ClinicalTrials.gov Requirements

Anthony Keyes, MBA, PMP, Program Manager, Clinical Research Projects

ClinicalTrials.gov Basics

- There a 2 systems
  - —Clinicaltrials.gov – Public-facing side
  - — Register.clinicaltrials.gov – Protocol Registration and Results System (PRS)
- There are 2 functions of the PRS
  - —Registration
  - —Results Reporting

ClinicalTrials.gov Program

- 3.5 FTEs
- Mission: Increase compliance, decrease institutional liability
- Assist the PI and study team with…
  - —Account creation and maintenance
  - —Initial registration
  - —Response to PRS reviewer comments (time-limited)
  - —Reminders to update and enter results
  - —Results reporting
    - Required for Applicable Clinical Trials (ACTS)
    - Required for any clinical trial receiving full or partial NIH funding
  - —Changes to PI/Study team (including when a PI leaves)
  - —Direct services ($50/hour)

ClinicalTrials.gov - Johns Hopkins Policy

IRB Policy 103.25: Organization Policy on Registration of Clinical Trials

- Updated to reflect the "Final Rule"
- Outlines:
  - What studies to register
  - When studies need to register, update, report results
  - Assigning the Responsible Party as the "Sponsor" (Johns Hopkins University)
  - Other Policy requirements

42 CFR Part 11
Clinical Trials Registration and Results Information Submission

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ClinicalTrials.gov Regulations

Entity	Registration	Results Reporting	Penalties
Food and Drug Administration (FDA)	Within 21 days of enrollment	Within 365 days of primary completion date for ACTs	• $11,569/study/day • Criminal proceedings
National Institutes of Health (NIH)	Within 21 days of enrollment	Within 365 days of primary completion date for clinical trials receiving NIH funding	Loss of grant funding (to include the institution)
Centers for Medicare & Medicaid Services (CMS)	All qualifying clinical trials	Study-specific	
National Cancer Institute (NCI)		Within 365 days of primary completion date of NCI-supported clinical trials (in a peer-reviewed journal and/or ClinicalTrials.gov)	Loss of grant funding
World Health Organization (WHO)	All clinical trials		
International Committee of Medical Journal Editors (ICMJE)	Prior to enrollment	None	Ineligibility to publish
Foundations (i.e., Gates)	Study-specific	Study-specific	Loss of funds

ClinicalTrials.gov - FDA Final Rule

Food and Drug Administration Amendments Act of 2007 (FDAAA) and Final Rule (42 CFR Part 11)

- Released September 2016, Effective January 2017, Compliance date April 2017
- Applies to Applicable Clinical Trials (ACTs)
- Registration must be within 21 days of first enrollment
- Record must be updated at least annually
- Record must be updated within 30 days (e.g., completion dates, recruitment status)
- Comments must be responded to within 15 calendar days (registration) or 25 calendar days (results)
- Results due 365 days from primary completion date

ClinicalTrials.gov - NIH Policy

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information NOT-OD-16-149, Release Date: April 16, 2016, Effective January 18, 2017

- Complementary to the Final Rule (released the same day)
- Applies to NIH-funded clinical trials regardless of study phase, type of intervention (even if not an ACT), includes behavioral interventions
- Does not apply to a clinical trial that uses NIH-supported infrastructure but does not receive NIH funds to support its conduct.
- Responsible Party is considered the Sponsor ("grantee organization for NIH-funded trials")
- Requires reporting of baseline race and ethnicity data (if collected)
- Requires submission of full protocol and statistical analysis plan at time of results reporting
- Instructs NIH to post results within 30 days of submission even if they do not meet quality control standards (this has yet to happen)

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Zarin D et al., Trial Reporting in ClinicalTrials.gov — The Final Rule. November 17, 2016
N Engl J Med 2016; 375:1998-2004. http://www.nejm.org/doi/full/10.1056/NEJMsr1611785

ClinicalTrials.gov - Dissemination Statement

- Applicants seeking NIH funding will be **required to submit a plan** for the dissemination of NIH-funded clinical trial information that will address how the expectations of the policy will be met.
- Upon receipt of an award, an awardee will be obligated to **adhere to their plan** through the terms and conditions of the award.
- The **required plan** can be a brief statement explaining whether the applicant intends to register and submit results information to ClinicalTrials.gov as outlined in the policy

Dissemination Plan Request sent to an Investigator (Northwestern)

As you may be aware, all clinical trial applications submitted on or after January 18, 2017 are to include a dissemination plan for clinical trials to be submitted for documentation in the official grant file. Please see guide notice NOT-OD-16-149 . Our records indicate that we have not received this required documentation for the above-referenced grant. The plan can be brief, but at a minimum it ***must contain sufficient information to assure that****:*

(1) the applicant will ensure that clinical trials under the award are registered and results information is submitted to ClinicalTrials.gov as outlined in the policy and according to the specific timelines stated in the policy;

(2) informed consent documents for the clinical trial(s) will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov; and

(3) ***the recipient institution has an internal policy in place*** *to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.*

Please submit a dissemination plan for the above mentioned grant via the AOR by (Date).

Courtesy of Priya Tripathi (Northwestern)

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ClinicalTrials.gov - NIH Clinical Trial Definition

Use the following four questions to determine the difference between a clinical study and a clinical trial:

1) Does the study involve human participants?
2) Are the participants prospectively assigned to an intervention?
3) Is the study designed to evaluate the effect of the intervention on the participants?
4) Is the effect being evaluated a health-related biomedical or behavioral outcome?

Note that If the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

ClinicalTrials.gov - NIH Clinical Trial Definition

Resources to Clarify the Definition

Case Studies
These simplified case studies illustrate the differences between clinical trials and clinical studies.

Decision Tree

FAQs
These FAQs further clarify the application of the clinical trial definition.

NOT-OD-15-015 Notice of Revised NIH Definition of "Clinical Trial" (Released 10/23/14)

ClinicalTrials.gov - Steps of Compliance

Steps to Compliance for NIH Awardees

NIH awardees must take specific steps to ensure compliance with NIH implementation of the NIH Policy on Dissemination of Clinical Trials Research and Section 801 of FDAAA, as implemented by 42 CFR Part 11.

Click on the titles to display contents. **Display All / Hide All**

Step 1 Determine if the competing application, contract proposal, funded grant, or awarded contract supports a clinical trial.

Step 2 Determine which regulations and/or policies apply to your NIH-funded clinical trial.

Step 3 Certify compliance in NIH grant applications, contract proposals and progress reports.

Step 4 Determine who is responsible for clinical trial registration and results reporting.

Step 5 Ensure the responsible entity registers the clinical trial no later than 21 days after enrolling the first subject.

Step 6 Ensure the responsible entity updates information in the clinical trial record at least once every 12 months.

Step 7 Ensure the responsible entity reports summary results not later than a year after clinical trial completion date.

https://grants.nih.gov/policy/clinical-trials/reporting/steps.htm

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ClinicalTrials.gov New Requirements

Two major changes impact applications submitted for due dates on or after January 25, 2018.

1. **Applicants are required to use FORMS-E.**
   New NIH "FORMS-E" Grant Application Forms and Instructions Coming for Due Dates On or After January 25, 2018 - NIH Guide Notice NOT-OD-17-062, Release Date: April 27, 2017

2. **Applications that include one or more clinical trials must be submitted in response to funding opportunity announcements (FOA) that allow for clinical trials.**
   Reminder: Policy on Funding Opportunity Announcements (FOA) for Clinical Trials Takes Effect January 25, 2018 - NIH Guide Notice NOT-OD-18-106, Release Date: November 30, 2017

Application form packages are designated alphabetically to indicate the most recent version (e.g., FORMS-D, FORMS-E)

ClinicalTrials.gov New Requirements

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Focus of changes:

- Consolidation of human subjects, inclusion enrollment, and clinical trial information previously collected across multiple agency forms
- Expansion and use of discrete form fields for clinical trial information to
  - provide the level of information needed for peer review;
  - lead applicants through clinical trial information collection requirements;
  - present key information to reviewers and agency staff in a consistent format; and
  - align with ClinicalTrials.gov (where possible) and position us for future data exchange with ClinicalTrials.gov
- Incorporation of recent Grants.gov changes to R&R Budget and SBIR/STTR Information forms

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ClinicalTrials.gov New Requirements

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Reminder: Policy on Funding Opportunity Announcements (FOA) for Clinical Trials Takes Effect January 25, 2018 - NIH Guide Notice NOT-OD-18-106, Release Date: November 30, 2017

"This notice reminds the community that, effective for due dates on or after January 25, 2018, NIH will require all applications involving one or more clinical trials be submitted through a Funding Opportunity Announcement (FOA) specifically designed and designated for clinical trials. This policy improves our ability to identify proposed clinical trials, ensure that key pieces of trial-specific information are submitted with each application, and uniformly apply trial-specific review criteria."

New ICMJE Policy

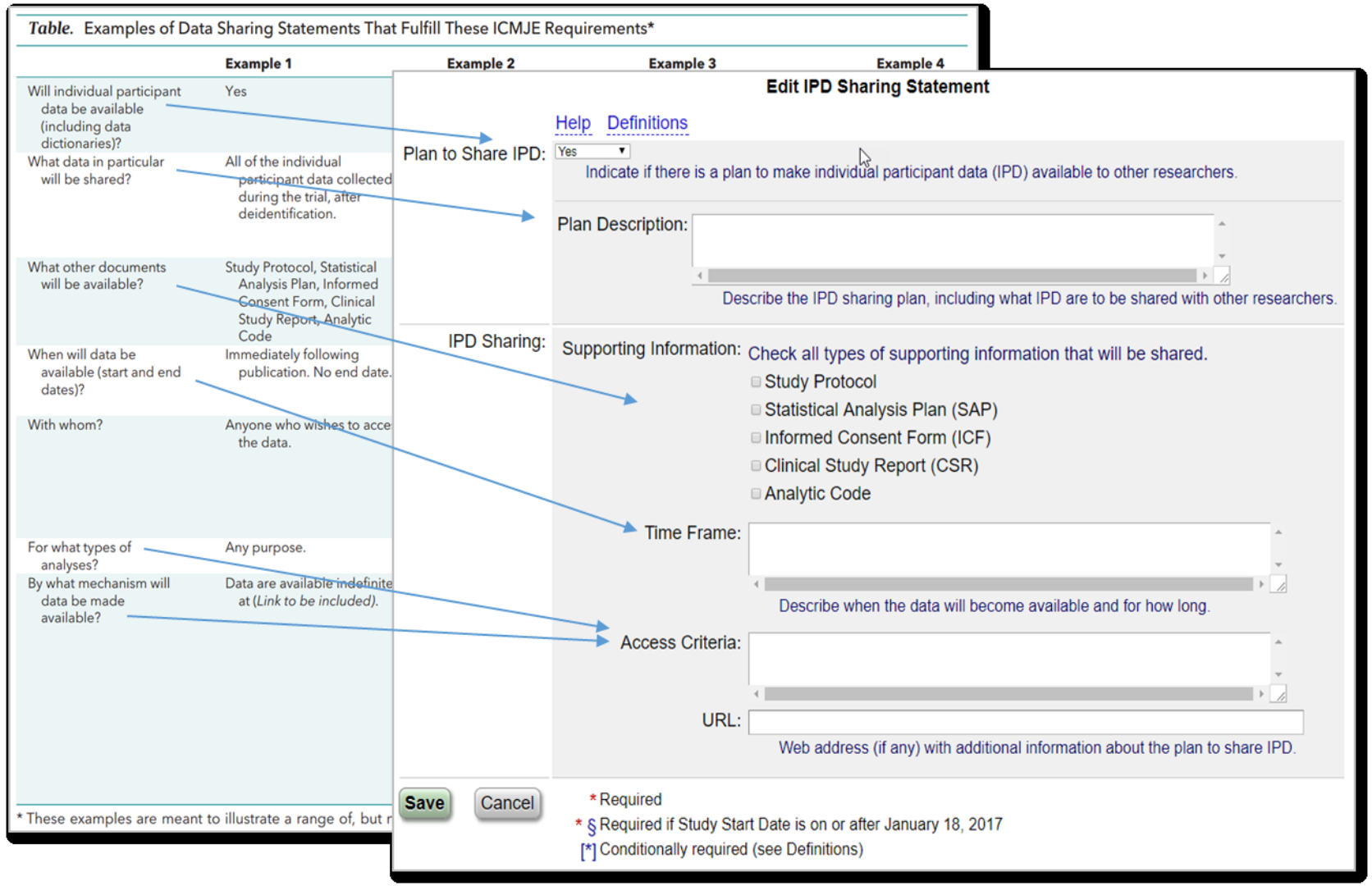

Table. Examples of Data Sharing Statements That Fulfill These ICMJE Requirements*

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes			
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.			
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code			
When will data be available (start and end dates)?	Immediately following publication. No end date.			
With whom?	Anyone who wishes to acce the data.			
For what types of analyses?	Any purpose.			
By what mechanism will data be made available?	Data are available indefinite at (*Link to be included*).			

* These examples are meant to illustrate a range of, but r

Edit IPD Sharing Statement

Help Definitions

Plan to Share IPD: Yes

Indicate if there is a plan to make individual participant data (IPD) available to other researchers.

Plan Description:

Describe the IPD sharing plan, including what IPD are to be shared with other researchers.

IPD Sharing:

Supporting Information: Check all types of supporting information that will be shared.

- Study Protocol
- Statistical Analysis Plan (SAP)
- Informed Consent Form (ICF)
- Clinical Study Report (CSR)
- Analytic Code

Time Frame:

Describe when the data will become available and for how long.

Access Criteria:

URL:

Web address (if any) with additional information about the plan to share IPD.

Save Cancel

* Required

* § Required if Study Start Date is on or after January 18, 2017

[*] Conditionally required (see Definitions)

- Data Sharing Statement: publication requirement
  - For trials that start enrolling participants on or after January 1, 2019, ICMJE will require **data sharing statements** *in the ClinicalTrials.gov registration* as a condition of publication
    - (These statements will be required in manuscripts submitted to ICMJE journals starting in July 2018)
  - In ClinicalTrials.gov, the data sharing statement is entered in the IPD Sharing Statement module

Courtesy of Scott Patton (Stanford)

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ClinicalTrials.gov Recommendations

1) Include a line item for “ClinicalTrails.gov registration, updating and Results Reporting” into all grants for clinical trials
2) Reach out to the Program with any/all questions
3) Register early (at the time of IRB submission)
4) Include multiple people on the “Access List”
5) Set reminders for the annual verification
6) Perform other updates within 30 days
7) Begin results entry 3 months prior to due date

registerclinicaltrials@jhmi.edu

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NIH Policy Sample Language – Example 1

Dissemination of study results through ClinicalTrials.gov registration and reporting at a minimum will include the following components:

- *X (insert name or role, can be a designee) will be responsible for handling ClinicalTrials.gov requirements for this project under the PI's oversight. S/he will register the trial prior to enrolling the first subject. Once a record is established, s/he will confirm accuracy of record content; resolve problems; and maintain records including content update and modifications. S/he will also be responsible for aggregate results reporting and AE reporting at the conclusion of the project.*
- *Add specifics related to this trial.*

Courtesy of Sarah White (Harvard)

NIH Policy Sample Language – Example 2

- As applicant for this award, I will ensure that clinical trials under the award are registered and results information is submitted to ClinicalTrials.gov as outlined in the policy and according to the specific timelines stated in the policy. Registration will occur no later than 21 days following enrollment of the first subject. Once a study record is established, required updates will be performed at least once every 12 months, or more frequently as required, confirming the completeness and accuracy of the study record. Summary results will be submitted by the standard results submission due date, and any required results updates will be submitted within the time frames specified in the ClinicalTrials.gov regulations.
- The sponsor institution has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with requirements contained in NIH Policy on the Dissemination of Clinical Trial Information (NOT-OD-16-149).
- Informed consent documents for this clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov.

Courtesy of Scott Patton (Stanford)

Resources

- High-level Summary of Form Changes in FORMS-E Application Packages
- Annotated Form Sets for NIH Grant Applications
- Do I Have the Right Form Version For My Application?
- Application Forms, Form Updates, and Choosing the Correct Forms FAQs
- NIH Guide to Grants and Contracts
- The National Cancer Institute Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials (Jan 28, 2015)
- NIH Office of Extramural Research (OER): Requirements for Registering & Reporting NIH-funded Clinical Trials in ClinicalTrials.gov
- Summary Table of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information
- NIH Data Sharing Policy