CLINICAL INVESTIGATION

Clinical trial transparency and the evaluation of new medicines

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In the ongoing debate about clinical trial transparency, it should be remembered that an estimate of the publication rate of all clinical trials (regardless of phase, size, duration, design, sponsor, and so forth) gives little information about our ability to assess accurately the relative value of any individual medicine.

It has been recognized for many years that the scientific literature contains a preponderance of reports of positive results, and that selective publication can lead to study publication bias [1,2], which sometimes results in over-estimation of the benefit of individual medicines. Although Song's extensive literature review [2] confirmed that trials were more likely to be published (and more likely to be published quickly) if the results were positive, the data reviewed was drawn from searches carried out in 2008 and 2009, and looked at studies on bias published between 1998 and 2009, including many trials from a period prior to the existence of trial registries. This review also pointed out that the actual impact of bias depends upon specific circumstances and that "the prospective registration of clinical trials and the endorsement of reporting guidelines may reduce research dissemination bias in clinical research".

Many clinical trials form part of the pharmaceutical industry's business of developing and registering new medicines. These include small (Phase I & II) trials investigating safety, tolerability, efficacy and optimal dosage in small numbers of patients; the larger randomized, controlled Phase III trials which are the main basis for regulatory assessment; and large postapproval Phase IV studies. However, many other clinical trials are also carried out by hospitals, research institutes or individual investigators, and in addition, established medicines are used as comparators in the investigation of further new medicines. So the complete collection of clinical trials conducted globally is an extremely heterogeneous mixture of studies of different sizes, phases, durations and complexities.

It is noteworthy that the majority of small Phase II trials are designed to support the decision to progress to Phase III (or not). As such, they may not be submitted for publication individually, and would not normally be included in meta-analyses or systematic reviews.

Nevertheless, there is now broad agreement that all clinical trials in patients should be conducted to predefined protocols and that the results of all this research should be publicly available to benefit future patients and to avoid unnecessary repetition of trials [3,4]. Over the last 20 years, various initiatives have been introduced to establish the following principles:

- All clinical trials in patients (including key elements of trial design) should be registered on public registries at the time the trial begins recruitment;
- At least summary results of all trials should be posted on similar registries or databases;
- All trials should be submitted for publication in the scientific literature, regardless of whether the results are positive or not.

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In the USA, a national registry [5] has been functional since 2000 and registration of specified new trials is a legal requirement [6]; posting of summary results of these trials became a requirement in the US FDA Amendment Act of 2007 [7]. In Europe, trial registration in the European register (EudraCT) within the scope of the EU Clinical Trials Directive [8] has been implemented since 2004, although this only became publicly accessible in recent years, and it is acknowledged that data on trials between 2004 and 2011 may be incomplete [9]. Only very recently has the registry software been updated to allow posting of summary results [10], while work is ongoing to replace the original Directive with a new European Clinical Trials Regulation [11]. In 2005, the International Committee of Medical Journal Editors published a policy requiring mandatory registration of clinical trials as a condition for manuscript submission [12].

Unfortunately, implementation of measures to fulfill these principles has been piecemeal; different registries have been developed by various parties in various countries, and, except for the FDA requirement, selection and use of these registries has been largely left to the discretion of the primary sponsor or responsible party for any given clinical trial.

Regarding the development of new medicines, the global pharmaceutical industry committed to disclosure of clinical trial information through trial registration and posting of summary results in the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Joint Position Paper of 2005, updated in 2008 and 2009 [13] and to publication of results in the IFPMA Joint Position Paper of 2010 [14]. Implementation of these principles remains the responsibility of the individual companies, and is included in codes of practice (e.g., IFPMA, ABPI [15,16]).

Apart from the US and European registries, others currently available include Current Controlled Trials [17], characterized by ISRCTN identifiers, at least 15 other country-specific registries and more than a dozen set up by pharmaceutical companies themselves. There is also the WHO portal, which links back to many of the primary registries. Not surprisingly, none of these registries is comprehensive, (and there is considerable duplication) so if one wishes to gather as much information as possible about a specific medicine, any search must include a number of these sources. It should be noted that studies which set out to measure the success of an individual registry do not measure overall clinical trial transparency, nor do they fully assess the potential for publication bias associated with any individual medicines.

In fact, many such studies have investigated subsets of trials such as those conducted in a specific time period, or trials posted on a single registry, or disclosure of results through publication in the literature, or disclosure solely through a single registry. Hence, comparing results from study to study is subject to many limitations. Therefore, the figures used to support claims such as 'only half of all trials are published', are often misleading, and may substantially underestimate the overall proportion of trials whose results are actually available in the public domain. For example, the study by Bourgeois *et al.* (one of those used to support the claim that half of trials are not published) notes that although 66.5% of industry-sponsored trials were published, results for many of those not published were available electronically – combined this gives a disclosure figure of 88% [18].

Since few studies have investigated the overall level of transparency related specifically to medicines approved for use in patients, at the end of 2012 we set out to do just this. Our study [19] examined the industry-sponsored clinical trials related to all new medicines (new active substances) approved by the EMA (European Medicines Agency) for use in patients in 2009, 2010 and 2011. This was a quantitative assessment of disclosure of results, based upon either posting of summary results in registries or publication in the scientific literature. This overall assessment of transparency demonstrated that results for almost 90% (784/882) of company-sponsored trials in patients were available in the public domain. This figure is considerably higher than some of the figures quoted in other studies, and similar to the 88% mentioned above [18].

We conclude that any assessment of overall transparency must investigate multiple sources of trial information and include both posting of summary results in registries and publication of results in the scientific literature. In addition, it is clear even from the single largest and most useful registry [5] that the links between trial registry and publication in the scientific literature are not yet sufficiently well-established to rely on one or the other [20]; publications are not always logged in the registry and trial registry identifiers are not always listed in the freely available abstract fields of the publications.

So where are we in 2014? A great deal of progress has been made, albeit rather more slowly than we would perhaps have liked over the last 30 years or so since the Simes paper [1]. It is now highly unlikely that, at least in Europe and North America, any new clinical trial in patients could be carried out without being registered, and then effectively hidden if the results were unfavorable. In particular, any trial (at least from Phase II onwards), that is part of the global development plan for any new medicine will be registered, most likely on the ClinicalTrials.gov website [5].

Nevertheless, the variety of registries now available causes complications in making any overall assessment, and ideally, all sponsors should be working to the same standards of routine disclosure (through a single registry or at least to a common format), while the links between publications in the literature and registry entries should become standard.

While transparency for industry-sponsored trials has clearly improved, progress on overall transparency should not be confused with the question of the availability of more detailed clinical study reports and patient level data sets required from selected studies for some meta-analyses and systematic reviews. However, as long as the development of new medicines is largely carried out by the global pharmaceutical industry, additional requirements for sharing patient level data to facilitate further research need to be considered in the context of legitimate commercial concerns, as well as ensuring patient confidentiality [21].

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