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Clinical Research Newsletter

A Newsletter for Clinical Research Professionals

Clinical Trials Office, Columbia University

ClinicalTrials.gov Registration – What's New?

We will be offering 3 informational sessions to discuss the Final Rule and the NIH Policy, on 12/07/16, 12/13/16 and 12/16/16. All sessions will be held at 2pm in the Hammer Health Sciences Building, Room LL205. To sign up for a session, please contact CRCHelp@columbia.edu.

In an effort to increase the availability of information about clinical trials via ClinicalTrials.gov, the U.S. Department of Health and Human Services (HHS) issued a Final Rule on September 16, 2016 that describes requirements for registering certain clinical trials and submitting summary results information for certain clinical trials to ClinicalTrials.gov. The Final Rule, which will be codified at 42 CFR Part 11, becomes effective on January 18, 2017 and has a compliance date of April 18, 2017, which is 90 days after the effective date.

The National Institutes of Health (NIH) simultaneously released a complementary policy. This applies to all clinical trials funded wholly or partially by NIH where applications or proposals are received by the NIH on or after the effective date, as well as NIH-conducted trials where trials are initiated on or after the effective date. The NIH Policy also becomes effective on January 18, 2017, but does not outline a compliance period.

Which trials must be registered?

Currently, HHS requires that clinical trials that meet the definition of Applicable Clinical Trials (ACTs) be registered on ClinicalTrials.gov. The definition of ACT includes:

- Phase 2,3 and 4 interventional studies;
- Controlled clinical studies involving drugs, biological products and medical devices regulated by the Food and Drug Administration (FDA); and
- Studies having at least one site in the United States or one of its territories, investigate a product manufactured in and exported from the US, or are conducted under an Investigational New Drug (IND) or Investigational Device Exemption (IDE).

Excluded studies include Phase 1 drug trials, small feasibility/pilot studies of devices, behavioral interventions and non-interventional (observational) clinical research. While the Final Rule provides further clarification on ACTs, it does not change the definition of an ACT.

Important clarifications include the following:

- All interventional studies with pre-specified outcome measures, including those with one intervention group, would be considered "controlled."
- Trials that are initially registered as Phase 1/Phase 2 trials are considered to be Phase 2 trials and would be considered to be an ACT.

The complementary NIH Policy applies to *all* clinical trials funded by NIH, including studies that are not covered by the Final Rule.

Announcements

- Information sessions on the Final Rule and the NIH Policy will be offered in December. To attend a session, please RSVP here.
- Version 7 (October 2016) of the Clinical Research Handbook is now available. To access the handbook, please visit our website or EVPR's website.
- An optional Good Clinical Practice (GCP) training module is now available in Rascal: *TC3450 – Good Clinical Practice (GCP)*
- Starting January 1, 2017, the NIH will require NIH-funded researchers involved in clinical trials to be trained in GCP. The Rascal course, TC3450, can be used to fulfill the NIH's requirement. More information can be found on the last page of this newsletter.
- RecruitMe is currently live. To post your trial or schedule a training session, please contact Dominic Mathurin.

In addition to ACTs under the Final Rule, the NIH Policy applies to *all* other trials including:

- Phase 1 trials of drug and biological products;
- Small feasibility studies of device products; and
- Clinical trials of behavioral, surgical, and other types of health and medical interventions.

Who is responsible for registering ACTs?

The Final Rule does not change the definition of the person or entity responsible for registering an ACT. The Responsible Party is the person or entity who initiates the trial (Sponsor), conducts the trial (Principal Investigator), or does both (Sponsor-Investigator for IND/IDE trials).

For NIH grants, the awardee or the investigator is responsible for meeting the expectations of the NIH Policy. Applicants seeking NIH funding are *required* to submit a plan outlining how they will meet the policy's expectations. Awardees are *obligated* to adhere to the plan through the terms and conditions of the award.

It can be assumed that the Principal Investigator (PI) is the responsible party for all clinical trials that are not industry sponsored. An exception would be where Columbia University is a subaward site under a prime award made to another university; the PI at the other university would be the responsible party for registration purposes.

Which ACTs are subject to the Final Rule and NIH Policy?

Registration Information: The Final Rule only applies to ACTs with a Study Start Date on or after January 18, 2017. Trials that were initiated before January 18, 2017 will follow the Food and Drug Administration Amendments Act (FDAAA) statute.

Results Information: The Final Rule only applies to ACTs with a Primary Completion Date on or after January 18, 2017.

It is important to look at both the Study Start Date and Primary Completion Date when determining which requirements apply to a record.

Example: If the Study Start Date for a trial is June 2014 but the Primary Completion Date is July 2017, registration information will follow FDAAA regulations, but results information will follow the Final Rule.

The NIH Policy applies to clinical trials that do not necessarily meet the FDAAA's definition of an ACT. All NIH-funded clinical trials, whether they are assessing biomedical or behavioral outcomes, or whether they are employing an FDA regulated product, are covered by the policy. However, the policy does not apply to those clinical trials that were initiated before the effective date of January 18, 2017.

When does registration information need to be submitted to ClinicalTrials.gov?

The Final Rule does not change the deadline for registration of ACTs, which is no later than 21 days after enrolling the first participant. In the record, it is important to ensure that the Study Start Date notes the date that consent was obtained from the first study participant, rather than the date of IRB approval. The NIH Policy follows the same timeframe as the Final Rule.

What does registration information consist of?

The following information is requested to be submitted in the Registration portion of a record:

- Descriptive information about the trial
- Recruitment information
- Location and contact information
- Administrative data

In addition to some new data elements (indicated by new), the existing data elements that are newly required for completion by the Final Rule include:

Study Identification

- Official Title
- Secondary IDs and ID Type - including unique identifiers from NIH grant numbers, if applicable

Study Status

- Overall Recruitment Status
- Why Study Stopped, if terminated, withdrawn, suspended
- Study Start Date
- Study Completion Date
- Expanded Access Status - indicating current availability status

Sponsors/Collaborators

- Responsible Party Contact Information new—not disclosed to the public

Oversight

- Studies a U.S. FDA-regulated Device Product new
- Studies a U.S. FDA-regulated Drug Product new
- Device Product Not Approved or Cleared by U.S. FDA new
- Product Manufactured in and Exported from the U.S. new
- Pediatric Post-market Surveillance of a Device Product new

Study Design (All sub-elements)

- Expanded Access Type new - individual patient, intermediate, treatment use
- Primary Purpose - new dropdown option: device feasibility
- Enrollment

Arms and Interventions

- Other Names (used to identify the intervention), if any
- Intervention Description

Outcome Measures

- Primary Outcome Measure (POM) Description
- Secondary Outcome Measure (SOM) Description

Eligibility

- Accepts Healthy Volunteers

The NIH Policy follows the same registration requirements as the Final Rule.

When must clinical trial registration information be updated?

	Trials initiated before January 18, 2017 (FDAAA)	**Trials initiated after January 18, 2017 (Final Rule)**
General updates	Once per year	Once per year
15 calendar day updates	N/A	Only for a change in the approval or clearance status of a device product not approved or cleared by the FDA
30 calendar day updates	Any change in the following: ● Overall Recruitment Status ● Primary Completion Date	Any change in the following: ● Study Start Sate ● Intervention Name ● Availability of Expanded Access ● Overall Recruitment Status ● Individual Site Status ● IRB Review Status ● Primary Completion Date ● Study Completion Date ● Responsible Party (RP) ● Contact for RP
Comments (errors, deficiencies and/or inconsistencies identified) related to registration information	N/A	Correct or address within 15 calendar days
Comments (errors, deficiencies and/or inconsistencies identified) related to results information	N/A	Correct or address within 25 calendar days

The NIH Policy follows the same timeline for registration updates as the Final Rule.

When does results information need to be reported to ClinicalTrials.gov?

In general, results information must be submitted no later than 1 year after the primary completion date of an ACT. The Primary Completion Date is the date that the final subject was examined or received an intervention for the purpose of collecting the data for the primary outcome measure.

The submission deadline may be delayed for up to 2 additional years (a total of 3 years after the trial's Primary Completion Date) if the responsible party submits a certification to ClinicalTrials.gov that either:

1) a drug, biological, or device product studied in the clinical trial is not yet approved, licensed, or cleared for marketing by the FDA and is still under development by the manufacturer; or

2) that the manufacturer is the sponsor of the clinical trial and has sought or will seek approval, licensure, or clearance for a new use of a product studied in the trial within 1 year.

In addition, responsible parties can request an extension to the results information submission deadline for "good cause." The request must contain a description of the reason(s) why clinical trial results information cannot be provided according to the deadline, and an estimate of the date on which the clinical trial results information will be submitted.

While the Final Rule does not change the standard deadline for reporting primary outcome measure data, it does establish deadlines for submitting results information for secondary outcome measures and/or adverse event information that have not been collected by the Primary Completion Date. The NIH Policy follows the same timeline for results information submission as the Final Rule.

Type of Results Information	Deadline
Primary Outcome Measure	Up to 1 year from the primary completion date
Secondary Outcome Measure	Up to 1 year from the study completion date new
Adverse Event (AE) Information	Up to 1 year after date of AE data collection new

What does results information consist of?

If collected, the following information is requested to be submitted in the Results portion of a record:

- Participant flow to track progress of subjects through the trial by treatment group
- Demographic and baseline characteristics for the entire population of subjects in the trial
- Outcomes and statistical analyses for each primary and secondary outcome measure included in the statistical analysis plan (SAP)
- Adverse Event (AE) information [1]
- Protocol and SAP [2]
- Administrative information (e.g., point of contact to obtain information about results posted)
- Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared device products

[1] Adverse event information consists of one table that summarizes all serious adverse events (SAEs) experienced by subjects enrolled in the clinical trial, and another table that summarizes non-serious AEs that exceed a frequency of 5% in any arm of the clinical trial. The Final Rule adds a third table for summarizing all-cause mortality, with the number and frequency of deaths due to any cause by arm.

[2] The Final Rule requires the submission of a copy of full protocol and SAP (if separate from the protocol) at the time of results information submission. These documents must include all amendments that have been approved by the IRB, and must be submitted in PDF; it is important that the latest version is submitted at the time of results submission.

In addition to some new data elements (indicated by new), the existing data elements that are newly required for completion by the Final Rule include:

Participant Flow
- Arm/Group Title and Description
- Pre-Assignment Details, in any
- Participant Data new - description of the unit of assignment, if other than 'participants', and number of units that started and completed the clinical trial, by arm

Baseline Characteristics
- Arm/Group Title and Description
- Overall Number of Units Analyzed new, if unit is other than 'participants'
- Analysis Population Description
- Race and Ethnicity, if collected under protocol
- Other measures assessed at baseline and used in the analysis of POM
- Measure Type and Measure of Dispersion - new dropdown option: count of participants, count of units, and geometric least squares mean
- Number of Baseline Participants (and Units) new, if unit is other than 'participants'

Outcome Measures
- Arm/Group Title and Description
- Analysis Population Description
- Outcome Measure Description - metric used to characterize specific outcome measure
- Type of statistical test conducted - superiority, non-inferiority, equivalence, or other new

Adverse Events
- Time Frame
- Additional Description (e.g., different definition of AE/SAE)
- Assessment Type - collection approach, whether systematic or non-systematic
- Arm/Group Title and Description
- All-cause mortality new
- Organ system - new dropdown menu option: product issues

The NIH Policy follows the same results submission requirements as the Final Rule.

What are potential consequences of noncompliance?

Records will be identified as noncompliant on www.ClinicalTrials.gov under the Final Rule and the NIH Policy, and failure to comply may provide a basis for enforcement actions. Specifically, responsible parties may face civil monetary penalties of up to $10,000 per day. Moreover, grant funding can be withheld if required reporting cannot be verified for federally funded trials. Similarly, noncompliance may lead to suspension or termination of grant or contract funding under the NIH Policy, which could be considered in future funding decisions.

ICMJE Recommendations

The International Committee of Medical Journal Editors (ICMJE) proposes comprehensive trial registration as a solution to the problem of selective awareness of research data. The ICMJE Recommendations encourage journal editors to require that all clinical trials be entered in a public registry before the start of participant enrollment in order for the trials to be considered for publication.

This policy applies to any "clinical trial" starting enrollment after July 1, 2005. ICMJE defines a clinical trial as *"any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome."* Health-related interventions include any intervention used to modify a biomedical or health-related outcome (e.g., drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase 1 trials), would be exempt.

Although ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, it does not require results reporting for registered trials.

The Final Rule does not affect the ICMJE clinical trial registration policy. Interested parties are encouraged to explore the policies of the ICMJE and of the journals to which they seek to submit papers.

Summary Table of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information

Element	Final Rule	NIH Policy	ICMJE
Scope/ Applicability	• Applicable clinical trials of FDA-regulated drug, biological, and device products and pediatric post-market surveillance studies of devices required by the FDA under the FD&C Act. • Does not apply to phase 1 trials or small feasibility device studies. • Applicable clinical trials are (1) clinical trials of drug and biological products that are controlled, clinical investigations, other than phase 1 investigations, of a product subject to FDA regulation; and (2) prospective clinical studies of health outcomes comparing an intervention with a device product against a control in humans (other than small feasibility studies) or any pediatric post-market surveillance studies required by FDA under the FD&C Act. • Applies to public and private sector sponsors and other entities who meet the definition of a responsible party.	• All clinical trials funded wholly or partially by NIH • Includes phase 1 clinical trials and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions • Applies to NIH-funded clinical trials where applications or proposals are received by NIH on or after the policy's effective date • Applies to NIH-conducted clinical trials initiated on or after the policy's effective date • Identifying clinical trial record as non-compliant in ClinicalTrials.gov • For federally funded trails, grant funding can be withheld if required reporting cannot be verified • Civil monetary penalties of up to $10,000/ day (amount to be adjusted going forward)	Interventional studies (any intervention type or phase)
Timeframe for registration on ClinicalTrials.gov	Not later than 21 days after enrollment of the first participant.	Same	Prior to enrollment of first participant
Registration data elements to be submitted to ClinicalTrials.gov	Elements defined in the final rule. Consists of descriptive information, recruitment information, location and contact information, and administrative data.	Same	Similar; the WHO Trial Registration Data Set (TRDS) https://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf
Timeframe for results information submission to ClinicalTrials.gov	Not later than 12 months after primary completion date; possible delay of up to an additional 2 years for trials of unapproved products or of products for which initial FDA marketing approval or clearance is being sought, or approval or clearance of a new use is being sought.	Same	N/A (Encouraged, but policy restricted to registration)
Results information data elements to be submitted to ClinicalTrials.gov	Elements defined in the final rule. Includes participant flow, demographic and baseline characteristics, outcomes and statistical analyses, adverse events, the protocol and statistical analysis plan, and administrative information.	Same	N/A (Encouraged, but policy restricted to registration)
Potential Consequences of Noncompliance	• Identifying clinical trial record as non-compliant in ClinicalTrials.gov • For federally funded trails, grant funding can be withheld if required reporting cannot be verified • Civil monetary penalties of up to $10,000/day (amount to be adjusted going forward)	• May lead to suspension or termination of grant or contract funding • Can be considered in future funding decisions • Identifying clinical trial record as non-compliant in ClinicalTrials.gov	May not be eligible for journal publication
Effective Date	January 18, 2017. Compliance date is 90 days from the effective date.	January 18, 2017	N/A

Disclosing registration in the Informed Consent Form

For any clinical trial subject to the Final Rule or the NIH Policy, the following statement must be reproduced word for word in the applicable informed consent documents: “A description of this clinical trial will be available on http://ClinicalTrials.gov, as required by U.S. law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.”

Additional Resources

- We will be offering 3 informational sessions to discuss the Final Rule and the NIH Policy, on 12/07/16, 12/13/16 and 12/16/16. All sessions will be held at 2pm in the Hammer Health Sciences Building, Room LL205. To sign up for a session, please contact CRCHelp@columbia.edu.
- *CUMC Clinical Research Handbook - Version 7* has been updated to incorporate necessary changes from the Final Rule and the NIH Policy regarding ClinicalTrials.gov registration (*See pages 73-76 in the Handbook*).
- Registered Protocol and Registration and Results System (PRS) users may access additional resources regarding Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting and Final Rule Information on the PRS website.
- Training materials and online presentations, such as the Final Rule Webinar Series hosted by the National Library of Medicine (NLM), are available on the ClinicalTrials.gov website.

Updates

- Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials was released on September 16, 2016. This policy establishes the expectation that investigators on NIH-funded clinical trials to complete training in Good Clinical Practice (GCP) every 3 years. The new policy, which takes effect on January 1, 2017, requires GCP training for all NIH-funded investigators and clinical trial site staff with responsibilities for the conduct, management and oversight of NIH-funded clinical trials. The University has an established GCP course, TC3450, which links to the Collaborative Institutional Training Initiative (CITI) training website and satisfies the NIH requirement. The course must be accessed through the Rascal Training Center. The requirement may also be met through GCP training from third-party providers with documentation of completion within the past three years. Completion of TC3450 or another approved GCP course will be reflected on the Rascal IRB Data Sheet. The policy affects individuals on active trials as well as future awards. For questions, please contact NIH-GCP@columbia.edu.

  NOTE: GCP training does not replace Human Subjects Protection training (TC0087).

Clinical Trials Office (CTO)

Our mission is to facilitate quality clinical trial research by providing the CU research community with comprehensive administrative services that help move trials quickly from initial proposal through contract execution. We also provide regulatory support for FDA-regulated research.

We’re on the Web!

Visit us at:

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Research Funnies