizations were more likely to report positive findings than trials funded by non-profit organizations. Specifically, the authors found that 67% of profit studies favored the newer treatment, while only 49% of non-profit studies did [13]. Since no-profit clinical studies are not aimed at the industrial development of the drug but at the improvement of proper use of medicine in 'real-world conditions', particularly in populations usually not involved in clinical trials (such as pediatrics, elderlies, and/or pregnant women, patients with comorbid conditions or patients under multiple drug therapies), there is an urgent need to improve this sector.

5. Comment of external expert on each negative trial

Data Monitoring Committees (DMC), introduced as components of clinical trials, were aimed to review the safety, effectiveness, and trial issues data. Similarly to DMC, a further approach, which can implement the right interpretation of all clinical trial data, is the establishment of a section dedicated to a external advisory expert board opinion. The involvement of external experts who are allowed to analyze and discuss each failed trial could potentially help the readers to understand how much confidence can be placed in the clinical trial results. Therefore, an external opinion for each clinical trial, especially for the negative ones, will help to understand the statistical power of a trial, monitor efficacy, for example, in terms of achievement of primary end point, and also safety, through the evaluation of adverse event rates. In this context, the independence of an external expert will more deeply define if the study results appropriately meet research standards.In conclusion, sharing clinical trial results, especially the negative ones, as well as statistical analysis and methodological data, is one of the main aims of the current clinical research. Sharing these data will generate several benefits, leading to a better understanding of benefit/risk profile of a new treatment [14]. On the contrary, a misconducting clinical trial can lead to inefficiency in research resource allocation as well as significant changes of the regulatory decision-making processes [15].

Benefits deriving from clinical trial data sharing are clear. The instruments in order to guarantee transparency of clinical study's characteristics as well as its efficacy and safety results are now available. Before the new CTR No. 536/2014 will be real, definitively effective, clinical trials registration, DSUR and IB publication, promotion of independent clinical research, and the possibility for an external expert to comment on each negative trial may represents important instruments which can guarantee clinical trial data transparency.

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Declaration of interest

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