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EDITORIAL

Clinical trial transparency and access to anonymized individual participant data☆

Transparencia en los ensayos clínicos y el acceso a los datos individuales anonimizados de los participantes

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For the advance of science in general, and medicine in particular, the results of research have to be published (or made public). However, many researchers do not publish the results of clinical trials (publication bias), while others publish only significant results (outcome reporting bias).[1] These two types of bias affect clinical practice, given that the data available (that is, the data published) tends to be favourable to the interventions under study. These biases are fought with the obligation to register clinical trials before they begin in a free public registry, and to publish the results obtained.[2] These two requirements have radically changed the panorama of clinical research in this century, especially for clinical trials with medicines (and healthcare products), which are the only ones subject to regulations by the public administrations. The situation is much worst for trials that study non-regulated interventions such as behaviour, physiotherapy and surgery.[3] Other proposals, such as requiring the main author of a manuscript that communicates research results to sign a ''declaration of transparency'',[4] have had very limited effects. This is shown in the data from a very reduced number of clinical trials published in the BMJ,[5] the only one of the five ''greatest'' journals that implemented it. Consequently, there is no other conclusion to be reached than that registering a trial and publishing its results are the two key mechanisms available to the scientific community to know about what is attempted to be researched, and what is really researched—or what is ''forgotten'' to be researched or communicated.

It is true that there is still a way to go in the correct fulfilment of registration of publication of results of clinical trials. However, the International Committee of Medical Journal Editors (ICMJE), a pioneer in requiring trial registration, has launched a new proposal for the scientific community: to publish the results of any clinical trial the researchers will be required to be willing to release to other researchers the anonymized individual raw data of the participants in the clinical trial that back up the results presented in the article.[6] Interest in this proposal was huge, because it was preaching to the choir: releasing anonymized individual raw data of clinical trial participants had already been put into practice by many promoters (industry, foundations and public institutions). Furthermore, the European Medicines Agency has also committed to this, although it has been 2 years since the Agency has reported any advances in the matter. Consequently, when the ICMJE extended to invitation to send comments about this proposal, they received 319 replies from individuals interested in carrying out clinical trials around the world, with replies from patients included among them.[7]

As is well known, outcome reporting bias appears both in industry-promoted trials as well as in those financed

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through public funding.[8] A few scandals over certain results from industry-promoted clinical trials that were not published and that later, when the outcomes became known, gave rise to changes in the product data sheets of the medicines involved, have had a decisive influence on making the agents interested in clinical research be, in the majority, favourable to the maximum degree of transparency. And, in this context, there are two attention-gathering facts that reveal the difficulties that, in practice, the proposal from the ICMJE about access to the raw anonymized individual participant data from clinical trials can have. The protagonist of the first fact falls to an academic group that repeatedly refuses to facilitate this type of data to one of the promoters, a pharmaceutical company. It is important to emphasise that the trial outcomes were crucial for the regulation agencies—that had no access to the raw anonymized individual participant-level data from the clinical trial[9]—in their decision to limit the therapeutic use of the drug under study. The second striking fact is that the journal that published that trial, the New England Journal of Medicine (NEJM), displayed a rather arrogant behaviour and in addition published—a week before publishing the ICMJE's proposal in its pages—an editorial on the raw anonymized individual participant data from clinical trials[10] that has raised blisters.

In March of 2016, Doshi[9] published the (post-) history of CHEST. This was a clinical trial in which hydroxyethyl starch and saline solution were compared for the treatment of blood volume loss in 7000 critical patients. It was directed by Myburgh (the George Institute in Australia) and published by the NEJM in 2012.[11] CHEST was partially funded by Fresenius Kabi, a company that manufacturers hydroxyethyl starch, which called the results published in the NEJM into question. The contract signed with the George Institute prevented Fresenius Kabi from having access to the trial data. Given that the George Institute was unwilling to given them to him, Fresenius Kabi approached the BMJ to have the data re-analysed by an independent team. The BMJ proposed that this be done through YODA, the model for access to data from clinical trials at the University of Yale (New Haven, CT, USA).[9] This pathway has turned out to be useless, as Myburgh refuses to turn over the data to YODA and claims that there are restrictions as to who can have access to the CHEST data. His understanding is that Fresenius Kabi could bias the independent researchers that, using YODA, would carry out the reanalysis of the data. While this was going on in 2012–2013, Fresenius Kabi addressed the NEJM, explaining his doubts as to how the adverse events had been assigned to both treatment groups. The NEJM replied that there was no need to publish any correction at all to the original article that described the results.[9] Curiously, just 6 days after the publication of the article by Doshi,[9] the NEJM published an online correction of the adverse events outcomes from CHEST.[12]

However, the fact is that while the proposal from the ICMJE on release of raw anonymized individual participant data from clinical trials was being printed in the NEJM presses, its editor published an editorial[10] that, as was mentioned earlier, enflamed (part of) the scientific community. The NEJM understands that when what is involved is releasing the raw anonymized individual data of the participants in a clinical trial, it is necessary to distinguish between the researchers that performed re-analysis with the collaboration of the research team that carried out the clinical trial and obtained the data, and those that will merely perform a secondary analysis apart from the trial research team. The NEJM called those conducting secondary analyses ''research parasites'', while indicating that the first group worked ''in symbiosis'' with the research team that actually carried out the trial: NEJM understands that ceding the raw anonymized data must be symbiotic, not parasitical.[10] This posture was immediately answered by the scientific community, not just in editorials in journals[13,14] and blogs,[15,16] but also in Twitter with the hashtag *#IAmAResearchParasite*, which leaves no doubt as to the (ironic) intention of its promoters and followers. It is noteworthy that the NEJM expresses an opinion that does not coincide at all with the ICMJE proposal, which does not limit access to the raw anonymized individual data from the trial participants—in spite of the fact that the NEJM is a founding member of the ICMJE. In the face of the flood of protests, the editor of the NEJM was forced to publish another online editorial four days after the first, in which he indicated that the journal was committed to the release of the raw anonymized individual participant-level data from the clinical trials, that third-party re-analysis of the data could ''improve the health of human beings substantially''; however, he insisted that the greatest benefit would be obtained through ''symbiotic'' collaboration, that is to say, that which happens between those that obtained the data with the researchers that will carry out the secondary analyses.[17] This editorial was published several months later in the paper version of the NEJM, accompanied by four articles of opinion in which the difficulties for gaining access to such data in reality were raised,[18] the creation of a world-wide portal for all clinical trials—whoever the promoter might be[19]—was mentioned and—what a surprise!—two examples of ''symbiotic'' collaborations were given.[20,21]

So, sharing the raw anonymized individual participant data from the clinical trials is the latest requirement that, in a not so far-off future, the ICMJE plans to impose on the journals that belong to this committee. Its success will depend on the speed with which the requirement is adopted and on the number of journals that, not belonging to the ICMJE, really comply with it. For society there is no other path than that which leads to the maximum transparency in clinical trials. This will be achieved when all the trials are properly registered, all the outcomes are published (or are made public) and their raw anonymized individual participant-level data is available to third parties. However, it is ironic that the ICMJE encourages the sharing of this type of individual participant-level data when it still does not require its members to implement quality controls that prevent (or, at least, minimise) the publication of articles with outcome reporting bias.[22] This is indeed urgent so that clinicians and patients have access to reliable information about clinical trials; but this does not seem to be on the ICMJE's agenda.

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