

Glossary

Clinical Trials Terminology

absorption The process by which medications reach the blood stream when administered other than intravenously, for example, through nasal membranes. *See also ADME in acronym glossary.* (pharmacokinetics)

action letter An official communication from FDA to an NDA sponsor announcing an agency decision. *See also approval letter, approvable letter, not-approvable letter.*

admission criteria Basis for selecting target population for a clinical trial. Subjects must be screened to ensure that their characteristics match a list of admission criteria and that none of their characteristics match any single one of the exclusion criteria set up for the study. *See also inclusion criteria.*

adverse drug reaction (ADR) In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (*see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*). (ICH)

adverse event (AE) Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH) *See also serious adverse event, serious adverse experience.*

adverse reaction *See adverse drug reaction.*

AIDS Acquired immune deficiency syndrome. *See also SIDA and HIV in acronym glossary.*

algorithm Step-by-step procedure for solving a mathematical problem; also used to describe step-by-step procedures for making a series of choices among alternative decisions to reach an outcome.

aliquot A part that is a definite fraction of a whole, as in aliquot samples for laboratory testing or analysis.

alpha error *See Type 1 error.* (statistics)

analyte A substance being analyzed; in chromatography, a single component (compound) of a mixture.

applet A small application, typically downloaded from a server. (IT)

approvable letter An official communication from FDA to an NDA sponsor that lists minor issues to be resolved before an approval can be issued.

approval (in relation to institutional review boards) The affirmation decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements. (ICH)

approval letter An official communication from FDA to inform an NDA sponsor of an agency decision that allows commercial marketing of the product.

audit (of a clinical trial) A systematic and independent examination of trial-related

activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). (ICH)

audit certificate Document that certifies that an audit has taken place (at an investigative site, CRO, or clinical research department of a pharmaceutical company).

audit report A written evaluation by the sponsor's auditor of the results of the audit. (ICH)

audit trail Documentation that allows reconstruction of the course of events. (ICH)

balanced study Trial in which a particular type of subject is equally represented in each study group.

bandwidth An indicator of the throughput (speed) of data flow on a transmission path; the width of the range of frequencies on which a transmission medium carries electronic signals. All digital and analog signals have a bandwidth. (IT)

baseline assessment Assessment of subjects as they enter a trial and before they receive any treatment.

Bayesian statistics Statistical approach named for Thomas Bayes (1701–1761) that has among its features, giving a subjective interpretation to probability, accepting the idea that it is possible to talk about the probability of hypotheses being true and of parameters having particular values.

beta error *See Type 2 error.* (statistics)

between-subject variation In a parallel trial design, differences between subjects are used to assess treatment differences.

bioanalytical assays Methods for quantitative measurement of a drug, drug metabolites, or chemicals in biological fluids.

bioavailability Rate and extent to which a drug is absorbed or is otherwise available to the treatment site in the body.

bioequivalence Scientific basis on which generic and brand-name drugs are compared. To be considered bioequivalent, the bioavailability of two products must not differ significantly when the two products are

Glossary Notes

Some glossary entries are followed by source annotations in parentheses to indicate that the definition is an official one. “ICH,” for example, indicates that the definition is quoted verbatim from the ICH Guideline for Good Clinical Practice, and a 21 CFR citation indicates a quotation from the Code of Federal Regulations. Other annotations indicate the definition applies to a certain discipline—for example, statistics or information technology (IT).

given in studies at the same dosage under similar conditions.

biostatistics Branch of statistics applied to the analysis of biological phenomena.

blind study One in which the subject or the investigator (or both) are unaware of what trial product a subject is taking. *See also double-blind study, single-blind study, triple-blind study.*

blinded medications Products that appear identical in size, shape, color, flavor, and other attributes to make it very difficult for subjects and investigators to determine which medication is being administered.

blinding/masking A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). (ICH)

browser Computer program that runs on the user's desktop computer and is used to navigate the World Wide Web. *See also Web browser.* (IT)

cache Storage area on a computer's hard drive where the browser stores (for a limited time) Web pages and/or graphic elements. (IT)

carry-over effect Effects of treatment that persist after treatment has been stopped, sometimes beyond the time of a medication's known biological activity.

case record form *See case report form.*

case report form (CRF) A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject. (ICH)

categorical data Data evaluated by sorting values (for example, severe, moderate, and mild) into various categories.

causality assessment Determining whether there is a reasonable possibility that the drug caused or contributed to an adverse event. It includes assessing temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, and the presence (or absence) of a more likely cause.

circadian rhythm Biological timing and rhythmicity that, in human beings, is characterized by cycles of approximately 24 hours. *Synonym: biological clock.*

clean database (or file) One from which errors have been eliminated and in which measurements and other values are provided in the same units.

client A program that makes a service request of another program (the server) that fulfills the request. Web browsers (such as Netscape Navigator and Microsoft Explorer) are clients that request HTML files from Web servers. (IT)

clinical investigation *See clinical trial.*

clinical investigation brochure *See investigator's brochure.*

clinical research associate (CRA) Person employed by a sponsor, or by a contract research organization acting on a sponsor's behalf, who monitors the progress of investigator sites participating in a clinical study. At some sites (primarily in academic settings), clinical research coordinators are called CRAs. *See monitor.*

clinical research coordinator (CRC) Person who handles most of the administrative responsibilities of a clinical trial, acts as liaison between investigative site and sponsor, and reviews all data and records before a monitor's visit. *Synonyms: trial coordinator, study coordinator, research coordinator, clinical coordinator, research nurse, protocol nurse.*

clinical significance Change in a subject's clinical condition regarded as important whether or not due to the test article. Some statistically significant changes (in blood tests, for example) have no clinical significance. The criterion or criteria for clinical significance should be stated in the protocol.

clinical study *See clinical trial/study.*

clinical trial Systematic study of a test article (treatment, drug, device) in one or more human subjects. *Synonyms: clinical study, clinical investigation.* (21 CFR 312.3)

clinical trial/study Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s), with the object of ascertaining its safety and/or efficacy. The terms "clinical trial" and "clinical study" are synonymous. (ICH)

clinical trial/study report A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (*see the ICH Guideline for Structure and Content of Clinical Study Reports*). (ICH)

clinical trial exemption (CTX) A scheme that

allows sponsors to apply for approval for each clinical study in turn, submitting supporting data to the Medicines Control Agency (MCA), which approves or rejects the application (generally within 35 working days). Approval means that the company is exempt from the requirement to hold a clinical trial certificate (CTC). (UK)

clinical trial materials Complete set of supplies provided to an investigator by the trial sponsor.

clinical trial report *See final report.*

coding In clinical trials, the process of assigning data to categories for analysis. Adverse events, for example, may be coded using MedDRA. *See acronym glossary.*

cohort Group of subjects in a clinical trial followed up at regular, predetermined intervals.

cohort study *See prospective study.*

comparative study One in which the investigative drug is compared against another product, either active drug or placebo.

comparator (product) An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial. (ICH)

Competent Authority (CA) The regulatory body charged with monitoring compliance with the national statutes and regulations of European Member States.

compliance (in relation to trials) Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements. (ICH)

confidentiality Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity. (ICH)

Conformity Assessment The process by which compliance with the Essential Requirements (ERs) is assessed. *See also Notified Body.*

consent form (CF) Document used during the consent process that is the basis for explaining to potential subjects the risks and potential benefits of a study and the rights and responsibilities of the parties involved.

consumer safety officer FDA official who coordinates the review process of various applications.

contract A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract. (ICH)

contract research organization (CRO) A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. (ICH)

control group The group of subjects in a controlled study that receives no treatment, a standard treatment, or a placebo.

controlled study A study in which a test article is compared with a treatment that has known effects. The control group may receive no treatment, standard treatment, or placebo.

coordinating center Headquarters for a multisite trial that collects all data.

coordinating committee A committee that a sponsor may organize to coordinate the conduct of a multicenter trial. (ICH)

coordinating investigator An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial. (ICH)

correlation The relationship of one variable to another, not to be confused with causation. (statistics)

crossover trial In crossover trials, each subject receives both treatments being compared or the treatment and control. Such trials are used for patients who have a stable, usually chronic, condition during both treatment periods.

curriculum vitae (cv) Document that outlines a person's educational and professional history.

daltons Units of atomic mass.

data and safety monitoring board (DSMB) Researchers—ideally independent of the trials they monitor—who periodically review data from blinded, placebo-controlled trials. A DSMB can stop a trial if toxicities are found or if treatment is proved beneficial. See also *independent data-monitoring committee*.

data base A collection of data, typically organized for easy search and retrieval.

database Data stored in computer form for retrieval, processing, and/or analysis.

Data Encryption Standard (DES) A widely used method of data encryption using a private (secret) key. Each message uses one of 72 quadrillion or more possible encryption keys that are chosen at random. The sender and receiver must both know and use the same private key. DES applies a 56-bit key to each 64-bit block of data. The U.S. government judged the key so difficult to break that it restricted the key's export to other countries.

data monitoring Process by which case

report forms are examined for completeness, consistency, and accuracy.

data monitoring committee See *independent data-monitoring committee*.

Declaration of Helsinki A set of recommendations or basic principles that guide medical doctors in the conduct of biomedical research involving human subjects. It was originally adopted by the 18th World Medical Assembly (Helsinki, Finland, 1964); the recently revised document (52nd WMA General Assembly, Edinburgh, Scotland, October 2000).

demographic data Characteristics of subjects or study populations, which include such information as age, sex, family history of the disease or condition for which they are being treated, and other characteristics relevant to the study in which they are participating.

direct access Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subject's identities and sponsor's proprietary information. (ICH)

distribution In pharmacokinetics, the processes that control transfer of a drug from the site of measurement to its target and other tissues. See also *ADME in acronym glossary*. (pharmacokinetics)

documentation All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct and/or results of a trial, the factors affecting a trial and the actions taken. (ICH)

domain name The way a particular Web server is identified on the Internet. For example, www.tripod.com names the World Wide Web (www) server for Tripod (tripod), which is a commercial (com) entity. (IT)

dosage regimen (a) The number of doses per given time period; (b) the time that elapses between doses (for example, every six hours) or the time that the doses are to be given (for example, at 8 a.m. and 4 p.m. daily); or (c) the amount of a medicine (the number of capsules, for example) to be given at each specific dosing time.

double-blind study A study in which neither the subject(s) nor the investigator(s) know what treatment a subject is receiving.

dynamic HTML Collective term for a combi-

nation of new tags and options, style sheets, and programming that lets you create Web pages in Hypertext Mark-up Language (HTML) that are more responsive to user interaction than previous versions of HTML. (IT)

effectiveness The desired measure of a drug's influence on a disease condition as proved by substantial evidence from adequate and well-controlled investigations.

efficacy A product's ability to produce beneficial effects on the course or duration of a disease.

endpoint An indicator measured in a subject or biological sample to assess the safety, efficacy, or other objective of a trial. See also *surrogate marker*.

equipoise A state in which an investigator is uncertain about which arm of a clinical trial would be therapeutically superior for a patient. An investigator who has a treatment preference or finds out that one arm of a comparative trial offers a clinically therapeutic advantage should disclose this information to subjects participating in the trial.

essential documents Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (ICH)

ethics committee See *institutional review board*.

exclusion criteria A list of criteria, any one of which excludes a potential subject from participation in a study. See also *inclusion criteria*.

excretion The act or process of eliminating waste products from the body. See also *ADME in acronym glossary*. (pharmacokinetics)

explanatory trial Term used to describe a clinical study designed to demonstrate the efficacy of a product. See also *pragmatic trial*.

external consistency The consistency of a procedure between sets of data.

File Transfer Protocol (FTP) A standard protocol for exchanging files between computers on the Internet. Used to transfer Web page files to the computer that acts as a server for everyone on the Internet. Also commonly used to download programs and other files to your computer from other servers. FTP is usually one of the programs that come with TCP/IP. See *TCP/IP in Glossary of Acronyms, Abbreviations & Initials*.

final report Complete, comprehensive description of a completed trial that describes the experimental materials and statistical design. It also presents and

evaluates the trial results and statistical analyses.

firewall A set of related programs, located at a network gateway server, that protects a private computer network from users from other networks. Also the security policy that is used with the programs. (IT)

first-in-humans study The first Phase 1 study in which the test product is administered to human beings.

first-in-man study See *first-in-humans study*.

Food and Drug Administration (FDA) The United States regulatory authority charged with, among other responsibilities, granting IND and NDA approvals.

gas chromatography (GC) A process by which the components of a mix are separated from one another by volatilizing the sample into a carrier gas stream and passing the gas through a column containing a substance that selectively retains (adsorbs) and releases the volatile constituents.

good clinical practice (GCP) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. (ICH)

good clinical research practice (GCRP) Term sometimes used to describe GCP. See also *good clinical practice*.

Harmonized Standard A European Norm (EN) that has been accepted by all Member States and published in the Official Journal of the European Communities.

Health Level 7 (HL7) A clinical data interchange messaging system in which messages are structured according to a predefined format and sent from one system to another. The sending system needs to know only how to convert its data into an HL7 message; the receiving system needs to know only how to extract the data.

healthy volunteer A healthy person who agrees to participate in a clinical trial for reasons other than medical and receives no direct health benefit from participating. See also *human subject*.

heterologous Consisting of different elements, or of elements in differing proportions.

human subject A human subject, defined in 21 CFR 50.3, is an "individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient." *Synonym: subject/trial subject.*

Consent

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed. —Article 22, Declaration of Helsinki

Huriet Law France's regulations covering the initiation and conduct of clinical trials.

hypertext Links in a document that permit you to jump immediately to another document. In most Web browsers links are displayed as colored, underlined text. (IT)

HyperText Markup Language (HTML) A set of codes that describe the way type, graphics, and other elements are displayed on a Web page. (IT)

impartial witness A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. (ICH)

inclusion criteria The criteria that prospective subjects must meet to be eligible for participation in a study. See also *exclusion criteria*.

independent data-monitoring committee (IDMC) A committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. (ICH)

independent ethics committee (IEC) An independent body (a review board or a committee, institutional, regional, national, or supranational) constituted of medical/scientific professionals and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations, and regulatory requirements pertaining to independent

ethics committees may differ among countries, but should allow the independent ethics committee to act in agreement with GCP as described in the [ICH] guideline. (ICH) See also *institutional review board*.

informed consent A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form. (ICH) Under 21 CFR 50.20, no informed consent may include any "language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence."

inspection The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies). (ICH)

institution (medical) Any public or private entity or agency or medical or dental facility where clinical trials are conducted. (ICH)

institutional review board (IRB) An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. (ICH) *Other names for such bodies include independent review board, independent ethics committee, committee for the protection of human subjects.*

Ethics Committees

Bodies convened to protect human clinical research subjects work under a variety of other names. For convenience and consistency, *Applied Clinical Trials* generally uses the terms *institutional review board* and *ethics committee*. Other names and abbreviations for such bodies are shown below.

CCI	committee on clinical investigations
CCPPRB	Comité Consultative pour la Protection des Personnes dans les Recherches Biomédicales (France)
CHR	committee on human research
CPPHS	committee for the protection of human subjects
CRB	central review board
EAB	ethical advisory board
EC	ethics committee
HEX	human experimentation committee
IEC	independent ethics committee
IRB	independent review board; institutional review board
LREC	local research ethics committees (UK)
MREC	multicentre research ethics committees (UK)
NRB	noninstitutional review board, also known as an independent review board
REB	research ethics board (Canada)

interactivity Interactions in cyberspace with other people, information, and computers. Examples of interactivity include sending an email message and filling out an *Applied Clinical Trials* subscription form at www.superfill.com/subscribe/apct.htm. (IT)

interim clinical trial/study report A report of intermediate results and their evaluation based on analyses performed during the course of a trial. (ICH)

internal consistency A property of data that does not contradict itself.

Internet A global system of computer networks that provides the infrastructure for email, the World Wide Web, and other online activities.

Internet service provider (ISP) A company that provides access to the Internet for individuals and organizations. ISPs range in size from small local services to huge national providers, like Netcom and AT&T, and international full-service providers like America Online (AOL).

investigational product A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. (ICH)

investigator A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals

at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (ICH). 21 CFR 312.63 expands on the ICH definition by stating that an investigator is the individual “under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.” See also *sponsor-investigator*.

investigator/institution A term used in the ICH guideline to indicate “the investigator and/or institution, where required by the applicable regulatory requirements.” (ICH)

investigator’s brochure A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects. (ICH)

IRB See *institutional review board*.

legally acceptable representative An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial. (ICH)

longitudinal study Investigation in which data are collected from a number of subjects over a long period of time (a well-known example is the Framingham Study).

masking See *blinding/masking*.

matched-pair design A type of parallel trial design in which investigators identify pairs of subjects who are “identical” with respect

to relevant factors, then randomize them so that one receives Treatment A and the other Treatment B. See also *pairing*.

matching See *pairing*.

mean The sum of the values of all observations or data points divided by the number of observations, an arithmetical average.

median The middle value in a data set when they are arranged in order of magnitude. That is, just as many values are greater than the median and lower than the median value (with an even number of values, the conventional median is halfway between the two middle values).

medical practice computer system A PC- or network-based computer system used to manage electronic patient files. Defined by the European Forum for GCP, such a system is neither sponsor-supplied nor trial-specific.

Medicines Control Agency (MCA) The United Kingdom regulatory authority that approves or rejects CTX/CTC and PL applications.

megatrials Massive randomized clinical trials that test the advantages of marginally effective experimental drugs by enrolling 10,000 or more subjects. Synonym: large-sample trials.

Memorandum of understanding (MOU) An MOU between FDA and a regulatory agency in another country allows mutual recognition of inspections.

meta-analysis A statistical process for pooling data from many clinical trials and summarizing it through formal statistical means. Also called overview. (statistics)

metabolism The sum of the processes by which a substance is handled in the living body. See also ADME in acronym glossary. (pharmacokinetics)

mode The most frequently occurring value in a data set. (statistics)

modem From modulator/demodulator. A device that converts the digital data that your computer uses into analog data that can travel on telephone lines. (IT)

monitor Person employed by the sponsor or CRO who is responsible for determining that a trial is being conducted in accordance with the protocol. A monitor’s duties may include, but are not limited to, helping to plan and initiate a trial, assessing the conduct of trials, and assisting in data analysis, interpretation, and extrapolation. Monitors work with the clinical research coordinator to check all data and documentation from the trial. See also *clinical research associate*.

monitoring The act of overseeing the

Nuremberg Code—Directives for Human Experimentation

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Reprinted from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181–182. Washington, D.C.: U.S. Government Printing Office, 1949.

progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). (ICH)

monitoring committee See *independent data-monitoring committee*.

monitoring report A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs. (ICH)

multicenter trial A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator. (ICH) *Synonym: multicenter study.*

n-of-1 study A trial in an individual subject is administered a treatment repeatedly over a number of episodes to establish the treatment's effect in that person, often with experimental and control treatments randomized.

New Drug Application (NDA) An application to FDA for a license to market a new drug in the United States.

nonclinical study Biomedical studies not performed on human subjects. (ICH)

not-approvable letter An official communication from FDA to inform an NDA

sponsor that the important deficiencies described therein preclude approval unless corrected.

Notified Body (NB) A private institution charged by the Competent Authority with verifying compliance with the applicable Essential Requirements stated in the Medical Device Directive. This process, called Conformity Assessment, has EU-wide validity once completed by the NB.

null hypothesis A null hypothesis (for example, "subjects will experience no change in blood pressure as a result of administration of the test product") is used to rule out every possibility except the one the researcher is trying to prove, an assumption about a research population that may or may not be rejected as a result of testing. Used because most statistical methods are less able to prove something true than to provide strong evidence that it is false. See also *research hypothesis*.

Nuremberg Code Code of ethics for conducting human medical research set forth in 1947.

objective measurement A measurement that cannot be influenced by investigator bias; for example, blood glucose levels or ECG tracings.

open study A trial in which subjects and investigators know which product each

subject is receiving; opposite of double-blind study.

open-label study See *open study*.

opinion (in relation to independent ethics committee) The judgment and/or the advice provided by an independent ethics committee. (ICH)

original medical record See *source documents*.

outcomes research See *pharmacoeconomics*.

overview See *meta-analysis*. (statistics)

p value The lowest level of significance at which a given null hypothesis can be rejected; that is, the probability of observing a result as extreme or more extreme than that observed if the null hypothesis is true. See *statistical significance*. (statistics)

pairing A method by which subjects are selected so that two subjects with similar characteristics (for example, weight, smoking habits) are assigned to a set, but one receives Treatment A and the other receives Treatment B.

parallel trial Volunteers are randomized to one of two differing treatment groups (usually medicine and placebo) and usually receive the assigned treatment during the entire trial. Also called parallel group trial, parallel design trial.

parameter A constant in a model, or a constant that wholly or partially characterizes a function of probability distribution. (mathematics and statistics)

patient Person under a physician's care for a particular disease or condition. See also *subject/trial subject, healthy volunteer*.

patient file Contains demographic, medical, and treatment information about a patient or subject. It may be paper-based or a mixture of computer and paper records.

period effect Designated period during the course of a trial in which subjects are observed and no treatment is administered.

pharmacodynamics (PD) The branch of pharmacology that studies reactions between drugs and living structures, including the processes of bodily responses to pharmacological, biochemical, physiological, and therapeutic effects.

pharmacoeconomics Branch of economics that applies cost-benefit, cost-utility, cost-minimization, and cost-effectiveness analyses to compare the economics of different pharmaceutical products or to compare drug therapy to other treatments. Sometimes referred to as outcomes research.

pharmacogenetics The study of the way drugs interact with genetic makeup or the genetic response to a drug.

pharmacokinetics (PK) The study of the processes of bodily absorption, distribution, metabolism, and excretion (ADME) of compounds and medicines.

pharmacology The science that deals with the characteristics, effects, and uses of drugs and their interactions with living organisms.

pharmacovigilance Term used for adverse event monitoring and reporting in some countries.

Phase 1 unit A facility designed specifically for conducting studies involving normal, healthy volunteers. It may be operated by a sponsor company, a contract research organization (CRO), or a special unit of a hospital.

phases of clinical trials Clinical trials are generally categorized into four (sometimes five) phases. An investigational medicine or product may be evaluated in two or more phases simultaneously in different trials, and some trials may overlap two different phases.

Phase 1 studies. Initial safety trials on a new medicine in which investigators attempt to establish the dose range tolerated by about 20 to 80 healthy volunteers for single and multiple doses.

Although usually conducted with healthy volunteers, Phase 1 trials are sometimes conducted with severely ill subjects, for example, those with cancer or AIDS. When pharmacokinetic issues are being addressed (for example, metabolism of a new antiepileptic medicine in stable epileptic subjects whose microsomal liver enzymes have been induced by other antiepileptic medicines), trials may be conducted in less-ill subjects.

Pharmacokinetic trials are usually considered Phase 1 trials regardless of when they are conducted during a medicine's development.

Phase 2a studies. Pilot clinical trials to evaluate efficacy and safety in selected populations of about 100 to 300 subjects who have the disease or condition to be treated, diagnosed, or prevented. Often involve hospitalized subjects who can be closely monitored. Objectives may focus on dose-response, type of patient, frequency of dosing, or any of a number of other issues involved in safety and efficacy.

Phase 2b studies. Well-controlled trials to evaluate safety and efficacy in subjects who have the disease or condition to be treated, diagnosed, or prevented. These trials usually represent the most rigorous demonstration of a medicine's efficacy. Synonym: pivotal trials.

Phase 3 studies. Multicenter studies in populations of perhaps 1000 to 3000 subjects (or more) for whom the medicine is eventually intended. Phase 3 trials generate additional safety and efficacy data from relatively large numbers of subjects in both controlled and uncontrolled designs and are used to support a PLA. Trials are also conducted in special groups of subjects or under special conditions dictated by the nature of a particular medicine and/or disease. Phase 3 trials often provide much of the information needed for the package insert and labeling of the medicine.

Phase 3b studies. Trials conducted after submission of a new drug application (NDA), but before the product's approval and market launch. Phase 3b trials, sometimes called peri-approval studies, may supplement or complete earlier trials, or they may seek different kinds of information (for example, quality of life or marketing). Phase 3b is the period between submission for approval and receipt of marketing authorization.

Phase 4 studies. After a medicine is marketed, Phase 4 trials provide additional details about the product's safety and efficacy. They may be used to evaluate

formulations, dosages, durations of treatment, medicine interactions, and other factors. Subjects from various demographic groups may be studied. An important part of many Phase 4 studies is detecting and defining previously unknown or inadequately quantified adverse reactions and related risk factors. Phase 4 studies that are primarily observational or nonexperimental are frequently called postmarketing surveillance.

Phase 5 studies. Postmarketing surveillance is sometimes referred to as Phase 5.

placebo A pharmaceutical preparation that contains no active agent. In blinded studies, it is generally made to look just like the active product.

postmarketing surveillance Ongoing safety monitoring of marketed drugs. See *Phase 4 studies, Phase 5 studies*.

pragmatic trial Term used to describe a clinical study designed to examine the benefits of a product under real world conditions.

preclinical studies Animal studies that support Phase 1 safety and tolerance studies and must comply with good laboratory practice (GLP). Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies or trials). Because many animals have much shorter life spans than humans, preclinical studies can provide valuable information about a drug's possible toxic effects over an animal's life cycle and on its offspring.

prospective study Investigation in which a group of subjects is recruited and monitored in accordance with criteria described in a protocol.

protocol A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term "protocol" refers to protocol and protocol amendments. (ICH)

protocol amendment A written description of a change(s) to or formal clarification of a protocol. (ICH)

qualitative variable One that cannot be measured numerically (race and sex, for example).

quality assurance (QA) All those planned and systematic actions that are established to ensure that the trial is performed and the

data are generated, documented (recorded), and reported in compliance with good clinical practice (GCP) and the applicable regulatory requirement(s). (ICH)

quality control (QC) The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled. (ICH)

quantitative variable One that can be measured (blood pressure, for example).

random allocation Assignment of subjects to treatment (or control) groups in an unpredictable way. Assignment sequences are concealed, but available for disclosure in the event a subject has an adverse experience.

random number table Table of numbers with no apparent pattern used in the selection of random samples for clinical trials.

random sample Members of a population selected by a method designed to ensure that each person in the target group has an equal chance of selection.

randomization The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. (ICH)

raw data Records of original observations, measurements, and activities (such as laboratory notes, evaluations, data recorded by automated instruments) without conclusions or interpretations.

recruitment (investigators) Process used by sponsors to select investigators for a clinical study.

recruitment (subjects) Process used by investigators to enroll appropriate subjects into a clinical study, i.e., those selected on the basis of the protocol's inclusion and exclusion criteria.

recruitment period Time period during which investigators must complete enrollment of their quota of subjects for a trial.

recruitment target Number of subjects that must be recruited into a study to meet the requirements of the study protocol. In multicenter studies, each investigator has a recruitment target.

regulatory authorities Bodies having the power to regulate. In the ICH GCP guideline the expression "regulatory authorities" includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities. (ICH)

representative See *legally acceptable representative*.

research hypothesis The research hypothesis is the conclusion a study sets out to support (or disprove); for example, "blood pressure will be lowered by [specific endpoint] in subjects who receive the test product." See also *null hypothesis*.

risk In clinical trials, the probability of harm or discomfort for subjects. Acceptable risk differs depending on the condition for which a product is being tested. A product for sore throat, for example, will be expected to have a low incidence of side effects. However, unpleasant side effects may be an acceptable risk when testing a promising treatment for a life-threatening illness.

safety Relative freedom from harm; in clinical trials, this refers to an absence of harmful side effects resulting from use of the product and may be assessed by laboratory testing of biological samples, special tests and procedures, psychiatric evaluation, and/or physical examination of subjects.

script A program or a sequence of instructions that are interpreted or carried out by another program. (IT)

search engine An online service that compares your search criteria with its database of information about the Internet and displays the results. (IT)

serious adverse event (SAE) or serious adverse drug reaction (serious ADR) Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. (ICH)

serious adverse experience The Nordic Guidelines for Good Clinical Trial Practice define a serious AE as "Any experience that suggests a significant hazard, contra-indication, side effect or precaution."

server A computer program that provides services to other computer programs in the same or other computers. See also Web server.

single-blind study One in which subjects do not know whether they are receiving the active drug or a placebo.

source data All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH)

source documents Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH)

sponsor An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (ICH) According to 21 CFR 50.3, a corporation or agency whose employees conduct the investigation is considered a sponsor and the employees are considered investigators.

sponsor-investigator An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (ICH) Under 21 CFR 50.3, the term is used only for an individual person; it does not apply to corporations or agencies.

standard deviation Indicator of the relative variability of a variable around its mean; the square root of the variance. (statistics)

standard operating procedures (SOPs) Detailed, written instructions to achieve uniformity of the performance of a specific function. (ICH)

statistical significance State that applies when a hypothesis is rejected. Whether or not a given result is significant depends on the significance level adopted. For example, one may say "significant at the 5% level." This implies that a level of significance has been applied such that when the null hypothesis is true there is only a 1 in 20 chance of rejecting it and/or that the observed result has led to rejection of the null hypothesis.

stochastic Involving a random variable; involving chance or probability.

study coordinator See *clinical research coordinator*.

subinvestigator Any individual member of the clinical trial team designated and supervised by the investigator at a trial site

to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). (ICH) See also *investigator*.

subject/trial subject An individual who participates in a clinical trial, either as recipient of the investigational product(s) or as a control. (ICH) See also *healthy volunteer*, *human subject*.

subject identification code A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data. (ICH)

surrogate marker A measurement of a drug's biological activity that substitutes for a clinical endpoint such as death or pain relief.

t-test A statistical test used to compare the means of two groups of test data.

trial coordinator See *clinical research coordinator*.

trial site The location(s) where trial-related activities are actually conducted. (ICH)

triple-blind study A study in which knowledge of the treatment is concealed from the people who organize and analyze the data of a study as well as from subjects and investigators.

Type 1 (or Type I) error Error made when a null hypothesis is rejected but is actually true. Also called false positive. (statistics)

Type 2 (or Type II) error Error made when an alternative hypothesis is rejected when it is actually true. Also called false negative. (statistics)

Type 3 (or Type III) error Some statisticians use this designation for an error made when calling the less effective treatment the more effective one. (statistics)

unequal randomization A technique used to allocate subjects into groups at a differential rate; for example, three subjects may be assigned to a treatment group for every one assigned to the control group.

unexpected adverse drug reaction An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (ICH)

uniform resource locator (URL) Address of a Web page—actmagazine.com, for example.

validation of data Procedure carried out to ensure that the data contained in the final clinical trial report match original observations.

validity The accuracy of the relationship between two or more variables.

variance A measure of the variability in a sample or population. It is calculated as the mean squared deviation (MSD) of the individual values from their common mean. In calculating the MSD, the divisor n is commonly used for a population variance and the divisor $n-1$ for a sample variance.

volunteer See *healthy volunteer*.

vulnerable subjects Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. (ICH)

Warning Letter A written communication from FDA notifying an individual or firm that the agency considers one or more products, practices, processes, or other

activities to be in violation of the Federal FD&C Act, or other acts, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation may result in administrative and/or regulatory enforcement action without further notice. (FDA)

washout period A period in a clinical study during which subjects receive no treatment for the indication under study and the effects of a previous treatment are eliminated (or assumed to be eliminated).

Web browser A computer program that interprets HTML and other Internet languages and protocols and displays Web pages on your computer monitor. (IT)

Web page A single page on a Web site, such as a home page. (IT)

Web server A computer program that delivers HTML pages or files. Sometimes the computer on which a server program runs is also referred to as a server. (IT)

Web site A collection of Web pages and other files. A site can consist of a single Web page, thousands of pages, or custom-created pages that draw on a database associated with the site. (IT)

weighting An adjustment in a value on the basis of a judgment by the investigator. (statistics)

well-being (of the trial subjects) The physical and mental integrity of the subjects participating in a clinical trial. (ICH)

within-subject differences In a crossover trial, variability in each patient is used to assess treatment differences. (statistics)

World Wide Web All the resources and users on the Internet that are using HTTP protocols. Also called the Web and WWW. □

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