

# Regulatory Writing

## New developments in public disclosure of clinical trials

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In April this year, the World Health Organisation (WHO) issued a statement on the public disclosure of clinical trial results (the full statement is available from <http://www.who.int/ictrp/results/reporting/en/>). In essence, this statement reiterates the previous WHO statement on

registration of trial methods prior to initiation and extends it to include the timely publication of results, both in clinical trial registries and in peer reviewed journals. The aim is to ensure that negative results are not underreported, thereby distorting efficacy conclusions derived from publicly available data. The statement also calls for sponsors to make the results of past trials available. Finally, the statement suggests more rigorous identification of trial registry identification in subsequent publications and data sharing initiatives, presumably to make meta-analyses easier. The statement was accompanied by a detailed rationale published in PLoS<sup>1</sup> and a commentary, also in PLoS,<sup>2</sup> by Ben Goldacre, a prominent campaigner for full disclosure of clinical trial results.

### Current disclosure levels

Well before publication of this statement, there has been a general shift towards greater disclosure and transparency. Several factors have driven these changes, not least, the Food and Drug Administration Amendments Act (FDAAA) in 2007, which in its Section 801 required all applicable trials to report summary results at ClinicalTrials.gov within a year of the primary completion date. However, the rationale for the statement, published in PLoS cites evidence that even trials registered in this new transparency era still often fail to publish results. In a recent estimate of compliance with mandatory reporting requirements on the ClinicalTrials.gov registry, the investigators used an algorithm to identify 'highly likely applicable clinical trials', that is trials legally obliged to report results according to the FDAAA.<sup>3</sup> Only 13% of the trials identified by this algorithm reported

summary results within the statutory 12 months of trial completion. This percentage rose to 38% when the whole study period was considered.

The percentage of reporting was higher for industry-sponsored trials and also for later-phase studies. On manual review of a subset of the trials selected by the algorithm, for industry-sponsored trials, some 45% were not actually required to report results, leading the authors to conclude that 'approximately 79% to 80% of industry-funded trials reported summary results or had a legally acceptable reason for delay'. When I did a quick manual search of industry-sponsored trials on [clinicaltrials.gov](http://clinicaltrials.gov) that had completed at least one year ago and that did not have any results posted, the sponsors in my admittedly not particularly exhaustive sample were all small companies. Most large companies now take disclosure very seriously and most will have dedicated disclosure groups to ensure that they meet their reporting obligations. Smaller companies, however, will be unlikely to have such resources available. In cases of start-ups with a single product in their pipeline, if the study fails, the company will likely disappear and the study results will never see the light of day. Thus, there may be a reporting bias in favour of trials with products that are more likely to continue in clinical development (and hence for trials that may have an impact on clinical practice later). This, in combination with a higher reporting rate for later phase clinical trials, suggests that a high percentage of industry trials relevant for clinical practice are now being disclosed.

Compliance is lower for trials with institutional sponsors (such as the National Institute for Health [NIH] for example). As many of these trials will be intended to answer 'real-world' questions rather than being part of a drug-development programme, whose goal is to get a drug registered, the gaps in knowledge are potentially more significant. Industry has shown that it can react to new reporting requirements (for example, by setting up dedicated disclosures groups), but in the case of institutions, bureaucratic inertia, as well as limited funds, may be a substantial barrier to change.

It has been argued that disclosure of early-phase clinical trials is important from a safety point of view. For example, if a particular drug is associated with a life-threatening reaction, caution should also be exercised with another drug that shares the same target (as tragically illustrated by the case of TGN1412, where greater transparency with a previous trial in a similar molecule may have helped prevent the severe reactions seen<sup>4</sup>). In this case, some sort of adverse drug reaction registry may be of help and would probably not require extensive resources as serious adverse events would have to be notified to the health authorities anyway.

### Publishing in peer-reviewed journals

One novelty of the WHO statement is that these results should also be published in peer-reviewed journals (with open access) within 12 months to address the well documented issue of publication bias. These timelines for publishing look very tight given that the turnaround time between manuscript submission and publication can be anywhere between 2 and 6 months. As might be expected given the relative complexities of publishing in a peer-reviewed journal and the lack of legal requirements, the publication rates compared to results disclosure on trial registries are lower.<sup>5</sup> Ben Goldacre<sup>2</sup> suggests the this battle may not be worth fighting, arguing that journal articles are often ‘spun’ and may not report the primary outcome measure. He also points out that academic publishing decisions can be arbitrary, even though many journals may pay lip service to consideration of negative trials.

### Retrospective disclosure

The most substantial novelty in the statement is the requirement that the results for old trials are made available on the grounds that evidence-based decisions today are based on potentially biased data collected in the past. Although this argument is persuasive, implementation in practice is fraught with problems. Ben Goldacre recognises that throwing resources at disclosure of trials with no bearing on current clinical practice is not an efficient approach.<sup>2</sup> He suggests a directed approach, whereby preliminary retrospective registration of clinical trials can serve as a guide for researchers who wish to request more details and results.

Even with this directed approach, disclosure may not always be feasible. First, retrospective trial

registration is likely to leave gaps in the record. And even if a trial is identified and further details requested, the pertinent information may be hard to retrieve. Many companies will have undergone restructuring or mergers, and the employees responsible for an old project will almost certainly have changed project, company, or even country. And this is not to mention changes in archiving systems and the fact that, at best, some of the older studies will only be available as scanned versions. In principle, the health authorities should also have these trials archived somewhere, but many of the problems applicable to data retrieval by companies would apply. Furthermore, the rigorous requirements of ICH only started to be universally applied from the mid 1990’s onwards. Prior to that, it would also be a bit hit and miss which information was recorded, whether the primary endpoint was properly reported, and even whether there was a pre-defined statistical analysis plan.

### Conclusion

Progress in the disclosure of clinical trial results is undeniable. Although there is always room for improvement, disclosure rates for the most recent industry-sponsored trials are relatively high. Attention is now shifting to the disclosure of the results of past trials. Although this is a desirable goal, it will be difficult to achieve in practice.

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### References

1. Moorthy VS, Karam G, Vannice KS, Kieny M-P. Rationale for WHO’s new position calling for prompt reporting and public disclosure of interventional clinical trial results. *PLoS Med.* 2015;12(4):e1001819.
2. Goldacre B. How to get all trials reported: audit, better data, and individual accountability. *PLoS Med.* 2015; 12(4):e1001821.
3. Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. Compliance with results reporting at ClinicalTrials.gov. *N Engl J Med.* 2015;372(11): 1031-9.
4. Goodyear M. Learning from the TGN1412 trial. *BMJ.* 2006;332(7543):677-8.
5. Jones CW, Handler L, Crowell KE, Keil LG, Weaver MA, Platts-Mills TF. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ.* 2013; 347:f6104.