

The Lost Decade: Clinical Trials Data Access After *Seife v HHS*

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Realization of the full value of data from clinical trials requires that the data be accessible to the broader research community, not just to the investigators who conducted and the entities that sponsored the research. Data access facilitates benefits such as validation and reproduction of results and dissemination of knowledge. These benefits make the recent decision in *Seife v HHS*¹ particularly significant. In *Seife*, the US District Court for the Southern District of New York invalidated an HHS Final Rule that exempted certain clinical trials conducted between 2007 and 2017 from reporting requirements established by the Food and Drug Administration Amendments Act of 2007 (FDAAA). This decision has the potential to make clinical trial data from hundreds of trials conducted by industry, academic institutions, and other parties publicly available, and headlines have understandably been upbeat. However, we caution that the decision's significant limitations—coupled with a historic lack of enforcement—temper our optimism.

The Decision

In 2007, Congress—worried that unfavorable clinical trial results were being withheld from the public through selective publication practices—sought to make clinical trial data more accessible.² Thus, the FDAAA includes a requirement that the sponsors (or sponsor-designated principal investigators) of certain clinical trials publish their results on ClinicalTrials.gov, a government website offering information about publicly and privately supported clinical studies.² Whereas the FDAAA requires publication of “Basic Results”—including data about sample demographics and primary and secondary outcomes—the statute gave HHS discretion to determine when “Expanded Results” must be reported.²

In 2016, HHS issued a Final Rule under the FDAAA taking the position that Basic Results reporting would not be required for clinical trials completed after the FDAAA's effective date in 2007 and before the Final Rule's effective date in 2017 if the product evaluated in the trial was not approved or cleared by the FDA at the time of the trial's completion.² Because products are typically

TAKEAWAY POINTS

- ▶ Realization of the full value of data from clinical trials requires that the data be accessible to the broader research community, not just to the investigators who conducted and the entities that sponsored the research.
- ▶ The *Seife v HHS* decision has the potential to make clinical trial data from hundreds of trials conducted by industry, academic institutions, and other parties publicly available, and headlines have understandably been upbeat.
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studied *before* they receive marketing authorization, this created a significant exemption from the FDAAA's reporting requirements.

In December 2018, a complaint was filed against HHS, the FDA, and the National Institutes of Health alleging that the Final Rule was contrary to the intent of the FDAAA and impermissibly narrowed the scope of studies for which Basic Results must be reported.¹ The plaintiffs sought to invalidate the exemption from Basic Results reporting requirements and to force HHS to start taking enforcement action against parties not in compliance with their reporting obligations.

In late February 2020, a federal judge held that the government agencies had in fact misinterpreted the FDAAA and set aside HHS' Final Rule interpretation.¹ The court concluded that the Final Rule was inconsistent with the FDAAA on 2 grounds.¹ First, under the plain language of the FDAAA, HHS had no discretion as to whether to require the publication of Basic Results.¹ Second, the FDAAA required publication of trial results for a product that “is approved,” meaning that the product is *presently* approved.¹ Thus, even if the product was not approved at the time of the trial's completion but was approved at the time that HHS finalized its rule, the FDAAA required results reporting. The court noted that the purpose of the FDAAA was to force researchers to disclose product information regardless of whether it was “positive” or “negative” and that not requiring publication of trial results from before the 2017 rule would frustrate this purpose.¹

Implications

A recent study found that 36% of trials subject to the FDAAA—a total of 1523 trials of medicines and medical devices—were missing results, and 23% had posted their results late.³ Only 41% of trials reported results on ClinicalTrials.gov within 1 year.³

Examples of noncompliant clinical trials abound. For instance, the results of the randomized phase 3 trial that prompted the FDA to approve tipiracil hydrochloride (TAS-102) for patients with refractory metastatic colorectal cancer were not posted within the 1-year allotted time frame (ClinicalTrials.gov identifier: NCT01607957).¹ Similarly, results information for a randomized study in pediatric patients with acute myelogenous leukemia of later FDA-approved decitabine (Dacogen) should have been submitted within a year of the trial's primary completion date, but no results information appears in ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01177540).¹ Another example is a study that evaluated treatment in patients with metastatic renal cell carcinoma with bevacizumab and the investigational drug CRLX101, to which FDA granted fast-track designation later, compared with treatment with a standard-of-care therapy (ClinicalTrials.gov identifier: NCT02187302).¹

Oncology is the most dominant therapy area for both industry- and non-industry-sponsored clinical trials.⁴ The other largest therapy areas for trials are cardiovascular, infectious disease, and metabolic disorders.⁴

The practical effect of the ruling is to deem sponsors uncompliant with federal law if they have not posted results to ClinicalTrials.gov. In theory, the stakes for sponsors are high. The FDAAA directs HHS to issue notices of noncompliance to parties not in compliance with their reporting obligations and to post public notices of noncompliance on ClinicalTrials.gov; further, it allows imposition of steep monetary penalties and withholding of research funds. However, consistent with longstanding legal doctrine, the court held that government's decisions not to enforce are generally unreviewable. Yet, without enforcement, the first part of the decision may have little practical effect.

HHS has not yet announced whether it will appeal the *Seife* decision. If the government allows the decision to take effect without appealing or if it is upheld on appeal, it remains to be seen whether the agencies will compel the publication of a decade's worth of clinical trials data. Prior studies have shown that compliance with FDAAA reporting requirements is poor, largely due a lack of enforcement by regulators.^{3,5}

Some sponsors put out of compliance with the *Seife* decision may voluntarily publish their results on ClinicalTrials.gov. Even in the absence of enforcement, "naming and shaming" has proven effective at increasing compliance with the FDAAA.⁶ Regrettably, voluntary compliance may be *Seife's* greatest legacy. Given competing priorities at HHS, a historical lack of enforcement, and the courts' inability to review enforcement decisions, there is reason to be skeptical that HHS will take affirmative steps to require publishing of results from the lost decade.

The FDAAA laid the groundwork for greater transparency, but that potential has gone largely unrealized to date. There are significant ethical consequences to the ongoing lack of access to clinical trial data. Transparency increases the value of research participants' contributions. Research participants "volunteer their time, their effort and the[ir] bodies" for the good of science and society, and making the results widely available helps justify the risks and burdens that they assume.⁷ Data access can also spur innovation, as researchers learn and build on each other's work, avoiding duplication and the concomitant waste of resources.⁸ Increased data availability can facilitate protection of participants by illuminating risks and promoting informed consent. It may also foster trust among taxpayers who fund research. With *Seife*, regulators have a new opportunity to reset sponsors' expectations and to improve compliance with clinical trial results reporting. This is an opportunity they should seize.

Conclusions

The *Seife* plaintiffs were ethically and legally in the right to call for the publication of clinical trial data from 2007 to 2017. *Seife* is, at the very least, a symbolically important decision—especially for oncology, which leads the clinical trial landscape—but its practical impact will be dampened if the government does not take steps to enforce it. ■

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