

## NIH Definition of Clinical Trial

### Case Studies

**Case #1:** 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?

Answer: **No,**

- The study does not involve human subjects (only archived and de-identified blood samples are used).
- The study does not include an intervention.

**Case #2:** A study is planned to randomly assign individuals to an experimental intervention to promote weight loss or to a control intervention. After a year, participants' behaviors will be assessed to measure their adherence to exercise regimens. Is this study a clinical trial?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to an intervention.
- The study identifies a health-related behavioral outcome (adherence to exercise regimens).

**Case #3:** 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. are randomly assigned to receive the experimental intervention or to receive one of two control interventions. Each community has a population between 100,000 and 500,000 individuals. The experimental intervention includes public awareness campaigns and educational pamphlets. Is this study a clinical trial?

Answer: **Yes,**

- The study involves human subjects within communities (clusters).
- The study involves interventions to which subjects (in clusters) are prospectively assigned.
- The study identifies a health-related behavioral outcome (smoking behavior).

**Case #4:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to an intervention.
- The study identifies a health-related biomedical outcome (Tumor size and the incidence of metastatic disease).

**Case #5:** 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 concentrations in the blood (pharmacokinetics (pK)). Is this study a clinical trial?

Answer: **Yes,**

- The study involves human subjects (healthy volunteers).
- Subjects are prospectively assigned to an intervention.
- The study identifies a health-related biomedical outcome (maximum tolerated dose).

Note: If the study was examining only pK, it would not be a clinical trial.

**Case #6:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to two different diagnostic strategies, digital vs. film-screen mammography.
- The study identifies a health-related biomedical outcome (incidence and progression of breast cancers).

**Case #7:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to interventions.
- The study identifies a health-related biomedical outcome (frequency of flare-ups).

**Case #8:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to a biomedical intervention.
- The study identifies a health-related biomedical outcome (tumor size).

**Case #9:** 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?

Answer: **No**,

- The study involves human subjects.
- Subjects are prospectively assigned to an intervention (reading a specific announcement).
- 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.

**Case #10:** 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 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?

Answer: **Yes**,

- The study involves human subjects.
- Subjects are prospectively assigned to an intervention.
- The study identifies a health-related biomedical outcome (blood amyloid levels).

**Case #11:** 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. Is this study a clinical trial?

Answer: **No**,

- The study does not involve human subjects. The study is designed to evaluate the device.
- 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.
- The study does not identify a health-related biomedical or behavioral outcome.

**Case #12:** 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?

Answer: **Yes**,

- The study involves human subjects.
- Subjects are prospectively assigned to interventions (integration of CPAP and imagery training).

- The study identifies a health-related biomedical outcome (decreased hypernasality).

**Case #13:** A study aims to examine mechanisms of Serotonin 1A receptor neurotransmission in social anxiety disorder (SAD) by examining how human limbic neurocircuitry processes affect mood stimuli after acute perturbation of the serotonin 1A system. In a double-blind, counterbalanced, repeated-measures design, both controls and subjects with social phobia will be randomly assigned to receive either buspirone or placebo 30 minutes prior to a functional MRI scan. Images showing blood flow to the amygdala and frontocortical regions will be compared. Is this study a clinical trial?

Answer: **No,**

- The study involves human subjects.
- Subjects are prospectively assigned to an intervention (drug or placebo).
  - The study is not designed to examine the effects of buspirone on individuals, but rather to examine short-term changes in blood flow to the brain using fMRI.
- The study does not identify a health-related biomedical or behavioral outcome.
  - Short-term changes in blood flow to the brain are not a health-related outcome.

**Case #14:** 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?

Answer: **Yes,**

- The study involves human subjects (clusters of individuals about whom researchers are collecting behavioral information).
- Subjects are prospectively assigned to interventions (one of three services).
- The study is primarily designed to measure a health-related behavioral outcome (purchase and use of eyeglasses).

**Case #15:** A study primary objective 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 to castrate levels 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to an intervention.
- The study identifies health-related outcomes (dose-response relationship of testosterone and bone turnover).

**Case #16:** Participants are randomly assigned to different methods of the informed consent process to assess the impact of interactive and multimedia components. The study measures participant preferences and understanding of the content. Is this study a clinical trial?

Answer: **No**,

- The study involves human subjects.
- Subjects are prospectively assigned to interventions.
- The study does not identify a health-related biomedical or behavioral outcome.

**Case #17:** An investigator prospectively assigns a healthy group (n=7) to sleep deprivation of 2 hours per night for 5 nights after which measurements of cortisol, testosterone, and insulin and glucose levels are collected to determine the mechanism of insulin resistance. Is this study a clinical trial?

Answer: **No**,

- The study involves human subjects.
- Subjects are prospectively assigned to interventions (sleep deprivation)
- The study does not identify a pre-determined health-related biomedical or behavioral outcome that reflects the effect of an interventions on human subjects' biomedical or behavioral status, or quality of life

**Case #18:** A placebo-controlled study is designed to evaluate the effect of statin rechallenge 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 be recruited for participation in n-of-1 trials. 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 trial, 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?

Answer: **Yes**,

- The study involves human subjects.
- Subjects are prospectively assigned to interventions.
- The study identifies a, health-related biomedical outcome (drug-associated myalgia).

**Case #19:** 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?

Answer: **No**,

- The study involves human subjects.
- The study does not involve prospective assignment of human subjects to an intervention.
- The study does not identify a, health-related biomedical or behavioral outcome; rather, the study is designed to evaluate the device.

Note: 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.

**Case #20:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to interventions based on their level of circulating metastatic cells that are measured with an approved, in vitro diagnostic device.
- The study identifies health-related biomedical outcomes (primary tumor size and the progression of metastatic disease).

**Case #21:** 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 survival of patients who opt to get radiotherapy. Is this study a clinical trial?

Answer: **No,**

- The study involves human subjects.
- Subjects are not prospectively assigned to interventions (Patients and their healthcare providers select the therapy and investigators observe outcomes).
- The study identifies health-related biomedical outcomes (6-month survival).

Note: If the study prospectively assigned patients to receive surgery or radiation, the study would be a clinical trial.

**Case #22:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to interventions.
- The study identifies health-related biomedical outcomes (incidence and severity of migraines).

Note: If patients were only monitored while they took medication prescribed by their physician (such as in case #21), there would be no prospective assignment, and this study would not be a clinical trial.

**Case #23:** 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?

Answer: **Yes,**

- The study involves human subjects.
- Subjects are prospectively assigned to interventions.
- The study identifies a health-related biomedical outcome (improved mobility).

**Case #24:** 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?

Answer: **No,**

- The study involves human subjects research that would be exempt under 45 CFR 46.101(b)(2)<sup>1</sup>.
- Subjects (city population) are prospectively assigned to an intervention (exposure to anti-smoking messages).
- 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.

**Case #25:** Investigators are planning a study to evaluate the effects of providing cash incentives on the rate of STD testing in a specific city. Cash is provided to those agreeing to undergo STD testing. The rate of STD testing after providing cash incentives will be compared to the rate observed in the two years prior to the study. Any individual who tests positive will receive counseling and free treatment. Is this a clinical trial?

Answer: **Yes,**

- The study involves human subjects.
- The study involves an intervention (the combination of cash incentives tied to STD testing).
- The study identifies a health-related outcome. The proposed study not only evaluates cash incentives as a recruitment method, but also provides counseling and/or therapy, which has a direct health implication.

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<sup>1</sup> “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.”  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101>