

**21st Century Cures Act, Section 2052
Third Report on Clinical Trials**

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Abbreviations and Acronyms

ACT	Applicable Clinical Trial
API	Application Programming Interface
BESH	Basic Experimental Studies with Humans
BIMO	Bioresearch Monitoring
BTRIS	Biomedical Translational Research Information System
CBER	[FDA] Center for Biologics Evaluation and Research
CDER	[FDA] Center for Drug Evaluation and Research
CDRH	[FDA] Center for Devices and Radiological Health
CTRP	Clinical Trials Reporting Program
DIA	Drug Information Association
eRA	Electronic Research Administration
FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDAMA	Food and Drug Administration Modernization Act of 1997
FD&C Act	Federal Food, Drug, and Cosmetic Act
HHS	U.S. Department of Health and Human Services
ICOs	Institutes, Centers and Offices
IRP	Intramural Research Program
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NLM	National Library of Medicine
NNLM	Network of the National Library of Medicine
OER	Office of Extramural Research
OIR	Office of Intramural Research
PHS	Public Health Service [Act]
PRS	Protocol Registration and Results
RPPR	Research Performance Progress Report
SMART	Sequential, Multiple Assignment, Randomized Trial

I. Introduction

The U.S. Department of Health and Human Services (HHS) takes seriously its stewardship of the clinical trial enterprise. As part of these stewardship efforts, HHS has issued regulations on the registration of and summary results information submission for certain clinical trials to the ClinicalTrials.gov data bank, which is a web-based resource that provides the public with easy access to information on certain publicly and privately supported clinical studies on a wide range of diseases and conditions.¹ The public availability of this information is intended to inspire clinical trial innovation by reducing unnecessary duplication of studies; strengthening scientific rigor; and promoting efficiency, accountability, and transparency in research, as well as to enhance participant enrollment.

HHS has initiated a suite of activities to educate responsible parties and encourage compliance with the registration and summary results information submission requirements under section 402(j) of the Public Health Service (PHS) Act (42 U.S.C. § 282(j)),² including its implementing regulations (42 CFR Part 11).³ The Congressional mandate in section 2052 of the 21st Century Cures Act (P.L. 114-255) (Cures Act) requires the Secretary of HHS to submit two types of reports: 1) the Report on Activities to Encourage Compliance, which was submitted to and received by Senate and House committees prior to the due date of December 13, 2018, and 2) the Reports on Clinical Trials,⁴ for which this is the last of three biennial reports. The Cures Act requires the Reports on Clinical Trials to describe activities undertaken by HHS to educate responsible parties about ClinicalTrials.gov registration and summary results information submission requirements, as well as to provide data associated with clinical trial registration and summary results information submission. HHS welcomes the opportunity to outline its efforts to encourage compliance with section 402(j) of the PHS Act, including its implementing regulations. In addition, the U.S. National Institutes of Health (NIH) has implemented a broad set of reforms for NIH-funded research to improve many aspects of clinical trial stewardship throughout the life span of a clinical trial.⁵

This third and final Report on Clinical Trials includes information on activities conducted by NIH and the U.S. Food and Drug Administration (FDA) between October 1, 2020, and September 30, 2022, to encourage compliance by responsible parties with section 402(j) of the PHS Act, including its implementing regulations, and activities undertaken to educate responsible parties about the ClinicalTrials.gov data bank registration and summary results information submission requirements. This report also includes the total number of applicable clinical trials (ACTs) with complete data bank registration information registered on ClinicalTrials.gov between January 18, 2017, and September 30, 2022; and the total number of

¹ <https://clinicaltrials.gov/>

² <https://www.gpo.gov/fd/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapIII-partA-sec282.pdf>

³ <https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission>

⁴ <https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf>

⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5101947/>

ACTs registered for which summary results information was submitted to the data bank between January 18, 2017 and September 30, 2022.⁶

II. Background

The Food and Drug Administration Modernization Act of 1997 (FDAMA), (P.L. 105-115), required HHS, through NIH, to establish a registry of clinical trial information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases and conditions.⁷ The registry, ClinicalTrials.gov, was developed and made available to the public in February 2000.

The ClinicalTrials.gov registration requirements were expanded after Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA), P.L. 110-85, which was enacted on September 27, 2007, amending the PHS Act by including expanded clinical trial registry data bank provisions in section 402(j).⁸ Title VIII of FDAAA requires more types of trials to be registered and additional trial registration information to be submitted to ClinicalTrials.gov.⁹ FDAAA also requires the submission of summary results information for certain trials, which led to the development of the ClinicalTrials.gov results data bank that contains summary information on study participants and study outcomes, including adverse events.¹⁰ NIH made the results data bank available to the public, as required by FDAAA, in September 2008. HHS issued regulations, the “Final Rule for Clinical Trials Registration and Results Information Submission”¹¹ (or Final Rule) (42 CFR Part 11) in September 2016. The Final Rule clarifies and expands the requirements of Title VIII of FDAAA for registering and submitting summary results information for ACTs. The Final Rule took effect on January 18, 2017, and responsible parties were expected to be in compliance with the regulations as of April 18, 2017.

FDAAA also amends the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. § 331) to include specific prohibited acts for failing to submit required registration or summary results information to the ClinicalTrials.gov data bank, submitting false or misleading information to the ClinicalTrials.gov data bank, and failing to submit the certification to FDA required under section 402(j)(5)(B) of the PHS Act (42 U.S.C. § 282(j)(5)(B))¹² or knowingly submitting a false

⁶ The ACT numbers presented in this report are estimates based on a programmatic evaluation of the clinical trial data submitted to ClinicalTrials.gov by responsible parties. This programmatic evaluation did not include a detailed assessment of individual ClinicalTrials.gov study records to verify a trial’s ACT status. As such, the actual number of ACTs may be different.

⁷ <https://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf>

⁸ <https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>

⁹ <https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82>

¹⁰ <https://clinicaltrials.gov/ct2/about-site/results>

¹¹ <https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016-22129.pdf>

¹² For information on this requirement, see FDA’s Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff, Form FDA 3674 – Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions, available at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm>.

certification. In FDA's final guidance entitled Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank¹³ issued in August 2020, FDA stated that when it believes that the responsible party for an ACT may have failed to comply with 42 U.S.C. § 282(j), including its implementing regulations found in 42 CFR Part 11, FDA generally intends to send a Preliminary Notice of Noncompliance (Pre-Notice) Letter, which describes the potential violation and requests that the recipient review the record in the ClinicalTrials.gov data bank and make any necessary corrections within 30 days after receiving the letter. As stated in the final guidance, Pre-Notice Letters notify the recipient that after the 30-day period has elapsed, FDA intends to conduct a further review and assessment of the information submitted to the ClinicalTrials.gov data bank and other information available to FDA. The final guidance further states that if FDA determines that there was a failure to comply with FDAAA's requirements, FDA will issue a Notice of Noncompliance (see section III.3.4) pursuant to 42 U.S.C. § 282(j)(5)(C)(ii) to a responsible party who failed to submit required information or submitted false or misleading information to the ClinicalTrials.gov data bank, and FDA will provide the recipient with an opportunity to correct the identified violation. Per the final guidance, failure to comply with the requirements relating to ACTs may result in an FDA enforcement action, including civil money penalties, injunction, and/or criminal prosecution.

Section 2052 of the Cures Act, enacted December 13, 2016, requires the Secretary of HHS, acting through the Director of NIH and in collaboration with the Commissioner of Food and Drugs, to submit two types of reports to the Senate Committee on Health, Education, Labor, and Pensions (HELP) and the House Committee on Energy and Commerce:

- (1) Report on Activities to Encourage Compliance: describes education and outreach, guidance, enforcement, and other activities undertaken to encourage compliance with section 402(j) of the PHS Act. This report included data from September 27, 2007, through April 18, 2017, and was submitted to and received by the Senate and House committees before the due date of December 13, 2018.
- (2) Reports on Clinical Trials describe:
 - a. the total number of ACTs with complete ClinicalTrials.gov registration information registered during the period for which the report is being prepared;
 - b. the total number of ACTs registered during the reporting period for which results have been submitted to the data bank;
 - c. activities undertaken by the Secretary to educate responsible parties about ClinicalTrials.gov registration and results submission requirements, including issuance of guidance documents, informational meetings, and training sessions; and
 - d. activities described in the Report on Activities to Encourage Compliance (i.e., education and outreach, guidance, enforcement, and other activities) undertaken to encourage compliance with section 402(j) of the PHS Act.¹⁴

¹³ <https://www.fda.gov/media/113361/download>

¹⁴ <https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf>

In the Reports on Clinical Trials, registration and summary results information submission data will be broken down by the fiscal year (FY) in which the ACT was registered and in which summary results information has been submitted. A total of three Reports on Clinical Trials are required to be submitted: the first report was submitted to and received by the Senate and House committees by April 18, 2019; the second report was submitted to and received by the Senate and House committees by April 18, 2021; and this last report is due by April 18, 2023.

III. Activities Conducted to Educate Responsible Parties and Encourage Compliance: October 1, 2020–September 30, 2022

Throughout this report, “activities conducted to educate responsible parties and encourage compliance” refers to the activities undertaken to educate responsible parties about ClinicalTrials.gov registration and summary results information submission requirements, as well as the activities to encourage compliance with section 402(j) of the PHS Act and its implementing regulations, as required by section 2052 of the Cures Act and as described in section II of this report. These activities include presentations delivered at conferences, participation in workshops and webinars, development and dissemination of educational outreach materials, and other routine activities.

NIH and FDA were able to extensively educate responsible parties and encourage compliance during the reporting period despite the need to alter many planned or intended activities between 2020 and 2022 because of the COVID-19 public health emergency. Because non-mission critical federal employee travel was not permitted and many professional meetings were postponed or canceled, presentations were rescheduled or, when possible, conducted virtually rather than in person. In some cases, activities were combined (e.g., conducting a single webinar for two groups rather than delivering the two previously planned presentations).

III.1 Presentations at Conferences

NIH and FDA staff delivered presentations at more than 40 different conferences between October 1, 2020, and September 30, 2022, to educate responsible parties and encourage compliance with section 402(j) of the PHS Act and its implementing regulations. These presentations provided a wide array of information, including, but not limited to, discussion of the responsibilities of the responsible party related to compliance with the regulatory requirements for clinical trial registration and summary results information submission, COVID-19-related resources and information, and descriptions of the ClinicalTrials.gov modernization effort to improve the user experience for clinical trial registration and summary results information submission. Conference attendees included responsible parties as defined by section 402(j) of the PHS Act, clinical research professionals, institutional review board members and administrators, clinical research coordinators, systematic reviewers and meta-researchers, journal

editors, librarians, policy makers, leaders at academic medical centers, behavioral and biomedical researchers, clinicians, and ethicists, among others. Organizations including HHS agencies, research and educational institutions, professional associations and societies, among others, hosted these conferences. The list of presentations delivered includes, but is not limited to:

- Nine (9) presentations at conferences and symposia hosted by the Society of Clinical Research Associates¹⁵
- Five (5) presentations at conferences hosted by NIH and FDA for a wide range of collaborators, both internal and external to the agencies
- Five (5) presentations at conferences hosted by the National Council for University Research Administrators¹⁶
- Four (4) presentations at conferences hosted by the Society of Quality Assurance¹⁷
- Three (3) presentations at conferences hosted by the Society of Research Administrators International¹⁸
- One (1) presentation at a conference hosted by the Federal Demonstration Partnership¹⁹

III.2 Workshops and Webinars

In addition to delivering presentations at conferences, NIH and FDA staff presented at more than 16 workshops and webinars to educate responsible parties and to encourage compliance with section 402(j) of the PHS Act, including its implementing regulations. While the majority of these were hosted by NIH, one was hosted by the Drug Information Association (DIA).²⁰ The audiences for these workshops and webinars included responsible parties as defined by section 402(j) of the PHS Act, clinical research professionals, protocol navigators, the basic research community, institutional administrators, scientists, regulatory affairs professionals, and others. Information shared through these workshops and webinars typically included ClinicalTrials.gov registration and results information submission requirements as outlined in section 402(j) of the PHS Act and its implementing regulations, and an overview of ClinicalTrials.gov enhancements to improve the quality of summary results information submissions.

Among the webinars hosted by NIH, the National Library of Medicine (NLM) hosted an NIH-Funded Basic Experimental Studies with Humans (BESH): Registration and Results Reporting Webinar summarizing findings from NLM's analysis of challenges in registering and reporting results information for BESH on ClinicalTrials.gov and presented issues to consider. In addition, from February 2021 to December 2021, NLM hosted five webinars to provide updates on the ClinicalTrials.gov modernization effort and demonstration of the ClinicalTrials.gov Beta website, which was launched in December 2021. The ClinicalTrials.gov Results Database Train-the-Trainer Workshop,²¹ usually held in person, was held virtually (including both asynchronous

¹⁵ <https://www.socra.org/>

¹⁶ <https://www.ncura.edu/default.aspx>

¹⁷ <https://www.sqa.org/>

¹⁸ <https://www.srainternational.org/home>

¹⁹ <https://thefdp.org/default/>

²⁰ <https://www.diaglobal.org/>

²¹ <https://clinicaltrials.gov/ct2/manage-recs/present#ResultsTrainTrainer>

learning and virtual live sessions) in August 2021 due to the COVID-19 public health emergency. Topics addressed during the workshop included an Overview of the Clinical Trial Disclosure Landscape, a Protocol Registration and Results (PRS) System Overview, NIH Requirements for Clinical Trials Registration and Reporting, PRS Results Module Introductions, and Example Studies for Results Data Entry.

III.3 Educational Outreach Materials

Educational outreach materials were developed and shared via the ClinicalTrials.gov website or through other modes of communication, such as stakeholder websites or publications, to encourage compliance with section 402(j) of the PHS Act and its implementing regulations.

III.3.1 ClinicalTrials.gov Updates

NIH continually evaluates and makes enhancements to ClinicalTrials.gov. These enhancements can include, but are not limited to, providing resources to aid responsible parties with registration and summary results information submission, improving the ClinicalTrials.gov user experience, and disseminating information more effectively. Enhancements made in the last two years included technical developments, updating informational webpages, developing training materials, and contributing to informational resources such as blogs and user newsletters.

Several enhancements to ClinicalTrials.gov search capabilities were made to improve users' ability to find summary results information on the site, including implementation of a new application programming interface (API) to provide a mechanism to develop computer-based queries to help the public access posted information for ClinicalTrials.gov study records.²² The API that was first introduced as a beta model in July 2019 became the operational API in May 2021. The Downloading Content for Analysis webpage has been updated to reflect this change, including links to the current XML schema and crosswalk linking data elements to corresponding API fields. As of January 1, 2022, the previous API is no longer supported.

NIH NLM also made several updates to the Support Materials webpage²³ of the ClinicalTrials.gov public site, including new sections about the NIH Scientific Data Sharing Policies²⁴ and the NIH Office of Extramural Research (OER) Electronic Research Administration (eRA) Research Performance Progress Report (RPPR) Submission Validations for Clinical Trial Registration and Results Reporting.²⁵ The Data Element Definitions, Templates, and Checklists Section on the Support Materials webpage was also updated to include a new checklist entitled, Plain Language Checklist for Lay Brief Summaries.²⁶ The checklist identifies best practices to help investigators write brief summaries in study records that can be easily understood by the general public. Additionally, content about the prioritization of the review of COVID-19-related submissions and information from the NIH Director's November 2020 statement encouraging researchers to expeditiously share COVID-19-related

²² <https://clinicaltrials.gov/api/gui>

²³ <https://clinicaltrials.gov/ct2/manage-recs/resources>

²⁴ <https://clinicaltrials.gov/ct2/manage-recs/resources#NIHScientificDataSharingPolicies>

²⁵ <https://clinicaltrials.gov/ct2/manage-recs/resources#NIHPolicy>

²⁶ https://prsinfo.clinicaltrials.gov/Plain_Language_Checklist_for_Lay_Brief_Summaries.pdf

results were added to the Responses to Top Questions from Responsible Parties Related to Coronavirus (COVID-19)²⁷ in May 2021.

The ClinicalTrials.gov Frequently Asked Questions (FAQs) webpage,²⁸ developed to aid users with registration and summary results information submission requirements and to provide pertinent information to support compliance with section 402(j) of the PHS Act and its implementing regulations, was updated in October 2020, January 2021, January 2022, April 2022, and June 2022. These new and updated FAQs address topics ranging from delayed submission of results information to all-cause mortality tables.^{29,30,31,32,33}

In addition, NIH NLM made updates to the Expanded Access Information and Submission Deadlines³⁴ section of the FAQs webpage as described below:

- Provide further clarity to responsible parties on the Federal court decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020) *Seife*.³⁵
- Clarify that responsible parties may only submit certifications for delayed submission of results information prior to the date of (i.e., the day before) the standard submission deadline for results information. The standard submission deadline for results information is no later than one year after the ACT's primary completion date.
- Clarify that responsible parties may only submit good cause extension requests for delayed submission of results information prior to the date (i.e., the day before) that results information would otherwise be due.

The NIH NLM also updated the ClinicalTrials.gov History, Policies, and Laws webpage³⁶ in October 2020 to further clarify for responsible parties the summary results information submission requirements following the Federal court decision in *Seife*.

The NIH NLM conducted other general educational and outreach material-related efforts, including developing and updating training materials available to assist responsible parties who use PRS³⁷ to submit registration and summary results information to ClinicalTrials.gov. In December 2020, two new study design examples for results data entry were added to the Training Materials webpage: *Micro-Randomized* and *Sequential, Multiple Assignment, Randomized Trial (SMART)*.³⁸ In October 2021, materials from the August 2021 Results

²⁷ <https://prsinfo.clinicaltrials.gov/TopQuestionsFromResponsibleParties-Covid19.pdf>

²⁸ <https://clinicaltrials.gov/ct2/manage-recs/faq>

²⁹ https://clinicaltrials.gov/ct2/manage-recs/faq#fr_42

³⁰ https://clinicaltrials.gov/ct2/manage-recs/faq#fr_43

³¹ https://clinicaltrials.gov/ct2/manage-recs/faq#fr_44

³² https://clinicaltrials.gov/ct2/manage-recs/faq#fr_49

³³ https://clinicaltrials.gov/ct2/manage-recs/faq#fr_48

³⁴ <https://clinicaltrials.gov/ct2/manage-recs/faq#expandedAccess>

³⁵ On February 24, 2020, the *Seife* decision held that FDAAA requires responsible parties to submit to the ClinicalTrials.gov data bank summary results information for ACTs completed before January 18, 2017, if the ACT studies a product that is approved, licensed, or cleared by FDA at any time, including after the ACT's primary completion date.

³⁶ <https://clinicaltrials.gov/ct2/about-site/history#2020Seife>

³⁷ <https://register.clinicaltrials.gov/>

³⁸ <https://clinicaltrials.gov/ct2/manage-recs/present#ResultsExmplStudies>

Database Train-the-Trainer virtual workshop³⁹ were also made available on the Training Materials webpage.

The PRS Guided Tutorials,⁴⁰ available via the Support Materials webpage, were updated in March 2021.⁴¹ These tutorials provide step-by-step instructions to help PRS users enter registration and summary results information and contain new and updated content and features in response to feedback obtained through focus groups and survey responses. Two new sections within the PRS Guided Tutorials include: “Quick Overview Guides” designed to help users get the most from the tutorials, and the “PDF Library” providing all tutorial content in a single place and available for download. Other updates include improving images and re-sizing functionality, adding study examples from materials developed for the behavioral sciences community, and revising the Introduction and tutorial content for added clarity and guidance. Audio narration has been removed as maintenance updates were too resource intensive considering its limited usage. The PRS User’s Guide,⁴² a document that describes how to use the PRS and provides step-by-step instructions for PRS functions, was updated in October 2020 and again in June 2021.

Updates were also made to the How to Register Your Study webpage in June 2022, specifically to the ClinicalTrials.gov Considerations for Observational Studies and Expanded Access Records section.

In October 2021, the definition for *Results First Posted with QC Comments* was made available in the Glossary;⁴³ the terms, *Results First Posted* and *First Posted*, were updated for clarity; and the *Results First Posted with QC Comments* date was added to the Key Record Dates section for every ClinicalTrials.gov study record.

The NIH NLM published blog posts, user newsletter updates, and new documentation to share updates about ClinicalTrials.gov’s modernization efforts more broadly. The first of two posts published in the NLM Director’s blog, *Musings from the Mezzanine*, in February 2021 and described the progress of the ClinicalTrials.gov modernization efforts.⁴⁴ The second blog post, published in December 2021, described the goals and highlights of the Beta PRS and Beta ClinicalTrials.gov releases.⁴⁵ Links to these blog posts were added to the ClinicalTrials.gov Modernization webpage. An *NLM Technical Bulletin* article describing new features of the Beta ClinicalTrials.gov webpage published in December 2021.⁴⁶ In March 2022, a Beta Release Notes webpage was added to detail updates to the ClinicalTrials.gov webpage.⁴⁷ A PRS Beta Release Notes webpage was added in July 2022 to detail updates to the PRS Beta webpage.⁴⁸

³⁹ <https://clinicaltrials.gov/ct2/manage-recs/present#ResultsTrainTrainer>

⁴⁰ <https://prsinfo.clinicaltrials.gov/tutorial/content/index.html#/>

⁴¹ <https://clinicaltrials.gov/ct2/manage-recs/resources#GuidedTuts>

⁴² <https://prsinfo.clinicaltrials.gov/prs-users-guide.html>

⁴³ <https://clinicaltrials.gov/ct2/about-studies/glossary>

⁴⁴ <https://nlmdirector.nlm.nih.gov/2021/02/10/progress-towards-a-modernized-clinicaltrials-gov/>

⁴⁵ <https://nlmdirector.nlm.nih.gov/2021/12/08/clinicaltrials-gov-modernization-effort-beta-releases-now-available/>

⁴⁶ https://www.nlm.nih.gov/pubs/techbull/nd21/nd21_clinical_trials_beta.html

⁴⁷ <https://beta.clinicaltrials.gov/release-notes>

⁴⁸ <https://register.clinicaltrials.gov/prs/beta/public/release-notes>

III.3.2 Additional Information Released

The NIH OER published blog posts, Guide Notices, and made available new website resources, such as videos, to help educate NIH applicants and awardees about compliance activities. Blog topics explored registration and summary results information reporting for BESH, progress towards the modernization of ClinicalTrials.gov, and notifications about the eRA Human Subjects System. In October 2021, enhanced validations on noncompliance with clinical trial registration and summary results information submission requirements⁴⁹ took effect in the eRA Human Subjects System that could delay RPPR submission and/or award if the responsible party is late meeting either requirement. New Guide Notices include the *Continued Extension of Certain Flexibilities for Prospective Basic Experimental Studies With Human Participants*⁵⁰ and *Guidance electronic Research Administration (eRA) Research Performance Progress Report (RPPR) Submission Validations for Clinical Trial Registration and Results Reporting*.⁵¹ New resources include the *NIH Requirements for Clinical Trials Registration and Reporting* training video added in 2021.⁵²

The NIH NLM is leading an effort to modernize ClinicalTrials.gov, in part, to provide more effective educational support and better management of study records. In September 2021, NIH published the “Report on the ClinicalTrials.gov Modernization Effort, Summary of Progress: 2019–21.”⁵³ This report describes NIH’s modernization approach, including strategic goals; discusses users’ challenges and feedback; and shares product development plans and progress.

The NIH Office of Intramural Research (OIR) added required language regarding the registration of a trial on ClinicalTrials.gov to the consent templates on the Consent Templates and Guidance webpage.⁵⁴ In January 2022, NIH OIR issued the new NIH Policy Manual Chapter for the Intramural Research Program (IRP) for reporting results information in ClinicalTrials.gov entitled, *Clinical Trial Registration and Results Information Reporting*.⁵⁵ The new chapter is intended to promote NIH IRP responsible parties’ compliance with the clinical trial registration and summary results information submission requirements.

III.3.3 Journal and Professional Association Publications

An article authored by NIH staff was published in the journal *Contemporary Clinical Trials*, that supports educating responsible parties and encouraging compliance with section 402(j) of the PHS Act and its implementing regulations.⁵⁶ This publication compares reporting of race and ethnicity information in ClinicalTrials.gov prior to and after the date responsible parties were required to submit race and ethnicity information (if collected under the protocol) pursuant to 42 CFR 11.48(a)(2)(iii). Another article authored by NIH staff published in the *British Medical*

⁴⁹ <https://nexus.od.nih.gov/all/2021/11/09/enhanced-checks-for-compliance-with-clinical-trial-registration-and-reporting-in-rppr/>

⁵⁰ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-088.html>

⁵¹ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-008.html>

⁵² https://www.nlm.nih.gov/oet/ed/ct/2021_prs_tt/pre-work_registration/registration-and-reporting.html

⁵³ https://www.nlm.nih.gov/od/bor/clinicaltrialswg/NLM_BOR_CTG_WG_Modernization_Update_Report.pdf

⁵⁴ <https://irbo.nih.gov/confluence/display/ohsrp/Consent+Templates+and+Guidance>

⁵⁵ <https://policymanual.nih.gov/3007>

⁵⁶ Fa in KM, Nelson J, Tse T, Williams RJ. Race and ethnicity reporting for clinical trials in ClinicalTrials.gov and publications. *Contemp Clin Trials*. 2020 Dec 5;101:106237. (PMID 33290865)

Journal discusses issues to consider when data submitters, including responsible parties, register and submit summary results information to ClinicalTrials.gov for clinical trials using master protocol designs. In particular, the article proposes an approach for reporting each master protocol sub-study as separate study records and shows examples of benefits and limitations.⁵⁷

III.3.4 FDA Guidance and Other Documents

In April 2021, the FDA released a public statement by the Acting Commissioner of Food and Drugs⁵⁸ regarding the first-ever Notice of Noncompliance issued by FDA pursuant to section 402(j)(5)(C)(ii) of the PHS Act and published the ClinicalTrials.gov – Notices of Noncompliance and Civil Money Penalty Actions webpage on FDA’s website.⁵⁹ This webpage includes a table that lists the Notices of Noncompliance issued by FDA to-date and the amount of any civil money penalties assessed by FDA. The table also contains links to the Notices of Noncompliance and associated Response Letters (if any).

III.4 Routine Activities

Between October 1, 2020, and September 30, 2022, NIH conducted several routine activities (e.g., email and media communications, external and internal consultations, external and internal training) to encourage compliance with section 402(j) of the PHS Act and its implementing regulations.

III.4.1 Routine Email and Media Communications

NIH and FDA staff, in coordination with their respective communications offices, routinely respond to questions about ClinicalTrials.gov from a variety of media outlets. The NIH ClinicalTrials.gov customer service desk receives daily inquiries from responsible parties submitting data via the PRS. Each month, ClinicalTrials.gov staff reply to approximately 12,400 general, account-related, and registration-related emails and approximately 400 results information-related emails.⁶⁰ The NIH NLM actively monitors these emails to identify frequently requested information for developing new FAQs and clarifying existing user documentation. Responses to public and media inquiries about general ClinicalTrials.gov requirements are also provided via the FDA Office of Clinical Policy mailbox (approximately 25 questions per month).⁶¹

As of September 2022, the *Hot Off the PRS!* email bulletin, which replaced the FDAAA Update listserv on August 1, 2019, sent out 21 communications. This email bulletin provides responsible parties with updates related to FDAAA, as well as notifications about available resources,

⁵⁷ Williams RJ, Dobbins HD, Tse T, Chon SD, Loose D, Sarosy GA, Prindiville SA, Rockhold FW, Zarin DA. Approach for reporting master protocol study designs on ClinicalTrials.gov: qualitative analysis. *BMJ*. 2022 Jun 10; 377:e067745. (PMID: 35688481)

⁵⁸ <https://www.fda.gov/news-events/press-announcements/fda-takes-action-failure-submit-required-clinical-trial-results-information-clinicaltrials.gov>

⁵⁹ <https://www.fda.gov/science-research/fdas-role-clinicaltrials.gov-information/clinicaltrials.gov-notices-noncompliance-and-civil-money-penalty-actions>

⁶⁰ register@clinicaltrials.gov

⁶¹ gcpquestions@fda.hhs.gov

outreach materials, and other activities. From August 2020 to September 2022, the number of subscribers has grown from 3,265 to 8,987.

During the reporting period, the NIH OIR also sent monthly email notifications on registration and summary results information submission compliance to intramural scientific directors, clinical directors, investigators, and clinical trial staff.

III.4.2 Routine External Consultations

NIH staff provide a variety of external consultations, including approximately four web-based meetings each month to help responsible parties submit summary results information to ClinicalTrials.gov or address quality control (QC) review comments; monthly teleconferences with the DIA Clinical Trial Disclosure Community to encourage compliance and educate biopharmaceutical and device industry professionals responsible for U.S. and international trial disclosure compliance;^{62,63} monthly teleconference consultations with the Clinical Trials Registration and Results Reporting Taskforce (a national consortium of members from academic medical centers, universities, hospitals, and non-profit organizations focused on the implementation of domestic clinical trials registration and summary results information submission requirements in the ClinicalTrials.gov data bank);⁶⁴ meetings with the French Health Research Registry regarding how ClinicalTrials.gov and NIH could support their work; and meetings with the Canadian Cancer Research Alliance to discuss updates to maintain and facilitate interoperability and the impact of ClinicalTrials.gov modernization on the Canadian Partnership Against Cancer website and database, which extracts ClinicalTrials.gov data.

FDA staff met with the Department of Veterans Affairs and the Biomedical Advanced Research and Development Authority to provide an overview of ClinicalTrials.gov requirements and FDA's compliance role.

III.4.3 Routine Internal Consultations

The NIH OIR meets regularly with NIH Institute and Center intramural research investigators to encourage compliance with section 402(j) of the PHS Act, including its implementing regulations. One-on-one consultations are held routinely to assist and inform NIH intramural investigators responsible for data submission to ClinicalTrials.gov. In addition, presentations and one-on-one consultations are regularly scheduled with other NIH intramural research staff and Institute and Center leadership to ensure broad familiarity with registration and summary results information submission requirements.

The NIH Clinical Trials Operations Workgroup, a trans-NIH group composed of staff from NIH Institutes, Centers and Offices (ICOs), meets quarterly to support the implementation of specific clinical trial requirements, including the ClinicalTrials.gov registration and summary results information submission requirements for NIH grantees, and to ensure that grantee and regulatory requirements are harmonized across NIH ICOs.

⁶² <http://communities.diaglobal.org/>

⁶³ <https://www.diaglobal.org/>

⁶⁴ <https://ctrtaskforce.org>

The NIH Clinical Trials Implementation Group, led by NIH OER, meets monthly to provide guidance and make decisions regarding the implementation of clinical trials initiatives.

The National Cancer Institute (NCI) Clinical Trials Reporting Program (CTRP) is a comprehensive database of information on all interventional clinical trials directly or indirectly supported by NCI open to accrual as of 2009.⁶⁵ NIH staff hold periodic consultations to coordinate CTRP and ClinicalTrials.gov activities. A product derived from these consultations allows investigators to export protocol registration information from CTRP to the PRS, making data submission from CTRP to ClinicalTrials.gov more streamlined and efficient.⁶⁶

NIH staff provided consultation to NCI on clinical trials registration efforts and user research and met with the National Center for Advancing Translational Sciences (NCATS) regarding the COVID-19 Clinical Trial Tracker, which is filled with data curated primarily from ClinicalTrials.gov and the World Health Organization as well as supplemental information from certain national registries around the world.

III.4.4 Routine Internal Training

There were multiple training opportunities provided specifically for NIH and FDA staff on clinical trial registration and summary results information submission requirements. These included, but were not limited to, training for NIH contracting officers, contract specialists, and contracting officer representatives on the NIH Document Generation System, which maintains contract and solicitation clauses and provisions for the NIH acquisition community; annual training provided for health care journalists who are fellows of the Association of Health Care Journalists and NIH partnership, and the Annual Network of the NLM (NNLM) New Staff Orientation for recent hires at NNLM Regional Medical Libraries;⁶⁷ multiple trainings on policies and procedures for grants and contracts to ensure their inclusion in NIH clinical research efforts; the Reviewer Certification Program – Advanced Topics in Clinical Trials, which trains FDA Center for Devices and Radiological Health (CDRH) review staff and includes information on tracking ClinicalTrials.gov registration; training for Center for Biologics Evaluation and Research (CBER) Bioresearch Monitoring (BIMO) staff on ClinicalTrials.gov requirements; and training for Center for Drug Evaluation and Research (CDER) BIMO staff on the ClinicalTrials.gov requirements and internal procedures for evaluating ClinicalTrials.gov compliance and implementing compliance actions.

In August and December 2021, NIH NLM staff presented to the NIH Clinical Center Protocol Navigators who support the development, management, and guidance of intramural clinical studies. Presenters discussed PRS-user related topics such as sharing individual participant data and provided an overview of outcome measures and statistical analyses.

The NIH OIR held weekly Biomedical Translational Research Information System (BTRIS) trainings on ClinicalTrials.gov, and provided one-on-one trainings on National Heart, Lung, and

⁶⁵ <https://www.cancer.gov/about-nci/organization/ccct/ctrp>

⁶⁶ <https://prsinfo.clinicaltrials.gov/prs-users-guide.html#NCI>

⁶⁷ <https://nnlm.gov>

Blood Institute (NHLBI) standard operating procedures covering protocol registration and results information submission.

III.4.5 Routine ClinicalTrials.gov Enhancements and Updates

Data submission system improvements to enhance the clinical trial data submission process and experience for responsible parties typically are made to the PRS every 3-4 months, and the PRS User's Guide is typically updated every 3-4 months to reflect those improvements.⁶⁸ Information about FDAAA,⁶⁹ the FAQs, Training Materials, and Support Materials webpages of the ClinicalTrials.gov public site is updated as needed. Specific updates made during the reporting period are discussed in detail earlier in the report (see section III.3.1 for more details).

The Final Rule (42 CFR Part 11) information webpage in the PRS, which was created specifically to provide PRS users general information about the Final Rule as well as details on data submission requirements,⁷⁰ is updated approximately every 24 months. Individuals may subscribe to the *Hot Off the PRS!* email bulletin to receive notifications when new information is added.⁷¹

The main sections of the ClinicalTrials.gov website are continually updated, and features enhanced, in response to stakeholder feedback. These improvements are made to better support anyone using the public site to find clinical trials or trial data, background information, or information on legal and policy requirements. Evaluation of the site and enhancements are ongoing, and updates to the site are announced via the *NLM Technical Bulletin*⁷² and/or on the ClinicalTrials.gov What's New webpage.⁷³

III.5 Other Activities

FDA conducted several non-routine internal presentations and trainings for various staff groups, including BIMO staff in CBER, CDER, CDRH, and the Office of Regulatory Affairs (ORA). These presentations and trainings covered subjects including, but not limited to, FDA's enforcement strategy and internal procedures for evaluating ClinicalTrials.gov compliance, handling issues of potential noncompliance, and recent compliance activities.

In April 2022, FDA gave a presentation to the Clinical Trials Registration and Results Reporting Task Force on the agency's compliance program for ClinicalTrials.gov.

FDA and NIH staff continue to participate in a Clinical Trials Transformation Initiative⁷⁴ (CTTI)-led effort started in June 2021 to identify and explore the key challenges to clinical trial registration and results information reporting and to identify potential solutions. Completion of this effort is anticipated in mid-2023.

⁶⁸ <https://prsinfo.clinicaltrials.gov/prs-users-guide.html>

⁶⁹ <https://clinicaltrials.gov/ct2/manage-recs/fdaaa>

⁷⁰ <https://prsinfo.clinicaltrials.gov/>

⁷¹ https://public.govdelivery.com/accounts/USNLMOCPL/subscriber/new?topic_id=USNLMOCPL_30%20

⁷² https://www.nlm.nih.gov/pubs/techbull/current_issue.html

⁷³ <https://clinicaltrials.gov/ct2/about-site/new>

⁷⁴ <https://ctti-clinicaltrials.org/our-work/quality/challenges-meeting-u-s-clinicaltrials-gov-reporting-requirements/>

NIH staff participated in additional engagement and outreach activities, including an exhibit booth at the Medical Library Association annual meeting.⁷⁵

III.6 Surveillance and Enforcement

FDA has conducted surveillance and enforcement activities to encourage compliance with section 402(j) of the PHS Act and its implementing regulations. FDA uses a risk-based approach to evaluate potential noncompliance and issue Pre-Notice Letters and Notices of Noncompliance, as appropriate, as well as take other regulatory or enforcement action(s) available under the law. Between October 1, 2020, and September 30, 2022, FDA conducted 187 BIMO inspections of sponsors and sponsor-investigators, during which FDA assessed ClinicalTrials.gov compliance.

Although FDA has moved toward a more consistent state of operations since the beginning of the COVID-19 public health emergency, the public health emergency continues to have an impact on the agency's ability to conduct inspections. For example, in response to the spread of the omicron variant, FDA paused domestic surveillance inspections in late December 2021 to ensure the safety of its employees and the employees of the firms it regulates. FDA resumed domestic surveillance inspections in February 2022. More generally, FDA's inspectional operations continue to adapt to evolving travel requirements and testing protocols, along with the impact of COVID-19 infections on industry personnel and FDA inspectional staff.^{76, 77, 78, 79}

FDA has also undertaken several activities during the reporting period to develop internal procedures for its compliance and enforcement program. These activities include developing Center-specific risk-based enforcement strategies for identifying potential noncompliance through surveillance of clinical trials registered on the ClinicalTrials.gov website and, if necessary, taking appropriate compliance actions (e.g., issuing a Pre-Notice Letter). FDA also continues development work on Office of Orphan Products Development-specific processes for educating orphan product development grantees on ClinicalTrials.gov requirements and monitoring grantees' compliance with those requirements. Joint FDA-NIH efforts have included developing interagency communication plans to ensure coordinated compliance processes and timely communications related to the implementation and enforcement of FDAAA and the regulations in 42 CFR Part 11.

Between October 1, 2020, and September 30, 2022, FDA issued 52 Pre-Notice Letters related to 66 ACTs. Although Pre-Notice Letters have generally been effective at securing voluntary compliance by responsible parties, FDA did issue four Notices of Noncompliance under section 402(j)(5)(C)(ii) of the PHS Act to the responsible parties for four ACTs during the period covered by this report. Copies of the Notices of Noncompliance are available on FDA's

⁷⁵ <https://www.nlm.nih.gov/oet/exhibits/mla/2021/nlm-updates.html>

⁷⁶ To provide FDA investigators with the most reliable and accurate information, FDA developed a rating system to assist in determining when and where it was safest to conduct prioritized domestic inspections until the agency resumed domestic surveillance inspections in July 2021.

⁷⁷ <https://www.fda.gov/news-events/press-announcements/fda-roundup-january-4-2022>

⁷⁸ <https://www.fda.gov/news-events/press-announcements/fda-roundup-january-21-2022>

⁷⁹ <https://www.fda.gov/news-events/press-announcements/fda-roundup-february-4-2022>

website.⁸⁰ In each instance, the recipient of the Notice of Noncompliance remedied the noncompliance identified in the Notice. FDA did not bring any civil money penalty actions during the period covered by this report.

In response to the four Notices of Noncompliance issued by FDA, the NIH posted to ClinicalTrials.gov information about the violations identified in each Notice of Noncompliance issued by FDA. This information was added to the study records for the four ACTs associated with the Notices of Noncompliance. The NIH NLM also implemented a feature that allows users to search ClinicalTrials.gov for trials with “FDAAA 801 Violations” (i.e., trials that are the subject of a Notice of Noncompliance issued by FDA).⁸¹

The NIH is actively implementing processes to verify compliance with ClinicalTrials.gov registration and results information submission requirements by NIH grantees, including additional enhancements in response to an HHS Office of the Inspector General audit,⁸² and coordinating compliance action with FDA as appropriate. The NIH implemented enhanced internal procedures, such as new forms, strengthened reporting systems, and centralized compliance workflows, to verify and improve compliance with ClinicalTrials.gov registration and summary results information submission among NIH-funded extramural investigators. The procedures standardize approaches across NIH ICOs for verifying grantee compliance with both the NIH policy and section 402(j) of the PHS Act. Electronic system validations are in place to automatically flag a record to ensure that no awards are issued without resolving clinical trial registration and reporting requirements and to enable NIH ICOs to track compliance activities.

IV. ClinicalTrials.gov Registration and Summary Results Information Submission Data: January 18, 2017–September 30, 2022

IV.1 Total Number of ACTs with Complete Registration Information Submitted

During the period covered by this report, 24,540 studies with submitted information indicating they are ACTs were registered and posted publicly on ClinicalTrials.gov. Of those, 2,759 were registered in FY 2017 (and had a study start date on or after January 18, 2017), 4,268 were registered in FY 2018, 4,285 were registered in FY 2019, 4,495 were registered in FY 2020, 4,672 were registered in FY 2021, and 4,061 were registered in FY 2022 (see Table 1). An additional 463 ACTs had complete registration information submitted during the time period of this report but are not included in the fiscal year totals because they are studying a device

⁸⁰ <https://www.fda.gov/science-research/fdas-role-clinicaltrials.gov-information/clinicaltrials.gov-notices-noncompliance-and-civil-money-penalty-actions>

⁸¹ The term “FDAAA 801 Violations” was added to the ClinicalTrials.gov glossary in December 2020 at <https://clinicaltrials.gov/ct2/about-studies/glossary>.

⁸² <https://oig.hhs.gov/oas/reports/region6/62107000.pdf>

product that is not approved or cleared by FDA (42 CFR 11.35(b)(2)(i)) and, therefore, are eligible for delayed posting on ClinicalTrials.gov.

To calculate these annual registrations, NIH staff identified studies posted on ClinicalTrials.gov with the submitted information specified below (i.e., the data elements described in 42 CFR 11.22 that can be used to assist in identifying an ACT):

- Study Type is “Interventional.”
- At least one of the following applies:
 - Facility Information – Country is “United States” (or is one of the U.S. territories, including American Samoa, Guam, Northern Mariana Islands, Puerto Rico, or the U.S. Virgin Islands.)
 - U.S. Food and Drug Administration Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) is “Yes.”
 - Product Manufactured in and Exported from the U.S. is “Yes.”
- Studies a U.S. FDA-regulated Drug Product is “Yes,” *or* Studies a U.S. FDA-regulated Device Product is “Yes.”
- Primary Purpose is *not* “Device Feasibility” (for device products), *or* Study Phase is *not* “Phase 1” (for drug and biological products).
- Overall Recruitment Status is *not* “Withdrawn.”
- Study Start Date is on or after January 18, 2017.

For the purpose of this report, ACTs with complete ClinicalTrials.gov registration information are those that have completed the QC review process, have an assigned NCT number, have the above data elements completed, and have been publicly posted on ClinicalTrials.gov during the period of this report (i.e., from January 18, 2017, to September 30, 2022).

IV.2 Total Number of Registered ACTs with Summary Results Information Submitted

In general, ACTs with complete ClinicalTrials.gov registration information must have their summary results information submitted to the data bank no later than 1 year after the trial’s Primary Completion Date (the standard results information submission deadline). The Primary Completion Date is the date on which the last subject in a clinical trial was examined or received an intervention to collect final data for the primary outcome measure of the study. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.

Not all ACTs that are 1 year or more beyond the Primary Completion Date are required to have submitted summary results information. Under the provisions in 42 CFR 11.44, the standard summary results information submission deadline may be delayed if the responsible party (1) certifies that it is seeking, or may at a future date seek, initial approval, licensure, or clearance of the FDA-regulated product studied in the trial; (2) certifies that it has filed, or will file within 1 year, an application or premarket submission seeking approval, licensure, or clearance of a new use for a previously approved, licensed, or cleared product; or (3) requests an extension of the

deadline for submitting summary results information for good cause.⁸³ In addition, the Primary Completion Date (and certain other data elements used to identify trials for this report) in a study record must be updated throughout the course of the study, as specified in 42 CFR 11.64, based on the actual progress of the study (e.g., if participant enrollment takes longer than initially anticipated, the Primary Completion Date may need to be delayed). As a result, the total number of ACTs and those ACTs with summary results information due within a specific fiscal year might have changed from the information provided in the previous 21st Century Cures Act, Section 2052 Report on Clinical Trials.

Overall, as of September 30, 2022, 8,464 ACTs with a Study Start Date on or after January 18, 2017, had reached their standard results submission deadline (i.e., one year after the trial's Primary Completion Date) (see Table 2).⁸⁴ Of these, 4,801 ACTs had summary results information submitted and posted on ClinicalTrials.gov following completion of the QC review criteria process. Another 721 ACTs had summary results information submitted but are still undergoing the QC review procedures established by the NIH to assess information submitted for apparent errors, deficiencies, or inconsistencies as described in 42 CFR 11.64(b).⁸⁵ Additionally, 388 ACTs had a delay in the standard results information submission deadline based on one of the mechanisms described above.

V. Summary

HHS is committed to educating the community about clinical trial registration and summary results information submission requirements to encourage regulatory compliance; promote efficiency and accountability in the clinical trial enterprise; and ensure greater transparency into clinical trials to participants and the public. HHS takes the implementation of these regulations

⁸³ In certain circumstances, a responsible party may delay the standard results information submission deadline (generally 1 year after the Primary Completion Date). The options to delay submission of summary results information are:

- Certify Initial Approval: The clinical trial studies an FDA-regulated drug product (including a biological product) or device product that was not approved, licensed, or cleared by FDA for any use before the Primary Completion Date of the clinical trial, and the sponsor intends to continue with product development and is either seeking, or may at a future date seek, FDA approval, licensure, or clearance of the drug product (including a biological product) or device product under study (42 CFR 11.44(c)).
- Certify New Use: The clinical trial studies an FDA-regulated drug product (including a biological product) or device product that previously has been approved, licensed, or cleared, for which the manufacturer is the sponsor of the clinical trial and for which an application or premarket notification seeking approval, licensure, or clearance of the use being studied (which is not included in the labeling of the approved, licensed, or cleared drug product (including a biologic product) or device product) has been filed or will be filed within 1 year with FDA (42 CFR 11.44(b)).
- Extension: Request, for good cause, an extension of the deadline for submitting summary results information. The extension request must demonstrate good cause and meet the specified conditions (42 CFR 11.44(e)).

⁸⁴ This is the sum of values in the first row of Table 2 for FY 2017 to FY 2022.

⁸⁵ Starting on January 1, 2020, submitted summary results information for ACTs for which results information is not consistent with the QC review criteria are available on ClinicalTrials.gov with a general notice that the QC review process has not concluded a long with brief, standardized major comments.

seriously, executes implemented enhancements to processes to encourage compliance, and implements registering and summary results information reporting of clinical trials. As described in this report, HHS has undertaken broad and extensive measures to educate, consult with, and encourage compliance by responsible parties with the data bank registration and summary results information submission requirements as outlined in section 402(j) of the PHS Act and its implementing regulations. These measures have included issuing guidance documents, holding informational meetings, hosting training sessions, and more. This report also presents data on the total number of ACTs registered during the period of this report that have complete ClinicalTrials.gov registration information, as entered by the responsible parties, and the total number of ACTs started during the period of this report for which summary results information has been submitted to ClinicalTrials.gov, broken down by fiscal year.

HHS is committed to continuing to evaluate and strengthen these processes to ensure greater compliance moving forward, including undertaking additional actions to educate and engage with responsible parties to encourage compliance with section 402(j) of the PHS Act and its implementing regulations.

VI. Table 1. Total Number of ACTs*⁺ Registered on ClinicalTrials.gov: January 18, 2017–September 30, 2022*^{+^†}

FY 2017 [§]	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
2,759	4,268	4,285	4,495	4,672	4,061

* Includes registered studies that meet the following criteria:

- Study Type is “Interventional.”
- At least one of the following applies:
 - Facility Information – Country is “United States” (or is one of the U.S. territories, including American Samoa, Guam, Northern Mariana Islands, Puerto Rico, or the U.S. Virgin Islands.)
 - U.S. Food and Drug Administration IND or IDE is “Yes.”
 - Product Manufactured in and Exported from the U.S. is “Yes.”
- Studies a U.S. FDA-regulated Drug Product is “Yes,” or Studies a U.S. FDA-regulated Device Product is “Yes.”
- Primary Purpose is not “Device Feasibility” (for device products), or Study Phase is not “Phase 1” (for drug and biological products).
- Overall Recruitment Status is not “Withdrawn.”
- Study Start Date is on or after January 18, 2017.

Note: A total of 463 ACTs with study start dates on or after January 18, 2017, submitted complete registration information during the time period of this report but are not included in the table because they are studying a device product that is not approved or cleared by FDA (42 CFR 11.35(b)(2)(i)) and therefore are eligible for delayed posting.

+ Registrations as of September 30, 2022, is provided for ACTs based on the fiscal year of the Study Start Date.

^ The totals presented in Table 1 are based on a programmatic evaluation of clinical trial data submitted to ClinicalTrials.gov by responsible parties. This programmatic evaluation did not include a detailed assessment of individual ClinicalTrials.gov study records to verify a trial's ACT status. As such, the actual number of ACTs may be different.

† Includes only ACTs with a Study Start Date on or after January 18, 2017, with complete ClinicalTrials.gov registration information, that is, they have completed the QC review process, have an assigned NCT number, have the above data elements completed, and have been publicly posted on ClinicalTrials.gov during the period of this report. Certain data elements used to identify ACTs for this report must be updated throughout the course of the study, as specified in 42 CFR 11.64, based on the actual progress of the study. As a result, the total number of ACTs registered within a specific fiscal year might differ between the 21st Century Cures Act, Section 2052 Reports on Clinical Trials.

§ Partial fiscal year: January 18, 2017–September 30, 2017.

VII. Table 2. Total Number of Registered ACTs with Summary Results Information Submitted to ClinicalTrials.gov: January 18, 2017–September 30, 2022

ACT Results Status* ⁺	FY 2017 [†]	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
ACTs that reached the standard results submission deadline	0	139	963	1,999	2,512	2,851
Results submitted and posted (QC review concluded)	0	92	692	1,378	1,484	1,155
Results submitted (QC review not yet concluded) [^]	0	10	55	124	183	349
Submission deadline delayed [~]	0	2	16	39	149	182

* Results status as of September 30, 2022, is provided for ACTs based on the fiscal year in which the standard results submission deadline was reached. Generally, summary results information for ACTs is not required to be submitted until 1 year after the trial's Primary Completion Date, or later if the conditions for delayed submission are met. The Primary Completion Date (and certain other data elements used to identify trials for this report) must be updated throughout the course of the study, as specified in 42 CFR 11.64, based on the actual progress of the study. As a result, the total number of ACTs and those ACTs with summary results information due within a specific fiscal year might differ between the 21st Century Cures Act, Section 2052 Reports on Clinical Trials. Additionally, ACTs in earlier Reports on Clinical Trials listed as "QC review not yet concluded" and "Submission deadline delayed" may have had results posted during the period of this report and would be listed as "Results submitted and posted" in the current Report on Clinical Trials.

⁺ *The totals presented in Table 2 are based on a programmatic evaluation of clinical trial data submitted to ClinicalTrials.gov by responsible parties. This programmatic evaluation did not include a detailed assessment of individual ClinicalTrials.gov study records to verify a trial's ACT status. As such, the actual number of ACTs may be different.*

[†] *Partial fiscal year: January 18, 2017–September 30, 2017. Note: As of September 30, 2017, all ACTs registered in FY 2017 were either still ongoing or not yet 1 year beyond their Primary Completion Date and therefore not yet subject to the summary results information submission requirements.*

[^] *ACTs may have summary results information submitted but not yet posted because the summary results information is still undergoing the QC review procedures established by NIH to assess submitted information for apparent errors, deficiencies, or inconsistencies as described in 42 CFR 11.64(b). Starting on January 1, 2020, submitted summary results information for ACTs for which results are not consistent with the QC review criteria are available on ClinicalTrials.gov with a general notice that the QC review process has not concluded along with brief, standardized major comments.*

[~] *A responsible party may delay the standard results submission deadline through one of three options:*

- *Certify Initial Approval: The clinical trial studies an FDA-regulated drug product (including a biological product) or device product that was not approved, licensed, or cleared by FDA for any use before the Primary Completion Date of the clinical trial, and the sponsor intends to continue with product development and is either seeking, or may at a future date seek, FDA approval, licensure, or clearance of the drug product (including a biological product) or device product under study (42 CFR 11.44(c)).*
- *Certify New Use: The clinical trial studies an FDA-regulated drug product (including a biological product) or device product that previously has been approved, licensed, or cleared, for which the manufacturer is the sponsor of the clinical trial and for which an application or premarket notification seeking approval, licensure, or clearance of the use being studied (which is not included in the labeling of the approved, licensed, or cleared drug product (including a biologic product) or device product) has been filed or will be filed within 1 year with FDA (42 CFR 11.44(b)).*
- *Extension: Request, for good cause, an extension of the deadline for submitting summary results information. The extension request must demonstrate good cause and meet the specified conditions (42 CFR 11.44(e)).*