

# *Transparency for Clinical Trials and NIH-Sponsored Research*

by

Stuart Buck

Vice President of Research Integrity, Laura and John Arnold Foundation

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## **I. Introduction**

At the Laura and John Arnold Foundation (LJAF), we are dedicated to improving the reliability and validity of scientific evidence across fields that inform governmental policy, philanthropic endeavors, and individual decision-making.<sup>1</sup> As part of LJAF's continued efforts to ensure that scientific research is fundamentally sound—and in light of the fact that far too many details about clinical trials are hidden from public view—this piece will address the critical issue of transparency in drugs, interventions, and medical device clinical trials.

One recent study strikingly found that only 22 percent of taxpayer funded trials were in compliance with a federal law requiring findings to be reported on the government registry of public and private clinical studies, *ClinicalTrials.gov*.<sup>2</sup> Such a broad lack of transparency has serious consequences for patient outcomes because it leaves doctors—and even government agencies such as the Centers for Disease Control—unaware of the full range of effects and side effects of commonly used pharmaceuticals.<sup>3</sup> One egregious example arises from the treatment of heart disease. According to some estimates, if a particular 1980 trial on anti-arrhythmic drugs had been published before 1993, a dangerous drug might have been taken off the market earlier, saving between 20,000 and 75,000 lives per year in the United States.<sup>4</sup>

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<sup>1</sup> LJAF is the primary funder of the Meta-Research Innovation Center at Stanford University, an organization focused on improving the quality of medical research; and the Center for Open Science, an organization that is working to improve the scientific process and promote accurate, open findings in scientific research.

<sup>2</sup> Prayle et al., “Compliance with mandatory reporting of clinical trial results on *ClinicalTrials.gov*: cross sectional study,” *BMJ* 344 (3 Jan. 2012), at <http://www.bmj.com/content/344/bmj.d7373>. Ross et al. (2009) found that only 40% of industry-funded trials and 47% of NIH-funded trials are published. Ross et al., “Trial Publication after Registration in *ClinicalTrials.gov*: A Cross-Sectional Analysis,” *PLoS Medicine* (8 Sept. 2009), at <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000144>. A subsequent study found that a third of NIH-funded trials remained unpublished even after a median 51 months since the trials were completed. Ross et al., “Publication of NIH funded trials registered in *ClinicalTrials.gov*: cross sectional analysis,” *BMJ* 344 (3 Jan. 2012), at <http://www.bmj.com/content/344/bmj.d7292>.

<sup>3</sup> To this day, the CDC's website claims that Tamiflu can prevent flu and decrease the risk of death (see <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>), even though a full review of the evidence indicates that those claims are overstated. See Jefferson et al., “Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments,” *BMJ* 348 (9 April 2014), at <http://www.bmj.com/content/348/bmj.g2545>.

<sup>4</sup> Kay Dickersin & Drummond Rennie, “Registering Clinical Trials,” *JAMA* 290 v. 4(July 23/30, 2003): 516-523.

While the underreporting of results is a serious concern, even the trials that are published can be misleading. In many cases, analysis will be selectively written so as to highlight a positive finding while ignoring less desirable results.<sup>5</sup> The reason that trial sponsors get away with publishing biased results is that the current transparency requirements are too weak. There is no enforceable requirement that all findings be published as planned or that the publication include an explanation for any alterations.

Implementing the three principles of reproducible science discussed below, and further examined in Section II, would help address reporting biases; make clinical trials more reliable, open, and complete; make the practice of medicine more evidence-based; and save thousands more lives every year.

- **Pre-registration**

Pre-registration requires researchers to declare certain details, such as the trial's goal and expected outcome, at the outset. Such a public declaration can later be used to identify whether a seemingly positive finding occurred merely by chance or because of an altered trial design. Pre-registration is thus critical to maintaining the integrity of the trial. Otherwise, researchers who have financial or ideological interests at stake could change various parameters along the way so as to make a drug look more effective and safe than it really is. Registration has been mandatory for certain trials conducted by drug and device manufacturers since the Food and Drug Administration Amendments Act of 2007 (FDAAA) (enacted at 42 U.S.C. § 282(j)).

- **Sharing of data and statistical code**

Patient-level data (*i.e.*, datasets containing information about every patient in the trial) and code should be made publicly available to a much greater extent than is currently the case. Sharing patient-level data and code would allow researchers to see the full results of a trial, discover errors or discrepancies that would never have been noticed otherwise, and to extend analyses and make new discoveries. Moreover, scholars are incentivized to conduct studies in a more careful, diligent manner if they know that other researchers will have access to the same data and code.

- **Sharing of all final results**

Even if patient-level datasets are not available, sponsors should be required to publish all results, even from “failed” trials on drugs that are not approved. Failure to disclose all results harms patients, stifles scientific advances, and causes society to waste resources on the wrong remedies. For example, if a trial on a particular statin is never published because the pharmaceutical company was unhappy about a negative result or the presence of side effects, doctors and patients might use that statin without knowing the potentially negative outcomes. Government decision-makers also are affected when clinical trial results are not disclosed, as was the case when the United States purchased \$1.3 billion worth of Tamiflu because a selective review of studies claimed that it stopped the spread of flu and prevented deaths. Academic investigators

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<sup>5</sup> Dwan et al., “Evidence for the Selective Reporting of Analyses and Discrepancies in Clinical Trials: A Systematic Review of Cohort Studies of Clinical Trials,” *PLoS Medicine* (24 June 2014), at <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001666>.

later gained access to the rest of the unpublished clinical trials about Tamiflu and found that its only proven effect was to reduce the length of a person's flu by 16 hours. If the results of all Tamiflu clinical trials had been publicly disclosed, the government might not have purchased the drug in such a large supply.

## **II. Specific Suggestions for Strengthening Federal Drug Approval and Federally-Funded Research<sup>6</sup>**

Federal funding, Food and Drug Administration (FDA) approval, and ClinicalTrials.gov should all be reformed so that evidence on drug effectiveness is available, reliable, and trustworthy. Here are some specific suggestions.

### **1. Register pre-clinical animal studies**

Pre-clinical animal studies are often low quality and are plagued by problems such as the use of small sample sizes, a failure to use randomization, or the repetition of an experiment until a desired result is achieved.<sup>7</sup> A rigorous registration system would incentivize researchers to plan stronger experiments up front and would help others evaluate whether the results justify a human trial. For example, the National Institutes of Health (NIH) recently spent \$25+ million on a drug trial that it learned was based on faulty animal research. This oversight would not have happened if the original animal research had been pre-registered with full disclosure of the intended methods and statistical analysis.

### **2. Register Phase I or other feasibility studies**

Many drugs that apparently work in early Phase I feasibility trials fail when they undergo more rigorous testing in later phases.<sup>8</sup> Phase I trials currently are not required to be registered on ClinicalTrials.gov. Mandating registration would make public more information about Phase I trials and could help protect patients from taking part in larger Phase II/III trials that might be unnecessary or unsafe.

### **3. Require registration of trials conducted outside the U.S.**

Many clinical trials are conducted in developing countries that lack stringent guidelines for research. Although it is difficult to certify the quality control for such trials,<sup>9</sup> mandatory registration would represent a first step toward regulatory oversight and would provide the medical community with important information about how the trial was designed.

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<sup>6</sup> LJAF presents this information solely for educational purposes, and does not take a position for or against any particular piece of legislation.

<sup>7</sup> See Malcolm R. Macleod, "Preclinical research: Design animal studies better," *Nature* 510 (5 June 2014): 35.

<sup>8</sup> See Hay et al., "Clinical development success rates for investigational drugs," *Nature Biotechnology* 32 (2014): 40-51.

<sup>9</sup> See Lorenzo et al., "Hidden risks associated with clinical trials in developing countries," *Journal of Medical Ethics* 36 (2010): 111-15.

- 4. Require all registered trials to upload consent documents to ClinicalTrials.gov**  
Patient consent documents shed light on how a trial was planned and also show whether a patient agreed to allow additional research to be performed on a dataset.
- 5. Require all registered trials to submit the trial protocol to ClinicalTrials.gov**  
Trial protocols, which are the lengthy planning documents written before a clinical trial's launch, should routinely be made available on ClinicalTrials.gov. While making public trial protocols mandatory would provide much more information about trial design, the Department of Health and Human Services rejected a proposal to require protocol submissions.<sup>10</sup> Therefore, further policy action may be necessary.
- 6. Require all registered trials to submit final results to ClinicalTrials.gov**  
Federal law<sup>11</sup> requires trial sponsors to declare a trial's results on ClinicalTrials.gov after FDA approval; however, this reporting requirement is too narrow and should apply even when a drug or device is not approved. Failed clinical trials provide valuable information, and without their publication, future researchers may waste time and money subjecting patients to unsafe and unnecessary trials on treatments that are already known not to work.
- 7. Require all registered trials to submit Clinical Study Reports to ClinicalTrials.gov**  
Clinical Study Reports offer detailed descriptions of what occurred during the study and every finding that emerged. Even when trials are published in the scholarly literature, they often fall far short of describing the full results and side effects described in the Clinical Study Report.<sup>12</sup> The FDA should require all registered trials to submit Clinical Study Reports in full to ClinicalTrials.gov so that doctors and patients are not misinformed about the true effectiveness or side effects of a drug. If concerns arise over the dissemination of private or business confidential information in the reports, they could be redacted before public release.
- 8. Require all registered trials to make statistical code publicly available**  
Statistical code (*i.e.*, in software such as R, Stata, or others) used to analyze the results of a clinical trial should routinely be made public so that others can review it for correctness. Even prestigious scholars have made mistakes because of coding errors.<sup>13</sup>
- 9. Require all registered trials to make patient-level datasets available to other researchers**

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<sup>10</sup> See <https://www.federalregister.gov/articles/2014/11/21/2014-26197/clinical-trials-registration-and-results-submission#h-35>.

<sup>11</sup> 42 U.S.C. § 282(j)(3)(E).

<sup>12</sup> See Wieseler et al., "Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data," *PLoS Medicine* (8 Oct. 2013), at <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001526>.

<sup>13</sup> See Greg Miller et al., "A Scientist's Nightmare: Software Problem Leads to Five Retractions," *Science* 314 (22 Dec. 2006): 1856-57.

Requiring all registered trials to make patient-level datasets publicly available would be the “gold standard” for turning clinical trials into reproducible research.<sup>14</sup> Data-sharing is becoming increasingly important in medical research, and the Institute of Medicine recently released a major report recommending that patient-level data-sharing be the “expected norm.”<sup>15</sup>

Policymakers should consider creating a data-sharing mandate that applies to all FDA-regulated and NIH-sponsored clinical trials, as well as to all clinical trials conducted with the involvement of anyone employed at an academic institution that receives federal funding. Furthermore, data from trials should be routinely deposited into trusted digital repositories that assign persistent digital identifiers so that the data can be appropriately protected and its use tracked. Policymakers at the FDA and/or NIH should consider creating a unified clinical trial data system so that data and metadata are created and stored in a consistent manner across all trials.<sup>16</sup>

One objection is that patient-level data are subject to privacy protections under the Health Insurance Portability and Accountability Act (HIPAA).<sup>17</sup> Certain steps could be taken to protect patients. For example, it is possible to de-identify and statistically anonymize datasets. Datasets made available to other researchers also could be subject to a confidentiality agreement. Indeed, several drug companies, such as GlaxoSmithKline, are voluntarily making some of their clinical trial datasets available to outside researchers.

A further objection is that creating a second version of a clinical trial dataset would be expensive and time-consuming, but with the appropriate lead time on a new rule—plus the improved workflow software that exists today—researchers should be able to prepare datasets as a clinical trial progresses. This would be a small price to pay for having more accurate information about the drugs the government purchases and Americans ingest.

#### **10. Strengthen enforcement requirements.**

The FDA and the NIH should be given broader enforcement authority and funding so that they can better prevent pharmaceutical companies from ignoring the legal requirements to submit trials within a year. For example, the FDA and NIH could be required to file annual reports describing how often trial sponsors comply with pre-registration requirements, along with a list of imposed fines or withheld grant funds.

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<sup>14</sup> See Peter C Gøtzsche, “Why we need easy access to all data from all clinical trials and how to accomplish it,” *Trials* 12 no. 249 (2011), at <http://www.trialsjournal.com/content/12/1/249>.

<sup>15</sup> Institute of Medicine, *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* (Jan. 14, 2015), at <http://www.iom.edu/Reports/2015/Sharing-Clinical-Trial-Data.aspx>.

<sup>16</sup> The work of the Clinical Data Interchange Standards Consortium would likely be the starting point for such a system.

<sup>17</sup> For a good discussion of the risks, see Mello et al., “Preparing for Responsible Sharing of Clinical Trial Data,” *New England Journal of Medicine* 369 (2013): 1651-1658, at <http://www.nejm.org/doi/full/10.1056/NEJMhle1309073>.

In addition to the fact that many trial sponsors fail to publish their complete findings, a recent investigation revealed that the FDA regularly fails to inform the public or academic journals about significant fraud, misstatements, or data irregularities that occur in clinical trials.<sup>18</sup> The FDA should rectify this oversight and put in place procedures that would ensure the public record is corrected whenever an investigation reveals any significant impropriety in the conduct or analysis of a clinical trial.

#### **11. Require the FDA to Make Decisions Based on Rigorous Evidence.**

Some have argued that the FDA should be empowered to make decisions based on evidence such as observational studies, case histories, patient registries, and the like. Such a policy would be a mistake. Even randomized controlled trials, which are the most rigorous form of evidence, can be compromised by distorted analyses and the selective publication of results. So, the opportunities for misrepresentation and inappropriate statistical analysis would be exponentially higher if companies seeking any form of FDA approval for either drugs or devices were allowed to rely on much less rigorous forms of evidence. Except in narrow cases of effectiveness that is obvious to any observer,<sup>19</sup> the FDA should not make approval decisions without rigorous randomized trials.

### **III. Conclusion**

Increasing transparency in clinical trials is a critical part of ensuring the safety of drugs, interventions, and medical devices, and the government should take action to rectify the current lack of oversight of clinical trial reporting.

For all trials regulated by the FDA or conducted at institutions funded in part by the NIH or other federal agencies, policymakers should: (A) expand registration requirements by requiring researchers to make protocols, statistical code, and Clinical Study Reports publicly available; (B) move quickly towards making patient-level data available to qualified independent researchers; and (C) expand registration requirements to include pre-clinical animal studies, Phase I trials, and international trials.

Not only would strengthening transparency requirements improve the reproducibility and reliability of clinical trials, it would provide doctors with crucial information about how best to protect human life and health. Policymakers, clinicians, and patients alike should mobilize to support clinical trial transparency as a way to prevent needless harm, make our health system more efficient, and improve patients' wellbeing.

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<sup>18</sup> Charles Seife, "Research Misconduct Identified by the US Food and Drug Administration," *JAMA Internal Medicine* (Feb. 9, 2015), at <http://archinte.jamanetwork.com/article.aspx?articleID=2109855>.

<sup>19</sup> Gleevec is an example.