Transparency in Clinical Research. Recent policy initiatives focus on improving the use of clinical research for patients, providers, and health systems.

WHAT’S THE ISSUE?
Reporting biases in the published literature—whereby the results of research are inconsistently or selectively reported—is a well-known phenomenon and has been a source of concern in the health care field since at least the 1980s, particularly in the realm of therapeutic drug trials. Despite several efforts over the ensuing decades to address this issue, it is estimated that up to half of all clinical trials conducted and completed have never had their results published.

This lack of transparency in clinical research has serious implications for patients, providers, and health systems more generally. Although previous efforts have failed to fully address the problem, recent policy initiatives in both the United States and abroad offer new opportunities to address outstanding issues.

WHAT’S THE BACKGROUND?
Reporting biases exist across multiple fields of research and can take a variety of forms, including selective or delayed publication, as well as publications that contain misleading or inadequate information on findings or study design. Although estimates vary, studies have found that up to half of all clinical trials never have their results published. Past evaluations have also found that clinical studies showing positive results are twice as likely to be published compared to those that do not, and positive findings are also more likely to be reported promptly.

Studies have also found that the trial results reported to regulatory agencies can differ significantly from the results that are publicly reported in journals. A recent analysis of fifteen drugs approved in 2012 by the Food and Drug Administration (FDA) found that, per drug, a median of 35 percent of the trials used to support their regulatory approval were not made publicly available through either a database or the published literature, sometimes in violation of federal requirements.

There have also been high-profile examples over the years of companies failing to adequately report study findings to regulatory agencies. In 2012, for example, GlaxoSmithKline (GSK) pleaded guilty to criminal charges and agreed to pay $3 billion in fines, in part for failing to report safety data about its diabetes drug Avandia. However, the failure to publish or adequately report trial results data is not limited to industry-funded trials; in fact, nonindustry trials may be even less likely to report results in a timely fashion.

Failure to publish trial results is also considered an ethical violation. People participate in trials in part out of a belief that doing so will benefit future patients. Withholding
findings after individuals have participated in trials is considered by most to be a violation of a researcher’s responsibility to those participants. More broadly, nonreporting, delayed reporting, and biased or misleading reporting also lead to significant waste of resources and data in biomedical research. A 2009 analysis estimated that the cumulative effect of flawed trial designs, nonpublication, and poor reporting of results meant that more than 85 percent of research funds went toward research that was not widely disseminated.

The general lack of transparency in clinical research has several important implications. Most critically, it can leave patients and their providers with an incomplete picture of a treatment’s benefits and risks, and can lead to unnecessary health system spending on ineffective or even harmful therapies.

**Previous Efforts to Increase Transparency in Clinical Research**

There have been several attempts over the years to address the lack of transparency in clinical research, largely through the public registration of trials and mandated reporting of results. The prospective public registration of clinical trials offers several benefits.

First, it allows other researchers to obtain more complete information on previously conducted research, which facilitates systematic reviews and replication of study results. Prospective registration can also discourage trial conductors from making post-hoc changes to their research methodology that can lead to biased reporting of results and can make it easier for patients to find active or planned trials for which they might qualify. A range of countries, as well as international and national-level organizations, maintain clinical trial registries. However, the quality and comprehensiveness of the information available in these registries varies, and previous efforts to encourage or mandate trial registration have not been as successful as was hoped.

In 2005, for example, the International Committee of Medical Journal Editors (ICMJE) (a group that includes many of the leading medical journals) instituted a policy that stated that its member journals would only publish trials that had been registered in a public trials registry at or before the time of first patient enrollment. Although trial registration did increase substantially, particularly for trials conducted in Europe and North America, the impact of the policy has been limited to a subset of trials. Enforcement of the ICMJE’s policy is inconsistent, and only about 30 percent of English-speaking journals require or encourage registration. Furthermore, some trials may not be conducted with the aim of publication and would not necessarily be influenced by the policy.

One of the largest and most comprehensive clinical trial registries is ClinicalTrials.gov, which was established in 1997. Following the passage of the FDA Amendments Act (FDAAA) in 2007, the site was expanded to include a broader range of trials, registration information, and summary results, including adverse events. Under the FDAAA, a non–Phase I clinical trial must be registered if it has at least one site in the United States or is investigating a drug, device, or biological agent that is subject to FDA oversight and is initiated or ongoing as of September 2007. Results must be reported within twelve months of trial completion, and failure to comply can result in a penalty of up to $10,000 per day.

However, the FDAAA has several limitations. For example, it excludes many trials conducted outside of the United States, as well as all Phase 1 trials and small feasibility studies. The law also did not establish an official auditing process to ensure compliance, and enforcement is lacking. No penalties for noncompliance have been levied, and several studies have confirmed that compliance with the FDAAA is generally poor.

One analysis, for example, found that only 13 percent of the trials that met the FDAAA’s inclusion criteria had reported results within twelve months after trial completion, and 38 percent reported results within the five-year study period. FDAAA regulations also do not apply retroactively. Studies completed prior to 2007 are exempt from reporting requirements, which omits decades of research.

**What Efforts Are Under Way to Address the Issue?**

In recent years, there has been renewed efforts to improve transparency and access to trial data, both in the United States and abroad. However, the scope of these efforts has broadened beyond registration and the publication of analyzed results to include sharing of the underlying data.

Making these data available offers several additional benefits. It allows future researchers to learn from past failures and successes, and it facilitates third-party reanalysis that
can help generate new findings or hypotheses that need additional testing as well as reinforcing (or challenging) regulatory decision making. This approach can also serve as an important check on biased analysis and reporting. The recent reanalyses of trials for Tamiflu and Paxil, for example, offer compelling examples of how increased transparency can provide an important counterbalance to reporting biases.

The AllTrials campaign, which advocates for greater transparency, has attracted support from more than 600 organizations in the United States and abroad, including medical journals, research institutions, advocacy organizations, and some pharmaceutical companies. Increased advocacy and attention surrounding this issue have also led to a range of policy and regulatory reforms. The World Health Organization recently updated its policy on the public disclosure of clinical trial results, which reaffirmed the ethical imperative of full reporting; proposed reporting time frames; called for publication of historical data as well as future research; and outlined strategies for linking trial registries to their published results.

The European Medicines Agency, which is “responsible for the protection of public and animal health through the scientific evaluation and supervision of medicines,” has implemented two key policies that allow for broader access to trial data. In 2010 the agency announced that it would make a wide range of regulatory documents available upon request, including clinical study reports, which are comprehensive documents comprising trial protocols, methods, and results. Over the ensuing two years, the agency released more than two million pages of documents, although the release of some trial data was delayed as a result of lawsuits (subsequently dropped) from the drug industry.

In December 2012 the European Medicines Agency announced that, in addition to its existing publication policy, it would require the proactive publication of the full clinical trial data following the agency’s decision to approve or deny a marketing application. A final policy outlining its approach was published in 2014. Under this policy, the agency will publish clinical study reports and de-identified participant data submitted as part of any marketing application made after January 2015, which registered users will be able to access. Data that may be considered commercially confidential or would compromise patient privacy will be redacted, although guidance on how (and how much) data should be redacted is still being finalized.

The FDA has also taken some steps to share data more broadly, although to a lesser extent than the European Medicines Agency. In 2013 the FDA sought public comment on a proposal supporting additional transparency for product-masked, de-identified patient data. Pooling these data would not allow for evaluation of specific products but could allow for research on specific diseases. However, the FDA indicated in January 2014 that it does not intend to implement a policy of routine preparation and release of de-identified and masked study data, as this would be resource intensive and the FDA does not consider such work to be a part of its core mission.

Other US-based organizations have been more proactive. In 2013 the Institute of Medicine (IOM) convened a working group to develop guiding principles and strategies for the responsible sharing of clinical trial data. The final report was published in January 2015. It includes four broad recommendations focused on how various stakeholders (such as research sponsors, medical journals, academic institutions, regulatory agencies, and institutional review boards) can foster a culture of data sharing and ensure that this sharing maximizes benefits and minimizes risks; the time frames in which clinical trial data should be published; the development of adequate and transparent data-sharing policies and procedures; and the need for an international collaboration to address the associated infrastructure, technological, sustainability, and workforce challenges.

The Department of Health and Human Services (HHS) has also released several proposals for public comment that are aimed at increasing transparency. The first proposes new regulations for registering and submitting results to ClinicalTrials.gov of clinical trials that qualify for mandatory reporting under the FDAAA. The new regulations would require an expanded amount of information be submitted at the time of registration and following study completion. HHS sought input on the advantages and disadvantages of requiring submission of additional information, such as full clinical trial protocol documents.

A second proposal would extend these requirements to all trials funded by the National Institutes of Health (NIH), instead of just those that would qualify for mandated reporting. $3 billion Amount paid by GlaxoSmithKline after pleading guilty to criminal charges for failing to report safety data about its diabetes drug Avandia.

“It is estimated that up to half of all clinical trials conducted and completed have never had their results published.”
under the FDAAA. Yet another proposed rule would require public posting of participant consent forms. NIH director Francis Collins has also indicated that both the FDA and the NIH will begin taking more aggressive steps to ensure compliance with reporting requirements, particularly for NIH grant recipients.

A number of drug companies have also made proactive commitments to share clinical trial data more broadly. GSK and Roche were among the earliest companies to commit to data sharing, and several more have followed. Some companies have also collaborated to pool data on shared platforms. Project Data Sphere, for example, is an oncology-focused collaboration that includes trial data from twelve sponsors.

In 2013 the US and European industry trade groups (Pharmaceutical Research and Manufacturers of America and European Federation of Pharmaceutical Industries and Associations) published a joint set of principles for clinical trial data sharing and outlined several commitments that they encourage member companies to adopt. Under these commitments, member companies would share patient- and study-level clinical trial data, full clinical study reports, and trial protocols for drugs approved in the United States and Europe with qualified researchers. To date, companies have adopted differing approaches to the type and amount of data they will provide and the procedures for external researchers to access the data.

The move toward greater transparency has extended beyond trials of medical products to include a range of other interventions (such as psychosocial or behavioral interventions), and there have been recent proposals to expand transparency policies to include other types of research, such as observational studies.

**WHAT’S THE DEBATE?**

There is little debate that reporting biases are a serious concern in clinical research, and although the move toward greater transparency has not been without controversy, debate has mostly shifted toward questions of how and under what circumstances trial data should be shared. There are several key challenges that must be addressed to ensure that data sharing is done in a way that maximizes public benefit while minimizing the risks associated with increased transparency.

An oft-cited concern is how to ensure that patients’ rights are adequately protected—in particular, how to share patient-level data without compromising privacy. Current methods of anonymization are imperfect, and new approaches may be required. There are also questions over whether consent for data sharing should be a condition of trial participation going forward, or if patients should be allowed to enroll in a study but opt out of broader data sharing for the purposes of secondary analyses. Allowing opt-outs could compromise the validity of those secondary analyses.

However, requiring data sharing as a condition of consent may be a disincentive for patients to participate in a trial, particularly among vulnerable populations who have been subjected to unethical research practices in the past and may be more mistrusting of clinical research. Minority populations are already underrepresented in clinical trials—a fact that can negatively affect the generalizability of trial results—and it will be necessary to devise strategies that allow for data sharing without further exacerbating inequalities in research participation.

Another key concern relates to the risk that trial data will be misused or improperly analyzed. Misleading or incorrect conclusions based on these data could lead to unnecessary health scares and undermine public trust in clinical trials. The existing data-sharing initiatives or platforms typically include a vetting process, whereby researchers must submit formal requests that are subject to review and approval. Such controlled access approaches can help address concerns over improper use, but they also raise a separate set of concerns: namely, whether the data that are being shared will be useful to third-party researchers.

The major platforms established by industry groups currently come with restrictions on the type of data that is available and how it will be shared. For example, all companies redact certain information to prevent inadvertent patient identification, but some are also redacting what they deem to be “commercially confidential information,” the definition of which can vary according to the company. Researchers must also access and read the data through a secure portal instead of downloading the data to their own computers, which can make reanalyses cumbersome and more time consuming.
However, it remains to be seen whether these controlled-access policies and procedures will significantly impede research. As of October 31, 2015, 169 research proposals had been submitted through ClinicalStudy DataRequest.com (a web-based portal used by twelve major companies). No results have yet been published, but eighty-five data-sharing agreements have been signed, and seventy-five projects are currently under way. These proposals vary in terms of their objectives, and they include systematic reviews of multiple trials as well as detailed reanalyses of data from a single trial.

The emergence of these data-sharing platforms has also led to debate over which entities should mediate access to data on the safety and efficacy of medical products, which could be considered a public good. Some have questioned whether pharmaceutical companies should be relied upon to serve this purpose, arguing that regulatory agencies are better suited to ensure that data on safety and efficacy are genuinely open to outside scrutiny.

Regardless of which entities control access to the data, there are significant financial and logistical challenges associated with aggregating, indexing, and anonymizing the data from disparate trials, most of which are stored in multiple independent databases and were collected using differing standards. Older trial data may also exist in legacy systems, which may not be fully integrated into current databases or may exist only in paper records. There are ongoing questions over how to prioritize trials that should be targeted for this process, how and to what extent data should be pooled across institutions, where these data sets should be housed, who will oversee their maintenance, and how these systems and operations should be funded.

WHAT’S NEXT?

In the near term, legislative efforts by the US government are under way to improve clinical trial data sharing. The 21st Century Cures Act, which was passed by the House in July 2015, contains provisions that would direct the NIH to improve the standardization of data housed in ClinicalTrials.gov. These changes are intended to facilitate use of the database by the public as well as communication between the database and other health information technologies (such as electronic health records).

The legislation also directs the FDA and the NIH to establish a repository of all data from certain clinical trials that have been sponsored by either HHS or other developers that have granted the HHS permission to share their data. These data would then be made available for further study by scientific and medical researchers. This effort would run as a pilot program for seven years, after which it could be adopted as a permanent piece of the research infrastructure.

The focus is now on the Senate, which has been developing its own bill aimed at reforming the biomedical research infrastructure. It remains to be seen how the two versions will be reconciled and whether these provisions will be preserved. Regardless, the existing proposals would not substantially affect the FDA’s ability to share data beyond its current initiatives. Congressional action may be required to move this issue forward.

Over the longer term, it is unclear how the existing and emerging data-sharing initiatives will evolve, and their ultimate usefulness will depend on a range of issues that are still under discussion. There are ongoing questions, for example, over some of the details of the European Medicines Agency’s data-sharing policies, including how anonymization and redacting of sensitive information will be handled and how disputes over data sharing will be resolved. The agency’s final policy on this issue is forthcoming.

The major industry data-sharing programs are also largely untested, and it remains to be seen whether those platforms and systems are structured in a way that can allow for meaningful research. Further incentives or enforcement mechanisms may also be necessary to encourage academic researchers to share data more broadly. Careers in academia depend on an individual researcher’s ability to publish based on data collected over months or years, which does not generally encourage broad sharing.

As experience with these data-sharing programs grows, it will likely be necessary to identify and disseminate best practices. The recent IOM report called for the establishment of forums of diverse stakeholders, led by trusted, impartial entities, that could facilitate this exchange and help drive consensus on solutions to outstanding challenges. However, it is unclear which entity would lead such efforts or how the process would be funded.
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