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Sponsor Kristi Stiffler: NE Administrator
Area Cancer Consortium - Institutional
Applicability FHCC Institutional Policies

Posting Results and Adverse Events on ClinicalTrials.gov

SCOPE:

This policy applies to all Fred Hutchinson Cancer Center ("Fred Hutch"), University of Washington, and Seattle Children's workforce members supporting Cancer Consortium clinical research activities.

PURPOSE:

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.

DEFINITIONS:

Applicable Clinical Trial: For any trials of drugs and biologics: controlled clinical investigations, other than Phase I investigations, of a product subject to FDA regulation.

For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

> **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)

Cancer Consortium: An NCI-designated Comprehensive Cancer Center that comprises Fred Hutch (FH), University of Washington (UW), and Seattle Children’s (SC).

Cancer-related Study: A study that meets one or more of the following characteristics:

- Funded by NCI; or
- Primary site of a multi-site trial has classified the study as cancer or cancer-related; or
- The trial cohort will include both patients with a cancer diagnosis and others without a cancer diagnosis AND includes a primary or secondary analysis of the portion of the cohort with a cancer diagnosis; or
- Research of secondary conditions related to cancer treatment in patients with a cancer diagnosis who have received that treatment; or
- Cancer prevention studies that specifically include a primary outcome of cancer diagnosis; or
- Bone Marrow Transplant (BMT) not related to cancer treatment.

Clinical Research Support (CRS): Fred Hutch-based department providing central management and oversight functions for coordinating, facilitating, and reporting on the Consortium’s clinical research.

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.

> **Note:** This definition of "clinical trial" is broader than the term "applicable clinical trial" as defined in the regulation. (Source: NOT-OD-16-149)

ClinicalTrials.gov: A publicly available registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov captures significant summary protocol information before and during the trial as well as summary results and adverse event information of a completed trial. Federal laws and regulations as well as editors of prominent medical journals require registration of a clinical trial.

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted

by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

NCI: National Cancer Institute

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). When an applicable clinical trial or other clinical trial is not conducted under an IND or IDE, the single person or entity who initiates the trial, by preparing and/or planning the trial, and who has authority and control over the trial, will be considered the sponsor. (Source: 42 CFR 11.4)

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)

POLICY:

Any Cancer Consortium (CC) investigator, in the role of PI who initiates or conducts an investigator-initiated clinical trial shall be designated as the Responsible Party (RP). The RP must ensure the accuracy of all ongoing trial information in the ClinicalTrials.gov system, including, but not limited to, registration, recruitment status, summary of adverse event information, completion dates, 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.

REQUIREMENTS:

Registration

The RP is responsible for registration with ClinicalTrials.gov PRS within the timeframes specified in 42

CFR Part 11 for a 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 Centers for Medicare & Medicaid Services (CMS) or International Committee of Medical Journal Editors (ICMJE), both of which require registration prior to enrolling participants.

Clinical trials for which the CC 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 (NCTN) trials, and trials coordinated by other Cancer Centers.

Registrations managed by Clinical Research Support (CRS)

Although the RP is responsible for ensuring registration, CRS staff support the initial ClinicalTrials.gov registration of investigator-initiated, cancer-related clinical trials that are sponsored by the Fred Hutchinson Cancer Center and University of Washington institutions or investigators. Clinical trials sponsored by Seattle Children's are not supported by CRS.

CRS staff submit the protocol, consent, and a specific set of trial data to the Clinical Trials Reporting Program (CTRP) to fulfill NCI reporting 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 staff assign a National Clinical Trial (NCT) Identification (ID) after the trial record has been reviewed and accepted.

In consideration of the following rules and policies, CRS staff register trials with NCI-CTRP immediately following approval by the Consortium Scientific Review Committee 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 continue to support amendments, updates, and status changes in ClinicalTrials.gov until it is time to transfer management of the trial record to the RP for results reporting.

Registrations managed by the Principal Investigator

Fred Hutchinson Cancer Center PIs who meet the definition of RP for non-cancer-related clinical trials need a ClinicalTrials.gov account in order to register their trials. CRS staff must be notified in order to create individual user accounts under the Fred Hutch Cancer Center institutional account and provide basic system instructions to investigators and study teams.

Updates to Trial Information

The FDAAA and 42 CFR Part 11 specify update requirements. In general, the RP 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. For trial records supported by CRS, it is the responsibility of the RP to inform CRS staff of the occurrence of the actual Primary and/or Study Completion Date so that the ClinicalTrials.gov record can be updated within this time frame. Notice of changes in recruitment status must be provided as soon as possible, but no later than 30 days after such changes.

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. The RP is expected to comply and upload a version to ClinicalTrials.gov or Regulations.gov to satisfy this requirement for trials initially approved by the Institutional Review Board (IRB) on or after January 21, 2019.

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

Reporting Results and Adverse Events

The RP for an Applicable Clinical Trial (ACT) 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 still 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. Results submissions are ongoing until accepted by ClinicalTrials.gov staff without any major issue comments.

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

CRS staff do not report results or adverse events for any trials. CRS staff monitor compliance requirements and create individual user accounts when management of a trial is transferred to the RP for results reporting. CRS provides this as a service and is not accountable to ensure that compliance is met. The RP is accountable for meeting compliance requirements. The Clinical Research Oversight Committee (CROC) will be notified regarding studies that are delinquent in meeting approaching compliance requirements and deadlines.

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 (including statistical

analyses, if applicable), 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.

The RP 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 within 11 months after the Primary Completion Date may result in escalation to CROC.

Interim reporting deadlines

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 individual 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.

Public posting of results information

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 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.

Departing Investigator Responsibilities

If an investigator who serves as sponsor and/or RP for a clinical trial leaves the CC 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, the role will be transferred to another individual in the CC, or the record will be transferred to another institution. When appropriate, Fred Hutchinson Cancer Center or University of Washington 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 CC.

Penalties and Consequences

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 CC 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 $13,237 for 2023. 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.
- 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 CC 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 Fred Hutchinson Cancer Center Office of General Counsel, 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.

REFERENCES:

ClinicalTrials.gov Protocol Registration and Results System (PRS): https://register.clinicaltrials.gov

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

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

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

Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT):

https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

42 CFR Part 11 Clinical Trials Registration and Results Information Submission

45 CFR Part 102 Adjustment of Civil Monetary Penalties for Inflation

45 CFR Part 46 Protection of Human Subjects

FDA Guidance: Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank: https://www.fda.gov/media/113361/download

Office for Human Research Protections (OHRP): Informed Consent Posting Instructions: https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/informed-consent-posting-guidance/index.html

Approval Signatures

Step Description	Approver	Date
	Natalie Simpson: Policy & Practices Mgr	09/2023
	Kristi Stiffler: VP, Clinical Research	09/2023
	Kristi Stiffler: VP, Clinical Research	09/2023
	Nora Olsen: NE Research Monitor	09/2023