

FRED HUTCH UNIVERSITY OF WASHINGTON CANCER CONSORTIUM	Clinical Trials Reporting ClinicalTrials.gov/FDAAA 801
	Posting Results and Adverse Events on ClinicalTrials.gov

Approval			
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Printed Name	John T. Slattery, PhD		

Background

Section 801 of the Food and Drug Administration Amendments Act (FDAAA) of 2007, also known as U.S. Public Law 110-85, contains requirements for registering trials, updating trial information and reporting trial results in ClinicalTrials.gov. The ClinicalTrials.gov “basic results” database was launched in September 2008. The final rule for Clinical Trials Registration and Results Information Submission (42 CFR 11), which clarifies and expands the requirements in FDAAA, was released in September 2016. Both registration and results reporting are accomplished through the ClinicalTrials.gov Protocol Registration System (PRS).

The NIH Policy on the Dissemination of NIH Funded Clinical Trial Information (NOT-OD-16-149) expands the scope of trials for which aggregate results and summary adverse event information must be reported by including all clinical trials funded in whole or in part by the NIH. Although specific trials covered by the NIH policy may or may not also be considered as applicable under the statute (FDAAA) and regulation (42 CFR 11), the NIH policy reporting requirements are those of the statute and regulation.

Noncompliance with these requirements could result in civil monetary penalties and withholding or recovery of funds from federal grants.

Responsible Personnel

Principal Investigator

Responsible Party

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Clinical Research Oversight Committee
 Medical Director, Clinical Research Support
 Vice President, Clinical Research
 Consortium ClinicalTrials.gov Administrator, Clinical Research Support

Abbreviations and Acronyms

- ACT: Applicable Clinical Trial (42 CFR 11.10)
- CMS: Center for Medicare and Medicaid Services
- CROC: Clinical Research Oversight Committee
- CRS: Clinical Research Support
- FDA: Food and Drug Administration
- FDAAA: Food and Drug Administration Amendments Act
- FHCRC: Fred Hutchinson Cancer Research Center
- ICMJE: International Committee of Medical Journal Editors
- IRB: Institutional Review Board
- NCI: National Cancer Institute
- NCI-CTRP: NCI Clinical Trials Reporting Program
- NCT ID: National Clinical Trials ID, ClinicalTrials.gov
- NIH: National Institutes of Health, HHS
- PCD: Primary Completion Date (42 CFR 11.10)
- PI: Principal Investigator
- PRMS: Protocol Review and Monitoring System
- PRS: Protocol Registration and Results System, ClinicalTrials.gov
- RP: Responsible Party (42 CFR 11.10)
- SC: Seattle Children’s
- SCD: Study Completion Date (42 CFR 11.10)
- SRC: Scientific Review Committee
- SCCA: Seattle Cancer Care Alliance
- UW: University of Washington

Definitions

Applicable Clinical Trial: A term used in the FDAAA statute, which includes the following types of trials:

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- **Trials of drugs and biologics.** Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to Food and Drug Administration (FDA) regulation
- **Trials of devices.** 1) Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and 2) pediatric postmarket surveillance required by FDA

Note: A clinical investigation of a drug can be an Applicable Drug Clinical Trial under FDAAA even if it does not require an IND, and a clinical investigation of a device can be an Applicable Device Clinical Trial whether or not an IDE is required.

- For the complete statutory (FDAAA) definition and more information on the meaning of "applicable clinical trial," see 42 CFR 11.10 or "Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT)". (Source: ClinicalTrials.gov)
- The scope of FDAAA and 42 CFR 11 is limited to "Applicable Clinical Trials," a term which has a narrower definition than "Clinical Trial". The scope of the NIH Policy (NOT-OD-16-149) encompasses the broader definition of "Clinical Trial".

Cancer Consortium: An NCI-designated Comprehensive Cancer Center comprised of FHCR, UW, SC and SCCA.

Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. This definition encompasses phase 1 trials of FDA-regulated drug and biological products, small feasibility studies of FDA-regulated device products, and studies of any intervention not regulated by the FDA, e.g., behavioral interventions. This definition of "clinical trial" is broader than the term "applicable clinical trial" as defined in the regulation. (Source: NIH)

ClinicalTrials.gov: A public database developed by the U.S. NIH, provided through its National Library of Medicine (NLM), that meets FDAAA and ICMJE requirements.

Interventional Study Type: Participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health related outcomes. (Source: 42 CFR Part 11)

Primary Completion Date: 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 pre-specified protocol or was terminated. In the case of clinical trials 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 of the primary outcomes. (Source: 42 CFR Part 11)

Responsible Party: The sponsor of the clinical trial or the principal investigator (PI) of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the PI is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under 42 CFR 11 and FDAAA for the submission of clinical trial information. (Source: 42 CFR Part 11)

Sponsor: A person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators. (Source: 21 CFR 50.3)

Study Completion Date: The date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated. (Source: 42 CFR Part 11)

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Policy

Cancer Consortium Investigators are responsible for ensuring registration of any clinical trial in which their role is principal investigator, regardless of whether the Consortium PI meets the definition of responsible party. If the Consortium PI meets the definition of RP (sponsor or sponsor-designated PI), they are responsible for ensuring the accuracy of all ongoing trial information in the ClinicalTrials.gov system, including the recruitment status, summary of adverse event information, and trial results. The RP must ensure their record follows all applicable laws and regulations, appropriately reflects the scientific design and analytic approach, and is truthful and non-misleading.

Procedures

1. REGISTRATION

The Consortium PI is responsible for registering the trial directly in the ClinicalTrials.gov Protocol Registration System (PRS), within the timeframes specified in 42 CFR 11, if the PI meets the definition of RP for a non-cancer-related clinical trial that is applicable under the FDAAA statute or covered by the NIH policy.

Registration with ClinicalTrials.gov of clinical trials that are neither applicable under FDAAA nor covered by the NIH policy may still be required by policies such as those of CMS or ICMJE (both of which require registration prior to enrolling participants).

Clinical trials for which the Consortium PI does not meet the definition of RP are generally registered with ClinicalTrials.gov by the external lead organization, such as industry-sponsored trials, NCI National Clinical Trials Network trials, and trials coordinated by other Cancer Centers.

Registrations managed by Clinical Research Support (CRS)

Although the PI is responsible for ensuring registration, CRS staff manages the initial ClinicalTrials.gov registration of investigator-initiated, cancer clinical trials on behalf of the RP (the PI) and the sponsor for FHCRC and UW.

CRS staff submits the protocol, consent and a specific set of trial data to NCI-CTRP to fulfill the NCI requirements. In return, NCI-CTRP provides a trial summary report, which is used by CRS staff to create the initial ClinicalTrials.gov record. ClinicalTrials.gov staff review the trial record, which may involve more than one review cycle if comments are issued to which responses are required. The trial is considered to be completely registered when ClinicalTrials.gov assigns an NCT ID, after the trial record has been reviewed and accepted.

In consideration of the following rules and policies, CRS staff initially registers trials with NCI-CTRP immediately following SRC approval to allow enough time for production of the trial summary report, data processing, and reviews.

- The NCT ID is required by CMS for all billing claims.
- ICMJE requires registration before the first participant is enrolled as a condition of consideration for publication.
- Registration is required no later than 21 days after the first participant is enrolled to comply with the NIH funding policy and the FDA Amendments Act.

CRS staff continues to manage amendments, updates, and status changes in ClinicalTrials.gov until it is time to transfer management of the trial record to the PI (the RP) for results reporting.

Registrations managed by the Principal Investigator

Consortium PIs who meet the definition of RP for non-cancer-related clinical trials need a ClinicalTrials.gov account in order to register their trials. The Consortium ClinicalTrials.gov Administrator creates individual user accounts under the institutional account (either UWashington [FH/UWCC group] or FHCRC) and provides basic system instructions to investigators and study teams.

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2. UPDATES TO TRIAL INFORMATION

The FDAAA and 42 CFR Part 11 specify update requirements. In general, if the PI meets the definition of RP, the PI must review and verify all trial information in the ClinicalTrials.gov system not less than once every 12 months. The final rule also specifies certain data elements that must be updated within 30 calendar days of a change. Notice of changes in recruitment status must be provided as soon as possible, but no later than 30 days after such changes.

- For trial records managed by CRS, it is the responsibility of the PI to inform the CRS ClinicalTrials.gov administrator within 10 business days of any change in overall recruitment status or the occurrence of the actual Primary and/or Study Completion Date.

Under the Revised Common Rule (45 CFR Part 46), a version of the informed consent document used to enroll subjects must be posted on a publicly available Federal website after the study closes to accrual and no later than 60 days after the last study visit. Cancer Consortium PIs are expected to comply and upload a version to ClinicalTrials.gov to satisfy this requirement for trials initially approved by the IRB on or after January 21, 2019.

Additionally, the RP must respond to comments issued by a ClinicalTrials.gov reviewer within 15 days, to correct or address all apparent errors, deficiencies, and/or inconsistencies.

3. REPORTING RESULTS AND ADVERSE EVENTS

A Cancer Consortium PI who meets the definition of RP for an Applicable Clinical Trial under FDAAA and/or a Clinical Trial funded by NIH must submit clinical results and summary adverse event information directly in the ClinicalTrials.gov PRS according to FDAAA and 42 CFR Part 11.

Results are required for trials that are terminated, or stopped prematurely, after participants were enrolled. Results are not required for trials without enrolled participants. Additionally, the RP must correct or address all apparent errors, deficiencies, and/or inconsistencies within 25 days of notification or discovery.

- CRS does not report results or adverse events for any trials. The Consortium ClinicalTrials.gov Administrator monitors compliance requirements and creates individual user accounts when management of a trial is transferred to the PI for results reporting. CRS provides this as a service and is not accountable to ensure that compliance is met. The RP is accountable to meet compliance requirements. CROC will be notified regarding studies that are delinquent in meeting approaching compliance requirements and deadlines.

The Primary Completion Date and Study Completion Date must be identified and reported no later than 30 after each occurs. Both the Primary Completion Date and Study Completion Date are determined by when data were collected, not the date data were analyzed, a manuscript was published, enrollment was completed, or the study closed with the IRB.

Initial reporting deadline

The deadline for initial reporting is no later than 1 year after the Primary Completion Date (as defined in 42 CFR Part 11.10). An initial results submission requires clinical trial results, a summary of adverse events, and a copy of the updated protocol and statistical analysis plan (if not included in the protocol) to be submitted to ClinicalTrials.gov.

- Cancer Consortium PIs must be prepared to submit initial results data within 9 months after the Primary Completion Date to allow for PRS review, corrections, and posting by the regulatory deadline. Failure to initiate an initial results submission by 11 months after the Primary Completion Date will result in escalation to CROC.

Interim reporting deadlines

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If data collection is still continuing for any of the secondary outcomes or additional adverse events at the time of the Primary Completion Date, one or more additional submission deadlines will apply. If any amendments were made to the protocol and/or statistical analysis plan since the previous submission, the revised protocol must be submitted to ClinicalTrials.gov.

- For secondary outcome measures: 1 year after the date on which the final subject is examined or receives an intervention for the purposes of final collection of data for that secondary outcome measure.
- For additional adverse event information: 1 year after the date of data collection.

Final reporting deadline

The deadline for final reporting is no later than 1 year after the Study Completion Date (as defined in 42 CFR Part 11.10). The final results submission requires reporting of all clinical trial results and summary of adverse events, along with a copy of the updated protocol and statistical plan to be submitted to ClinicalTrials.gov.

Quality Control

Beginning in January 2020, results for ACTs with a start date on or after January 18, 2017 are publicly posted on ClinicalTrials.gov regardless of whether the quality control review process is complete. A general notice is included if the QC review process has not concluded, along with brief comments about “major” issues identified. All versions will be posted until the review process concludes and no “major” issues are identified by PRS.

4. DEPARTING INVESTIGATOR RESPONSIBILITIES

If an investigator who serves as sponsor and/or RP for a clinical trial leaves the Consortium before all required data have been reported to ClinicalTrials.gov, in conjunction with their Division Director, it must be determined whether the RP will continue to hold the role of RP, the role of RP will be transferred to another individual in the Consortium, or the record will be transferred to another institution. When appropriate, FHCR or UW can accept the role of RP.

Departing investigators must contact CRS at ctgov@fredhutch.org to arrange for any necessary record transfer and close out any studies before departing the Cancer Consortium.

5. PENALTIES AND CONSEQUENCES

Cancer Consortium Investigators who fail to comply with federal requirements may be subject to enforcement actions. Noncompliance or repeated violations can also result in administrative action by CROC. CROC reserves the right to impose discipline or sanctions as provided for in applicable policies from Consortium partners.

- Failure to comply with FDAAA requirements may result in financial penalties of up to \$10,000 per day, withholding of funds and sanctions imposed by the FDA. The Federal Food, Drug, and Cosmetic Act caps monetary penalties, permitting a maximum penalty of \$10,000 for all violations adjudicated within a single proceeding, or, if a RP fails to remedy its noncompliance within the notice period, \$10,000 per day of continuing noncompliance (detailed in FDA final guidance on Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank). These amounts may be updated to reflect inflation in accord with federal law, and the current inflation-adjusted amounts are \$12,316 for 2020. Inflation-adjusted maximums are found at 45 CFR 102.3.
- Failure to comply with NIH policy may result in withholding of cash payments, disallowing cost for an activity, suspending or terminating either in part or whole the current award, withholding a future award and having a non-compliance notice publicly available.
- Failure to comply with ICMJE requirements may result in an inability to publish in an ICMJE affiliated journal.

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- Failure to comply with CMS requirements can result in a lack of payment for a qualified research billing service and a need to refile the qualified research billing claim.

Notice of Noncompliance

Should any Cancer Consortium Investigator receive a “Preliminary Notice of Noncompliance (Pre-Notice) Letter” from the FDA, they should immediately contact CRS at ctgov@fredhutch.org. CRS will report receipt of the notification to CROC, the FH Office of General Council as well as applicable departmental leadership.

The RP will have 30 calendar days to take any necessary actions to address the potential violations cited by the letter before a public Notice of Noncompliance will be reported by the FDA.

Applicable Regulations & Guidelines

21 CFR 50 – Protection of Human Subjects

45 CFR 46 – Protection of Human Subjects

Federal Food, Drug, and Cosmetic Act (FD&C Act)

Food and Drug Modernization Act (FDAMA) of 1997

FDA Amendments Act of 2007, Section 801 (FDAAA or Public Law 110-85)

42 CFR 11 – Final Rule for Clinical Trial Registration and Results Information Submission

NOT-OD-16-149 – NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

NOT-CA-15-011 – NCI Clinical Trial Access Policy

FDA Guidance – Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

45 CFR 102.3 – Civil Monetary Penalty Authorities Administered

International Committee of Medical Journal Editors (ICMJE) clinical trial registration policy

CR 8401 – Center for Medicare and Medicaid Services (CMS)

Attachments/Related References

ClinicalTrials.gov Protocol Registration System (PRS): <https://register.clinicaltrials.gov>

Summary of FDAAA section 801 requirements: <http://clinicaltrials.gov/ct2/manage-recs/fdaaa>

ClinicalTrials.gov Protocol Registration Data Element Definitions: <https://prsinfo.clinicaltrials.gov/definitions.html>

ClinicalTrials.gov Results Data Element Definitions: https://prsinfo.clinicaltrials.gov/results_definitions.html

ClinicalTrials.gov PRS Guided Tutorials: <https://prsinfo.clinicaltrials.gov/tutorial/content>

Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT): https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

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Version Review History	
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Frederick Appelbaum, MD, Deputy Director, FH	05/20/2014
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