USA Terminology - Interventional versus Non-Interventional: FDA's Framework for Real World Evidence

Term	Definition	Context/Scope	Link
Framework for FDA's Real-World Evidence Program - Glossary			
Clinical Trial	A research study in which one or more human subjects are prospectively assigned to one or more **INTERVENTIONS** (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes. Clinical trials are interventional clinical studies.	Under the Cures Act, FDA's RWE Program must evaluate the potential use of RWD to generate RWE of product effectiveness to help support approval of new indications for drugs approved under FD&C Act Section 505(c) or to help to support or satisfy post-approval study requirements. FDA's RWE Program will also apply to biological products licensed under section 351 of the Public Health Service Act.	https://www.fda.gov/media/120060/download
Observational Study	A **NON-INTERVENTIONAL** clinical study design that is not considered a clinical trial.		
Patient Registry	An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more predetermined scientific, clinical, or policy purpose. Registries are generally defined either by diagnosis of a disease (disease registry) or usage of a drug, device, or other treatment (exposure registry).		
Real World Data (RWD)	Data relating to patient health status and/ or the delivery of health care routinely collected from a variety of sources.		
Real World Evidence (RWE)	Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.		

Term	Definition	Context/Scope	Link
Framework for FDA's Real-World Evidence Program - Glossary			
	RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective) (FDA Website – RWE)		

USA Terminology - Interventional versus Non-Interventional: 21 CFR 312

Term	Definition	Context/Scope	Link
21 CFR 312 – Investigational New Drug Application			
Clinical Investigation	Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice (as per 21 CFR 312.3(b))	Procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's) (as per 21 CFR §312.1) Refer to the exemptions in 21 CFR 312.2	https://www.ecfr.gov/cgi-bin/text-idx?SID=a4e40cf41e89e40c2e6f763d5f0576c5&mc=true&node=se21.5.312_13&rgn=div8
Investigational New Drug	*Investigational new drug* means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part (as per 21 CFR 312.3(b))		

USA Terminology - Interventional versus Non-Interventional: 45 CFR 46

Term	Definition	Context/Scope	Link
45 CFR 46 – Protection of Human Subjects (Common Rule)			
Clinical Trial	Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the **INTERVENTIONS** on biomedical or behavioral health-related outcomes (as per 45 CFR 46.102(b))	Research not regulated by the FDA e.g., Clinical trials/ investigations of investigational medicinal products. Applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research (as per 45 CFR 46.101(a))	https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1102
INTERVENTION	**INTERVENTION** includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes (as per 45 CFR 46.102(e)(2))		

USA Terminology - Interventional versus Non-Interventional: 21 CFR 50

Term	Definition	Context/Scope	Link
21 CFR 50 – Protection of Human Subjects			
Clinical investigation	Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration	Applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for	https://www.ecfr.gov/cgi-bin/text-idx?SID=cbf14eab457a7d82752ebae1d7425c34&mc=true&node=se21.1.50_13&rgn=div8

Term	Definition	Context/Scope	Link
21 CFR 50 – Protection of Human Subjects			
	as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies (as per 21 CFR 50.3(c))	human use, biological products for human use, and electronic products (as per 21 CFR 50.1(a)).	
Test Article	Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n) (as per 21 CFR 50.3(j))		

USA Terminology - Interventional versus Non-Interventional: 21 CFR 56

Term	Definition	Context/Scope	Link
21 CFR 56 – Institutional Review Boards			
Clinical Investigation	Clinical investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a	General standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use,	https://www.ecfr.gov/cgi-bin/text-idx?SID=932cafc1171bb23fec1ddaa3c186d0bb&mc=true&node=se21.1.56_1102&rgn=div8

Term	Definition	Context/Scope	Link
21 CFR 56 – Institutional Review Boards			
	research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part (as per 21 CFR 56.102(c)).	medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations (as per 21 CFR 56.101(a)).	
Test Article	Test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act (as per 21 CFR 56.102(l)).		

USA Terminology - Interventional versus Non-Interventional: Clinicaltrials.gov

Term	Definition	Context/Scope	Link
Clinicaltrials.gov – Glossary			
Clinical Study	A research study involving human volunteers (also called participants) that is intended to add to medical knowledge. There are two types of clinical studies: **INTERVENTIONAL** studies (also called clinical trials) and observational studies.	This glossary will help you understand words and phrases frequently used on ClinicalTrials.gov. Many of these words are also used by clinical researchers and others in the same or a similar manner. But the definitions below are provided to explain content on ClinicalTrials.gov only.	https://clinicaltrials.gov/ct2/about-studies/glossary
Clinical Trial	Another name for an **INTERVENTIONAL** study		

Term	Definition	Context/Scope	Link
Clinicaltrials.gov – Glossary			
INTERVENTION/ Treatment	A process or action that is the focus of a clinical study. **INTERVENTIONS** include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. **INTERVENTIONS** can also include non-invasive approaches, such as education or modifying diet and exercise.		
INTERVENTIONAL study (clinical trial)	A type of clinical study in which participants are assigned to groups that receive one or more **INTERVENTION**/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.		
Observational Study	A type of clinical study in which participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of **INTERVENTIONS**, but the investigator does not assign participants to a specific **INTERVENTIONS**/treatment. A patient registry is a type of observational study.		

European Terminology - Interventional versus Non-Interventional: Directive 2001/20/EC

Term	Definition	Context/Scope	Link
Directive 2001/20/EC – EU Clinical Trials Directive			
Clinical Trial	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy (as per Article 2(a) of Directive 2001/20/EC). This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State (as per Article 2(a) of Directive 2001/20/EC).	Conduct of clinical trials on medicinal products for human use. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. This Directive does not apply to non-interventional trials.	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
NON-INTERVENTIONAL Trial	A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data (as per Article 2(c) of Directive 2001/20/EC).		

Term	Definition	Context/Scope	Link
Directive 2001/20/EC – EU Clinical Trials Directive			
Investigational Medicinal Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form (as per Article 2(c) of Directive 2001/20/EC).		

European Terminology - Interventional versus Non-Interventional: Regulation EU/536/2014

Term	Definition	Context/Scope	Link
Regulation EU/536/2014 – EU Clinical Trials Regulation			
Risk to Subject Safety	The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the **INTERVENTION**. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure" or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence-based and supported by published scientific evidence on the safety and efficacy of that product,	Clinical trials on medicinal products for human use. This Regulation applies to all clinical trials conducted in the Union. It does not apply to **NON-INTERVENTIONAL** studies (as per Article 1 of Regulation EU/526/2014). This text is provided in the explanatory section of the regulation (Recitals) but is not supported in the body of the regulation with a definition of 'intervention'	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

Term	Definition	Context/Scope	Link
Regulation EU/536/2014 – EU Clinical Trials Regulation			
	and the **INTERVENTION** poses only very limited additional risk to the subject compared to normal clinical practice. Those **LOW-INTERVENTION** clinical trials are often of crucial importance for assessing stand-ard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. Those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products (as per Recital 11 of Regulation EU/536/2014)		
Clinical Study	'Clinical study' means any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal product (as per Article 2.2(1) of Regulation EU/536/2014)		
Clinical Trial	'Clinical trial' means a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does		

Term	Definition	Context/Scope	Link
Regulation EU/536/2014 – EU Clinical Trials Regulation			
	not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects. (as per Article 2.2(2) of Regulation EU/536/2014)		
LOW-INTERVENTION Clinical Trial	'**LOW-INTERVENTION** clinical trial' means a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisa-tion; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the		

Term	Definition	Context/Scope	Link
Regulation EU/536/2014 – EU Clinical Trials Regulation			
	subjects compared to normal clinical practice in any Member State concerned (as per Article 2.2(3) of Regulation EU/536/2014)		
NON-INTERVENTIONAL Study	'**NON-INTERVENTIONAL** study' means a clinical study other than a clinical trial (as per Article 2.2(5) of Regulation EU/536/2014)		
Investigational Medicinal Product	'Investigational medicinal product' means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial (as per Article 2.2(5) of Regulation EU/536/2014)		
Normal Clinical Practice	'Normal clinical practice' means the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder (as per Article 2.2(6) of Regulation EU/536/2014)		

Global Terminology – Interventional versus Non-Interventional: ICH E2F

Term	Definition	Context/Scope	Link
ICH E2F – Glossary			
INTERVENTIONAL Clinical Trial	An INTERVENTIONAL clinical trial is any research study that prospectively assigns people to one or more health-related INTERVENTIONS (e.g., preventive care, drugs, surgical procedures, behavioural treatments, etc.) to evaluate their effects on health-related outcomes.	Original definition sourced from CIOMS VII	https://database.ich.org/sites/default/files/E2F_Guideline.pdf