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# Yale University Human Research Protection Program

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## HRPP Policy 1000 Clinical Trial Registration and Reporting Requirements

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

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### 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.<sup>1</sup>

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

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### 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.

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### 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.<sup>2</sup> 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.<sup>3</sup> 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 Attachment 3 for examples of what types of studies are defined as clinical trials based on the NIH policy definition: See also [http://osp.od.nih.gov/sites/default/files/Case\\_Studies.pdf](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.<sup>4</sup>

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

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<sup>1</sup> For information regarding other registries, see *International Clinical Trials Registry Platform (ICTRP)* located at <http://www.who.int/ictrp/network/en/>.

<sup>2</sup> FDMAA 113 required that federally or privately funded clinical trials conducted under an investigational new drug applications (IND) 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>

<sup>3</sup> See, <https://clinicaltrials.gov/ct2/about-site/history#FinalRuleFDAAA801>; <https://clinicaltrials.gov/ct2/manage-recs/fdaaa#DevelopmentOfRegulations>; <https://prinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf>.

<sup>4</sup> 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](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.

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## 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.<sup>5</sup>

- 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**

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<sup>5</sup> 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](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](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.<sup>6</sup>

#### *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.<sup>7</sup>

#### *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.<sup>8</sup>

### **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.<sup>9</sup>

### **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)**

<sup>6</sup> 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 Attachment 3 for examples of what types of studies are defined as clinical trials based on the NIH policy definition. See also, [http://osp.od.nih.gov/sites/default/files/Case\\_Studies.pdf](http://osp.od.nih.gov/sites/default/files/Case_Studies.pdf).

<sup>7</sup> 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](http://www.icmje.org/news-and-editorials/icmje-recommendations_annotated_dec16.pdf)); See, <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>

<sup>8</sup> <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>

<sup>9</sup> 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](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.

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## 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.

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### 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](http://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

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### 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 occur 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](http://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.

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### 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).

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### **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.

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### **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](https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf)

### **Attachment 2:** Flowchart for Identifying an “Applicable Clinical Trial” Under the Final Rule.

See also, [https://grants.nih.gov/clinicaltrials\\_fdaaa/docs/Flow\\_chart-ACT\\_only.pdf](https://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf)

### NIH Policy

**Attachment 3:** Flowchart and Case Studies for Studies that Meet the NIH Policy Definition of a “Clinical Trial”.

See also, [http://osp.od.nih.gov/sites/default/files/Case\\_Studies.pdf](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/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 ClinicalTrials.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>

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## 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	<a href="mailto:HRPP@yale.edu">HRPP@yale.edu</a> 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	<a href="mailto:Yale.CTgov@yale.edu">Yale.CTgov@yale.edu</a>

## **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.

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## **Revision History**

Effective Date: 04/18/2017

**ATTACHMENT 1**  
**ClinicalTrial.gov Disclosure Requirements - Frequently Asked Questions**

	Final Rule/FDAAA	NIH-Funded Trials	ICMJE	CMS
<p><b>What Types of Clinical Trials or Studies Must Be Registered?</b></p>	<p><u>“Applicable Clinical Trials</u>                      All Phases of Research, Except Phase 1 (feasibility)</p> <ul style="list-style-type: none"> <li>○ 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.</li> <li>○ 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.</li> </ul> <p>In order to meet the definition of a FDAAA Applicable Clinical Trial one of the following conditions must exist:</p> <ul style="list-style-type: none"> <li>○ The trial has one or more sites in the U.S.</li> <li>○ The trial is conducted under an FDA Investigational New Drug Application (IND) or Investigational</li> </ul>	<p><u>Clinical Trial</u>                      All Phases</p> <ul style="list-style-type: none"> <li>○ All clinical trials funded in whole or in part by NIH.</li> <li>○ Includes phase 1 clinical trials <u>and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions.</u></li> </ul> <p><i>[This definition is broader than the Final Rule/FDAAA definition.]</i></p>	<p><u>Clinical Trial</u>                      All Phases</p> <ul style="list-style-type: none"> <li>○ 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</li> </ul>	<p><u>Qualifying Clinical Trials</u>                      All Phases</p> <p><i>Mandatory Criteria</i></p> <p>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)</p> <p>(2) The trial is not designed exclusively to test toxicity or disease pathophysiology and must have therapeutic intent; and</p> <p>(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.</p>

	<p>Device Exemption (IDE) application</p> <ul style="list-style-type: none"> <li>○ The trial involves a drug, biologic, or device that is manufactured in the U.S. or its territories and is exported for research</li> </ul> <p>FDAAA requirements for registration exclude the following (<u>unless funded either in whole or in part by NIH</u>):</p> <ul style="list-style-type: none"> <li>○ (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</li> <li>○ 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</li> <li>○ Trials that do not include drugs, biologics, or devices (e.g., behavioral interventions)</li> <li>○ Non-interventional (observational) clinical research, such as cohort or case control studies</li> </ul>		<p>medical intervention is not at the discretion of the investigator) will not require registration.</p> <p><b><i>[This definition is broader than the Final Rule/FDAAA or NIH definitions.]</i></b></p>	<p>There are also 7 desirable characteristics.</p>
<p><b>What Study Intervention Types Must Be Registered?</b></p>	<p>Drugs, Biologics, &amp; Devices that are regulated by the FDA</p>	<p>All (including trials not regulated by the FDA such as any behavioral or any study where the</p>	<p>All</p>	<p>All</p>

		<p>purpose is to modify one or more health-related biomedical or behavioral outcomes)</p> <p>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.</p>		
<b>What Funding Source Applies?</b>	All sources including University funds	NIH in whole or in part	All sources including University funds	All sources including University funds
<b>When Must Trials Be Registered?</b>	<p>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.</p> <p>(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</p>	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.)			
<b>When Must Results Be Submitted?</b>	<p>Not later than 12 months after the Primary Completion Date.</p> <p>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.</p>	Same as Final Rule/FDAAA	Not required	Not required
<b>What are the Potential Consequences of Noncompliance?</b>	<ul style="list-style-type: none"> <li>○ Identifying clinical trial record as non-compliant in ClinicalTrials.gov</li> <li>○ For federally funded trials, grant funding can be withheld if required reporting cannot be verified</li> <li>○ Civil monetary penalties of up to</li> </ul>	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 ( <i>amount to be adjusted going forward</i> )	compliant in ClinicalTrials.gov		
<b>What are the Effective Dates of the Disclosure Requirements Set Forth in the Final Rule and NIH Policy?</b>	01/18/2017	01/18/2017	N/A	N/A
<b>What are the Compliance Dates of the Final Rule and NIH Policy?</b>	<p>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 <i>primary completion date</i> on or after January 18, 2017.</p> <p>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, 2017 will follow the results submission requirements of FDAAA 2007).</p>	<p>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).</p> <p>The NIH policy does not apply to:</p> <ul style="list-style-type: none"> <li>○ NIH-funded clinical trials initiated before the effective date of January 18, 2017</li> <li>○ Clinical trials that use NIH-supported infrastructure but do not receive NIH funds to support their conduct</li> <li>○ Clinical trials of ongoing, non-competing awards.</li> </ul>	N/A	N/A



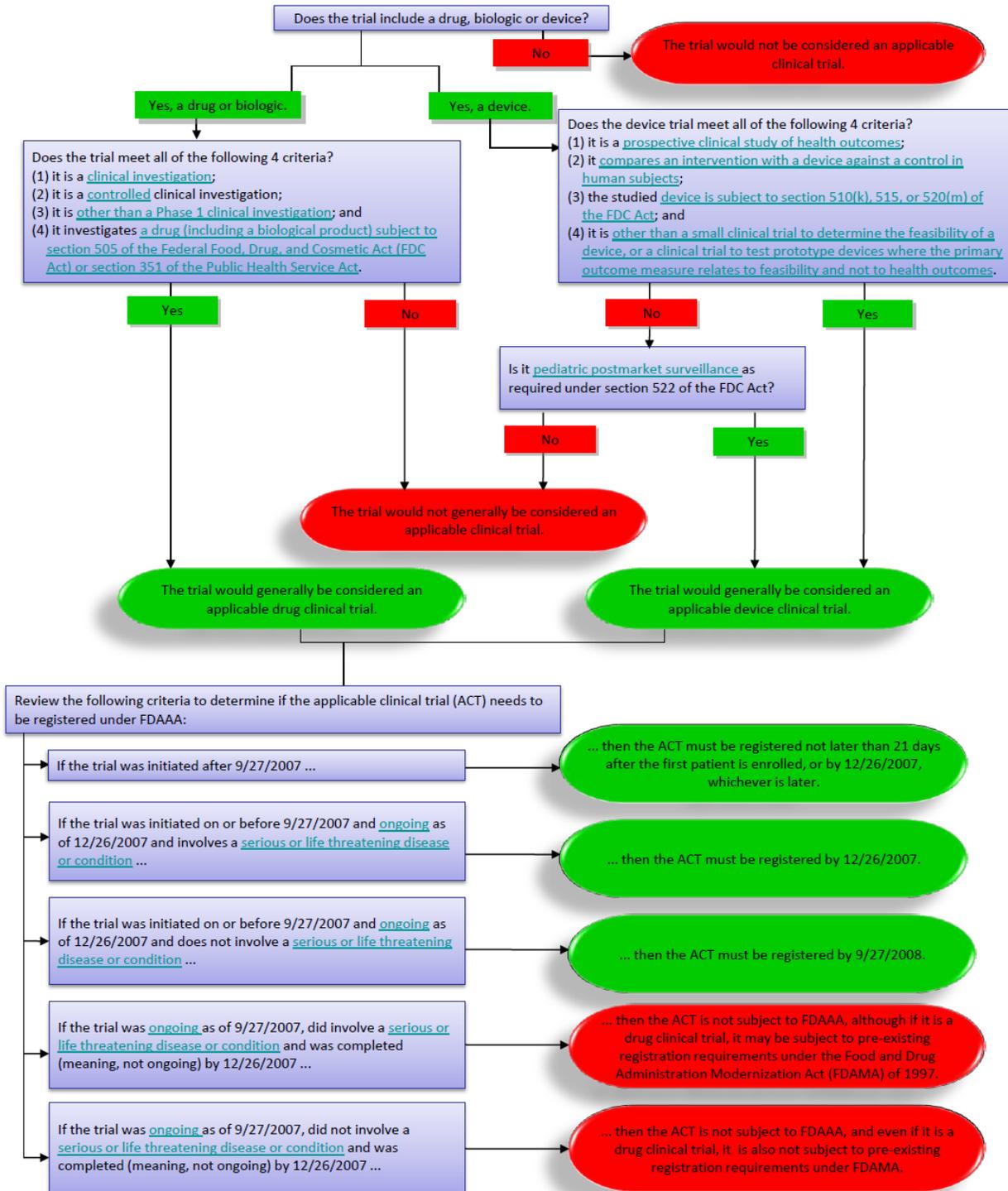
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**ATTACHMENT 2**

## Flowchart for Identifying an “Applicable Clinical Trial” under FDAAA

### Identifying an “Applicable Clinical Trial” under FDAAA

- This flowchart presents basic guidance on determining if a trial is considered an “applicable clinical trial” under FDAAA. It maps out the guidance provided in the “Elaboration of Definitions of Responsible Party and Applicable Clinical Trial”, and is also available as an interactive flowchart at: <http://grants.nih.gov/ClinicalTrials fdaaa/index.htm>
- This flow chart may not address every situation. The grantee’s sponsored research office, general counsel, or other similar official should be involved in determining whether or not the grant supports an applicable clinical trial that needs to be registered under FDAAA.



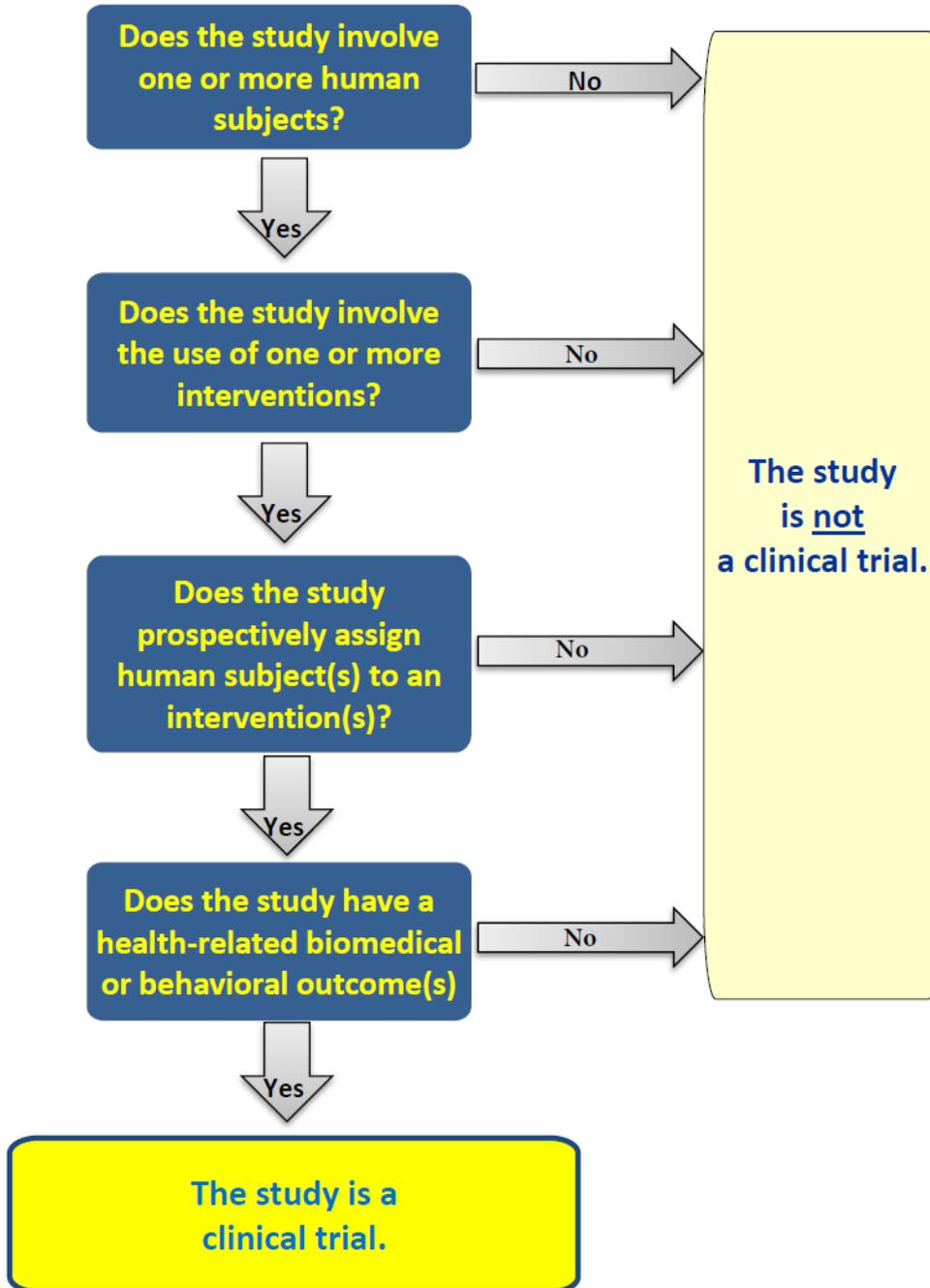


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**ATTACHMENT 3**

NIH Policy – Flow Chart and Case Studies for Studies that Meet the NIH Policy Definition of a “Clinical Trial”

**NIH Definition of Clinical Trial Decision Tree**



Type of Study	YES - Study IS A Clinical Trial	Type of Study	Study IS NOT A Clinical Trial
Behavioral / Interventional	<p><b>Case #2:</b> A study is planned to randomly assign individuals to an experimental intervention to promote weight loss or to a control intervention. After a year, <u>participants' behaviors will be assessed to measure their adherence to exercise regimens</u>. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to an intervention.</li> <li>○ The study identifies a health-related behavioral outcome (adherence to exercise regimens).</li> </ul>	Biomedical / Non-interventional	<p><b>Case #1:</b> A study will test de-identified, archived, human blood samples for which the researchers will not have access to identifying information. The study will evaluate the levels of cardiac troponin in patients undergoing cancer treatment with doxorubicin compared to cancer patients undergoing chemotherapy with agents other than doxorubicin. Is this study a clinical trial?</p> <p>Answer: <b>No,</b></p> <ul style="list-style-type: none"> <li>○ The study does not involve human subjects (only archived and de-identified blood samples are used).</li> <li>○ The study does not include an intervention.</li> </ul>
Behavioral / Interventional	<p><b>Case #3:</b> A large-scale study is designed to evaluate the effectiveness of community-based interventions in influencing smoking behavior. Thirty-four communities across the U.S. <u>are randomly assigned to receive the experimental intervention or to receive one of two control interventions</u>. Each community has a population between 100,000 and 500,000 individuals. <u>The experimental intervention includes public awareness campaigns and educational pamphlets</u>. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects within communities (clusters).</li> <li>○ The study involves interventions to which subjects (in clusters) are prospectively assigned.</li> <li>○ The study identifies a health-related behavioral outcome (smoking behavior).</li> </ul>	Non-biomedical or Non-behavioral outcome	<p><b>Case #9:</b> A study is designed to evaluate different types of printed public health announcements to identify the best designs for ensuring comprehension and retention of information in adults. Two printed announcements will be designed with identical information. One of the announcements will have a picture of a physician in a white coat showing his/her name and credentials (MD) and the other will not include the picture of the physician. Visitors to public libraries will be selected at random and asked to read one of the announcements and then to take a short survey assessing their comprehension and information retention. Is this study a clinical trial?</p> <p>Answer: <b>No,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to an intervention (reading a specific announcement).</li> <li>○ The study does not identify a health-related biomedical or behavioral outcome. The study is about understanding and remembering the content of the announcement, rather than affecting the health of the readers.</li> </ul>

<p>Behavioral / Interventional</p>	<p><b>Case #13:</b> An investigator is planning a study to maximize procurement and use of eyeglasses in “eye camps” in the catchment districts of an Eye Hospital. The study will use a cluster randomized, controlled design. Community eye camps (n = 21) will offer one of three types of service for the purchase of eyeglasses to correct refractive error: (1) issuing a prescription to individuals, who can take the prescription to an optometrist; (2) booking orders for eyeglasses and delivering them to individuals who purchase them; (3) providing on-the-spot fitting and offering to dispense eyeglasses at the same time. Follow-up questionnaires will be administered 6 weeks after provision of services to ascertain the level of procurement and use of eyeglasses. A secondary outcome will involve measurement of satisfaction with the services. Reasons for purchase/non-purchase will also be assessed. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects (clusters of individuals about whom researchers are collecting behavioral information).</li> <li>○ Subjects are prospectively assigned to interventions (one of three services).</li> <li>○ The study is primarily designed to measure a health-related behavioral outcome (purchase and use of eyeglasses).</li> </ul>	<p>Non-biomedical or Non-behavioral outcome / Evaluation of a device</p>	<p><b>Case #11:</b> A new intraoperative orthopedic imaging device is intended to provide improved feedback to the surgeon and to speed up artificial joint replacement procedures. A study is designed to assess the feasibility of using this device in humans. A study protocol is developed to utilize and record the output of the device during hip replacement surgeries. The device will collect data during surgeries at the same time that surgeons are using conventional imaging techniques. Postoperatively, data from the experimental device will be reviewed and compared to data collected from conventional imaging. Data collection will neither influence nor modify any surgical procedure. Is this study a clinical trial?</p> <p>Answer: <b>No,</b></p> <ul style="list-style-type: none"> <li>○ The study does not involve human subjects. The study is designed to evaluate the device.</li> <li>○ The orthopedic imaging device will not be in or near the operative field. The device will neither alter the patients’ environment nor influence the surgical procedures. Thus, the orthopedic imaging device is not an intervention.</li> <li>○ The study does not identify a health-related biomedical or behavioral outcome.</li> </ul>
<p>Behavioral Interventional</p>	<p><b>Case #24:</b> Investigators are planning a study to evaluate the effects of providing cash incentives for STD testing on the rate of agreement for counseling and treatment (if needed). Cash is provided to visitors if they agree to be tested, after which they will be offered free counseling and/or treatment. The rate of visitors undergoing counseling and/or treatment after providing cash incentives will be compared to the rate observed in the two years prior to the study. Is this a clinical trial?</p> <p>Answer: <b>Yes,</b></p>	<p>Non-Biomedical or Non-Behavioral outcome</p>	<p><b>Case #15:</b> Participants are randomly assigned to different processes for informed consent in order to assess the impact of interactive and multimedia components. The study measures participant preferences. Is this study a clinical trial?</p> <p>Answer: <b>No,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to interventions.</li> <li>○ The study does not identify a health-related biomedical or behavioral outcome.</li> </ul>

	<ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ The study involves an intervention (the combination of cash incentives tied to STD testing, counseling, and treatment).</li> <li>○ The study identifies a health-related outcome. The proposed study evaluates cash as a recruitment incentive for testing to determine the need for counseling and/or treatment, which has direct health implications.</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #4:</b> An investigator plans to administer a new experimental product to patients suffering from advanced stage Wilms tumors (rare and malignant kidney tumors). Due to the rarity of the disease, only five patients will be enrolled in the study. All patients will receive the new experimental product. Tumor size and the incidence of metastatic disease will be evaluated. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to an intervention.</li> <li>○ The study identifies a health-related biomedical outcome (Tumor size and the incidence of metastatic disease).</li> </ul>	<p>Non-biomedical or Non-behavioral outcome / Evaluation of a device</p>	<p><b>Case #18:</b> A study is designed to evaluate the efficacy of an in-vitro diagnostic device to detect circulating antibodies. Banked blood samples from identifiable, patients diagnosed with lupus and from patients who do not have lupus will be used to evaluate the device’s ability to detect circulating antibodies. Is this study a clinical trial?</p> <p>Answer: <b>No,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ The study does not involve prospective assignment of human subjects to an intervention.</li> <li>○ The study does not identify a, health-related biomedical or behavioral outcome; rather, the study is designed to evaluate the device.</li> </ul> <p><i>Note: <u>If the study was using the detection of circulating antibodies by the device to inform the use of therapy or to assess disease state (both are health-related outcomes), the study would be a clinical trial.</u></i></p>
<p>Biomedical / Interventional</p>	<p><b>Case #5:</b> A dose-escalation study is designed to determine the maximum tolerated dose of a new drug in healthy volunteers. The study will also measure the drug concentration in the blood (pharmacokinetics (pK)). Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects (healthy volunteers).T</li> </ul>	<p>Biomedical, but no randomization</p>	<p><b>Case #20:</b> A study is designed to examine the effectiveness of maximal surgical resection vs. radiation in the treatment of multiform glioblastoma (both are approved as standard therapies for multiform glioblastoma). Participating in the study will not dictate the course of therapy. The 6-month survival of glioblastoma patients who decide to undergo maximal surgical resection will be compared to the 6-month</p>

	<ul style="list-style-type: none"> <li>○ Subjects are prospectively assigned to an intervention.</li> <li>○ The study identifies a health-related biomedical outcome (maximum tolerated dose).</li> </ul>		<p>survival of patients who opt to get radiotherapy. Is this study a clinical trial?</p> <p>Answer: <b>No</b>,</p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are not prospectively assigned to interventions (Patients and their healthcare providers select the therapy and investigators observe outcomes).</li> <li>○ The study identifies health-related biomedical outcomes (6-month survival).</li> </ul> <p><i>Note: If the study prospectively assigned patients to receive surgery or radiation, the study would be a clinical trial.</i></p>
<p>Biomedical / Interventional</p>	<p><b>Case #6:</b> A new study will evaluate the performance of diagnostic tools used for the detection of breast cancer. The study will assign women between the ages of 40 and 50 to receive one film-screen mammography every two years for eight years. Another group of women, also between the ages of 40 and 50 will receive one digital mammogram every two years for eight years. Incidence and progression of breast cancers will be compared. Is this study a clinical trial?</p> <p>Answer: <b>Yes</b>,</p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to two different diagnostic strategies, digital vs. filmscreen mammography.</li> <li>○ The study identifies a health-related biomedical outcome (incidence and progression of breast cancers).</li> </ul>	<p>Exempt Research</p>	<p><b>Case #23:</b> Billboards containing anti-smoking messages will be placed at major intersections in city X to ensure public exposure. Researchers will evaluate the rate of smoking in the city annually for a period of five years. Is this a clinical trial?</p> <p>Answer: <b>No</b>,</p> <ul style="list-style-type: none"> <li>○ The study involves human subjects research that would be exempt under 45 CFR 46.101(b)(2): <i>“Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects’ responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.”</i> <a href="http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101">http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101</a></li> <li>○ Subjects (city population) are prospectively assigned to an intervention (exposure to antismoking messages).</li> <li>○ Although the study identifies a health-related outcome (changes in smoking rate), any observed changes cannot be construed as a result of reading anti-smoking messages.</li> </ul>

<p>Biomedical / Interventional</p>	<p><b>Case #7:</b> A study is designed to evaluate the efficacy of a new drug to limit the frequency of flare-ups in patients suffering from Secondary Progressive Multiple Sclerosis. Patients enrolled in this study will first be treated with the standard of care drug (drug A) for three months. Then, after a one month washout period, the same group of patients will receive the new drug (drug B) for another three months. The frequency of flare-ups will be evaluated while using drug A, compared to while using drug B. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to an intervention (Drug B).</li> <li>○ The study identifies a health-related biomedical outcome (frequency of flare-ups).</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #8:</b> Patients with advanced stage glioblastoma, who have not responded to standard of care therapeutic approaches, will receive an experimental drug. The drug will be administered weekly for six weeks. Tumor size will be measured every two weeks. Tumor size for each patient will be compared to the size of the tumor prior to treatment with the new drug. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to a biomedical intervention.</li> <li>○ The study identifies a health-related biomedical outcome (tumor size).</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #10:</b> An approved drug to treat cancer (drug A) has been shown also to decrease the size of amyloid plaques. A study is designed to treat patients with early stage Alzheimer with drug A. Patients’ blood will</p>		

	<p>be tested for amyloid levels before and after the initiation of treatment with drug A. Patients will serve as their own controls. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to an intervention.</li> <li>○ The study identifies a health-related biomedical outcome (blood amyloid levels).</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #12:</b> A study aims to define the effects of a velopharyngeal muscle strengthening program (VMSP), consisting of continuous positive airway pressure (CPAP) and imagery training, on physiologic, acoustic, and perceptual aspects of the velopharyngeal mechanism in patients with hypernasality. This is the first study that integrates multi-dimensional parameters to examine the CPAP-induced changes as CPAP therapy is used over time. The proposed study tests the hypothesis that VMSP will reduce the degree of hypernasality by improving the velopharyngeal valving mechanism through increasing velopharyngeal muscle size, decreasing the velopharyngeal orifice size, and decreasing nasalance scores. Physiologic, acoustic, and perceptual changes accompanying VMSP will be tracked and documented using magnetic resonance imaging (MRI), air pressure-flow technique, acoustic analysis, and listeners' perceptual ratings. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to interventions (integration of CPAP and imagery training).</li> <li>○ The study identifies a health-related biomedical outcome (decreased hypernasality).</li> </ul>		

<p>Biomedical / Interventional</p>	<p><b>Case #14:</b> The primary objective of a study is “to assess the dose-response relationships between testosterone and bone turnover, body composition, and other functions in normal young men.” To achieve this objective, healthy men, age 20-50, will be treated with a Gonadotropin Releasing Hormone agonist to lower testosterone and estradiol for 16 weeks and then with placebo or 1 of 4 gradually increasing doses of testosterone gel (1.25, 2.5, 5.0 or 10 gm/day). The 6th group will receive placebo only. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to an intervention (GNRH agonist and/or placebo).</li> <li>○ The study identifies health-related biomedical outcomes (dose-response relationship of testosterone and bone turnover).</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #16:</b> An investigator prospectively assigns a group of healthy individuals to sleep deprivation for a defined period of time in order to determine whether the level of stress hormones rise in response to decreased sleep. Blood levels of stress hormones will be measured. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Human subjects are prospectively assigned to an intervention.</li> <li>○ The study is designed to evaluate the effect of the intervention on study participants.</li> <li>○ The study identifies a health-related biomedical outcome.</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #17:</b> A placebo-controlled study is designed to evaluate the effect of statin challenge in patients with history of statin-related myalgia. Patients, who have stopped statin therapy for four or more months due to symptoms of myalgia, will</p>		

	<p>be recruited for participation in n-of-1 studies. Participants will undergo courses of treatment with statins or placebo, for up to ten months. Patients will be asked to complete a weekly visual analogue scale (VAS) evaluation for myalgia and specific symptoms. For each n-of-1 study, the difference in VAS scores between participants using statin and those in the placebo group will be calculated and compared. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to interventions.</li> <li>○ The study identifies a health-related biomedical outcome (drug-associated myalgia).</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #19:</b> A study is designed to optimize the dose of an approved therapeutic agent for cancer patients suffering from metastatic disease. The calculated optimal dose is hypothesized to correlate directly with the number of circulating metastatic cells detected by an approved in vitro diagnostic device. If the device detects a level of circulating metastatic cells above an experimentally-determined threshold, patients will receive the higher dose of chemotherapy. Patients with numbers of circulating metastatic cells below the threshold will receive the standard dose of the chemotherapeutic agent. Primary tumor size and the progression of metastatic disease will be evaluated over a period of three months. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to interventions based on their level of circulating metastatic cells that are measured with an approved, in vitro diagnostic device.</li> </ul>		

	<ul style="list-style-type: none"> <li>○ The study identifies health-related biomedical outcomes (primary tumor size and the progression of metastatic disease).</li> </ul>		
<p>Biomedical / Interventional</p>	<p><b>Case #21:</b> A study is designed to compare the effectiveness of two approved migraine medications in eliminating or decreasing the intensity of migraines. Patients suffering from migraines will be randomized to receive either frovatriptan (Frova) or eletriptan (Relpax) (both are approved as standard therapy for migraines) for six months. The incidence and severity of migraines will be compared between the two groups. Is this study a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to interventions.</li> <li>○ The study identifies health-related biomedical outcomes (incidence and severity of migraines).</li> </ul> <p><u>Note: If patients were only monitored while they took medication prescribed by their physician (such as in case #20), there would be no prospective assignment, and this study would not be a clinical trial.</u></p>		
<p>Biomedical / Interventional</p>	<p><b>Case #22:</b> A study is designed to examine improvements to mobility range in quadriplegic patients. Patients will be randomized to receive either a new mechanical exo-skeleton or an electrical impulse stimulation therapy for six months. Is this a clinical trial?</p> <p>Answer: <b>Yes,</b></p> <ul style="list-style-type: none"> <li>○ The study involves human subjects.</li> <li>○ Subjects are prospectively assigned to interventions.</li> <li>○ The study identifies a health-related biomedical outcome (improved mobility).</li> </ul>		