CURRENT SCIENCE

Volume 124 Number 11 10 June 2023

EDITORIAL

Clinical trial transparency – status and prospects

'I've been working in the area for clinical trial transparency for about seven years, and when I started off in this field it was intensely depressing, what you saw, coming out in terms of research. Because there was one paper after the other saying "oh, there's a problem, and then they'd quantify the problem in some way but they wouldn't tell you with which institutions, exactly, the problem was, they couldn't tell you who was responsible for the problem, and then, in the conclusion they'd write that 'well, we've got a problem and it could be solved if everyone just did things better in future.' " It was really not constructive. And over the past few years, we've seen a massive sea change in that....' The speaker was making introductory comments in a session entitled 'Brainstorming new ways to drive clinical trial reporting' (https://www.youtube.com/watch?v=HohWoE3bMi0). What is the speaker referring to, and how relevant is it for India?

Clinical trials test a new drug, vaccine or other medical product, or process, in a scientific way. Many clinical trials are required, by law, to be registered in a publicly accessible trial registry. There should be a record for each trial, which anyone can access for free. The World Health Organization (WHO) recognizes 18 of these registries which the public can access through a single portal, namely the International Clinical Trials Registry Platform. However, there are various problems with the records. Examples include the following: First, a record may be incomplete, outdated, or contain false or internally inconsistent information. Second, many registries require the results of the trial to be reported, within a year of completion, in the trial record. This is often not done, thereby contributing to 'research waste'. And third, data on a given trial from different sources – one or more registries, a publication, the regulator – may not be the same. This may be in addition to the fact that a trial may not have been registered as required.

Some examples of clinical research waste include: (a) In 2019, several years after completion, the results of 67 trials, that had enrolled almost 90,000 participants, had not been published or been reported in the United States (US) trial registry Clinical Trials.gov (doi:10.7326/L19-0618); and (b) in 2023, it was reported that over $ 360 million of National Institute of Health (NIH) funding essentially went to waste, because the results of 137 trials that had enrolled over 41,000 participants, had not been published (doi:10.1001/jama.2022.24025). In addition to not reporting results, trialists may have selectively reported, incompletely reported, or put a spin to their results (https://doi.org/10.1186/s13-063-022-06624-y). None of this is helpful in using the insights obtained from clinical trials to update clinical guidelines. There are also various other angles that contribute to waste, such as, the trials do not adequately enrol children, women, older adults, ethnic or racial minorities, rural residents, and so on, thereby bringing into question the ability to extrapolate the results to these various sub-groups. It is estimated that annually the lack of such inclusivity costs the US billions of dollars from the resulting excess mortality and morbidity (http://nap.nationalacademies.org/26479).

Various individuals or organizational actors have helped improve the situation. Prospective registration – that is, registration of a trial before the first person is enrolled – helps to prevent bias in the reporting of the results of a trial, and many prominent journals have required the prospective registration of a trial since 2005 (doi:10.1056/NEJMe058127). One notes, however, that they have been somewhat lax in enforcing this requirement (doi:https://doi.org/10.1136/bmj.m982).

Since 2016, a group at the University of Oxford has been working on 'trial trackers'. First, they implemented this for the trials hosted by ClinicalTrials.gov (https://fdaaa.trialstracker.net/), which is the largest WHO-recognized trial registry. Subsequently, they created the European Union Clinical Trials Register (https://eu.trialstracker.net/). The trackers, which are frequently updated, vary slightly in their search capabilities, but have the following kinds of search fields: sponsor name; number of trials per organization; number of trials per organization with results due; the percentage of results reported per organization; trials that have inconsistent data and the number of days a given trial's results are overdue.

Journalists and activists have used the data in the trial trackers to 'name and shame' the trials sponsored by specific companies or universities for which results have not been reported on time. They have also 'named and famed' organizations that have done well or shown significant improvement. The fact that one can now quantify the issue by organization, with specific details for each trial, is useful to those who are concerned about trial transparency and medical research waste. Institutions such as Johns Hopkins University track their records that are erroneous, or create systems that ensure better records in the future. The Johns Hopkins University, with a small number of staff, brought down the

number of problematic trials from 44% to 2% within five years (doi:10.1097/ACM.0000000000003806).

Governments have also initiated action. In 2017–18, the Science and Technology Committee of the House of Commons in the United Kingdom (UK) held hearings on this issue. One of those called to provide testimony was a professor at Oxford who had published several of the intensely depressing papers that highlighted problems with the system. Following this, in 2021, the UK government instituted a system that was a first of its kind. It was already a requirement that all ethics committees, after approving a trial must send details of the trial to the Health Research Authority (HRA). Now the HRA has taken on the responsibility of registering each trial with the British registry ISRCTN (https://www.transparimed.org/single-post/uk-clinical-trial-transparency). This move by the UK Government addresses the problem that a significant percentage of trials in the UK were not registered. It also helped to solve the problem of discrepancies in the data of the same trial from different sources.

Progress in Europe has been mixed, with some countries making faster progress than others (https://transparency-france.org/wp-content/uploads/2021/07/TranspariMED-NCA-report_final_20210705.pdf). Notably, a French medical journal has been regularly asking the drug regulator, the European Medicines Authority (EMA), for the release of trial data and has succeeded in influencing EMA policy (https://english.prescrire.org/en/26A06BA9AEE5C0FDC1-37141EB68F92D2/Download.aspx).

The US has been slow. Just last year, the Office of the Inspector General of the Department of Health and Human Services conducted an audit of a set of trials funded by NIH, and found that the results of about half the trials were not made public, or were delayed (https://oig.hhs.gov/oas/reports/region6/62107000.asp). In late 2022, four Republican members of the US Congress sent a letter to the NIH with a few pointed questions, such as: can you provide a list of clinical trialists who failed to report their results since 2007, how much did you fund these investigators, what action are you planning to take, and how will you ensure that the staff takes action (http://freepdfhosting.com/1fde8a921f.pdf). Earlier this year, a Democratic member of the House of Representatives sent a letter on the same general theme to the NIH. As such, not only has the need for trial transparency received attention at the highest level of government in the US, but it has also received support from both the parties. Based on these letters, it was expected that the NIH would soon work to prevent its grantees from violating the law. In May 2023, it was reported that NIH took action against two researchers who had failed to make public the results of their trials, and prevented them from taking up new projects (https://www.transparimed.org/single-post/gao-audit-nih). This gives hope that NIH, a major funder of biomedical research in the USA, will be more proactive on this issue in the days to come.

The need for greater clinical trial transparency has received further visibility through the activities of the student group, the 'Universities Allied for Essential Medicine' (UAEM). In particular the chapter at Yale University, in association with the Columbia University Law School, filed a citizens' petition to the Food and Drug Administration (FDA) on the matter of clinical trial transparency (https://www.uaem.org/news/uaem-north-america-pressures-fda-for-clinical-trial-transparency). The FDA is legally obliged to respond to this petition within six months.

Finally, the UK intends to take up the issue of improving clinical trials and their reporting globally by raising the issue at the 76th World Health Assembly this year.

India demonstrated leadership as early as 2007 when the Critical Trials Registry-India (CTRI) was established. From the time of its establishment it required details about the ethics committee(s) that had approved a given trial in the records hosted by CTRI. WHO implemented such a requirement later. However, surprisingly, CTRI has not yet provided a field for reporting the results of a trial in the record, although this is required by WHO. The world has now moved on from discussing the need to have this field in the trial record to enforcing the requirement to report the results of the trial. India needs to catch up on this front. Yet another issue concerns the more basic requirement of registering trials. As mentioned above, the law may require that a particular type of trial be registered. However such a trial may not be registered. Internationally, there have been some attempts to quantify this problem of non-registration. In New Zealand, it has been estimated that 9% of trials are not registered (https://www.transparimed.org/single-post/new-zealand-clinical-trials-audit-finds-high-reporting-rates-but-slow-reporting-speeds). In the UK, the figure was 20% (doi: 10.1136/bmjopen-2018-026840). However, now that the government of UK has taken the matter out of the clinical trialists' hands and will register trials itself, this problem is likely to be solved. In India, there has been no such attempt to quantify the issue of non-registration of trials that by law ought to be registered, and it is difficult to know whether there is a way for researchers to undertake such a study. Nevertheless, we believe that it is one of the biggest unanswered questions as far as the clinical trial ecosystem in India is concerned. If one does not know of a trial's existence, it is difficult to track its outcome. In the last few years, there has been a sea change in how the West is dealing with the issue of clinical trial transparency. India needs to catch up. If the country could organize something as complex as ensuring that over 2 billion vaccinations were conducted (https://www.mohfw.gov.in/) in a fairly short period of time, then fixing aspects of a clinical trial registry should not be a challenge.

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