

HUMAN SUBJECTS RESEARCH
DEFINITIONS, CATEGORIES, AND RESOURCE INFORMATION
Updated as of 2 January 2020

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I. BACKGROUND

The following information is a guide for Principal Investigators (PIs) funded through the Congressionally Directed Medical Research Programs (CDMRP). It is not intended to be a source for human subject use regulations; this is a guidance document. Human subjects research that is funded by the Department of Defense (DoD) must be in compliance with Title 32 of the Code of Federal Regulations, Part 219 (32 CFR 219), Protection of Human Subjects (<https://mrdc.amedd.army.mil/assets/docs/orp/32cfr219.pdf>), DoDI 3216.02 (<https://www.esd.whs.mil/Directives/issuances/dodi/>), the US Food and Drug Administration (FDA) and institutional requirements.

All United States Army Medical Research and Development Command (USAMRDC) supported research involving humans, human data, human specimens, or cadavers must be reviewed for compliance with Federal and DoD human subjects protection requirements and approved by the USAMRDC Office of Research Protections (ORP) before implementation.

For in-depth information, investigator guidance, and submission instructions, please refer to the Office of Research Protections (ORP) website and click on the Human Research Protection Office (https://mrdc.amedd.army.mil/index.cfm/collaborate/research_protections/) or the FDA website (<http://www.fda.gov>). The policies and procedures of the local Institutional Review Board (IRB) must also be consulted.

II. HUMAN SUBJECTS RESEARCH CONSIDERATIONS

A. Research Not Involving Human Subjects

Certain categories of research do not meet the regulatory definition of human subjects research, such as research with coded or de-identified data or specimens for which the investigator has no access to subject identifiers. Investigators must consult with their institution's IRB office for official determination regarding whether the project is considered research not involving human subjects.

B. Risk Status of Human Subjects Research

All research involving human subject use must follow 32 CFR 219 (the DoD version of the Common Rule) with the exception of exempt research (see below). Research involving human subjects is typically assigned a risk category of either no greater than minimal risk or greater than minimal risk (some institutions have expanded upon the minimal risk category). *Please note, only the IRB of record can officially assign the risk designation for a study.*

C. Exempt Human Subjects Research

Research involving human subjects may be exempt from IRB review if it meets certain categories. A list of the categories for exemption can be found in 32 CFR 219.101b. In brief, these may include research on normal educational practices, special cases of educational tests and/or surveys, the collection of existing data,

documents, records, or pathological specimens in a de-identified method. Exemption must be determined by the office of the institution's IRB of record. Investigators must review their institutional requirements and guidelines for filing with the IRB for exempt status.

D. Expedited IRB Review

Research involving human subjects may qualify for an expedited IRB review under certain categories, which are found in the Federal Register. Please review these at: <http://www.hhs.gov/ohrp/policy/expedited98.html>.

E. Decision Tree Charts

The office of Health and Human Services offers decision tree charts to aid investigators on the categorization of research and whether it involves human subject use. These are based on the Common Rule. The charts assist in determining whether the research may be classified as exempt, whether it must be reviewed by an IRB, if it needs to be reviewed through expedited procedures, and many other designations. Please review the charts found at: <http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html>.

III. HUMAN SUBJECTS RESEARCH DEFINITIONS

A. Clinical Trial

A clinical trial is 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.

B. Observational Studies

Observational studies are a type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given). These are not considered to be clinical trials.

IV. TYPES OF CLINICAL TRIALS

A. Drug Studies

For clinical trials designed to test the safety and/or efficacy of an investigational new drug or FDA-approved drug (this could include a chemical, biological, vaccine, or radiological substance), the phases of **clinical trials** include:

- 1. Phase 0** – Exploratory Investigational New Drug (IND) studies that allow for the study of pharmacokinetic and bioavailability data early in the research and development processes. Both human subject data and preclinical animal data

are used to determine the best drug and/or biologic candidates to advance further in the clinical trial phases. Accordingly, the exploratory IND studies occur prior to or early within the Phase I clinical trial, involve very limited human subject exposure, and have no therapeutic or diagnostic end.

Information on exploratory IND studies may be found at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf>

2. **Phase I** – Introduces a drug and/or biologic into humans and may be conducted in patients or in healthy volunteer subjects. The main focus of most Phase I clinical studies is the toxicity of a drug and/or biologic in humans, the determination of the metabolic actions of the drug and/or biologic, and the side effects of increasing doses to the maximum tolerated dose. The total number of subjects included in Phase I studies varies, but this is generally in the range of twenty to eighty.
3. **Phase II** – Includes controlled clinical studies conducted to obtain information on the efficacy of a drug and/or biologic for a particular indication or indications in patients with the disease, condition, or injury. This phase of testing also helps determine the common short-term side effects and risks associated with a drug and/or biologic. Phase II trials are conducted in a relatively small number of patients, usually involving populations with statistical power to support the outcomes.
4. **Phase III** – Expanded controlled and uncontrolled trials that focus on evaluating the overall benefit-risk relationship of a drug and/or biologic with respect to its effectiveness and safety. Phase III trials include several hundred to several thousand people.
5. **Phase IV** – Post-marketing trials that assess additional information on the risk, benefit, and optimal use of a drug and/or biologic. Phase IV trials may be conducted after a product is approved and on the market to test a drug and/or biologic in a different population (i.e., children).

B. Device Studies

The basic regulatory requirements to study the safety and performance of an investigational new device are discussed here: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm>

1. **Investigational Device Exemption (IDE)** – In accordance with Federal law, a device must have performance standards or premarket approval before it can be transported or distributed. An IDE allows a device to be shipped lawfully for the use in investigations of said device without the required performance standards or premarket approval; thus, an active IDE exempts the device from the FDA requirements. This allows for the investigation of the device for the

use in Premarket Approval (PMA) submission or 510k submission (see below for definitions).

An investigator should consult with their institution's IRB or the FDA to determine the appropriate regulatory pathway for US FDA-regulated investigational device research and submit appropriate documentation to the ORP for review.

- a. **IDE Exempt Studies.** Investigators should submit documentation of an IDE exemption (granted by the IRB or FDA) to the ORP.
- b. **Abbreviated IDE Studies.** Investigators should submit documentation of convened board IRB review and determination for the use of the investigational device in the study. The use of the device should be determined either non-significant risk or significant risk to participations.
- c. **Full IDE Studies.** Documentation of FDA correspondence and IDE number granted by the FDA is required for submission to ORP for review.

2. Definition of a Device Classification – Devices are assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The class to which the device is assigned will determine the required level of FDA clearance or approval. Regulations covering devices can be found at 21 CFR 800-1299 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPartFrom=800&CFRPartTo=1299>).

- a. **Class I General Controls.** Represent a minimal risk to the patient and are subjected to general controls of the FDA (manufacturer registration with the FDA, Good Manufacturing Practice [GMP], branding, labeling, and notification of the FDA prior to public marketing of the device). Examples of devices in this category include but are not limited to bandages, tongue depressors, and examination gloves, etc. Few Class I devices will need PMA or 510k (see below for definitions). Some modifications of Class I devices may require PMA or 510k.
- b. **Class II General Controls with Special Controls.** Represent moderate level of risk to the patient and therefore will be subjected to special controls (performance standards, postmarket surveillance, patient registries, guidance documents, and recommendations) prior to public marketing of the device. Devices in Class II may be life-supporting or life-sustaining and therefore may be subjected to regulatory assurances of safety and effectiveness. Devices in Class II require 510k submission. Examples of devices in this category include but are not limited to surgical needles, non-invasive imaging machines, infusion pumps, etc.
- c. **Class III General Controls and Premarket Approval.** Represent unknown risk to the patient because insufficient information is available to assess the

safety and effectiveness through general or special controls. Further investigation is needed with scientific review of the device's safety and effectiveness. Devices in Class III may be life-supporting, life-sustaining, preventive for the impairment of human health, or carry risk of causing illness or injury. Devices in Class III will need PMA or 510k submission. Examples of devices in this category include but are not limited to heart valves, stents, etc.

- d. **510k Clearance.** Devices submitted for 510k clearance are compared to a predicate device (a device previously cleared by the FDA or in use prior to 1976). The comparison of the subject device and the predicate device should show substantial equivalence of the devices and explain any differences. Human subject use is not required for the submission (but often is performed), but laboratory testing is required. The FDA clears 510k submission; it does not approve them.
- e. **Premarket Approval (PMA).** Devices submitted for PMA must show the safety and effectiveness of the new or modified Class III device. Human subject use data from a clinical trial and laboratory testing are required. PMA submission to the FDA includes documentation on the clinical testing of the device (protocols, safety and effectiveness data, adverse reactions, device failures, patient information, complaints, statistical analysis, and tabulated data, etc.). Studies under an IDE must be identified.

C. Behavioral Therapy Studies

A behavioral clinical trial is defined as a prospective accrual of patients in which a behavioral intervention (i.e., cohort or case-control study) has been designed to determine the outcome of an intervention or interaction (testing instrument, study tool, hazard, etc.) with respect to safety, effectiveness, and/or efficacy. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits the definition of a clinical trial. Clinical trials for behavioral research are not usually classified into phases unless a pharmaceutical agent is being tested.

V. TYPES OF OBSERVATIONAL STUDIES

A. Correlative Studies

Correlative studies may be associated with a clinical trial but do not seek the main outcomes of the clinical trial. A correlative study is defined as a prospective or retrospective collection of human anatomical substances (e.g., tissue, blood, nail clippings, bone marrow, behavioral documentation, other) to be used in research to answer a question regarding the disease, injury or condition, and/or intervention. It does not include the direct assessment of the *outcome of any intervention* for the prevention, diagnosis, treatment, or evaluation of the quality of life of the patient. Correlative studies may require informed consent of the human subject.

B. Epidemiological Studies

Epidemiological studies examine the distribution of disease, injury, or condition with respect to a defined population. The study hypothesis may center on the factors that affect health and/or how people make health-related decisions.

- 1. Cohort Studies** – A comparison of exposed versus non-exposed persons to a specific agent (testing instrument, study tool, hazard, etc.). The cohort study seeks to determine the outcome of the exposure.
- 2. Case-Control Studies** – The comparison of participants with the disease, injury, or condition versus participants without the disease, injury, or condition with respect to a specific agent (testing instrument, study tool, hazard, etc.). The case-control study seeks to determine the differences in the subpopulations to the intercession.