NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

Presentation to the Clinical Trials Registration Taskforce
December 15, 2016

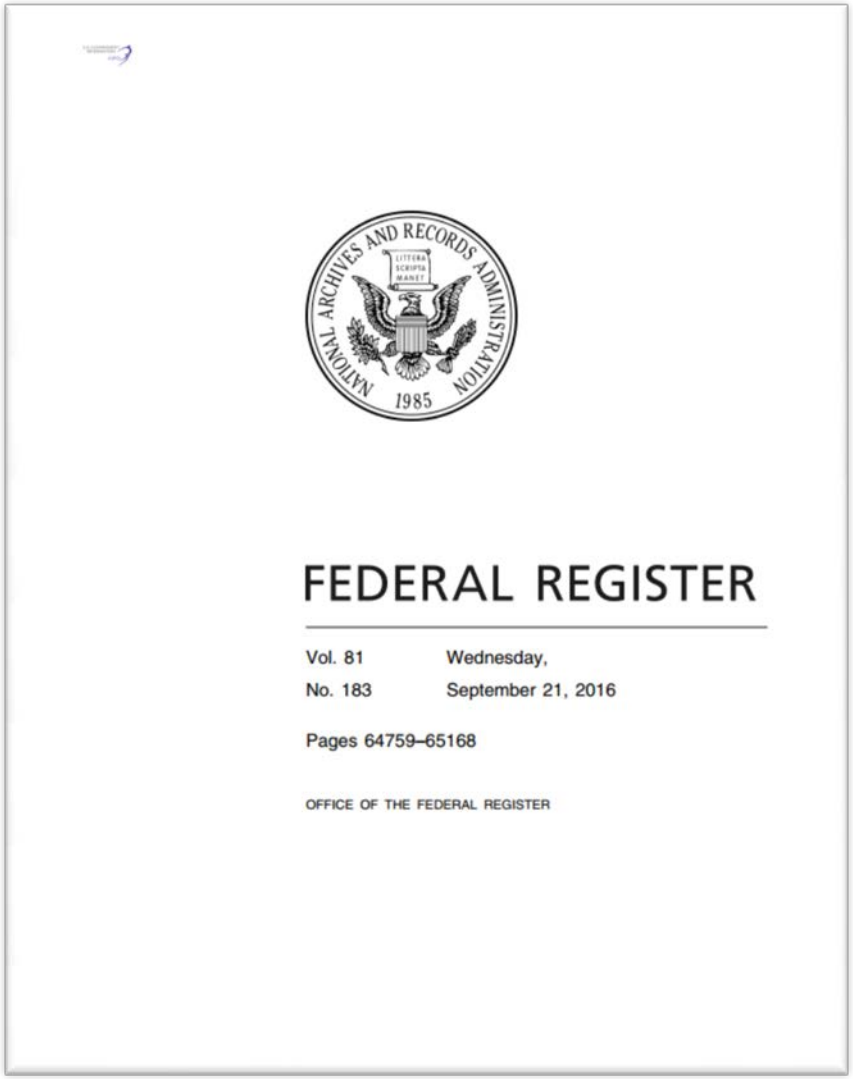
Sarah Carr
Valery Gordon, Ph.D., M.P.H.
Division of Clinical and Healthcare Research Policy
Office of Science Policy
Office of the Director
National Institutes of Health

NIH National Institutes of Health

Scientific and Public Health Benefits of Clinical Trial Transparency

- Enhances patient awareness
- Increases public access to information about interventions
- Informs the work of IRBs, policy makers, evidence based reviewers, meta-analysts
- Mitigates bias in medical evidence base (e.g., non-publication, especially negative results)
- Prevents duplication of unsuccessful trials and unsafe trials
- Informs design of future research and funding decision
- Meets ethical obligation to human subjects
  - Assure that clinical research results contribute to generalizable knowledge
  - Enhance human subjects protections by assisting review by IRBs
- Increases public trust in clinical research enterprise

Federal Register Publications
September 21, 2016



FEDERAL REGISTER

Vol. 81 Wednesday,
No. 183 September 21, 2016

Pages 64759–65168

OFFICE OF THE FEDERAL REGISTER

Clinical Trials Registration and Results Information Submission Final Rule
https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016-22129.pdf

NIH Policy on Dissemination of NIH-Funded Clinical Trial Information
https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016-22379.pdf

Purpose

- Establishes expectation that all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH, will ensure that their trials are registered at and results information submitted to ClinicalTrials.gov.

- Aims to promote broad and responsible dissemination of information from NIH funded clinical trials.

- Complements Clinical Trial Registration and Results Information Submission regulation (42 CFR Part 11).

Effective Date

January 18, 2017

Scope and Applicability

- Applies to all NIH-funded clinical trials regardless of study phase, type of intervention, or whether they are subject to the regulation.
- Applies to clinical trials funded through the extramural and intramural programs
  - Extramural: Applications for grants, other transactions, and contracts submitted on or after the effective date that request support for a clinical trial initiated on or after the effective date
  - Intramural: Clinical trials initiated on or after the effective date
- "Initiated" means enrollment of the first subject

Scope and Applicability (cont'd)

- Does not apply to a clinical trial that uses NIH-supported infrastructure, but does not receive NIH funds to support its conduct
  - Example: Facility in which clinical trial will be conducted was built with NIH funding, but the clinical trial itself is not funded by NIH
- Does not apply to NIH-funded clinical trials initiated before the effective date, but we encourage adherence

Scope and Applicability (cont'd)

- Encompasses clinical trials that are not "applicable clinical trials" under the statute and final rule, i.e., includes
  - Phase 1 trials of FDA-regulated drug and biological products.
  - Small feasibility studies of FDA-regulated device products.
  - Study of an intervention not regulated by the FDA (e.g., behavioral interventions)

Definition of a Clinical Trial

Clinical trial – A research study[1] in which one or more human subjects[2] are prospectively assigned[3] to one or more interventions[4] (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.[5]

1 See Common Rule definition of "research" at 45 CFR 46.102(d).
2 See Common Rule definition of "human subject" at 45 CFR 46.102(f).
3 The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
4 An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.
5 A "health-related biomedical or behavioral outcome" is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

Clinical Trial Decision Tree

- Does the study involve human participants?
- Are the participants prospectively assigned to an intervention?
- Is the study designed to evaluate the effect of the intervention on the participants?
- Is the effect that will be evaluated a health-related, biomedical, or behavioral outcome?

Note: observational studies and natural history studies are not clinical trials.

Responsibilities

- Applicants and offerors are required to submit a plan addressing how the expectations of the policy will be met.

- Awardees and investigators conducting NIH-funded clinical trials will be required to comply with all terms and conditions of award, including the plan.

- Responsibilities under the terms and conditions of award, fall into one of three categories, depending on whether, under the regulation, the clinical trial is an “applicable clinical trial” and the awardee or investigator is the “responsible party.”

Responsibilities (cont'd)

1. If the NIH-funded clinical trial **is an ACT** under the regulation and the awardee or investigator **is** the responsible party, the awardee or investigator will ensure that all regulatory requirements are met.
2. If the NIH-funded clinical trial **is an ACT** under the regulation but the awardee or investigator **is not** the responsible party, the awardee or investigator will coordinate with the responsible party to ensure that all regulatory requirements are met.
3. If the NIH-funded clinical trial **is not an ACT** under the regulation, the awardee or investigator will be responsible for carrying out the tasks and meeting the timelines described in regulation. Such tasks include registering the clinical trial in ClinicalTrials.gov and submitting results information to ClinicalTrials.gov.

Responsibilities (cont'd)

- Information will be posted on ClinicalTrials.gov
- Only one record for each trial, even those subject to the regulation and covered by the policy
- Informed consent documents are to include a specific statement relating to the posting of clinical trial information
  - Example: "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time." (From 21 CFR 50.25)

Definitions

Responsible Party: In the policy, the awardee or the investigator is responsible for meeting the expectations of this policy. In the regulation, a responsible party means, in part, the sponsor of the clinical trial or the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee.

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.

Registration Information: Includes descriptive information, recruitment information, location and contact information, and administrative data.

Results Information: Includes participant flow, demographic and baseline characteristics, outcomes and statistical analyses, adverse events, the protocol and statistical analysis plan, and administrative information.

Compliance with NIH Policy

- Required plan describing how applicant will meet the expectations of the NIH Policy will be a term and condition of award
- Failure to comply with terms and conditions of award may provide basis for enforcement actions, including termination, consistent with the Uniform Administrative Requirements, Cost Principles, and Audit Requirements for HHS Awards (45 CFR 75.371) and other authorities
  - See Section 8.5 of the NIH Grants Policy Statement
- Costs of compliance
  - Grantees are permitted to charge salaries of administrative and clerical staff as a direct cost
  - Administrative costs can be covered through indirect cost recovery

Compliance with NIH Policy (cont'd)

- If clinical trial is also an "applicable clinical trial," non-compliance with the statutory and regulatory requirements may lead to enforcement actions in 42 CFR 11.66

42 CFR 11.66 (c)

Under section 402(j)(5)(A) of the Public Health Service Act (42 U.S.C. 282(j)(5)(A)), if an applicable clinical trial is funded in whole or part by the Department of Health and Human Services, any required grant or progress report forms must include a certification that the responsible party has made all required registration and results submissions. If it is not verified that the required registration and results clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted, any remaining funding for a grant or funding for a future grant to such grantee will not be released. If the head of an HHS agency verifies that a grantee has not submitted such required clinical trial information, the agency head will provide notice to the grantee of the non-compliance and allow the grantee 30 days to correct the non-compliance and submit the required clinical trial information.

NIH Role in Compliance with 42 CFR part 11

- NIH will check grant and progress report forms for certification that information has been submitted
- NIH will verify that required information has been submitted before releasing any remaining funds for a grant or new funds for a future grant
- NIH will withhold funding from the grantee in the absence of verification
- If FDA determines that a responsible party is non-compliant and failure to submit required information is not remedied, NIH will inform the public through notices in ClinicalTrials.gov

Questions from Taskforce Members

- Does the policy apply to a “PI who is using NIH funds for a screening (not really a study)?”
- Does the policy apply to COBRE pilot grants that come from another institution within a university?
- Regarding the plan that is required to be submitted, how much detail is expected and where in the application should it be included?
- Why doesn’t NIH identify studies that will be accountable to the policy when grants are awarded?
- Will investigator A’s grant funds be withheld if Investigator B (same institution) has not fulfilled results reporting?
- To whom will NIH communicate about compliance issues?

Links to More Information

Final Rule

- https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016-22129.pdf
- https://clinicaltrials.gov/
- https://clinicaltrials.gov/ct2/manage-recs/present

NIH Policy

- https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016-22379.pdf
- http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials

Press Release Materials

- https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public

ClinicalTrials.gov Webinars

- https://www.nlm.nih.gov/bsd/disted/video/clinicaltrials/finalrulewebinar1.html
- https://www.nlm.nih.gov/bsd/disted/video/clinicaltrials/finalrulewebinar2.html
- https://www.nlm.nih.gov/bsd/disted/video/clinicaltrials/finalrulewebinar3.html

For More Information

Direct questions about the Rule to:

register@clinicaltrials.gov

Direct questions about the NIH Policy to:

clinicaltrials.disseminationpolicy@mail.nih.gov