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Client Alert

U.S. District Court Overturns HHS Interpretation of Final Rule that Permitted Sponsors of Certain Drug and Device Trials to Avoid Disclosure of Results on ClinicalTrials.gov

If Sustained, Court Decision Will Require Disclosure of Results for a Decade of Certain Clinical Trials

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Section 801 of the Food and Drug Administration Amendments Act of 2007 ("Section 801")[1], which is codified at 42 U.S.C. § 282(j) and took effect September 27, 2007, requires that sponsors of applicable clinical trials ("ACTs") register the trials and submit the basic results specified in the statute to the ClinicalTrials.gov data bank. The Department of Health and Human Services ("HHS") must publicly post this information in the data bank. As directed by the statute (although several years past the deadline), HHS promulgated a final rule on September 21, 2016—the Clinical Trials Registration and Results Information Submission rule ("Rule")[2], 42 C.F.R. Part 11—that took effect on January 18, 2017 and expanded the disclosure requirements. In the rule's preamble, HHS stated that it would not read its rule as imposing a retroactive obligation on sponsors to disclose publicly the basic results of ACTs for trials of products that were approved, licensed or cleared after the trials' completion date but before January 18, 2017, which HHS has referred to as "pre-Rule, pre-approval ACTs".

Certain parties challenged HHS's interpretation of Section 801 and its final rule. *See Seife et al. v U.S. Department of Health and Human Services et al.*[3] On February 24, 2020, Judge Naomi Reice Buchwald of the U.S. District Court for the Southern District of New York granted summary judgment[4] in the plaintiffs' favor. The court held that in the preamble of the Rule, HHS improperly exempted pre-rule, pre-approval ACTs from the statute's public disclosure requirements for basic results. The court concluded that Section 801 "unambiguously" requires that basic results of these clinical trials be publicly disclosed on ClinicalTrials.gov. It concluded:

> "The Court sets aside HHS's interpretation of the Final Rule as contrary to the unambiguous terms of the FDAAA, and enjoins defendants to comply with those terms, which require responsible parties to submit, and ClinicalTrials.gov to include, Basic Results for pre-Rule, pre-approval ACTs."

The case was filed[5] on December 7, 2018 by the Yale Media and Freedom Information Access and the NYU Technology Law and Policy Clinic, with support of the Yale Collaboration for Research Integrity, on behalf of plaintiffs[6] Charles Seife, an investigative journalist, and Dr. Peter Lurie, a former associate FDA commissioner and the current president of the Center for Science in the Public Interest. The defendants were the U.S. Department of Health and Human Services and its Secretary; the National Institutes of Health ("NIH") and its Director; and the U.S. Food and Drug Administration and its Commissioner ("FDA").

HHS has not yet announced whether it will appeal the district court's finding. If the district court's decision is not overturned, drug and device companies and other organizations that sponsor ACTs will have to determine if they complied with the statute and submitted basic results to ClinicalTrials.gov for trials that were completed on or after September 27, 2007 and before January 18, 2017 *and* studied a product that FDA approved, licensed, or cleared at any time after the ACT completion date. If basic results of these trials were not previously submitted, the basic results must be submitted by sponsors for public disclosure and posting by HHS on ClinicalTrials.gov.

BACKGROUND

Section 801 of FDAAA and the Final Rule

Congress enacted Section 801 because of its intent[7] to "increase the availability of information to the public" and to "communicate the risks and benefits of drugs" for the purpose of "help[ing] patients, providers, and researchers learn new information and make more informed healthcare decisions." Section 801 established new statutory requirements for public disclosure of information about certain clinical trials of drugs and medical devices subject to FDA regulation. These trials are defined in the statute as applicable clinical trials[8]. In accord with the statute, responsible parties[9] have been required to submit registration information for ClinicalTrials.gov since December 26, 2007, basic results[10] since September 27, 2008, and adverse events as an additional component of basic results since September 27, 2009 for all trials that are applicable clinical trials as of September 27, 2007, the statute's effective date.

- **Basic results** – Basic results include (1) demographic and baseline characteristics of the patient sample, including the number of patients who participated, dropped out, and were excluded from the analysis; (2) the primary and secondary outcomes of the study, including a table of values for each of the outcome measures for each arm of the trial and the results of statistical significance; (3) the point of contact for scientific information about the clinical trial results; and (4) whether there exists an agreement that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the trial results in any public or private forum or to publish the results in a scientific or academic journal. Thus, basic results include the core outcomes on which a trial succeeds or fails as well as whether or not the findings met prespecified statistical significance to show that the results were not the play-of-chance.
- **Completion date** – The term "completion date"[11] (also named in the statute as the primary completion date) refers to the "date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the prespecified protocol or was terminated." The completion date is important because, under the terms of the statute, it sets the clock for the date on which basic results and other information must be submitted. In general, basic results

must be submitted not later than one year after the earlier of the estimated or actual completion date of the trial, although the statute provides for some exceptions.

- **Expansion of the registry and results data bank** – Section 801 directed HHS to expand the registry and results data bank not later than three years after the statute's enactment. Notwithstanding Congress's instructions, however, HHS did not issue a final rule until September 21, 2016, and the rule did not take effect until January 18, 2017. HHS's final rule clarified existing statutory requirements and provided for the expanded registry and results data bank required by the statute. The new requirements included the disclosure of results for applicable clinical trials for products that are not approved, licensed, or cleared by FDA for any use as well as a major expansion of trial results and adverse events that must be disclosed. The additional requirements for disclosure of trial results—what are referred to as the expanded results—are not the subject of the court's ruling.

The Final Rule's Preamble: HHS's Interpretation of Marketing Status

A central issue for the court in *Seife* was the statutory definition of the product's marketing status and how HHS interpreted this in the rule's preamble[12]. The statute requires that basic results be submitted for all applicable clinical trials that study a drug or device "that is approved, licensed, or cleared by FDA." The final rule expanded this requirement to include ACTs that study a drug or device "that is not approved, licensed, or cleared by FDA." As explained in the court's decision, HHS interpreted the term "is approved, licensed, or cleared" to refer to whether the product was approved, licensed, or cleared on the date on which the ACT was completed. In HHS's view, which the court found to be contrary to the statute, basic results would not need to be submitted for ACTs that were completed before January 18, 2017 and that studied a product approved, licensed, or cleared after the study completion date.

The preamble states:

> "[f]or purposes of this final rule, the marketing status of a product will be determined based on its marketing status on the primary completion date [of the ACT]. Thus, if a drug product . . . or a device product is approved, licensed, or cleared for any use as of the primary completion date, we will consider that applicable clinical trial to be a trial of an approved, licensed, or cleared product. Similarly, if a drug product . . . or a device product is unapproved, unlicensed, or uncleared for any use as of the primary completion date, regardless of whether it is later approved, licensed, or cleared, we will consider that applicable clinical trial to be a trial of an unapproved, unlicensed, or uncleared product."

The court explained the implication of HHS's interpretation:

> "Thus, under HHS's interpretation, Basic Results for pre-Rule, pre-approval ACTs need not be disclosed regardless of whether those results indicate that an FDA-approved product that is used by possibly thousands of Americans is unsafe or ineffective."

THE DECISIONS OF THE COURT

Defendants' Motion for Dismissal: Standards of Review and Standing

The defendants moved to dismiss the plaintiffs' complaints, or in the alternative, for summary judgment. The plaintiffs filed a cross-motion for summary judgment. The defendants moved for lack of subject-matter jurisdiction by the district court under Federal Rule of Civil Procedure 12(b)(1), arguing that the plaintiffs lacked standing under Article III of the U.S. Constitution. The court concluded that plaintiffs suffered a concrete, particularized injury sufficient to establish standing under Article III because they were denied access to information that, in the court's view, HHS had an obligation to disclose and plaintiffs had a right to obtain. The court's decision reflects an aggressive application of the doctrine of

"informational standing" and will likely be challenged by the government on appeal. Although Congress undoubtedly intended to make information available to the public, it is not at all clear that plaintiffs' inability to access this information gives rise to an injury sufficient to confer Article III standing.

The Plaintiffs' First Cause of Action

The court addressed two causes of action that were asserted by the plaintiffs in their Complaint. (A third cause of action was voluntarily withdrawn by the plaintiffs.)

The plaintiffs' first cause of action contended that HHS's interpretation in the preamble of the final rule is contrary to the unambiguous terms of Section 801. As described above, this cause of action is specific to HHS's interpretation in the preamble that responsible parties are not required to submit basic results to ClinicalTrials.gov if the trial's completion date occurred before the effective date of the final rule and the product studied in the trial was not approved, licensed, or cleared for use at the time of the completion date.

- **Statutory requirement for disclosure of basic results** – The court agreed with the plaintiffs' assertion that the key provision in the statute is 42 U.S.C. § 282(j)(3)(C), which defines the obligations of HHS regarding basic results:

  > "Not later than 1 year after September 27, 2007, the Secretary [of HHS] shall include in the registry and results data bank for each applicable clinical trial for a drug that is approved under section 355 of Title 21 or licensed under section 262 of this title or a device that is cleared under section 360(k) of Title 21 or approved under section 360e or 360j(m) of Title 21, the following elements [of Basic Results] . . . ."

  The court also observed that an additional statutory provision, § 282(j)(3)(E)(iv), specifically addresses the situation where an ACT studied a product that was approved [licensed, or cleared] after, rather than before, the ACT's estimated or actual completion date. This provision also specifies the timing whereby the responsible party must submit basic results when the product that is studied is approved, licensed, or cleared. The court disagreed with the defendants' position that § 282(j)(3)(E)(iv) merely prescribes a deadline for submission of basic results that is applicable only if HHS exercises its discretion to require the submission of basic results for pre-approval ACTs by rulemaking. The court determined that this statutory provision did not afford HHS that discretion and that the statute explicitly imposes the obligation for responsible parties to submit basic results for pre-approval ACTs when the product is approved, licensed, or cleared by FDA, as well as the obligation for HHS to post these results on ClinicalTrials.gov.

- **Retroactive application of the statute** – The Court disagreed with the defendants' separate argument that the court should not determine that Section 801 requires responsible parties to submit basic results for pre-rule, pre-approval ACTs because the statute should not be construed to apply retroactively. The court determined that the obligation to submit basic results for pre-rule, pre-approval ACTs is not retroactive because "responsible parties knew since the FDAAA's enactment in 2007 that the statute required them to submit Basic Results for each ACT of a product that is approved [licensed or cleared]."

- **Court's interpretation coheres with Congress's purpose** – The court observed that its opinion is consistent with Congress's purpose in enacting Section 801. It concluded that Congress was concerned that negative trial results may not be released by sponsors and that the public therefore could not assess the safety and efficacy of drugs and devices. The court stated, "Plainly, requiring ClinicalTrials.gov to include Basic Results for pre-Rule, pre-approval ACTs ameliorates that concern and furthers those broader goals. Doing the opposite, by contrast, would exempt the responsible parties for every pre-approval ACT completed soon after September 27,

2007 and [before] January 18, 2017 from disclosing negative results regardless of whether thousands of Americans use the product, which would be utterly contrary to the FDAAA's aims."

The court reached this final judgment:

> "The Court accordingly finds that the FDAAA unambiguously requires responsible parties to submit, and defendants to include on ClinicalTrials.gov, Basic Results for pre-Rule, pre-approval ACTs."

The Plaintiffs' Second Cause of Action

The plaintiffs' second cause of action asserted that NIH's failure, to date, to post notices of noncompliance pursuant to the statute's NIH notice provision, §282(j)(5)(E)(i), and to create a search function for such notices on ClinicalTrials.gov pursuant to the notice search provision, § 282(j)(5)(E)(vi), was unlawfully withheld or unreasonably delayed. The court granted the defendants' motion for summary judgment and dismissal of this claim.

What's Next

Under the rules of appellate procedure, the defendants have 60 days to file an appeal with the U.S. Court of Appeals for the Second Circuit. If they file an appeal, the case will be briefed and argued through 2020, and likely decided in 2021. Interested parties may be able to participate in the appeal, either by seeking leave to intervene or by filing an amicus brief in support of either side.

- **Implications of an appeal** – The district court's decision puts companies and other organizations that are responsible parties of ACTs and that have not submitted basic results in a difficult position and, until any appeal is resolved, it is unclear what the likely impact of the decision will be. Significantly, the district court's decision does not strike down HHS's final rule or conclude that the final rule is invalid. Instead, the district court's decision purports to declare unlawful HHS's interpretation of the rule as set forth in the rule's preamble and imposes an injunction that requires defendants to comply with the court's interpretation of what the statute and the final rule require. If the defendants pursue an appeal, it is unlikely that the government will take any enforcement action against responsible parties of ACTs until all appeals are resolved. If the government decides not to appeal or if the district court is affirmed on appeal, however, there is a risk that responsible parties could face statutory penalties for not having previously submitted basic results for "pre-rule, pre-approval ACTs." The defendants' interpretive position appears to be driven by fair-notice concerns and a recognition that there has been general confusion over what information about trial results must be publicly disclosed, including because of the long delay that occurred between the statute's enactment and the effective date of the defendants' final rule. If the defendants lose on appeal and an appellate court concludes that the statute has always been unambiguous, responsible parties will be put in the potentially challenging position of having to argue that despite the statute's plain language, they were entitled to rely on the defendants' interpretation in failing to disclose basic results.
- **Potential penalties** – Section 801 penalizes actions or omissions including the failure to submit required clinical trial registration or results information; submission of false or misleading information to ClinicalTrials.gov; the failure to submit certifications of conformance to FDA in association with certain applications and submissions to the agency; or knowingly submitting a false certification to FDA. The statute provides for civil money penalties, notices on ClinicalTrials.gov of noncompliance, and potentially other penalties under the Federal Food, Drug and Cosmetic Act or laws punishing false statements to the government. In September 2018, FDA published a draft guidance[13] describing the agency's plan to review compliance during Bioresearch

Monitoring Program (BIMO) inspections and pursuant to specific complaints received by the agency. FDA generally intends to follow a procedure that includes notification of noncompliance to the responsible party of the ACT and opportunity for voluntary compliance prior to enforcement. There has not been significant public regulatory enforcement to date, but the court scrutiny in Seife and several other published analyses, which have criticized both lack of consistent compliance and lack of agency enforcement, could reasonably lead to increased enforcement pressure.

Because of the complexities of the district court's ruling, companies should take care in making decisions about how to proceed. At this time, it is unclear whether the government will appeal and to what extent it might exercise enforcement discretion for companies and other organizations that did not submit basic results for pre-rule, pre-approval ACTs.

If you have questions regarding the court's decision or would like guidance on the federal requirements for submission of clinical trial information to ClinicalTrials.gov, please contact Christina Markus, Ashley Parrish, Beverly Lorell, Elaine Tseng, or Jeffrey Bucholtz for more information.

[1] Section 801 of the Food and Drug Administration Amendments Act of 2007 was codified in section 402(j) of the Public Health Service Act (42 U.S.C. § 282(j)), and includes conforming amendments to the Federal Food, Drug, and Cosmetic Act (FDCA). Accessed at https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82.

[2] 81 FR 64982 (Sept. 21, 2016). Accessed at https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission.

[3] Seife & Lurie v. U.S. Department of Health and Human Services et al., No. 1:18-cv-11462, 2020 WL 883478 (S.D.N.Y. Feb. 24, 2020).

[4] Memorandum and Order. Seife v. U.S. Dep't of Health & Human Servs., 2020 BL 66856, S.D.N.Y., No. 18-cv-11462, 2/24/20. Accessed at https://cspinet.org/sites/default/files/Seife_and_Lurie_v_HHS_Order_on_SJ.pdf.

[5] Complaint. Case 1:18-cv-11462. Filed 12/07/18. Accessed at https://cspinet.org/sites/default/files/Seife_and_Lurie_v_HHS_Complaint.pdf.

[6] Article. "Transparency Advocates Win Victory for Public Access to Clinical Trial Data." Center for Science in the Public Interest. February 25, 2020. Accessed at https://cspinet.org/news/transparency-advocates-win-victory-public-access-clinical-trial-data-20200225.

[7] H. Rep. 110-225. Accessed at https://www.congress.gov/congressional-report/110th-congress/house-report/225/1.

[8] "Applicable clinical trial" is defined at 42 U.S.C. § 282(j)(1)(A)(i)-(iii).

[9] "Responsible party" is defined at 42 U.S.C. § 282(j)(1)(A)(ix).

[10] "Basic results" is defined at 42 U.S.C. § 282(j)(3)(C).

[11] "Completion date" is defined at 42 U.S.C. § 282(j)(1)(A)(v).

[12] See 81 Fed. Reg. 64982, 65067-65068 (Sept 21, 2016).

[13] "Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank. Draft Guidance for FDA Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to FDA." September 2018. Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/civil-money-penalties-relating-clinicaltrialsgov-data-bank.