



Clinical Research Training Office – Clinical Investigation Training Program (CITP) Glossary

The field of clinical investigation has a language all its own, replete with acronyms and jargon. The Clinical Investigation Training Program staff has put together the following compendium of commonly-used terminology in clinical research.

A

Adverse Effect: An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention.

Alternative Hypothesis: A statement of what a statistical hypothesis test sets out to establish. For example, in a clinical trial of a new drug, the alternative hypothesis might be that the new drug is more effective, on average, compared to the current drug used to treat the same condition. Also known as the research hypothesis.

B

Belmont Report: A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

Blinding: The process of preventing researchers and subjects participating in an experimental study from gaining knowledge of their treatment status.

- In a “single-blind” experimental study, the study subjects are unaware of their treatment assignment.
- In a “double-blind” experimental study, both the study subjects and the investigators monitoring the effects of the treatment are unaware of the treatment assignment.
- In a “triple-blind” experimental study, the study subjects, the investigators administering the treatment, and the investigators monitoring the effects of the treatment are unaware of the treatment assignment.

Blocking: The procedure by which experimental units are grouped into homogeneous clusters in an attempt to improve the comparison of treatments by randomly allocating the treatments within each cluster or “block.”

Boxplot: A way of summarizing a set of data measured on an interval scale. It is a type of graph used to show the shape of the distribution, and its central value and variability. The picture produced consists of the most extreme values in the data set (maximum and minimum values), the lower and upper quartiles, and the median. It is useful to indicate whether the data is skewed and if there are any unusual observations.

C

Categorical Data: A set of data is said to be categorical if the values or observations belonging to it can be sorted by category. Each value is chosen from a set of non-overlapping categories.

Chi-squared Test: A chi-squared test is any statistical hypothesis test in which the test statistic has a chi-square distribution when the null hypothesis is true, or any in which the probability distribution of the test statistic (assuming the null hypothesis is true) can be made to approximate a chi-square distribution as closely as desired by making the sample size large enough. Specifically, a chi-square test for independence evaluates statistically significant differences between proportions for two or more groups in a data set.

Clinical Research Associate: An individual who represents the sponsor and who is responsible for the accuracy and management of data and overall supervision of day-to-day activities of the study. Also called a monitor.

Clinical Trial: A controlled study involving human subjects designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

Close-ended Question: A question in which a selection of answers is provided for a respondent. The advantages are: production of more uniform answers than an open-ended question; ease of analysis; ease for the respondent; and possibly promoting higher survey completion rates. In contrast, the disadvantages include potential researcher bias, limiting of spontaneity, and difficulty of answer creation when the researcher is unaware of the range of potential responses.

Cohort: A group of subjects initially identified as having one or more characteristics in common who are followed over time. The Framingham Heart Study is a classic example of a cohort study.

Confidence Interval (informal definition): A range of values calculated from the data in which the investigator believes a true parameter value will lie with some specified probability. Informally (and incorrectly) a confidence interval is a probability statement about the true parameter value.

Confidence Interval (formal frequentist definition): A range of values calculated from the data that will contain the true parameter with a specified probability if the experiment were repeated a large number of times. Formally, a confidence interval is a probability statement about the range of values or region. It is customary to report confidence intervals whose coverage probability is 95 percent; that is, such an interval would enclose the true parameter value 95 percent of the time if the experiment were repeated a large number of times. Approximate 95 percent confidence intervals can be constructed by taking the mean ± 2 standard deviations. However, there are many circumstances in which intervals other than 95 percent are useful.

Contraindicated: Pertains to conditions present in certain individuals which may render a treatment inadvisable or dangerous. Contraindications are often said to be absolute or relative. An **absolute contraindication** exists where the proposed treatment must in no case be used. For example, penicillin is absolutely contraindicated in patients with a penicillin allergy, as it may produce anaphylactic shock and be fatal. A **relative contraindication** exists where a treatment may produce adverse effects, but the benefits of treatment outweigh the risks. For example, many antineoplastic agents are contraindicated in pregnancy, but the benefits of therapy in producing a possible remission of the cancer patient may outweigh the risk of teratogenicity.

Cross-Sectional Studies: Measure the prevalence of health outcomes or determinants of health, or both, in a population at a point in time or over a short period of time. This study is also referred to as a prevalence study, which refers to the comparison of exposed and non-exposed subjects.

D

Data Points: Any text or numbers generated during a study. Data points are often organized and plotted in graphical form.

Data and Safety Monitoring Board: A committee of scientists, physicians, statisticians and others that collect and analyze data during the course of a clinical trial to monitor for adverse effects and other trends that would warrant modification or termination of the trial or notification of the subjects about new information that might affect their willingness to continue in the trial.

Declaration of Helsinki: A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associates in various countries. It has been revised several times; most recently in 2000.

Dependent Variables: The outcomes that are measured in an experiment. Dependent variables are expected to change as a result of an experimental manipulation of the independent variable(s).

Discrete Data: A set of data is said to be discrete if the values/observations belonging to it are distinct and separate, i.e., they can be counted (1, 2, 3...). Examples might include the number of patients in a doctor's surgery; the number of flaws in one meter of cloth; gender (male, female); blood type (O, A, B, AB).

E

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as self-support, marriage or procreation.

Epidemiology: A scientific discipline that studies the factors determining the causes, frequency and distribution of diseases in a community or given population.

Exclusion Criteria: A list of specific conditions which make an individual ineligible to enroll in a research study.

Exculpatory: Pertaining to that which relieves of a responsibility, obligation or hardship; clearing from accusation or blame.

H

Histogram: A histogram is a way of summarizing data that are measured on an interval scale (either discrete or continuous). It is often used in exploratory data analysis to illustrate the major features of the distribution of the data in a convenient form. It divides up the range of possible values in a data set into classes or groups. For each group, a rectangle is constructed with a base length equal to the range of values in that specific group, and an area proportional to the number of observations falling within that group. Note: The histogram is only appropriate for variables whose values are numerical and measured on an interval scale. It is typically used with sample sizes >100 (when a stem and leaf plot is too cumbersome) and can be useful to detect any unusual observations such as outliers and gaps in the data set.

Human Subject: Under Department of Health and Human Services regulations, human subjects are living individuals about whom an investigator conducting research obtains: 1) data through intervention or interaction with the individual or 2) identifiable private information. Intervention includes both the physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact (e.g., questionnaires, interviews) between the investigator and the subject (45 CFR 46.102). Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. Under Federal Drug Administration (FDA) regulations a human subject is defined as "an individual who is or becomes a participant in research, either as a recipient of a test article or as a control (21 CFR 50.03, 21 CFR §56.103(e), 21 CFR §312.3(b)). A subject may be either a healthy individual or a patient." If the research involves a medical device, human subjects are individuals when they participate in an

investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (21 CFR §812.3(p)).

I

Inclusion Criteria: A list of specific conditions that an individual must meet to enroll in a research study.

Informed Consent: Informed consent means “knowing consent,” the exercise of a free power of choice without undue inducement, force, fraud, deceit, duress or other form of constraint or coercion. If the subjects are minors or are not capable of giving consent, parental, guardian or other legal representative consent is required. Use of a written consent form that includes all of the basic elements of informed consent must be documented by a signature of the subject or legally authorized representative.

Inter-Quartile Range (IQR): A measure of the spread or dispersion within a data set. It is calculated by taking the difference between the upper and lower quartiles. The IQR is the width of an interval which contains the middle 50 percent of the sample, so it is smaller than the range and its value is less affected by outliers.

Interval Scale: An interval scale is the measurement where the distance between two adjacent units of measurement (or "intervals") is the same but the zero point is arbitrary. Scores on an interval scale can be added and subtracted but cannot be meaningfully multiplied or divided.

Institutional Review Board (IRB): A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in research.

L

Linear Regression: A regression method which models the relationship between dependent variable Y , independent variables X_i , p and a random term ϵ . This method is called “linear” because the relation of the response (the dependent variable Y) to the independent variables is assumed to be a linear function of the parameters.

Logistic Regression: A statistical model on which the log odds of the response probability is predicted from a set of prognostic factors, $\text{Log} \{p/1-p\} = B_0 + B_1X_1 + B_2X_2 + \dots$, where p is the probability of response, X_1, X_2, \dots are the predictor (explanatory) variables, and B_1, B_2, \dots are parameters to be established from the data. Thus the effect of each prognostic factor is to multiply the baseline log odds.

Longitudinal Study: A study designed to follow subjects forward through time.

M

Mature Minor: Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor.

Meta-analysis: A comprehensive re-analysis of published and unpublished studies, usually based on obtaining individual patient data, to investigate and quantify consistency or lack of consistency among study results.

Minimal Risk: Risk is minimal when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Mode: The most frequently occurring value in a set of discrete data. There can be more than one mode if two or more values are equally common.

Monitor: Designated individual selected by a sponsor or contract research organization to oversee the progress of a clinical investigation.

Multivariable: Analyzing several predictor (explanatory) variables simultaneously. Suppose that an univariable analysis suggests that treatment A is better than treatment B: the hazard ratio is 2.2 (95% confidence interval 1.5-2.9) and $p=0.02$. However, when we simultaneously account for the effects of sex and treatment using multivariable analysis, we estimate the adjusted hazard ratio to be 1.35 (95% confidence interval 0.75-1.95) and $p=0.45$. We might conclude from these results that the apparent univariable effect of treatment is due to sex and that treatment A is not likely to be of real benefit.

Multivariate: Analyzing several outcome variables simultaneously, all as a function of one or more predictive variables. Note that multivariate does not mean “several predictive variables,” as it is often informally used, but refers to several outcome variables. When there are several predictors, the term “multiple” and “multivariable” are probably better descriptors.

N

Nesting: A design characteristic in which a particular effect lies hierarchically entirely within some other effect. In a simple parallel group comparison, patients receive only one treatment, meaning patients are nested within treatments. In a simple crossover design, patients receive both treatments, meaning patients are not nested within treatments.

Nominal Data: A set of data is said to be nominal if the values/observations belonging to it can be assigned a code in the form of a number where the numbers are simply labels. You can count but not order or measure nominal data. For example, in a data set males could be coded as 0, females 1; marital status of an individual could be coded as Y if married, and N if single.

Null Hypothesis: The proposition, to be tested statistically, that the experimental intervention has no effect, meaning that the treatment and control groups will not differ as a result of the intervention. Investigators usually hope that the data will demonstrate some effect from the intervention, thereby allowing the investigator to reject the null hypothesis.

Nuremberg Code: A code of research ethics developed during the trials of the Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.

O

One-sample t-test: A hypothesis test for answering questions about the mean where the data are a random sample of independent observations from an underlying normal distribution. The sample is drawn from a population of a given mean and an unknown variance (which therefore has to be estimated from the sample).

Open Design: An experimental design in which both the investigator(s) and the subjects know the treatment group to which subjects are assigned.

Open-ended Question: A type of question in which the researcher does not provide any response choices, giving the respondent the freedom to answer the question however they see fit. The advantages of this type of question are that it allows respondents the opportunity to express their own thoughts and that it helps avoid researcher bias. Disadvantages include: It requires respondents to exhibit more effort when responding; analysis may be difficult; and if in hard copy form, may be difficult to read.

Observational Study: A study design in which the investigator does not control the assignment of treatment to individual study subjects.

Ordinal Data: A set of data is said to be ordinal if the values/observations belonging to it can be ranked (put in order) or have a rating scale attached. You can count and order ordinal data, but not measure it.

Outlier: An outlier is an observation in a data set which is far removed in value from the others in the data set. It is an unusually large or an unusually small value compared to the other data points. It can be an error in measurement, in which case it will distort the interpretation of the data, having undue influence on many summary statistics, e.g., the mean. If an outlier is a genuine result, it is important because it might indicate an extreme behavior of the process under study. For this reason, all outliers must be examined carefully before embarking on any formal analysis.

P

Pharmacokinetic: Related to the absorption, distribution, metabolism and elimination of drugs by the body.

Pharmacology: The scientific discipline that studies the action of drugs on living systems (animals or humans).

Phase I (Clinical) Trial: The first stage in testing an unapproved (by the FDA) drug in man. The drug is administered to a small number of normal subjects to generate preliminary information on its safe dosage, toxicity, tolerance, absorption and metabolism. However, in some instances, if the drug is intended to treat a specific disease, it may be appropriate to test the drug in patients with that disease.

Phase II (Clinical) Trial: The second stage in testing a new drug in man generally carried out on patients with the disease or condition of interest to obtain information on the treatment efficacy and to supplement information on safety obtained from a phase I trial.

Phase III (Clinical) Trial: The third and usually final stage in testing a drug in man. The study is designed to include a control treatment and random allocation to treatment on a large subject population in different clinical settings. The drug is used as would be when marketed and the study is primarily concerned with assessments of dosage effects, efficacy and safety. Once this phase is completed, the drug manufacturers may request permission to market the drug by submission of a New Drug Application to the FDA.

Phase IV (Clinical) Trial: Generally carried out after FDA approval and licensure of the drug for that indication. The study is a randomized controlled trial designed to evaluate the long-term safety and efficacy of a drug for the given information.

Placebo: An inactive or inert substance, identical in appearance to the active form of the drug. It is administered to patients to determine whether effects observed during clinical trials are actually caused by the study drug or by the psychophysiological (psychosomatic) effects of the treatment.

Principal Investigator: The scientist or scholar with the primary responsibility for the design and conduct of a research project.

Private Information: Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may

readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Protocol: A protocol is the researcher's plan of a scientific experiment or treatment. A protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regime(s) and the proposed methods of data analysis.

P-value: The conditional probability that an observed effect or one larger is due to chance given that the null hypothesis is true. P-values are frequently misinterpreted as the unconditional probability of an error or the probability that the observed result is due to chance. It is important to recognize that the p-value assumes the null hypothesis is true and accounts for outcomes that have not been observed.

Q

Quality Assurance: A system of activities whose purpose is to provide assurance that the overall control of quality is being done effectively.

Quasi-experimental: A study that is similar to a true experimental study except that it lacks random assignments of subjects to treatment groups.

R

Randomization or Randomized Clinical Trials: Assignment of subjects to different treatments, interventions or conditions according to chance rather than with reference to some aspect of their condition, history or prognosis.

Range: The range of a sample (or data set) is a measure of the spread or the dispersion of the observations. It is the difference between the largest and the smallest observed value of some quantitative characteristic and is very easy to calculate. Note: a great deal of information is ignored when computing the range since only the largest and smallest data values are considered; the remaining data are ignored.

Risk: The probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk."

S

Sample Mean: An estimator available to estimate the population mean. It is a measure of the location in the data commonly referred to as the average. The sample mean is calculated by

taking the sum of all the data values and dividing by the total number of data values. The value depends equally on all of the data and may include outliers; therefore it may not appear representative of the central region of a distribution based on skewness and outliers.

Site Visit: A visit by agency officials, representatives or consultants to the location of a research activity to assess an investigation or the adequacy of IRB protection of human subjects.

Source Documents: The original recording of data about a research participant, e.g., history and physical reports, laboratory results, diagnostic test results, physician progress notes, nurses notes, etc.

Sponsor (of a drug trial): The developer of a new drug who distributes it to investigators and physicians for clinical trials, and who is responsible for securing FDA clearance for trials and reporting the results of those trials to the FDA. A sponsor may be a private pharmaceutical manufacturer, a research institute, a clinical investigator or a federal agency.

Sponsor: The company/person who initiates the study.

Standard Deviation: A measure of spread or dispersion within a set of data. It is calculated by taking the square root of the variance and is the most common measure of statistical dispersion. The more widely the values are spread out, the larger the standard deviation.

Standard Error: The standard deviation of the values of a given function of the data (parameter), over all possible samples of the same size.

Stem and Leaf Plot: A stem and leaf plot is a way of summarizing a set of data measured on an interval scale. It is often used in exploratory data analysis to illustrate the major features of the distribution of the data in a convenient and easily drawn form. A stem and leaf plot is similar to a histogram but is usually a more informative display for relatively small data sets (<100). It provides a table as well as a picture of the data and from it one can readily write down the data in order of magnitude, which is useful for many statistical procedures. One can also compare more than one set of data by the use of multiple stem and leaf plots. By using a back-to-back stem and leaf plot, we are able to compare the same characteristic in two different groups, for example, pulse rate after exercise of smokers and nonsmokers.

Stratification: Performing a statistical procedure separately in groups (strata) to reduce the effects of the group factor. As an adjunct to randomization, stratification can only effectively be used with blocking. As an analysis method, estimates are made within strata and pooled, when possible, across strata to reduce the influence of the stratifying variable.

Symmetry: Symmetry is implied when data values are distributed in the same way above and below the middle of the sample. Symmetrical data sets are: 1.) easily interpreted 2.) allow a balanced attitude to outliers, that is, those above and below the middle value (median) can be considered by the same criteria and 3.) Allow comparisons of spread or dispersion with similar data sets. Note: Many standard statistical techniques are appropriate only for symmetric distributional form.

T

Test Article: Any drug (including a biological product for human use), medical device for human use or any other article subject to regulation under the Food, Drug, and Cosmetic Act of 1938 or under sections 351 and 354-360F of the Public Health Service Act.

Therapeutic Intent: The research physician's intent to provide some benefit to improving a subject's condition (e.g., prolongation of life, shrinking of tumor or improved quality of life, even though cure or dramatic improvement cannot necessarily be effected). This term is sometimes associated with phase I drug studies in which potentially toxic drugs are given to an individual with the hope of inducing some improvement in the patient's condition, as well as assessing the safety and pharmacology of a drug.

Therapeutic Research: Research involving an intervention that has the likelihood of providing a therapeutic, diagnostic or preventive benefit to the subjects.

Two-sample t-test: A hypothesis test for answering questions about the mean when the data are collected from two random samples of independent observations, each from an underlying normal distribution. When carrying out a two-sample t-test it is typical to assume that the variance for the two populations is equal.

Type I Error: Concluding that a treatment effect or difference exists, when in reality, it does not (false positive).

Type II Error: Concluding that a treatment effect or difference does not exist, when in reality, it does (false negative).