GLOSSARY OF CLINICAL TRIAL AND STATISTICAL TERMS

Absolute risk difference The difference in size of risk between two groups. For example, if one group has a 15% risk of contracting a particular disease, and the other has a 10% risk of getting the disease, the risk difference is five percentage points.

Adjusted analysis An analysis that controls (adjusts) for baseline imbalances in important patient characteristics.

Adverse effect An adverse event for which the causal relation between the drug/intervention and the event is at least a reasonable possibility. The term adverse effect applies to all interventions.

Adverse reaction (adverse event) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time.

Approved drugs In the United States the FDA must approve drugs through a process that involves several steps, including preclinical laboratory and animal studies, investigational new drug (IND) application to start clinical trials for safety and efficacy, and filing of a new drug application (NDA) by the manufacturer of the drug. The drug is approved after the FDA approves the NDA.

Design, Execution, and Management of Medical Device Clinical Trials,
by Salah Abdel-aleem

Arm Any of the treatment groups in a randomized trial. Most randomized trials have two "arms," but some have three "arms," or even more.

Attrition The loss of participants during the course of a study (also called patients loss to follow-up). Participants that are lost during the study are often call dropouts.

Baseline

1. Information gathered at the beginning of a study from which variations found in the study are measured.
2. Initial time point in a clinical trial, just before a participant starts to receive the experimental treatment that is being tested.

Bias When a point of view prevents impartial judgment on issues relating to the subject of that point of view. In clinical studies, bias is controlled by several methods such as blinding and randomization.

Categorical data Data that are classified into two or more nonoverlapping categories. Race and type of drug (aspirin, paracetamol, etc.) are examples of categorical variables. If there is a natural order to the categories, for example, nonsmokers, ex-smokers, light smokers, and heavy smokers, the data are known as ordinal data. If there are only two categories, the data are dichotomous data.

Causal effect An association between two characteristics that can be demonstrated to be due to cause and effect, such as a change in one causes the change in the other. Causality can be demonstrated by experimental studies such as controlled trials (e.g., that an experimental intervention causes a reduction in mortality). However, causality can often not be determined from an observational study.

Censored A term used in studies whose outcome is the time to a particular event, to describe data from patients where the outcome is unknown. A patient might be known not to have had the event only up to a particular point in time, so "survival time" is censored at this point.

Chi-squared test A statistical test based on comparison of a test statistic to a chi-squared distribution. Used in RevMan analyses to test the statistical significance of the heterogeneity statistic.

Clinical investigator A medical researcher in charge of carrying out a clinical trial's protocol.

Clinical trial A research study to answer specific questions about new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people.

Clinically significant A result (e.g., a treatment effect) that is large enough to be of practical importance to patients and health care providers. The hypothesis of clinical studies is usually based on clinical significant effect. This is not the same thing as statistically significant. Assessing clinical significance takes into account factors such as the size of a treatment effect, the severity of the condition being treated, the side effects of the treatment, and the cost.

Cohort In epidemiology, a group of individuals with some characteristics in common.

Comorbidity The presence of one or more diseases or conditions other than those of primary interest. In a study looking at treatment for one disease or condition, some individuals may have other diseases or conditions that could affect their outcomes (comorbidity may be a confounder).

Compassionate use A method of providing experimental therapeutics prior to final FDA approval for use in humans. This procedure is used with very sick individuals who have no other treatment options. Often case-by-case approval must be obtained from the FDA for "compassionate use" of a drug or therapy.

Confidence interval (CI) A measure of the uncertainty around the main finding of a statistical analysis. Estimates of unknown quantities, such as the odds ratio comparing an experimental intervention with a control, are usually presented as a point estimate and a 95% confidence interval. This means that if someone were to keep repeating a study in other samples from the same population, 95% of the confidence intervals from those studies would contain the true value of the unknown quantity. Alternatives to 95%, such as 90% and 99% confidence intervals, are sometimes used. Wider intervals indicate lower precision; narrow intervals, greater precision.

Confidence limits The upper and lower boundaries of a confidence interval.

Confounder A factor that is associated with both an intervention (or exposure) and the outcome of interest. For example, if people in the experimental group of a controlled trial are younger than those in

the control group, it will be difficult to decide whether a lower risk of death in one group is due to the intervention or the difference in ages. Age is then said to be a confounder, or a confounding variable. Randomization is used to minimize imbalances in confounding variables between experimental and control groups. Confounding is a major concern in non-randomized studies.

Continuous data Data with a potentially infinite number of possible values within a given range. Height, weight, and blood pressure are examples of continuous variables.

Cross-over trial A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, the participants are randomly allocated to receive them in either the order A, B or the order B, A. Cross-over trials are particularly appropriate for study of treatment options for relatively stable health problems. The time during which the first interventions is taken is known as the first period, with the second intervention being taken during the second period.

Confidentiality regarding trial participants Refers to maintaining the confidentiality of trial participants including their personal identity and all personal medical information. The trial participants' consent to the use of records for data verification purposes should be obtained prior to the trial and assurance must be given that confidentiality will be maintained.

Contraindication A specific circumstance when the use of certain treatments could be harmful. Sometimes this term is confused with an entirely different term, namely the use of the product with precaution.

Control group The standard by which experimental observations are evaluated. In many clinical trials one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo.

Controlled trials Control is a standard against which experimental observations may be evaluated. In clinical trials one group of participants is given an experimental drug, while another group (i.e., the control group) is given either a standard treatment for the disease or a placebo.

Cost-effectiveness analysis An economic analysis that views effects in terms of overall health specific to the problem, and describes the costs for some additional health gain.

Data safety and monitoring board (DSMB) An independent committee composed of community representatives and clinical research experts that review data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.

Dependent variable The outcome or response that results from changes to an independent variable. In a clinical trial, the outcome (over which the investigator has no direct control) is the dependent variable, and the treatment arm is the independent variable.

Diagnostic trials Refers to trials that are conducted to find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trials usually include people who have signs or symptoms of the disease or condition being studied.

Distribution The collection of values of a variable in the population or the sample, sometimes called an empirical distribution.

Dose-ranging study A clinical trial in which two or more doses of an agent (e.g., a drug) are tested against each other to determine which dose works best and is least harmful.

Dose dependent A response to a drug that may be related to the amount received (i.e., the dose). Sometimes trials are done to test the effects of different dosages of the same drug. This may be true for both benefits and harms.

Dose-dependent range The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose–response relationships can be investigated using meta-regression.

Double-blind study A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome.

Drug–drug interaction A modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug.

Effectiveness The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do. For

example, if the device is intended for pain relief, it is expected that the device will actually relieve pain, with evidence demonstrating this effect.

Efficacy The extent to which an intervention produces a beneficial result under ideal conditions. Clinical trials that assess efficacy are sometimes called explanatory trials. Efficacy of a drug or treatment could be defined as the maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed.

Eligibility criteria Summary criteria for participants' selection; included are inclusion and exclusion criteria.

Empirical Based on experimental data, not on a theory.

Endpoint Overall outcome that the protocol is designed to evaluate.

Epidemiology The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population.

Experimental drug A drug that is not FDA licensed for use in humans, or as a treatment for a particular condition.

Equipoise A state of uncertainty where a person believes it is equally likely that either of two treatment options is better.

Equivalence trial A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Food and Drug Administration (FDA) The US Department of Health and Human Services agency responsible for ensuring the safety and effectiveness of all drugs, biologics, and medical devices, including those used in the diagnosis, treatment, and prevention of diseases.

Good clinical practice (GCP) Basically the rules for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials. GCP provide assurance that data and results are based on sound scientific and ethical research. They are a broad set of requirements, standards, and recommendations that apply to thousands of highly specific tasks.

Historical control A control person or group for whom data were collected earlier than for the group being studied. There is a large

risk of bias in studies that use historical controls due to systematic differences between the comparison groups, due to changes over time in risks, prognosis, health care, and so forth.

Hypothesis A supposition or assumption advanced as a basis for reasoning or argument, or as a guide to experimental investigation.

Inclusion/exclusion criteria The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

Informed consent The process of learning the key facts about a clinical trial before deciding whether to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether to participate, the doctors and nurses involved in the trial explain the details of the study.

Informed consent document A document that describes the rights of the study participants, and includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

Institutional review board (IRB) A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the United Sates must be approved by an IRB before they begin. Every institution that conducts or supports biomedical or behavioral research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants.

Intent to treat analysis Analysis of clinical trial results that includes all data from participants in the groups to which they were randomized even if they never received the treatment.

Interventions Primary interventions being studied.

Interim analysis Analysis comparing intervention groups at any time before the formal completion of a trial, usually before recruitment is complete. Often used with stopping rules so that a trial can be stopped if participants are being put at risk unnecessarily. Timing and frequency of interim analyses should be specified in the protocol.

Investigational new drug (IND) A new drug, antibiotic drug or biological drug, that is used in a clinical investigation. It also includes a biological product used in vitro for diagnostic purposes.

Logarithmic scale A scale in which the logarithm of a value is used instead of the value. In a logarithmic scale on a RevMan forest plot, the distance between 1 and 10 is the same as the distance between 10 and 100, or between 100 and 1000. A logarithmic scale may be used when the range of numbers being represented is large, or to represent ratios. See also linear scale.

Logistic regression A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention. It is widely used for dichotomous outcomes, in particular, to carry out adjusted analysis.

Masked Knowledge of the intervention assignment.

Medical device An intervention defined as:

- Used for diagnosis, cure, mitigation, treatment or prevention of a disease or condition
- Affects the structure and function of the body
- Does not achieve intended use through chemical reaction
- Is not metabolized

Mean An average value calculated by adding all the observations and dividing by the number of observations.

Mean difference (in meta-analysis) A method used to combine measures on continuous scales (e.g., weight), where the mean, standard deviation and sample size in each group is known. The weight given to the difference in means from each study (e.g., how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect.

Median The value of the observation that comes half way when the observations are ranked in order.

Meta-analysis The use of statistical techniques in a systematic review to integrate the results of included studies. Sometimes misused as a synonym for systematic reviews, where the review includes a meta-analysis.

Multivariate analysis Measuring the impact of more than one variable at a time while analyzing a set of data, such as looking at the impact of age, sex, and occupation on a particular outcome. Performed using regression analysis.

Natural history study Study of the natural development of something (such as an organism or a disease) over a period of time.

New drug application (NDA) An application submitted by the manufacturer of a drug to the FDA—after clinical trials have been completed—for a license to market the drug for a specified indication.

Normal distribution A statistical distribution with known properties commonly used as the basis of models to analyze continuous data. Key assumptions in such analyses are that the data are symmetrically distributed about a mean value, and the shape of the distribution can be described using the mean and standard deviation.

Noninferiority trial A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Null hypothesis The statistical hypothesis that one variable (e.g., which treatment a study participant was allocated to receive) has no association with another variable or set of variables (e.g., whether or not a study participant died), or that two or more population distributions do not differ from one another. In simplest terms, the null hypothesis states that the factor of interest (e.g., treatment) has no impact on outcome (e.g., risk of death).

Off-label use A drug prescribed for conditions other than those approved by the FDA.

Open-label trial A clinical trial in which doctors and participants know which drug or vaccine is being administered.

Orphan drugs An FDA category that refers to medications used to treat diseases and conditions that occur rarely.

Observational study A study in which the investigators do not seek to intervene, and simply observe the course of events. Changes or differences in one characteristic (e.g., whether or not people received the intervention of interest) are studied in relation to changes or differences in other characteristic(s).

Odds ratio The ratio of the odds of an event in one group to the odds of an event in another group. In studies of treatment effect, the odds in the treatment group are usually divided by the odds in the control group. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome. When the risk is small, odds ratios are very similar to risk ratios.

One-tailed test A hypothesis test in which the values for which we can reject the null hypothesis are located entirely in one tail of the probability distribution. Testing whether one treatment is better

than another (rather than testing whether one treatment is either better or worse than another) would be a one-tailed test. (Also called one-sided test.)

Open clinical trial There are several possible meanings for this term:

1. A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (i.e., not blinded). Random allocation may or may not be used in such trials. Sometimes called an "open label" design.
2. A clinical trial in which the investigator decides which intervention is to be used (nonrandom allocation). This is sometimes called an open label design (but some trials said to be "open label" are randomized).

Parallel group trial A trial that compares two groups of people concurrently, one of which receives the intervention of interest and one of which is a control group. Some parallel trials have more than two comparison groups and some compare different interventions without including a nonintervention control group.

Per-protocol analysis An analysis of the subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. This subset may be defined after considering exposure to treatment, availability of measurements, and absence of major protocol deviations. The per-protocol analysis strategy may be subject to bias as the reasons for noncompliance may be related to treatment.

Posterior distribution The outcome of Bayesian statistical analysis. A probability distribution describing how likely are different values of an outcome (e.g., treatment effect). It takes into account the belief before the study (the prior distribution) and the observed data from the study.

Prospective study In evaluations of the effects of interventions, a study in which people are identified according to current risk status or exposure, and followed forward through time to observe outcome. Randomized controlled trials are always prospective studies. Cohort studies are commonly either prospective or retrospective, whereas case-control studies are usually retrospective. In Epidemiology, "prospective study" is sometimes misused as a synonym for cohort study.

P-value The probability (ranging from zero to one) that the results observed in a study (or results more extreme) could have occurred by chance if in reality the null hypothesis was true. In a meta-analysis,

the *P*-value for the overall effect assesses the overall statistical significance of the difference between the intervention groups, while the *P*-value for the heterogeneity statistic assesses the statistical significance of differences between the effects observed in each study.

Pharmacokinetics The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.

Placebo A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness.

Placebo-controlled study A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants while the drug being tested is given to another group.

Placebo effect A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

Preclinical The testing of experimental therapies in the test tube or in animals—the testing that occurs before trials in humans may be carried out.

Prevention trials Trials to find better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

Protocol A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

Quality of life trials (or supportive care trials) Trials that explore ways to improve comfort and quality of life for individuals with a chronic illness.

Randomization A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better.

Randomized trial A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilized.

Side effects Any undesired actions or effects of a drug or treatment. Experimental drugs must be evaluated for both immediate and long-term side effects.

Single-blind study A study in which one party, either the investigator or participant, is unaware of what medication the participant is taking.

Standard treatment A treatment currently in wide use and approved by the FDA, considered to be effective in the treatment of a specific disease or condition.

Standards of care Treatment regimen or medical management based on state of the art participant care.

Statistical significance The probability that an event or difference occurred by chance alone.

Study endpoint A primary or secondary outcome used to judge the effectiveness of a treatment.

Sensitivity analysis An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are in correlation to uncertain decisions or assumptions about the data and the methods that were used.

Standard deviation (SD) A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE) The standard deviation of the sampling distribution of a statistic. Measurements taken from a sample of the population will vary from sample to sample. The standard error is a measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Statistically significant A result that is unlikely to have happened by chance. The usual threshold for this judgment is that the results, or more extreme results, would occur by chance with a probability of less than 0.05 if the null hypothesis was true. Statistical tests produce a *P*-value to assess this.

Stratification The process by which groups are separated into mutually exclusive subgroups of the population that share a characteristic, such as age group, sex, or socioeconomic status. It is possible to

compare these different strata to try and see if the effects of a treatment differ between the subgroups. See also subgroup analysis.

Stopping rule A procedure that allows interim analyses in clinical trials at predefined times, while preserving the type I error at some prespecified level.

Subgroup analysis An analysis in which the intervention effect is evaluated in a defined subset of the participants in a trial, or in complementary subsets, such as by sex or in age categories. Trial sizes are generally too small for subgroup analyses to have adequate statistical power.

Surrogate endpoints Often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up. For example, blood pressure is not directly important to patients, but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks.

Retrospective study A study in which the outcomes have occurred to the participants before the study commenced. Case-control studies are usually retrospective, cohort studies sometimes are, and randomized controlled trials never are.

***t*-Test** A statistical hypothesis test derived from the t distribution. It is used to compare continuous data in two groups (also called Student's t-test).

Toxicity An adverse effect produced by a drug that is detrimental to the participant's health. The level of toxicity associated with a drug will vary, depending on the condition that the drug is used to treat.

Two-tailed *t*-test A hypothesis test in which the values for which we can reject the null hypothesis are located entirely in both tails of the probability distribution. Testing whether one treatment is better or worse than another (rather than testing whether one treatment is only better than another) would be a two-tailed test (also called two-sided test).

Washout period/phase In a cross-over trial, the stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.