National Institute on Drug Abuse	Document Type Standard Operating Procedure (SOP)	Version: 1.0 Date: 12.14.16
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Title: Clinical Trial Registration and Reporting for NIDA Funded Clinical Trials		

PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to define the registration and reporting requirements for NIDA funded grants and contracts to ClinicalTrials.gov System. In an effort to make information about clinical trials widely available to the public, the U.S. Department of Health and Human Services (DHHS) issued a final rule (link is external) that specifies requirements for registering certain clinical trials and submitting summary results information to ClinicalTrials.gov. The new rule expands the legal requirements for submitting registration and results information for clinical trials involving U.S. Food and Drug Administration (FDA)-regulated drug, biological and device products.

The National Institutes of Health (NIH) has also issued a complementary policy (link is external) for registering and submitting summary results information to ClinicalTrials.gov for ALL NIH-funded trials, ***including those not subject to the final rule***. This SOP serves as a harmonized approach for all NIDA Divisions/Centers/Offices/Programs to meet the National Institutes of Health (NIH) Policy on Clinical Trial Reporting.

This DHHS Rule and its complementary NIH policy are intended to facilitate enrollment in clinical trials, allow for tracking of the progress of such trials, and address problems with the lack of timely dissemination of research findings.

SCOPE and APPLICABILITY

NIH is issuing this policy on the dissemination of NIH-funded clinical trial information to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTirals.gov. This policy establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH, regardless of study phase, type of intervention or whether they are subject to the statutory registration and results information submission requirements, must register these trials and their results submitted to ClinicalTrials.gov.

BACKGROUND

In September 2016, the DHHS issued a final rule that clarifies and expands the regulatory requirements and procedures for submitting registration and summary results information of clinical trials on ClinicalTrials.gov, in accordance with Food and Drug Administration Amendments Act (FDAAA) 801. The final rule is intended to make it clear to sponsors, investigators, and the public which trials must be submitted, when they must be submitted, and whether compliance has been achieved. For example, the final rule clarifies the definition of an Applicable Clinical Trial and provides structured criteria for determining which studies meet the definition.

The final rule also expands the FDAAA 801 requirements by requiring the submission of results information for trials of unapproved products. The regulation is effective on January 18, 2017 and responsible parties are expected to be in compliance by April 18, 2017.

The following documents provide background support to this SOP:

- Office of the Federal Register: Final Rule for Clinical Trials Registration and Results Information Submission (September 2016)
- NIH: Changes from Current Practice Described in the Final Rule (PDF) (September 2016)
- NIH News Release: HHS takes steps to provide more information about clinical trials to the public (September 16, 2016)
- Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. *N Engl J Med*; 2016 Nov 17;375(20):1998-2004. [Full Text]
- Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. *JAMA*; 2016 Oct4;316(13):1353-1354. [Full Text]

ROLES & RESPONSIBILITIES

For Awardee Staff: The Principal Investigator (PI) / Project Director (PD) as listed on the grant, cooperative agreement or contract award or Intramural Research Program (IRP) supported clinical trial is the "responsible party" for registering the trial and meeting the reporting requirements, including submitting results. The submission of the summary protocol and results information can be considered a part of the scientific process associated with a trial and is more than just an administrative task. Submitting registration information to the Protocol Registration and Results System (PRS) is relatively straightforward since there is typically not much interpretation required if the protocol is complete. The results section, while straightforward when it comes to entering appropriately compiled data, is more complex and is conceptually comparable to preparing the foundation for a scientific publication describing study results[1].

Someone who was actively involved in the study and is familiar with the intricacies of the study design and analysis, such as early closure of the study and its potential impact on study outcomes, is best suited to prepare the data in the results section. This person should also understand the manner in which adverse event information was collected and have the ability to map it into the appropriate data fields in ClinicalTrials.gov. These steps may be straightforward for a simple two-arm randomized, controlled study, but additional thought will need to be given to optimizing data presentation with complicated multi-step study designs or studies with distinct cohorts. Lessons learned have shown basic results entries have fewer errors and quality

review comments from ClinicalTrials.gov when the appropriate person (e.g., study statistician, principal investigator) enters the results information. Also, it is important to keep in mind that no matter who is involved with the submission process, the responsible party is ultimately accountable for the data submitted.

For NIDA Staff:

The Assigned Project Officers (POs) on the grant are responsible for ensuring that the PI/PD as listed on the grant has registered the trial, updated the trial and has submitted results in accordance with the final rule and NIH policy, utilizing the standardized NIDA Grant Award Checklist and/or progress reports.

The Project Manager (PM) on a multicenter contract or Interagency Agreement (IAA) is the "responsible party" for registering the trial, updating and submitting results in accordance with the final rule and NIH policy.

For research conducted at the NIDA Intramural Research Program (IRP) with NIDA IRP Principal Investigators, study information is entered into ClinicalTrials.gov by a designee at the Office of Protocol Services (OPS) based on the Initial Review Application and Protocol sent to them by the Addictions Institutional Review Board (IRB) office. OPS also develops a lay person summary for each study which is published on ClinicalTrials.gov.

PROCEDURE

FDAAA requires that a "responsible party" register and submit results for "applicable clinical trials" of drugs and devices. "Responsible party" and "applicable clinical trials" are defined in *FDAAA*, and further elaborated in NIH's "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial" document. Under *FDAAA*, the "responsible party" is responsible for submitting information for a clinical trial to the database. Briefly, the responsible party is defined as the sponsor or the principal investigator (if designated by the sponsor). For trials conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND or IDE holder is the sponsor.

For trials not conducted under an IND or IDE, the sponsor is the "initiator" of the trial (e.g., NIH grantee institution). Generally, applicable clinical trials include non-Phase 1/non-small feasibility, interventional studies of drugs, biological products or devices that have one or more sites in the US or are conducted under an IND or IDE. Specific criteria apply to applicable drug (including biologics) clinical trials and applicable device clinical trials. However, as part of the NIH complementary policy, **ALL** NIH-funded awardees and investigators conducting clinical trials, regardless of study phase, will be expected to register those clinical trials to ClinicalTrials.gov.

Under *FDAAA*, an applicable clinical trial must be registered in ClinicalTrials.gov via the Protocol Registration System (PRS) no later than 21 days after enrollment of the first participant[2]. After an applicable clinical trial is completed, the results must be submitted to ClinicalTrials.gov via the PRS no later than 12 months after

reaching the "completion date" or within 30 days of approval, licensure or clearance of the drug or device. The *FDAAA*-defined completion date is described in ClinicalTrials.gov as the "primary completion date" and is the date that the final subject was examined or received an intervention for purposes of final collection of data for the primary outcome.

The results information to be submitted is summary-level data for each arm of the trial in a tabular format that includes the following modules: participant flow (number of participants starting and completing), baseline characteristics, outcome measures and statistical analyses, and adverse events.

Table 1

	FDAAA	NIH / NIDA
What to Register	Applicable Clinical Trials	ALL NIH funded clinical trials
When to Register	At trial initiation (no later than 21 days of enrollment of the first subject); Update every 6 months for recruiting trials	At trial initiation (no later than 21 days of enrollment of the first subject); Updated at least every 6 months for recruiting trials
Results Reporting	Required for Applicable Clinical Trials Generally, submission within 12 months of the earlier of estimated OR actual trial completion date (of primary outcome) - independent of any cited publication	ALL NIH funded clinical trials Generally, submission within 12 months of the earlier of estimated OR actual trial completion date (of primary outcome) – independent of any cited publication
If Non-Compliant	Public Notice NIH funds withheld FDA sanctions, civil monetary penalties (up to $10,000 / day)	Public Notice NIH funds withheld

DOCUMENTATION

For Awardee Staff: The PI / PD will be responsible reporting their registration, update and the submission of results as part of the grant award progress report. The PI / PD should keep record (with dates) of their reporting and should include this with their progress reports for verification by the PO.

For NIDA Staff:

NIDA Project Officers will maintain records via progress reports and the NIDA grant application checklist. NIDA POs will check the PI's compliance with the reporting requirements by logging in to ClinicalTrials.gov to confirm the registration, updated status and results submission in accordance with timelines and regulations.

The NIDA Program Manager will maintain records of registration and results submission for contracts and IAAs.

A designee at the Office of Protocol Services enters study information into ClinicalTrials.gov for NIDA IRP Principal Investigators. The OPS also develops a lay person summary for each study which is published on ClinicalTrials.gov.

REFERENCES

(1) Tse T, Williams RJ, Zarin DA. Reporting basic results in ClinicalTrials.gov. *Chest*. 2009;136:295-303.

(2) Food and Drug Administration Amendments Act of 2007*. Public law 110-85.*

LINK

- Link on NIDA website where Extramural Staff can access SOP (insert link when available)
- https://clinicaltrials.gov/
- Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting
- Final Rule Webinar Series*:* https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar

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