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Under Pressure: Are Enhanced Global Efforts Enough For Trial Transparency?

by Ed Silverman

Increasing scrutiny is being placed on trial sponsors and regulators to improve trial data reporting. Researchers complain that, without access to specific data, results cannot be easily duplicated, which inhibits greater understanding of how medicines might work, adversely affecting treatment decisions and health care costs. Are penalties and public reprimands enough to change behavior?

The sudden flurry of notices was startling.

Over a six-month period last year, the US Food and Drug Administration flagged two pharmaceutical companies and a clinical investigator for failing to post results of their studies to a federal government database called ClinicalTrials.gov. What's more, the regulator threatened penalties if the results were not uploaded, as required by federal law.

The effort was noteworthy because it marked the first time the FDA had taken such a step. For years, the agency faced mounting complaints that too many drug makers and universities do not follow requirements for reporting results, an issue that has riled countless researchers and patient advocates who argue there is little to no transparency when it comes to registering trials and reporting results.

"That was a significant event," said Till Bruckner, who heads TranspariMed, a UK-based advocacy group that tracks and researches clinical trial transparency issues in different countries. "A major regulator was getting serious about transparency, and it demonstrates that quite a lot has changed in the last few years and that change is going forward, but there is more to do."

Indeed, various analyses of databases in different countries illustrate the point.

A study published last year found "notable gaps" in the quality and availability of clinical trial data in the European Union Clinical Trials Register. One recent analysis noted that several leading US universities and hospitals failed to report clinical trial results to the ClinicalTrials.gov database. And still another analysis found that only 26% of drug makers made results publicly available for all studies used to win regulatory approval for their medicines during a recent two-year period.

The issue erupted following scandals in which trial results remained hidden. A particularly sensational episode involved *GlaxoSmithKline plc*, which did not disclose study data showing a widely prescribed antidepressant pill was not effective in youngsters. The blunder contributed to a headline-grabbing guilty plea and a $3bn fine levied a decade ago by US authorities. The incident went a long way toward triggering interest in greater disclosure.

Only now, though, are some countries moving to address transparency issues.

Slow Moving FDA Efforts

The UK government recently launched new systems to automatically register new studies with an independent registry and to track all interventional studies involving British patients. Earlier this year, Belgian authorities disclosed plans to penalize trial sponsors that fail to report trial results. And Danish authorities have threatened sanctions against trial sponsors that fail to publish study results in a European database, although no fines have so far been levied.

Efforts to compensate for transparency failures are moving in fits and starts, and the US is a prime example. In 2007, a federal law called the FDA Amendments Act was adopted to require trial sponsors to register applicable studies on ClinicalTrials.gov within 21 days after the first human subject is enrolled. They are also required to submit summary results information to the database within 12 months after the trial's primary completion date.

A decade later, a rule also went into effect to strengthen reporting requirements. But adherence has been spotty, at best. More than 3,300 trial results out of roughly 13,200, approximately 25%, have not been reported, according to the FDAAA Trials Tracker database, a website created to keep tabs on FDA performance. The site also tallies the billions of dollars that the FDA could have collected if fines had been issued.

It was only last year that the FDA threatened any fines. The agency acted after issuing guidance to explain when penalties would be sought. A recent analysis found that, over the previous eight years, more than 90% of drug makers and universities that received 58 preliminary warnings from the agency about overdue clinical trial results responded by quickly providing the information to ClinicalTrials.gov. On average, it took just three weeks to furnish the data.

So far this year, the FDA has publicized only one additional notice sent to a trial sponsor about

failures to post results. Moreover, this latest compliance notice, which was sent to a small drug developer in mid-April, followed an initial preliminary notice by almost one year. To transparency advocates, this suggests any momentum created by the sudden spate of warnings sent last year may be lost. They are urging the FDA to move faster to avoid building an even bigger backlog of overdue study results.

“The FDA’s overall enforcement efforts are severely lacking,” says Reshma Ramachandran, postdoctoral fellow at the Yale University School of Medicine and a board member of Universities Allied for Essential Medicines, an organization that promotes clinical trial disclosure. She was also one of the co-authors of the recent analysis of FDA of compliance notices.

“Its selection of trials for enforcement action through preliminary and final notices been seemingly haphazard. Given that the agency’s goal of voluntary compliance has not been met by all sponsors, the FDA should do much more to encourage enforcement through simple measures such as issuing (preliminary) notices and follow through within a timely period with a non-compliance notice.”

An FDA spokeswoman noted the agency seeks to encourage voluntary compliance but declined to discuss the approach taken to issuing notices or explain why more notices have not been publicized.

The reality is that, despite the federal law, many results are not reported until as much as three years after a trial is completed, according to Deborah Zarin, a former director of ClinicalTrials.gov, who is now program director at the Multi-Regional Clinical Trials Center, a research and policy project run by Brigham and Women’s Hospital and Harvard University.

“We’ve learned since 2007 that, providing information one year after trial completion, without exception, is a standard that’s both achievable and can be used to create a floor. You don’t want to have to wait more than one year after trial completion for results. It’s become pretty much accepted that you register trials, but you still need to put a gun to their heads to get them to report results.”

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In her view, the US NIH is also complicit. Zarin noted that the agency must withhold funding from an institution that is not compliant with the federal law. Moreover, the NIH instituted a policy about reporting trial results six years ago, but only now is it being implemented. A key question is how the agency pursues – and measures – enforcement. The NIH did not respond to a request for comment.

UK Transparency Initiatives

Perhaps the most notable strides have been made recently in the UK, where the Health Research Authority is playing a game of catch up after an analysis completed two years ago found that 32% of all trials were not registered. Last fall, the HRA inaugurated a new system that automatically registers trials with the ISRCTN registry, which is part of a WHO network of globally recognized trial registries.

This was the second of two steps announced last year by the HRA. It also launched a new system to track whether trial results are being reported. The system makes it possible to keep tabs on all interventional trials involving UK patients, including studies of both medicines and medical devices, as well international trials with study arms in Britain. Both efforts are an outgrowth of a transparency effort called Make it Public that was outlined in July 2020.

However, the agency allows trial sponsors up to 30 months to defer registering a trial and publishing a summary. An HRA spokeswoman explained the goal was to align with similar rules in the EU, and even when a deferral is granted, a minimal amount of information is still recorded publicly. “This will make limited information publicly available and help to create a fuller picture of research taking place in the UK, while keeping sensitive information confidential,” she explained.

Yet there are no sanctions for wayward sponsors. The HRA spokeswoman insisted, though, that the agency has been able to “influence change” by tightening regulatory reporting. Final reports are expected 12 months after a trial has ended, notwithstanding any deferrals. And the HRA is working with the Medicines and Healthcare products Regulatory Agency on legislation to require results reporting 12 months after a trial ends and establish sanctions for “serious” violations that could harm patients.

One government critic applauded the effort but questioned the lack of sanctions. “I think the situation has improved significantly in the UK,” said Norman Lamb, a former Member of Parliament who chaired a committee that, in a 2018 report, skewered the government for failing to combat the lack of transparency surrounding clinical trials. “I think the problem is that this isn’t an issue which gets any traction with the public. It’s really important, but it’s not an issue that touches most people directly. So, there is no political pressure on governments to do anything.”

“I think it would make a difference if the HRA sanctioned companies, universities and National Health Service trusts. We need to send a very clear signal that non-compliance with reasonable responding rules is not an option. Once effective sanctions start to be imposed it would drive behavior change. I’m sure institutions sometimes fail to comply because there are no consequences. There have to be consequences for the culture to change.”

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Indeed, sabre rattling can work. After his committee threatened dozens of universities with hearings if they did improve results reporting, a recent analysis found 20 major universities disclosed 91% of their required trial results, up from just 29% shortly before the warnings were issued. And by last June, all 20 of the major universities had posted more than 70% of the required trial results on a European Union Clinical Trials Register, and five of those universities had a perfect reporting rate of 100%.

Divergent Country Approaches

Earlier this year, Belgium became the first EU country to disclose specific details about penalties that trial sponsors may face if they do not publicly disclose study results. Denmark has threatened fines and jail time, but so far has not taken such steps because trial sponsors are showing signs of improvement, according to a Danish Medicines Authority spokeswoman. She noted that results have been published for 212 of about 300 studies that were unpublished in 2017.

Three years ago, the Canadian government created a new online portal to access clinical study reports, documents that describe the methods and results of a clinical study or trial along with a short discussion of key findings related to the study. By last summer, Health Canada, the country’s regulator, had released clinical data from more than 160 submissions for drugs, biologics, vaccines, and medical devices.

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Yet the Canadian regulator never passed regulations to build on a 2014 law saying there is a duty to publicize clinical trial information, according to Matthew Herder, director of the Health Law Institute and associated pharmacology professor at the Nova Scotia-based Dalhousie University. "We want our regulator to provide a place to register trials and report results. Unfortunately, transparency is a bit of a puzzle. They have one part worked out better than most jurisdictions, but the other part is years behind."

Commercial Implications

Despite the various efforts to broaden transparency, though, there is substantial push back.

For instance, the US Trade Representative recently released a report about foreign trade barriers that expressed concern over changes to a EMA policy for disclosing clinical trial data, including confidential commercial information submitted to the EMA by pharmaceutical companies seeking marketing authorizations. At issue is a policy to release clinical study reports, although the Agency suspended the effort three years ago after it moved headquarters.

Since then, the EMA has only published clinical study reports for Covid-19 vaccines and treatments. But a USTR spokesman noted that the policy was not rescinded, suggesting the pharmaceutical industry will continue to push to eradicate the policy altogether. In years past, several drug makers went to court to prevent the EMA from releasing certain data, arguing that doing so would compromise confidential commercial information.

Ironically, a recent analysis found that, before the EMA suspended its policy it was not very good at releasing clinical study reports. Full clinical study reports were available for 81% of more than 900 trials examined. But the median time to publication was 511 days and less than 2% of the reports were published within the EMA's planned timeline of 60 days or less following a decision about marketing authorization.

Although Canada has won high marks for its portal disclosing clinical study reports, efforts elsewhere are spotty. Bruckner noted that Denmark, Sweden and the Netherlands have taken steps to disclose these reports, but Germany and Finland have refused. A few years ago, the FDA

ran a pilot program for releasing clinical study reports that were voluntarily made available by drug makers. But the program was discontinued after only one report was disclosed.

This suggests the potential for still another clash over transparency, since the stance adopted by the US Trade Representative contradicts the view held by the WHO and the International Coalition of Medicines Regulatory Authorities. Last year, these agencies urged drug makers to publish clinical study reports for new medicines and vaccines without redacting any confidential information.

The agencies released a joint statement in which they explained their goal is to ensure research results are publicly accessible so that decision makers — notably, health authorities and physicians — have greater understanding about drugs and vaccines. The agencies also argued releasing trial information that is not redacted would boost public confidence in medical products.

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The information needs to be published by the time marketing authorization is granted, because the data is needed for setting clinical guidelines and treatment decisions, argued Beate Wieseler, head of the drug assessment department at the Institute for Quality and Efficiency in Health Care, an independent German agency that assesses the effectiveness of medicines. "It is unclear to me how withholding clinical trial data from patients, physicians and the general public can be considered appropriate."

The upshot is that progress is being made, albeit slowly.

"If you're looking at these studies coming out and compare year-to-year performance, it does tend to show things are getting a little better. Overall, it's becoming a positive story. You can see it at all levels. Regulators in more countries are becoming proactive, funders are paying more attention, and more and more institutions are putting into place stronger processes to ensure results are made public," said TranspariMed's Bruckner.