Yale University Human Research Protection Program

HRPP Policy 1000 Clinical Trial Registration and Reporting Requirements

Responsible Office	Office of Research Administration	Effective Date	04/18/2017
Responsible Official	Director, Human Research Protection Program	Last Revision	04/18/2017

Scope

This policy applies to Yale conducted clinical trials subject to registration and disclosure requirements set forth in federal requirements set forth below.

- Final Rule for Clinical Trials Registration and Results Information Submission, 42 CFR Part 11
  Issued September 16, 2016; Effective January 18, 2017
- Final NIH Policy on the Dissemination of NIH-funded Clinical Trial Information, 81 FR 64922
  Published September 21, 2016; Notice Number NOT-OD-16-149, effective January 18, 2017
- The 2007 Food and Drug Administration Amendments Act (FDAAA), Section 801
  US Public Law 110-85
- The 1997 Food and Drug Administration Modernization Act (FDAMA), Section 113
  US Public Law 105-115

In addition, this policy's scope addresses the Centers for Medicare and Medicaid Services (CMS) clinical trial identifier requirement for all billing claims related to clinical trials outlined in the *Medicare National Coverage Determination (NCD) Manual*, Section 310.1–Pub. 100-03, as well as requirements established by the International Committee of Medical Journal Editors (ICMJE) related to trial registration outlined in *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journal*, December 2016.

Note: Compliance with trial registration and disclosure requirements that may be required by non-US agencies and organizations is not addressed by this policy.[1]

For an overview of the ClinicalTrial.gov trial disclosure requirements, see Attachment 1 ("ClinicalTrial.gov Disclosure Requirements - Frequently Asked Questions").

Policy Statement

Yale is committed to the disclosure of clinical trial information and results as an integral component of the research and education mission of the University and as required by applicable federal requirements. The goals of clinical trial registration and results dissemination enable Yale to fulfill regulatory requirements and its ethical obligations to research participants, the public, and the medical and scientific community by reducing publication bias and disseminating crucial scientific information regarding research studies.

Overview

Section 113 of the 1997 Food and Drug Administration Modernization Act (FDAMA) was the first federal law to require the NIH to create a public information resource regarding certain clinical trials regulated by the FDA.[2] In accordance with that Act, the NIH National Library of Medicine (NLM) developed ClinicalTrials.gov, and on February 28, 2000, the website was made available to the public. In 2007, the FDA Amendments Act of 2007, Section 801 (FDAAA) expanded the ClinicalTrial.gov submission requirements to require more types of trials to be registered, additional trial registration information, and the submission of summary results.

In September 2016, DHHS issued a Final Rule (42 CFR Part 11) that clarifies and expands the ClinicalTrials.gov registration and results submission requirements outlined in FDAAA 801.[3] The NIH issued a complementary policy (NOT-OD-16-149). The NIH policy is similar but broader than the Final Rule as it applies to all clinical trials funded in whole or in part by NIH regardless of study phase, type of intervention, or whether they are subject to the Final Rule. Specifically, the NIH definition of clinical trial includes those excluded from the Applicable Clinical Trial definition in 42 CFR 11.10 (phase 1 studies, small feasibility studies, *and trials that do not involve any FDA-regulated product such as trials involving only behavioral interventions*). See, the following for examples of what types of studies are defined as clinical trials based on the NIH policy definition: http://osp.od.nih.gov/sites/default/files/Case_Studies.pdf.

The effective date of the Final Rule and the NIH Policy is January 18, 2017. Compliance with the Final Rule is required by April 18, 2017. Failure to comply with the Final Rule and NIH Policy may have significant implications such as possible penalties including: criminal proceedings, civil penalties up to $11,000 per day, the withholding or loss of DHHS and NIH funds for the investigator and institution, and public notice of failure in the registry/results database.[4]

In addition to changes to DHHS regulations and NIH Policy, CMS requires a clinical trial number to be reported on all claims for items and services provided in clinical trials that are qualified for

[1] For information regarding other registries, see *International Clinical Trials Registry Platform (ICTRP)* located at http://www.who.int/ictrp/network/en/.
[2] FDMAA 113 required that federally or privately funded clinical trials conducted under an investigational new drug applications (IND) to test the effectiveness of experimental drugs for patients with serious or life-threatening diseases or conditions. See, https://clinicaltrials.gov/ct2/about-site/history#FinalRuleFDAAA801
[3] See, https://clinicaltrials.gov/ct2/about-site/history#FinalRuleFDAAA801; https://clinicaltrials.gov/ct2/manage-recs/fdaaa#DevelopmentOfRegulations; https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf.
[4] For more information regarding the history of ClinicalTrials.gov, see https://clinicaltrials.gov/ct2/about-site/history and https://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#5053.

coverage as specified in the *Medicare National Coverage Determination (NCD) Manual*, Section 310.1-Pub. 100-03. It should also be noted the ICMJE requires registration of an interventional study (not limited to ACTs) prior to enrollment of the first patient in an online repository such as ClinicalTrials.gov to publish in an ICMJE journal.

Definitions

Applicable Clinical Trial (ACT)

An "Applicable Clinical Trial" is the term defined in 42 CFR Part 11.10 to designate the category of trials that are subject to registration and result reporting requirements.[5]

- For Trials of Drugs and Biologics:
  An "Applicable Drug Clinical Trial" is defined as a controlled clinical investigation, other than a phase I investigation, of a drug or biologic that is the subject of an approved new drug application (NDA) or biologics license application (BLA) or requires an approved NDA or BLA in order to be legally marketed.

- For Trials of Devices:
  An "Applicable Device Clinical Trial" is a prospective clinical study of health outcomes that compares an intervention with a device against a control in human subjects. The studied device is subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FDC Act). Applicable clinical trials do not include small clinical trials to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes. Pediatric postmarket surveillance studies are applicable device clinical trials.

  Note: A study in which a device is used or a drug administered on a patient as part of routine medical care and not under a study or protocol is not an applicable clinical trial. Expanded access protocols under section 561 of the FDC Act are also not applicable clinical trials. A trial may still be an applicable clinical trial even if all the sites are outside the U.S. and its territories, depending on where and under what circumstances the device or drug is manufactured.

Clinical Trial

42 CFR 11.10 Definition

"Clinical trial" means: "a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes." 42 CFR 11.10(a).

NIH Policy Definition

"Clinical Trial" means: "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.'' This definition encompasses phase I trials of FDA-regulated drug and biological products, small feasibility studies of FDA-regulated device products, and studies of any intervention not regulated by the FDA, e.g., behavioral interventions. ***The NIH definition of "clinical trial" is broader than***

[5] See, Checklist for Evaluation Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT Under 42 CFR 11.22(b) for Clinical Trials Initiated on or after January 18, 2017, https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf; flowchart Identifying an "Applicable Clinical Trial" under FDAA, https://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf.

the term "Applicable Clinical Trial" as defined in the regulation" and includes those excluded from the Applicable Clinical Trial definition in the Final Rule (phase 1 studies, small feasibility studies, and trials that do not involve any FDA-regulated product such as trials involving only behavioral interventions). NIH Policy, NOT-OD-16-149.[6]

ICMJE Definition
A "Clinical Trial" defined by ICMJE is "Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration." See, *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journal*, December 2016.[7]

CMS Clinical Trials Policy Definition
The CMS Clinical Trials Policy defines a "Qualifying Trial" as follows: (1) The subject or purpose of the trial is the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids); (2) The trial is not designed exclusively to test toxicity or disease pathophysiology and must have therapeutic intent; and (3) Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers, although trials of diagnostic interventions may enroll healthy patients to have a proper control group. *Medicare National Coverage Determination (NCD) Manual*, Section 310.1-Pub. 100-03.[8]

Clinical Trial Information
Clinical trial information means the data elements, including clinical trial registration information and clinical trial results information, that the responsible party is required to submit to ClinicalTrials.gov, as specified in section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)) and this part. 42 CFR 11.10.[9]

ClinicalTrials.gov
ClinicalTrials.gov is a searchable, public registry, and results database of clinical studies. See "Protocol Registration and Results System" below.

The Food and Drug Administration Modernization Act of 1997 (FDAMA)

[6] See, https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html; 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. See also, the following case studies for examples of what types of studies are defined as clinical trials based on the NIH policy definition: http://osp.od.nih.gov/sites/default/files/Case_Studies.pdf.
[7] See, *Recommendation for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journal*, updated December 2016 (http://www.icmje.org/news-and-editorials/icmje-recommendations_annotated_dec16.pdf.); See, http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/
[8] https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM8401.pdf; https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS014961.html
[9] Specific registration information is available at the following URL: https://www.ecfr.gov/cgi-bin/text-idx?SID=07f25d8d5bb316afacc2ce6e7c672123&mc=true&node=se42.1.11_128&rgn=div8

Section 113 of the Act requires registration in a public database of any clinical trial conducted under an investigational new drug (IND) application if it is for a drug to treat a serious or life-threatening disease or condition and it is a trial to test effectiveness.

The Food and Drug Administration Amendments Act of 2007 (FDAAA)
Section 801 of the Act requires registration and results reporting of all Applicable Clinical Trials (ACTs) of drugs, biologics, and devices.

International Committee of Medical Journal Editors (ICMJE) publishing requirements
The ICMJE is a group of medical journal editors whose clinical trial registration policy requires prospective, health-related interventional clinical trials to be registered into a public registry before the start of participant enrollment, as a condition for publication in their member's journals. This policy has also been adopted by a majority of non-ICMJE journals.

NCT number
National Clinical Trial (NCT) number, another term for the ClinicalTrials.gov registry number unique to each record. The format for the ClinicalTrials.gov registry number is "NCT" followed by an 8-digit number, e.g.: NCT00000419.

Primary Completion Date
The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome measure, 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 upon which data collection is completed for all of the primary outcomes. The due date for reporting results for an ACT is 12 months from the Primary Completion Date (not the Study Completion Date).

Protocol Registration and Results System (PRS)
The system used to enter the clinical trial information that is posted for public access on the ClinicalTrials.gov website: https://register.clinicaltrials.gov/.

Responsible Party
"Responsible Party" (RP) is the term used in 42 CFR Part 11.10 and NIH Policy (NOT-OD-16-149) to designate the entity or individual responsible for the clinical trial and for submission of clinical trial information. A RP is the sponsor OR a designated principal investigator of the clinical trial.

The RP may be an organization (such as a drug or device manufacturer, a university or academic medical center, or a government research organization such as the NIH), or an individual. The Principal Investigator may be designated as the RP of a trial if so designated by a sponsor, grantee, contractor, or awardee (provided that "the principal investigator 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" for submitting information under the law).

Study Completion Date
Final date on which data was (or is expected to be) collected.

Policy Sections

1000.1 Identification of Responsible Party for ClinicalTrials.gov registration and reporting

A "Responsible Party" (RP) as defined herein is the term used to designate the entity or individual responsible for registering the clinical trial, maintaining the registration until completion, and reporting results.

- For Yale PI-initiated studies, the RP generally should be:
  - "Sponsor-Investigator" for Yale PI-initiated clinical trials conducted under an IND or IDE
  - "Sponsor" for all other studies

- For studies that involve an Investigational New Drug (IND) or Investigational Device Exemption (IDE), the RP may be the PI or someone other than the PI (e.g., Yale University, industry sponsor, etc.). (Typically, the name of the IND/IDE holder should be entered as the RP.)

- For industry-sponsored or multi-site trials the industry sponsor or lead site generally is responsible for registration and results submission. (**Note:** the Yale PI should consult with commercial sponsors to assure that posting of a trial is in accordance with terms of the study contract.)

In the event a PI who is designated as the RP of a registered trial leaves Yale, or no longer meets the definition of who may serve as the RP, the PI will ensure that the registration and reporting obligations are either transferred to the new institution, to another investigator at Yale who has the authority to serve as the RP and receives prior approval in accordance with University policy, or to Yale. If a PI who is designated as a RP for a study transfers from another institution to Yale, the PI must receive approval to serve as the RP in accordance with University policy. If a study is transferred and a Yale PI cannot be identified as the RP, Yale will be identified as the RP.

The Yale Center for Clinical Investigation (YCCI) (in collaboration with and the Yale Center for Analytical Sciences (YCAS)) is prepared to assist the RP with trial disclosure activities.

1000.2 Types of clinical trials subject to disclosure requirements

The RP must use ClinicalTrials.gov to register and/or submit trial results when satisfying disclosure requirements set forth in federal requirements. As defined in the definition section herein, the following types of clinical trials are subject to registration and disclosure requirements:

- "Applicable Clinical Trials" (ACTs) as defined in 42 CFR 11.10

- "Clinical Trials" that are funded either in whole, or in part, by NIH and meet the NIH Policy definition

Note: The definition of Clinical Trial under the NIH Policy is broader as it includes ACTs under the Final Rule **AND** those trials excluded by the Final Rule listed below:

  - (Non-serious/life-threatening) Phase 1 drug trials, including studies in which drugs are used as research tools to explore biological phenomena or disease processes

  - Small clinical trials to determine the feasibility of a device or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes
  - Trials that do not include drugs, biologics, or devices (e.g., behavioral interventions)

- For publication purposes, "Clinical Trials" that meet the ICMJE definition

  Note: "ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. The ICMJE accepts registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html) or in ClinicalTrials.gov.

- "Qualifying Trials" as defined by CMS for research-related claims billed to CMS

1000.3 Registration of clinical trial results

For clinical trials subject to NIH Policy and the Final Rule, the RP must:

- Register the study on ClinicalTrials.gov no later than 21 days after the first subject enrollment.
- Update registration information no less than once every 12 months with the understanding that certain information may be required to be updated more frequently.
- Complete an expanded access registration if an investigational drug product studied in an applicable drug clinical trial is available through an expanded access.

  The RP should only create one expanded access record for each investigational drug product however, that multiple ACTs can be linked to the same record if they study the same product.

IMPORTANT CONSIDERATIONS:

- If an investigator plans to publish, s/he should be aware that the ICMJE requires that the clinical trial registration by the PI or designee occurs prior to the enrollment of the first subject. Failure to do so will restrict publications in journals that follow ICMJE recommendations. As noted above, the ICMJE accepts registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html) or in ClinicalTrials.gov.
- CMS requires registration of Qualifying Trials before claims are submitted to Medicare. (For Qualifying Trials, the National Clinical Trial (NCT) number must be included by the PI or designee on claims for items and services provided in clinical trials that are qualified for coverage as specified in the "Medicare National Coverage Determination (NCD) Manual," Section 310.1-Pub. 100-03.) If a clinical trial does not qualify, then the costs for all items and services related to the clinical trial cannot be billed to Medicare.

1000.4 Results reporting

For clinical trials subject to NIH Policy and the Final Rule:

- Summary results for the primary outcome measure(s) must be entered by the RP no later than twelve (12) months after the study's Primary Completion Date (the last subject's last visit).
- Results for secondary outcome measures must be entered by the RP one (1) year after the date on which the final research participant is examined or receives intervention for the purposes of final collection for the secondary outcome measure.
- Certain information may be required to be updated more frequently.

Note: ICMJE and CMS do not have results reporting requirements.

In order to comply with these requirements, the RP will rely on the IRB record of approved studies in IRES-IRB and the Clinical Trial Management System (Oncore).

1000.5 University obligations to provide assistance and oversight

Yale University serves as the designee to provide assistance and ensure compliance with ClinicalTrial.gov disclosure requirements and this policy. This will be accomplished and coordinated in conjunction with the Yale Center for Clinical Investigation (YCCI), the Yale Center for Analytical Sciences (YCAS), the Human Research Protection Program (HRPP), the Office of Research Compliance, and each investigator conducting research. The Yale Center for Clinical Investigation (YCCI) (in collaboration with and the Yale Center for Analytical Sciences (YCAS)) is charged with providing support regarding ClinicalTrial.gov registration and reporting activities for Yale University investigators and their staff who are involved in the conduct, oversight, or management of research involving human subjects.

1000.6 Consequences of noncompliance

The failure to comply with federal requirements for trial registration and reporting in ClinicalTrials.gov may result in:

- Penalties to the RP of up to $11,000 per day (amount may be adjusted)
- The withholding of remaining or future NIH funding to the institution or investigator or recovery of monies already allocated
- Public notice of failure in registry/results database.
- Injunction action or criminal prosecution brought by the Department of Justice (DOJ) for prohibited acts.

The consequences for the failure to register a trial may also result in rejection of the publication by ICJME if the PI plans to publish or a denial of claims by CMS.

In addition to the above, the University may address the failure to comply with clinical trial disclosure requirements as follows: Escalation to the Yale Institutional Official, University Research Compliance Officer, HRPP Director, or designee for a determination regarding whether a study should be administratively suspended, if all of the PI's new IRB submissions should be held, and/or a determination of whether any further action is required.

Resources

- **Attachment 1**: ClinicalTrial.gov Disclosure Requirements - Frequently Asked Questions

- **Final Rule/FDAA**
  Checklist for Evaluating an "Applicable Clinical Trial" Under the Final Rule
  https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

- **Flowchart for Identifying an "Applicable Clinical Trial" Under the Final Rule**
  https://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf

- **NIH Policy**
  Case Studies for Studies that Meet the NIH Policy Definition of a "Clinical Trial"
  http://osp.od.nih.gov/sites/default/files/Case_Studies.pdf

- **ICMJE**
  ICMJE Clinical Trial Registration Requirements
  http://www.icmje.org/news-and-editorials/icmje-recommendations_annotated_dec16.pdf
  http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

- **CMS**
  CMS Requirements for Qualifying Trials which will render claims for items and services to CMS
  https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS014961.html
  https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM8401.pdf

- **Additional ClincalTrials.gov Resources**
  - Frequently Asked Questions https://clinicaltrials.gov/ct2/manage-recs/faq
  - How to Apply for an Account https://clinicaltrials.gov/ct2/manage-recs/how-apply
  - How to Edit Your Study Record https://clinicaltrials.gov/ct2/manage-recs/how-edit
  - How to Submit Your Results https://clinicaltrials.gov/ct2/manage-recs/how-report
  - Training Materials https://clinicaltrials.gov/ct2/manage-recs/present

Related Information

None.

Contacts

Subject	Contact	Telephone or Email
Office of Research Administration (Institutional Official)	Senior Associate Provost for Research Administration	203-785-3012
Human Research Protection Program	Director, Human Research Protection Program	HRPP@yale.edu 203-785-4688
Office of Research Compliance	University Research Compliance Officer	203-785-5322
Yale Center for Clinical Investigation	Director, Yale Center for Clinical Investigation	203-785-3482
Yale Center for Analytical Sciences (YCAS)	ClinicalTrial.gov Team	Yale.CTgov@yale.edu

Roles and Responsibilities

Office of Research Administration (Institutional Official)

The Institutional Signatory Official is the senior official who has the authority to commit Yale to the legally binding FWA terms and conditions. The IO has the authority to require compliance of the organization and all of its components to the terms of the FWA regarding research.

Human Research Protection Program (HRPP)

The Yale Human Research Protection Program (HRPP) is responsible for the protection of the rights and welfare of human subjects in research projects and compliance with regulatory and policy requirements for studies conducted at Yale, by Yale faculty, staff and students, and by investigators from several affiliate institutions.

Office of Research Compliance

The Office of Research Compliance (ORC) provides support to the Office of Research Administration and is responsible to review and participate in the implementation of emerging regulatory requirements and monitor regulatory compliance through assessments.

Yale Center for Clinical Investigation (YCCI)

The Yale Center for Clinical Investigation (YCCI) (in collaboration with and the Yale Center for Analytical Sciences (YCAS)) is charged with overseeing ClinicalTrial.gov registration and reporting for Yale University investigators and their staff who are involved in the conduct, oversight, or management of research involving human subjects.

Revision History

Effective Date: 04/18/2017

ATTACHMENT 1
ClinicalTrial.gov Disclosure Requirements - Frequently Asked Questions

	Final Rule/FDAAA	NIH-Funded Trials	ICMJE	CMS
What Types of Clinical Trials or Studies Must Be Registered?	"Applicable Clinical Trials" All Phases of Research, Except Phase 1(feasibility) ○ Trials of Drugs/Biologics: Controlled, clinical investigations of a product subject to FDA regulations, other than Phase I. This may include interventional studies with dietary supplements. ○ Trials of Devices: Prospective controlled trials with health outcomes, which compares an intervention with a device against a control, other than small feasibility studies. Includes Pediatric post-market surveillance studies. In order to meet the definition of a FDAAA Applicable Clinical Trial one of the following conditions must exist: ○ The trial has one or more sites in the U.S. ○ The trial is conducted under an FDA Investigational New Drug Application (IND) or Investigational	Clinical Trial All Phases ○ All clinical trials funded in whole or in part by NIH. ○ Includes phase 1 clinical trials *and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions*. ***[This definition is broader than the Final Rule/FDAAA definition.]***	Clinical Trial All Phases ○ Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the	Qualifying Clinical Trials All Phases *Mandatory Criteria* 1) The subject or purpose of the trial is the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids) (2) The trial is not designed exclusively to test toxicity or disease pathophysiology and must have therapeutic intent; and (3) Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers, although trials of diagnostic interventions may enroll healthy patients to have a proper control group.

	Device Exemption (IDE) application ○ The trial involves a drug, biologic, or device that is manufactured in the U.S. or its territories and is exported for research FDAAA requirements for registration exclude the following (<u>unless funded either in whole or in part by NIH</u>): ○ (Non-serious/life-threatening) Phase 1 drug trials, including studies in which drugs are used as research tools to explore biological phenomena or disease processes ○ Small clinical trials to determine the feasibility of a device or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes ○ Trials that do not include drugs, biologics, or devices (e.g., behavioral interventions) ○ Non-interventional (observational) clinical research, such as cohort or case control studies		medical intervention is not at the discretion of the investigator) will not require registration. ***[This definition is broader than the Final Rule/FDAAA or NIH definitions***.]	There are also 7 desirable characteristics.
What Study Intervention Types Must Be Registered?	Drugs, Biologics, & Devices that are regulated by the FDA	All (including trials not regulated by the FDA such as any behavioral or any study where the	All	All

		purpose is to modify one or more health-related biomedical or behavioral outcomes) 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.		
What Funding Source Applies?	All sources including University funds	NIH in whole or in part	All sources including University funds	All sources including University funds
When Must Trials Be Registered?	At trial initiation (no later than 21 days of enrollment of the first subject); update at least every 12 months, although certain information may be required to be updated more frequently. (In addition, an expanded access registration is required if an investigational drug product studied in an applicable drug clinical trial is available through an expanded access program. Only one expanded access record will be created for each investigational drug product, although multiple applicable	Same as Final Rule/FDAAA	Prior to first subject enrollment	Before claims are submitted to Medicare

	clinical trials can be linked to the same record if they study the same product.)			
When Must Results Be Submitted?	Not later than 12 months after the 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 as Final Rule/FDAAA	Not required	Not required
What are the Potential Consequences of Noncompliance?	○ Identifying clinical trial record as non-compliant in ClinicalTrials.gov ○ For federally funded trials, grant funding can be withheld if required reporting cannot be verified ○ Civil monetary penalties of up to	NIH funds withheld for the PI and the Institution (May lead to suspension or termination of grant or contract funding; Can be considered in future funding decisions; Identifying clinical trial record as non-	Rejection of the publication	Denial of claims

	$11,000/day (***amount to be adjusted going forward***)	compliant in ClinicalTrials.gov		
What are the Effective Dates of the Disclosure Requirements Set Forth in the Final Rule and NIH Policy?	01/18/2017	01/18/2017	N/A	N/A
What are the Compliance Dates of the Final Rule and NIH Policy?	ACTs must be in compliance with the Final Rule by April 18, 2017. The new registration requirements described in the Final Rule apply to trials initiated on or after January 18, 2017, and the new results submission requirements of the final rule apply to trials that reach their *primary completion date* on or after January 18, 2017. Trials initiated before January 18, 2017 follow the registration requirements in place before the Final Rule went into effect (FDAAA 2007), and trials that reach their primary completion date before January 18, 20017 will follow the results submission requirements of FDAAA 2007).	The NIH policy applies to applications submitted on or after January 18, 2017 for clinical trials initiated on or after January 18, 2017, as well as to competing renewal applications that include a new clinical trial (a clinical trial initiated on or after the effective date of the policy). The NIH policy does not apply to: ○ NIH-funded clinical trials initiated before the effective date of January 18, 2017 ○ Clinical trials that use NIH-supported infrastructure but do not receive NIH funds to support their conduct ○ Clinical trials of ongoing, non-competing awards.	N/A	N/A