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POLICY FORUM

US Federal Government Efforts to Improve Clinical Trial Transparency with Expanded Trial Registries and Open Data Sharing

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Policy changes proposed by the US Department of Health and Human Services (HHS) and the National Institutes of Health (NIH) are the latest in a longstanding effort to bring transparency and openness to health care research [1, 2]. The proposals are designed to expand clinical trial registration requirements and promote sharing of clinical data generated from research. Health care advocates have long maintained that selective publication and reporting of clinical trials not only diminishes the integrity of medical research, but also might risk patient lives when it prevents safety concerns from being promptly identified [3, 4]. Hence, there are both ethical and pragmatic reasons to enhance research transparency.

Clinical trials are prospective, interventional studies involving at least one human participant that provide evidence about the safety and efficacy of new therapies. Although the ethics of patient treatment in such trials are generally agreed upon [5], the importance of research transparency is growing as it becomes increasingly feasible to share information, collaborate across institutions, and network among investigators. Historically, the imperative for transparency for both the public and the academic community was satisfied by publishing results in peer-reviewed journals [3]. By today's standards, however, the publication process is slow [6], often creating a significant lag in the dissemination of new research findings. Moreover, the majority of clinical trials are never published and those published are more likely to be reporting positive results [7-9]. Even when clinical trials are published, the articles may not be consistent with the raw data or the results reported to clinical trial registries [10, 11]. In the past, this lack of transparency has slowed access to information on investigational therapies (as with HIV drugs in the 1980s [12]), potentially led to inappropriate use of medications (as with drugs like gabapentin [13] and COX-2 inhibitors [14]), and delayed device recalls (as in the case of metal-on-metal hip replacements [15]). From both public health [16, 17] and human rights perspectives [12], the incomplete dissemination of clinical research results is no longer tolerable.

The Evolution of Clinical Trial Registries

The proposed policy changes by HHS and NIH focus on broadening requirements for clinical trial registration to enhance research transparency. [Trial registries](#) are typically web-based platforms that provide a public source of information on existing clinical

trials, ranging from those specific to particular diseases to those that aggregate trials in a given region. Numerous foundations and disease-specific groups have their own trial registries, with the NIH alone listing close to 40 independent trial registries [18]. Registration provides the public and the scientific community with critical information about both active and completed trials, including title, purpose, eligibility, investigator contact information, and relevant dates.

Historically, patient advocates have led the movement to increase research transparency in the US. The first federally supported registry, the AIDS Clinical Trials Information Service (ACTIS, enacted in 1989), was in part a result of patient lobbying [12, 19, 20]. A decade later, advocacy work by the breast cancer community led to expanded federal funding for a “public resource” for clinical trial data through the Food and Drug Administration Modernization Act of 1997 (FDAMA) [12, 21]. That “public resource” became ClinicalTrials.gov, a central repository run by the National Library of Medicine for information on clinical trials throughout the world [22].

The role and scope of ClinicalTrials.gov has gradually expanded over time, and it is now the largest trial registry in the world, with close to 200,000 registered studies [22]. Initially, the registry was primarily limited to NIH-funded clinical trials. However, in 2005, the International Committee of Medical Journal Editors required registration of trials prior to publication, which led to substantial increases in trial registration [23, 24]. The FDA Amendments Act of 2007 (FDAAA) section 801 expanded the types of “applicable clinical trials” subject to reporting requirements [22, 25], a category of studies initially defined by the Food, Drug and Cosmetic Act but amended over the years by legislation and interpreted by executive processes of rulemaking [1]. It also formalized the data elements (including descriptive, recruitment, contact, and administrative data) required for registration and added mandatory reporting of summary results for applicable trials [22, 25], a category of studies initially defined by the Food, Drug and Cosmetic Act but amended over the years by legislation and interpreted by executive processes of rule making. Such results reporting is particularly valuable, increasing public access to study conclusions that can be used to guide clinical decision making. Several thousand trials now report summary results on ClinicalTrials.gov [22].

However, limits to trial transparency remain. NIH does not currently require registration of all sponsored trials, and there are notable exceptions in the existing interpretation and enforcement of FDAAA clinical trial reporting mandates [26]. For example, trials of drugs and devices not yet approved by the FDA and trials of non-FDA-regulated products are not subject to current regulatory policies [27]. Additionally, some results reporting requirements—including detailed definitions of necessary outcomes measures, results summaries, and adverse events—were not fully specified in the FDAAA, nor were the mechanisms to verify compliance [25]. This has led to poor rates of results reporting on ClinicalTrials.gov across trial sponsors [28].

Proposed Changes

The 2014 HHS Notice of Proposed Rulemaking (NPRM) [1] and the NIH proposal for disseminating NIH-funded clinical trial information [2] revise the scope of FDAAA section 801 [25]. Key features of the NPRM and the NIH proposals include: (1) expansion of mandatory applicable trial registration and results reporting on ClinicalTrials.gov to include more trials—including trials of drugs and devices not yet regulated by the FDA and *all* trials receiving funding from the NIH; (2) collection of new data types, such as specifically-defined outcome measures, during trial registration and data submission; (3) a requirement that all applicable studies required to register must report expanded summary data, including additional efficacy outcomes and adverse events; and (4) implementation of procedures for timely and accurate data reporting to speed information dissemination [1, 2, 29, 30].

These changes are a significant step forward, enhancing clinical trial transparency and setting the stage for future improvements. The NPRM will not only require more clinical trials to publicly register and report results, but also improve access to this information by making many of these data elements searchable [26]. These new rules will have a significant effect on academic research centers and NIH-funded research, which have poor records of both registering trials and making data publicly available [31, 32]. Improved procedures and implementation of penalties for delays will ideally ensure widespread trial registration and results reporting across all study sponsors and sites.

Nevertheless, the policy proposals contain numerous loopholes that make it possible to avoid registration and some striking omissions. For example, many “exploratory” and phase 1 research trials will continue to be exempt to maintain commercial competitive advantage [1, 26, 27]. Moreover, the proposed policy changes do little to promote open data.

The Benefits of Open Data

Sharing of raw experimental data among researchers is now the norm in many scientific fields. From genomics and drug development to molecular and structural biology, researchers have made commitments to crowdsource studies, share data, and promote the principles of open science [33]. A recent study surveying researchers who conduct clinical trials revealed that nearly three-quarters of respondents believed that data submission to repositories should be mandatory [34], suggesting there is now broader consensus that data from trials should be made publicly accessible. Registration and reporting of summary data in repositories like ClinicalTrials.gov is a good start, but efforts are needed to make clinical data more widely available for research and public health purposes.

Data sharing has numerous benefits. It honors the altruism of study participants by fully leveraging their data for additional research. It also allows existing data to be used to pursue novel research through meta-analysis by groups such as the Cochrane Collaborative and creates opportunities to advance medical science and clinical research [3, 11]. Access to raw clinical trial data, coupled with crowdsourcing, big data, and advanced analytics, offers the promise of more sophisticated and granular analyses that may both identify ways to improve patient outcomes and recognize rare adverse events [3, 35]. Moreover, access to data allows researchers to reconstruct the scientific conclusions of a study independently, ensuring research integrity through data accountability [36]. For example, the negative health impacts of incomplete data—such as occurred with rofecoxib [13] and oseltamivir [11, 37]—may have been determined more rapidly if researchers had had access to de-identified records.

There are also economic reasons to support increased data sharing, including the creation of efficiencies in research and development that spur innovation [35, 38]. Clinical trial data has been proposed to be a public good [38, 39], meaning that its use by one party does not diminish its value to others. Independent analysis has shown that effectively leveraging data liquidity—or the availability of data to researchers, clinicians, and patients—could create up to \$450 billion of value in the US health care market [40]. Indeed, utilizing existing clinical data should be considered “a boon to drug developers” that would reduce the cost of running clinical trials [41].

Toward A Data-Sharing World

Clinical trial sponsors have begun to respond to requests for research transparency. In 2013, GlaxoSmithKline created a data-sharing platform, ClinicalStudyDataRequest.com, now used by 13 of the largest pharmaceutical companies worldwide to share information on dozens of clinical trials [42]. Third parties, like the Yale University Open Data Access (YODA) Project, have also worked to facilitate data sharing [43]. These platforms are promising, yet they are limited in both their scope and their access to data. The number of available trials represents only a small proportion of those completed to date, and some of the available trials have cumbersome data use agreements. Furthermore, the high cost of data-sharing platforms and insufficient funds hamper these efforts.

The value of shared data lies largely in the ability to analyze the aggregated results of several studies to convey a greater truth [33]; thus efforts are needed to incorporate sharing data and using shared data into the reward structures of academic credit and promotion. ClinicalTrials.gov, which already aggregates registry information and summary results for hundreds of thousands of trials, may be the ideal public data repository. Hosting open data is a role that the government is uniquely positioned to fulfill, given its vast resources and regulatory monopoly [44]. In addition, to leverage any data in such a repository efficiently, common data definitions and infrastructure that

ensures security and privacy will need to be developed. To host, maintain, administer, and analyze the vast amounts of clinical data produced every year will also require significant funding [44].

Conclusions

As access to clinical data becomes the next frontier in clinical research transparency, the burden for action shifts onto scientists, clinicians, and study sponsors. The case for full transparency has been argued from public health, human rights, and economic perspectives. As the risks of withholding study information and research results—and the opportunities inherent in open data sharing—become increasingly evident, the rationale for more comprehensive clinical trial transparency grows stronger and the needed steps forward become clearer. The proposed rule changes from HHS and NIH are a step in the right direction. A culture of open data is not just the most ethical approach; it also offers large potential benefits to science and society. Ultimately, the scientific community must advocate for and establish professional norms of data sharing and collaboration.

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