

## “CLINICAL TRIAL” DEFINITIONS

### 1. 81 FR 64981: DHHS - Clinical Trials Registration and Results Information Submission (effective 1/18/17) <sup>1, 2</sup>

**Applicable Clinical Trial (Device):** <https://www.federalregister.gov/d/2016-22129/p-1301>

A clinical trial or study that meets the conditions listed in either paragraph [(b)(1)](i) or (ii) of this section is an applicable device clinical trial:

- (i) The study is a **pediatric postmarket surveillance of a device product** as required by FDA under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3601).
- (ii) The study is a **clinical trial with one or more arms** that meets all of the following criteria:
  - (A) Study Type is **interventional**;
  - (B) Primary Purpose of the clinical trial is **other than a feasibility study**;
  - (C) The clinical trial Studies a **U.S. FDA-regulated Device Product**; and
  - (D) One or more of the following applies:
    - (1) At least one Facility Location is **within the United States or one of its territories**,
    - (2) A device product under investigation is a **Product Manufactured in and Exported from the U.S.** or one of its territories for study in another country, or
    - (3) The **clinical trial has a U.S. Food and Drug Administration IDE Number**.

**Applicable Clinical Trial (Drug/Biologic):** <https://www.federalregister.gov/d/2016-22129/p-1311>

A clinical trial with one or more arms that meets the following conditions is an applicable drug clinical trial:

- (i) Study Type is **interventional**;
- (ii) Study Phase is **other than phase 1**;
- (iii) The clinical trial **Studies a U.S. FDA-regulated Drug Product**; and
- (iv) One or more of the following applies:
  - (A) At least **one Facility Location for the clinical trial is within the United States** or one of its territories,
  - (B) A drug product (including a biological product) under investigation is a **Product Manufactured in and Exported from the U.S.** or one of its territories for study in another country, or
  - (C) The **clinical trial has a U.S. Food and Drug Administration IND Number**.

**A note about Expanded Access:** <https://www.federalregister.gov/d/2016-22129/p-14>

**“Expanded Access use under section 561 of the FDC Act does not fall within the definition of “applicable clinical trial” under section 402(j) of the PHS Act. However, information on the availability of investigational drug products (including biological drug products) for expanded access will continue to be required to be submitted to the Clinical Trials.gov database under authority of the section 402(j) registration requirements.”**

### 2. FDA – a federal agency under the DHHS (4/1/16) <sup>2, 3, 4</sup>

**Clinical Investigation** <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>

“Any experiment that involves a **test article** and **one or more human subjects** and that **either is subject to** requirements for prior submission to the Food and Drug Administration under section **505(i) (new drugs) or 520(g) (investigational use of devices intended for human use)** of the act, **or is not subject to** requirements for prior submission to the Food and Drug Administration under these sections of the act, but the **results** of which are **intended to be submitted later to, or held for inspection** by, the Food and Drug Administration as part of an **application for a research or marketing permit**. (The term does **not** include experiments that are subject to the provisions of **part 58** of this chapter, regarding **nonclinical laboratory studies**.”)

Note: section 505(i) = section **355** (new drugs); section 520(g) = section **360j** (devices intended for human use)

### 3. 81 FR 64922: NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information (effective 1/18/17) <sup>1, 2, 4</sup>

**Clinical Trial** <https://www.federalregister.gov/d/2016-22379/p-70>

“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 1 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**. [This definition of “clinical trial” is broader than the term “applicable clinical trial” as defined in the regulation.]”

**NOT-OD-18-010 (October 25, 2017):** <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-010.html>

NIH not only supports trials of safety and efficacy, it also supports **mechanistic exploratory studies** that meet the definition of a clinical trial and are designed to explore or understand a biological or behavioral process, the pathophysiology of a disease, or

the mechanism of action of an intervention. These studies may focus on basic and/or translational discovery research in healthy human subjects and in human subjects who are affected by the pathophysiology of diseases and disorders. By addressing basic questions and concepts in biology, behavior, and pathophysiology, these studies may provide insight into understanding human diseases and disorders along with potential treatments or preventive strategies. NIH also supports biomarker studies that meet the definition of a clinical trial and that may provide information about physiological function, target engagement of novel therapeutics, and/or the impact of therapeutics on treatment response. NIH thus supports studies that meet the definition of clinical trials (as noted above) but do not seek to establish safety, clinical efficacy, effectiveness, clinical management, and/or implementation of preventive, therapeutic, and services interventions.

Examples of **mechanistic clinical trials** include but are not limited to:

- Studies that use a manipulation (physiological or behavioral) to answer basic science questions about normal functions.
- Studies that use an experimental manipulation in order to understand normal functioning or the pathophysiology of a disease or disorder, but do not aim to demonstrate clinical improvement.
- Studies that involve the prospective use of efficacious interventions where the intent is to obtain and analyze biospecimens to identify genetic risk associations, novel biomarkers, examine the disease process, or characterize mechanisms of therapeutic response.
- Studies in which an intervention with demonstrated efficacy for a population is being studied to understand mechanisms of response, non-response, or risk of adverse effects of the efficacious intervention.

#### 4. 2007 ICMJE (WORLD HEALTH ORGANIZATION/WHO): <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>

**Clinical Trial:** "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 (in a trial registry). The ICMJE member journals implemented the expanded definition of clinically directive trials for all trials that began enrollment on or after 1 July 2008. Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration (in a trial registry) if they wish to seek publication in an ICMJE journal. **[Note: ICMJE journals that report the results of clinical trials may require a data sharing statement]** VA ORD uses same definition.

#### 5. 2007 Center for Medicare and Medicaid Services (CMS)

CMS issued a [National Coverage Determination \(NCD\) for Routine Costs in Clinical Trials, Section 310.1 \(July 2007\)](#). Claims for routine costs of qualifying clinical trials as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials covered by Medicare will require health care providers and suppliers to report a [ClinicalTrials.gov Identifier \(NCT Number\)](#).

CMS: [Further Information on Mandatory Reporting of an 8-Digit Clinical Trial Number on Claims \(January 2014\)](#)

- [Policy](#)
- [Medicare Coverage and Clinical Trials](#)
- Definition of a [Qualifying Clinical Trial](#)

#### 6. 82 FR 7149: Common Rule / Federal Policy for the Protection of Human Subjects (effective 1/19/18)

**Clinical Trial** <https://www.federalregister.gov/d/2017-01058/p-1335>

"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 the interventions on biomedical or behavioral health-related outcomes**"

<sup>1</sup> Specific to registration at [ClinicalTrials.gov](#); and describes penalties for noncompliance

<sup>2</sup> Requires compliance with 21 CFR [50](#) [written consent requires the [clinicaltrials.gov](#) language, per 21 CFR [50.25\(c\)](#) / [42 USC 282\(j\)\(1\)\(A\)](#)\* (pages 491-492 / NIH)], and 21 CFR [56](#) [IRB Review]

<sup>3</sup> [Medical Device, Drug, Biologic, IND, IDE, Off-Label vs Investigational Use](#)

<sup>4</sup> [FDA GCP training](#), or [NIH GCP Training](#), or [NIH SBE GCP training](#)

\* Code of Laws in which section 282 is under the purview of NIH; section 282 references the DHHS Applicable Clinical Trial definitions

Other definitions: NCI, DOD