Version dated 19jun2020

Glossary

This glossary of terms is intended to provide our campus research professionals with a quick reference to many of the most common terms and phrases used in research here on MCW/CW campus. This has been combined with materials from many sources including the NIH, FDA, DHHR, PRIM&R, ACRP and local materials.

As you use this glossary, if you have suggestions for revision or addition to improve the information contained herein, please advise the Research Coordinator Advisory Committee via dwagner@mcw.edu or jcrawford@chw.org.

Thanks,

Children's Research Institute – Research Coordinator Advisory Committee

Please select a letter below to begin your search.

Adverse Drug Reaction

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 disease or for the modification of physiologic function. An ADR is a type of ADE whose cause can be directly attributed to a drug and its physiologic properties. (WHO 2005) ADRs occur despite appropriate prescribing and dosing. A causal relationship is suspected for an ADR but is not required for an ADE. .

Adverse Drug Event

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. (WHO). ADEs may also be associated with inappropriate use of the drug or other confounders that occur during drug therapy but are not necessarily caused by the pharmacology of the drug itself. Adverse drug events may also be caused by medication errors.

Adverse Event (AE)

A negative experience encountered by an individual during the course of a clinical trial, that is associated with the drug. An AE can include previously undetected symptoms, or the exacerbation of a pre-existing condition. When an AE has been determined to be related to the investigational product, it is considered an Adverse Drug Reaction.

Per FDA regulations *Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. 21 CFR 312.32(a).

FDA regulations use different terms when referring to adverse event. For example, adverse effect is used in 21 CFR 312.64; adverse experience is used in § 312.32; and unanticipated problems is used in § 312.66. For the purposes of this guidance, the term adverse event is used, except when quoting specific regulations. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s).

The HHS regulations at 45 CFR part 46 do not define or use the term *adverse event*, nor is there a common definition of this term across government and non-government entities. In OHRP guidance the term *adverse event* in general is used very broadly and includes any event meeting the following definition: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). Adverse events encompass both physical and psychological harms.

Adverse Event Reports

Events must be reported in accordance with federal regulations, IRB policies, and sponsor requirements. MedWatch is the FDA's adverse event reporting program.

Advocacy and Support

Organizations and groups that actively support participants and their families with valuable resources, including self-empowerment and survival tools.

Amendments

These are changes to an IRB approved research protocol and must be submitted and approved by the IRB before implementation (e.g., revised consent document, change in personnel, additional risks

Arm

A group of people in a clinical **study** who receive the same intervention. Clinical **studies** may have one or more research **arms**.

Assent

A child's affirmative agreement to participate in a research study. Mere failure to object may not, absent affirmative agreement, be construed as assent.

Authorization Agreement

A written agreement between two or more institutions that is used to document the delegation of IRB review responsibilities. This agreement may also be referred to as a reliance agreement, IRB authorization agreement. See also Master Authorization Agreement.

Bank (Data or Specimen Repositories)

Per OHRP guidance, repositories collect, store, and distribute human data and/or specimens for research purposes. Operation of a repository and its management is subject to oversight by the IRB.

Basic Research (Bench)

Basic research is sometimes referred to as "basic science" "bench or fundamental research." Basic research attempts to provide answers to the mysteries of modern medicine, with the goal of a better understanding of a particular concept, as niche as it may be. Basic science experiments might study how cancer cells replicate on a molecular level, or how an abnormal protein folds to cause some congenital disease.

Belmont Report**

The *Belmont Report* was written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission, created as a result of the National Research Act of 1974, was charged with identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and developing guidelines to assure that such research is conducted in accordance with those principles. Informed by monthly discussions that spanned nearly four years and an intensive four days of deliberation in 1976, the Commission published the *Belmont Report*, which identifies basic ethical principles and guidelines that address ethical issues arising from the conduct of research with human subjects. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Benefit

A valued or desired outcome; an advantage.

The benefits of human subjects research fall into two major categories: benefits to subjects and benefits to society. Frequently, the research subjects are undergoing treatment, diagnosis, or examination for an illness or abnormal condition. This kind of research often involves evaluation of a procedure that may benefit the subjects by ameliorating their conditions or providing a better understanding of their disorders. Patients and healthy individuals may also agree to participate in research that is either not related to any illnesses they might have or that is related to their conditions but not designed to provide any diagnostic or therapeutic benefit. Such research is designed principally to increase understanding and store of knowledge about human physiology and behavior. Research that has no immediate therapeutic intent may, nonetheless, benefit society as a whole. These benefits take the form of increased knowledge, improved safety, technological advances, and better health.

Direct payments or other forms of remuneration offered to potential subjects as an incentive or reward for participation should not be considered a "benefit" to be gained from research.

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 blinding and randomization.

Biologic

Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

Blinding

The process through which one or more parties to a clinical trial are unaware of the treatment assignments. In a single-blinded study, usually the subjects are unaware of the treatment assignments. In a double-blinded study, both the subjects and the investigators are unaware of the treatment assignments. Also, in a double-blinded study, the monitors and sometimes the data analysts are unaware. "Blinded" studies are conducted to prevent the unintentional biases that can affect subject data when treatment assignments are known.

Corrective Action/ Preventative Action (CAPA)

Corrective and preventive actions are processes for identifying, documenting, and addressing defects, deficiencies, and nonconformities, used here in the context of conducting a research study.

Corrective Action: Elimination of an existing nonconformity or undesirable situation or error (for example a protocol deviation). **Preventive Action:** Identification and elimination of the cause(s) of potential nonconformities in order to prevent future occurrence.

Case Report Form (CRF)

A record of pertinent information collected on each subject during a clinical trial, as outlined in the study protocol.

Cede Review

In the context of a single or central IRB review, the act of transferring IRB review and oversight. Also known as deferral.

Children

Those who have not attained the legal age for consent to participate in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted. (ie. Wisconsin’s “ age of majority” is 18.

CITI (Collaborative Institutional Training Initiative)

The Collaborative Institutional Training Initiative (CITI) Program is a provider of web based training materials for research education. CITI and GCP certification is required prior to working in research.

Class I, II, or III Devices

The FDA categorizes medical devices into one of three classes – Class I, II, or III – based on their risks and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. Class I devices generally pose the lowest risk to the patient and/or user and Class III devices pose the highest risk. For more information about the medical device classification process, see Classify Your Medical Device.

Clinical Investigation (FDA)

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 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. 21 CFR 50.3(c). Also known as Clinical Trial or Clinical Study.

Clinical Research Associate (CRA)

Person employed by the study sponsor or CRO to monitor a clinical study at all participating sites. See also, monitor. Or also person employed by the study as study staff (Clinical Research Assistant), usually with less delegated authority than a CRC (see below).

Clinical Research Coordinator (CRC)

Site administrator for the clinical study. Duties are delegated by the investigator. Also called research, study or healthcare coordinator, and data manager, research nurse or protocol nurse. CRC's can also obtain certification by professional research organizations increasing their knowledge of the regulations and research operation details.

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 behavioral outcomes.

Clinical Trial Registration (ClinicalTrials.gov)

A website maintained by the NIH intended to register clinical trials to provide the public with detailed study information potentially assisting them in making participation decisions including timely updates and possibly a summary of results at trial end. There are specific requirements regarding which studies need to be registered and the timing of that registration that can be found on the website: https://clinicaltrials.gov. An investigator may be the party responsible for registering the clinical trial if this is investigator initiated and the investigator is also serving as the sponsor. Assistance with this requirement is available through the MCW office of research and the CTSI.

Code of Federal Regulations (CFR)

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules and regulations (sometimes called administrative law) published in the Federal Register by the executive departments and agencies of the federal government of the United States.

Coded Data

(1) Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Cohort

A group of subjects initially identified as having one or more characteristics in common who are followed over time.

Common Rule

The Federal Policy for the Protection of Human Subjects was published in 1991 and codified in separate regulations by 15 Federal departments and agencies – thus referred to as "The Common Rule". The HHS regulations, 45 CFR part 46, include four subparts: subpart A, also known as the Federal Policy or the "Common Rule"; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children. Each agency includes in its chapter of the Code of Federal Regulations [CFR] section numbers and language that are identical to those of the HHS codification at 45 CFR part 46, subpart A. For all participating departments and agencies the Common Rule outlines the basic provisions for IRBs, informed consent, and Assurances of Compliance. Human subject research conducted or supported by each federal department/agency is governed by the regulations of that department/agency. The head of that department/agency retains final judgment as to whether a particular activity it conducts or supports is covered by the Common Rule. Currently 19 federal agencies (including HHS) follow the pre-2018 requirements. A revision to parts of the Common Rule went into effect in 2018. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

Comparative Effectiveness Research**

Comparative Effectiveness Research (CER), as defined by the United States Department of Health and Human Services, is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. The purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances.

Confidentiality

Confidentiality pertains to the **treatment of information** that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure. A research investigator should protect subjects against loss of confidentiality. Lack of secure handling of completed personality tests, questionnaires, interview protocols or data and recorded materials augments risk and must be avoided. See HIPAA.

Continuing Noncompliance

Noncompliance becomes serious or continuing when it results in harm, increases risk of harm, adversely affects the rights or welfare of participants, may affect the subject willingness to participate in the study, or undermines the scientific integrity of the data. Continuing means repeated occurrences of non-compliance by the same investigator/study team or by the institution. This repetition may occur in the same or different protocols by the same investigator/study team. This repetition, if unaddressed may affect the protection of human subjects.

Continuing Review

Periodic review and approval of a research study by the IRB to evaluate if risks to participants remain reasonable in relation to potential benefits, and to evaluate if the study continues to meet regulatory and institutional requirements. The process of continuing review renews the approval period for a research study. If continuing review is required, and is not done, the study will expire and all study activities must stop. This results in non-compliance. Continuing review shall be conducted at intervals determined by regulation or more often if deemed appropriate by the IRB.

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 study-related duties and functions.

FDA definition: means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration. 21 CFR 312.3

Contraindication

A specific circumstance when the use of certain treatments could be harmful.

Control Group

A comparison group of study subjects who are not treated with the investigational agent or intervention. The subjects in this group may receive no therapy, a different therapy, or a placebo. These studies are also referred to as “blind” (subjects do not know which treatment they are receiving) or “double blind” (neither the subjects nor the researchers know the treatment assignments).

Convened IRB Review (also known as Full Board Review)

A convened IRB board meeting is one at which a majority of IRB members are present, including a member whose primary concern is in a non-scientific area, before official actions may be taken.

Coordinating Center

A **Coordinating Center** is the term used to refer to the entity responsible for overall data management, monitoring and communication amongst all participating centers, and general oversight of the conduct of a research project involving human subjects at multiple locations. Responsibilities associated with serving in the capacity of a coordinating center will depend on the type of research and level of risk to subjects. A coordinating center may be designated either by a sponsor or by mutual agreement of the participating centers.

Corporate Compliance

The Compliance/Internal Audit Department for Children's Hospital and Health System is an independent and objective function of the organization to ensure compliance with laws, regulations, policies and procedures and to

bring a systematic approach to assessing organizational risks and evaluating the operational and financial controls within the organization.

Crossover design

A type of clinical trial in which each subject is given, at different times, both an experimental and a control therapy.

Data and Safety Monitoring Board (committee) (DSMB/DSMC)

Group of independent individuals, external to the trial, who are experts in relevant areas. They review the accumulated data from one or more ongoing clinical trials on a regular basis and advise the sponsor about:

- The continued safety of the trial participants.
- The continued validity of the trial.
- The continued scientific merit of the trial.

Data and Safety Monitoring Plan

A **data and safety monitoring plan** (DSMP) is a specific **plan**, developed by the local principal investigator (PI) that outlines how study progress will be monitored throughout the course of the research to ensure the **safety** of subjects as well as the integrity and confidentiality of **data**.

Data Manager

An individual who handles the data gathered during a study. Responsibilities may also involve managing data entry, database generation and/or maintenance, compliance with regulations, and protective and integrity of private information and study data. Common in multi-site consortium studies.

Decisionally Impaired Persons

Decisionally impaired persons are those who have a diminished capacity to understand the risks and benefits for participation in research and to autonomously provide informed consent. This decisional impairment may result from a psychiatric, organic, developmental or other disorder that affects cognitive or emotional functions, or may result from the effect of drugs or alcohol. The impairment may be temporary, permanent or may fluctuate.

Declaration of Helsinki

A series of guidelines adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964. The Declaration addresses ethical issues for physicians conducting biomedical research involving human subjects. Recommendations include the procedures required to ensure subject safety in clinical trials, including informed consent and Ethics Committee reviews.

Deferral

See Cede Review.

De-identifed Data

Private information or specimens are not individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. (see Protected Health Information, PHI) This is differentiated from coded data (see above) or identifiable data (see below).

Demographic Data

Refers to the characteristics of study participants, including sex, age, family medical history, and other characteristics relevant to the study in which they are enrolled.

Department of Health and Human Services (DHHS)

The Department of Health & Human Services' administers 115 programs across its 11 operating divisions. The United States Department of Health & Human Services (HHS) aims to "protect the health of all Americans and provide essential human services, especially for those who are least able to help themselves." These operating divisions include:

Agency for Healthcare Research and Quality, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, Centers for Medicare and Medicaid Services, Indian Health Service, National Institutes of Health, Office of the Assistant Secretary of Health, Office of the Secretary, Program Support Center, Substance Abuse and Mental Health Services Administration, Office of the Assistant Secretary for Preparedness and Response.

Dependent Variables

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

Descriptive study

The available study designs are divided broadly into two types – observational and interventional. Of the various observational study designs, the descriptive design is the simplest. It allows the researcher to study and describe the distribution of one or more variables, without regard to any causal or other hypotheses

Double-Blind

See Blinding.

Drug

As defined by the Food, Drug and Cosmetic Act, drugs are "articles (other than food) intended for the use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or to affect the structure or any function of the body of man or other animals."

Drug or Device Accountability Records (DAR)

Required documentation for material accountability, quantity used and left over, and date of disposal.

Effective Dose**

Under the Kefauver-Harris Drug Amendments of 1962 (amending the Food, Drug, and Cosmetic Act of 1938), a drug is considered to be effective that has been designated as such by the Food and Drug Administration on the basis of "substantial evidence." Such evidence was defined by Congress as "… adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

Efficacy**

The capacity of an investigational product to produce an effect (eg, lower blood pressure). Efficacy can be assessed accurately only in ideal conditions (ie, when patients are selected by proper criteria and strictly adhere to the dosing schedule). Thus, efficacy is measured under expert supervision in a group of patients most likely to have a response to a drug, such as in a controlled clinical trial.

Emergency Use of a Test Article

Use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain prospective IRB approval (21 CFR 56.102(d). The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Endpoint

In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives.

Enrolled Subject*

A subject who has participated in a consent conversation, is eligible for the study and has given informed consent. For minimal risk studies without the requirement of written consent or retrospective studies, the term is often used to identify a subject who meets eligibility criteria for a study and whose data has been collected.

Epidemiology

Epidemiology is the method used to find the causes of health outcomes and diseases in populations. In epidemiology, the patient is the community and individuals are viewed collectively. By definition, epidemiology is the study (scientific, systematic, and data-driven) of the distribution (frequency, pattern) and determinants (causes, risk factors) of health-related states and events (not just diseases) in specified populations (neighborhood, school, city, state, country, global). It is also the application of this study to the control of health problems (Source: Principles of Epidemiology, 3rd Edition).

Essential Documents

. Essential documents serve to demonstrate compliance with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. These document files may be audited by the sponsor and regulatory authorities to confirm the validity of the clinical research conduct and integrity of the data. This policy is based on: 1) the U.S. Code of Federal Regulations (CFR), 2) regulatory guidance that applies to the involvement of human subjects in clinical research, and 3) other standards for GCP, including the International Conference on Harmonisation (ICH E6).

The standard practice is maintaining all essential documents related to the implementation and compliance of a study protocol in a centralized location, usually in physical binders kept securely in the section offices. Electronic essential document binders may also be organized on a secured drive replacing the necessity for most actual paper and physical binders to be kept.

Equipoise

Genuine uncertainty in the expert medical community about the preferred treatment (Freedman B. Equipoise and the ethics of clinical research. NEJM 1987;317(3):141-145.)

Clinical **equipoise** is the assumption that there is not one 'better' intervention present (for either the control or experimental group) during the design of a randomized controlled trial (RCT). A true state of **equipoise** exists when one has no good basis for a choice between two or more care options (J Man Manip Ther. 2011 Feb; 19(1): 55–57.

Exception from Informed Consent (EFIC) Requirements for Emergency Research

The regulations at 21 CFR 50.24 and the conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814 provide a narrow exception to the requirement that the investigator obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in emergency research. The regulations also provide additional protections for subjects enrolled in these studies. For example, the regulations require consultation with representatives of and public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation. They also require public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study. As well, the regulations require that an independent data monitoring committee exercises oversight of the clinical investigation.

Exclusion Criteria

Refers to the characteristics that would prevent a subject from participating in a clinical trial, as outlined in the study protocol.

Exculpatory Language (in informed consent)

Exculpatory language is language through which the subject 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. This is not permitted in informed consent, whether oral or written consent. - **45 CFR 46.116**

Exempt Research

Unless otherwise required by law or by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the categories defined at 45 CFR 46.104(d) are exempt from the requirements of 45 CFR 46, except that such activities must comply with the requirements of 45 CFR 46.104 and as specified in each category. An institution's policies and procedures may also define how an exemption determination may be made.

Expanded Access

Sometimes referred to as "compassionate use" (which not a regulatory term), expanded access is a potential pathway for a patient with an **immediately life-threatening condition or serious disease or condition** to gain access to an **investigational medical product** (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Expedited Review

Expedited review procedures are described in HHS regulations at 45 CFR 46.110 and FDA regulations at 21 CFR 56.110. Under an expedited review procedure, the IRB Chairperson, or one or more experienced reviewers designated by the Chairperson from among the members of the IRB, reviews the research protocol. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more categories published in the federal register, may be reviewed by the IRB through the expedited review procedure.

Experimental Drug

See Investigational Drug

Faculty Advisor

Faculty advisors are faculty members who supervise and oversee research being conducted by students or fellows. Advisors are responsible for guiding students through the IRB process, helping with research design, methodology, and ethical considerations.

Family Educational Rights and Privacy Act (FERPA)

A Federal law (20 U.S.C. § 1232g; 34 CFR Part 99) that protects the privacy of student education records. The law applies to all schools that receive funds under an applicable program of the U.S. Department of Education.

FDA Approval

In the U.S., the Food and Drug Administration (FDA) must approve a substance as a drug before it can be marketed. The approval process involves several steps including pre-clinical laboratory and animal studies, clinical trials for safety and efficacy, filing of a New Drug Application by the manufacturer of the drug, FDA review of the application, and FDA approval/rejection of application.

Class II and Class I medical devices are usually "cleared" by the FDA, which means the manufacturer can demonstrate that their product is "substantially equivalent to another (similar) legally marketed device" that already has FDA clearance or approval. Those already-cleared products are called a predicate.).

Federalwide Assurance

An assurance of compliance is a written document submitted by an institution that is engaged in non-exempt human subjects research conducted or supported by HHS. Through the assurance of compliance, an institution commits to HHS that it will comply with the requirements set forth in the regulations for the protection of human subjects at 45 CFR part 46. The Federalwide Assurance is the only type of assurance of compliance accepted and approved by OHRP.

Fellow

A graduate doctor continuing to study in a medical specialty, and conducting independent research with minimal teaching duties. This individual holds a temporary academic post and as such, may obtain a fellowship and associated research funding. Not all fellows have provider rights at Children's. Assess with Physician Support Office to assess if a fellow has rights.

Food and Drug Administration (U.S. FDA)

Within the Department of Health and Human Services. See web page for more information: https://www.fda.gov/about-fda/fda-basics/fda-fundamentals

Food Drug and Cosmetic Act (FD & C Act)

The Federal Food, Drug, and Cosmetic Act (FD&C Act) is a federal law enacted by Congress. It and other federal laws establish the legal framework within which FDA operates. The FD&C Act can be found in the United States Code, which contains all general and permanent U.S. laws, beginning at 21 U.S.C. 301. https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act

Good Clinical Practice (GCP)

Good Clinical Practice (ICH GCP E6) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with GCP assures that the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible. The International Conference on Harmonization (ICH) guidance provides a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions. This is different from FDA GCP. CW commits to compliance with the ICH-GCP E6 to the extent those guidelines do not conflict with and are parallel to the FDA GCP and HHS regulations 45CFR46 "Common Rule".

FDA GCP sources: https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

ICH GCP source: https://ichgcp.net/

Grant

Financial support provided for a research study designed and proposed by the principal investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant, except that the grant award is a contract and there are general and specific stipulations of actions expected/required.

Health Insurance Portability and Accountability Act (HIPAA)

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the Secretary of the U.S. Department of Health and Human Services (HHS) to develop regulations protecting the privacy and security of certain health information.[1] To fulfill this requirement, HHS published what are commonly known as the HIPAA Privacy Rule and the HIPAA Security Rule. The Privacy Rule, or *Standards for Privacy of Individually Identifiable Health Information*, establishes national standards for the protection of certain health information. The *Security Standards for the Protection of Electronic Protected Health Information* (the Security Rule) establish a national set of security standards for protecting certain health information that is held or transferred in electronic form. The Security Rule operationalizes the protections contained in the Privacy Rule by addressing the technical and non-technical safeguards that organizations called "covered entities" must put in place to secure individuals' "electronic protected health information" (e-PHI). Within HHS, the Office for Civil Rights (OCR) has responsibility for enforcing the Privacy and Security Rules with voluntary compliance activities and civil money penalties.

Each covered entity has oversight of HIPAA regulations and each covered entity chooses to interpret the HIPAA regulations as they see fit. Processes will differ from institution to institution.

Healthy Volunteers in Studies

Healthy volunteers provide researchers with crucial data because their health information can be used as a comparison. In some studies, researchers need to compare healthy volunteers with people who have a specific disease or condition. Research with healthy volunteers is designed to develop new knowledge, not to provide direct benefit to study participants. These volunteers serve as controls for patient groups. They are often matched to patients on such characteristics as age, gender, or family relationship. They are then given the same test, procedure, or drug the patient group receives. Investigators learn about the disease process by comparing the patient group to the clinical research volunteers.

Historical Control Study

Comparing a new treatment in a current series of patients with an old treatment in a previous series of patients (by review of medical records). (Note: the condition of subjects may be compared with their own condition on a prior regimen, the effectiveness of which has already been established.)

HRPP (Human Research Protections Program)

The **Human Research Protection Program (HRPP)** is an institutional-wide program coordinated by Children's Wisconsin and composed of the research leadership, Institutional Review Boards designated by the organization, and other entities that are responsible for protecting the rights and welfare of participants in research conducted or reviewed by Children's Wisconsin. The Institutional Review Board is a committee designated by the HRPP that reviews and makes determinations about human subject research. The HRPP provides administrative support for the IRB.

Human Subject

Human subject means a living individual about whom an investigator (whether professional or student) conducting research (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses,

studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (HHS 45CFR46 “Common Rule”)

Human subject means 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 individual or a patient. (FDA 21CFR56)

Hypothesis

A research hypothesis is a specific, clear, and testable proposition or predictive statement about the possible outcome of a scientific research study based on a particular property of a population, such as presumed differences between groups on a particular variable or relationships between variables.

Individually Identifiable Data

In general, **OHRP** considers private information or specimens to be **individually identifiable** as **defined** at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Inclusion Criteria

See eligibility criteria.

Informed Consent Process

A process by which a potential research subject is provided with adequate information about the research to allow the potential subject to make a voluntary, informed decision about participating in the research. The process involves facilitating the potential subject’s understanding of the information presented, allowing appropriate time for the potential subject to ask questions and discuss with family and friends if needed, and obtaining the potential subject’s voluntary agreement to participate. This process is ongoing throughout the subject’s participation as the study progresses or as the subject and/or situation requires. Federal regulations dictate required elements that must be part of the consent process and included in the consent document (for example: purpose of the research, expected duration of participation, procedures, risks, benefits). The required elements can be found at 21 CFR 50.25 and 45 CFR 46.116.

Informed Consent Document

Often referred to as the “consent form”. This is the document used, in addition to the informed consent discussion, to convey the information needed by the subject to make an informed, voluntary decision about whether to participate in the research and document their voluntary agreement to participate (or their children in the case of an LAR (Legally Authorized Representative) giving parental permission for their minor child. This document must include the required elements of consent as described in 21 CFR 50.25 and 45 CFR 46.116.

Institutional Review Board (IRB)

An IRB is a body established generally under laws, regulations, codes, and guidance to protect the rights and welfare of human research participants. Within a HRPP, responsibilities must be delegated for providing ethical review and oversight of research. In many organizations, the IRB along with the support personnel and systems provide these functions.

An Institutional Review Board (IRB) is made up of individuals who have training in scientific areas, individuals who have expertise and training in non-scientific areas, and members of the community who may represent people who would participate as subjects in research studies.

IRB Manager or Director or Administrator

At Children's, this position is titled Research Integrity Manager. This position assures compliance consistent with the regulatory framework and institutional policies surrounding human subjects research activity within Children's Research Institute and Children's Wisconsin; responsible for oversight of Children's HRPP, including the development and ongoing management of policies and procedures related to the responsible and ethical conduct of research within Children's Research Institute and Children's Wisconsin; ensures that appropriate training and education programming is available to research personnel; provides supervision for the administrative staff of the human research protection program and oversees daily operations of the office.

IRB of Record

(See Reviewing IRB)

International Conference on Harmonisation (ICH)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established in 1990 to bring together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. It established and published the Good Clinical Practice Guidelines (GCP) adopted by many agencies.

Interaction

Interaction includes communication or interpersonal contact between investigator and subject.

Intervention

The diagnostic or therapeutic device, biologic, and/or drug under investigation in a clinical trial that is believed to have an effect on outcomes of interest in a study. Term also describes 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 to study effect.

Investigational Device Exemption (IDE)

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a PreMarket Approval (PMA). Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Clinical evaluation of devices that have not been cleared for marketing requires:

- an investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
- informed consent from all patients;
- labeling stating that the device is for investigational use only;

- monitoring of the study and;
- required records and reports.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution. Sponsors need not submit a PMA or Premarket Notification 510(k), register their establishment, or list the device while the device is under investigation. Sponsors of IDE's are also exempt from the Quality System (QS) Regulation except for the requirements for design controls (21 CFR 820.30).

Investigational Drug (or Product)

A **drug** is defined as: A substance recognized by an official pharmacopoeia or formulary. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A substance (other than food) intended to affect the structure or any function of the body.

A drug or pharmaceutical is considered investigational if either condition applies:

- The device is not approved for marketing in the U.S. or
- The device is approved for marketing but is being *clinically* evaluated for a new indication.

Investigational Medical Device*

A medical device is considered investigational if either condition applies:

- The device is not approved for marketing in the U.S. or
- The device is approved for marketing but is being *clinically* evaluated for a new indication.

*see Medical Device

Investigational New Drug Application (IND)

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Investigator

See Principal Investigator and Research Personnel

The HHS regulations at 45 CFR part 46 ("Common Rule") use the term "investigator" to refer to an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB.
https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/investigator-responsibilities/index.html

In addition, the FDA regulations do include specific investigator responsibilities. These are listed in 21 CFR 312.60-69.pdf.

FDA's definition of investigator is found at 21 CFR 312.3:

"Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Investigators play a crucial role in protecting the rights and welfare of human subjects and are responsible for carrying out sound ethical research consistent with research plans approved by an IRB.Note: co-investigator is not a human subject regulatory term and is not recognized by Children's Wisconsin HRPP. However, NIH defines co-investigator relative to their grants policy.

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures.

In vitro

In glass, as in a test tube. An in vitro test is one that is done in glass or plastic vessels in the laboratory. In vitro is the opposite of in vivo.

In vivo

In the living organism. For example, an experiment that is done in vivo is done in the body of a living organism as opposed to in a laboratory method that does not use the living organism as the host of the test. In vivo is the opposite of in vitro.

Key Personnel

All individuals who contribute in a substantive, meaningful way to the scientific development or execution of the project, whether or not salaries are requested. This is a specific NIH term that relates to grant applications. See Research Personnel for local working definition.

Legally Authorized Representative (LAR)

An individual, guardian or judicial or other entity authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the research. (45 CFR 46.102(c).

Limited Data Use Agreement (DUA)

A Limited Data Use Agreement is used by a covered entity to comply with HIPAA Regulations and is used for research studies that require the disclosure of a limited data set. A limited data set only includes identifiers, such as dates and zip codes.

Medical Devices

The FDA defines a medical device as:

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Such devices may include diagnostic test kits, crutches, electrodes, prescribed beds, pacemakers, arterial grafts, intraocular lenses and orthopedic pins.

The FDA categorizes medical devices into one of three classes – Class I, II, or III – based on their risks and the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. Class I devices generally pose the lowest risk to the patient and/or user and Class III devices pose the highest risk.

MedWatch Program

The FDA's medical product safety reporting program for health professionals, patients and consumers.

Minimal Risk

Risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 45 CFR 46.102(j); 21 CFR 56.102(i)

Monitor (Monitoring)

Person employed by a sponsor, CRO or other relevant entity, who reviews study records to determine that a study 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 study, and assessing the conduct of studies including GCP and regulatory requirement. Monitors work with the study clinical research coordinator to check all data and documentation from the study.

Multi-Center Research

Research that is written to include conduct of a model protocol carried out at more than one institution. A research study conducted at more than one institution (nationally and/or internationally) using the same protocol, each with its own site Principal Investigator. See Children's Wisconsin HRPP Guidance entitled *Conducting Investigator-Initiated Multi-Center Collaborative Research Activities*.

National Institutes of Health (NIH)

The National Institutes of Health (NIH) is the principal federal agency for health research in the United States. The NIH is part of the Department of Health and Human Services. The NIH comprises 27 institutes and centers that provides funding for research and conducts studies.

National Research Act

In 1974, the National Research Act was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The group identified basic principles of research conduct and suggested ways to ensure those principles were followed. .

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)

The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.

Noncompliance

Noncompliance is defined as a failure to follow requirements in the conduct of research. This includes allegations of suspected non-compliance. This can take the form of either (1) Violations of/ failure to comply with federal regulations, state laws, institutional policies, requirements or determinations of the IRB; and (2) deviations/departures/divergences from the IRB approval protocol.

Non-Significant Risk Device Study (NSR)

A non-significant devices study is one that does not meet the definition for a significant risk device study. (See also Significant Risk Device study) https://www.fda.gov/media/75459/download

Nuremberg Code

As a result of the medical experimentation conducted by Nazis during World War II, the U.S. Military Tribunal in Nuremberg in 1947 set forth a code of medical ethics for researchers conducting research on humans. . The guidelines were based on beneficence and non-maleficence, but also stressed the legal doctrine of informed consent. The Nuremberg Code has not been officially accepted as law by any nation or as official ethics guidelines by any association. However, the Code is considered to be the most important document in the history of clinical research ethics. The Nuremberg Code and the related Declaration of Helsinki are the basis for the current US federal regulations. .. https://history.nih.gov/research/downloads/nuremberg.pdf

Off Label Use (non-FDA approved usage)

Use of an FDA regulated product for an indication not in the approved labeling. If used in this way a physician has the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the "practice of medicine"* does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

Office for Human Research Protection (OHRP)

The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services. OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research. OHRP is part of the Office of the Assistant Secretary for Health in the Office of the Secretary of HHS.

OHRP provides clarification and guidance, develops educational programs and materials, maintains regulatory oversight, and provides advice on ethical and regulatory issues in biomedical and behavioral research. OHRP also supports the Secretary's Advisory Committee on Human Research Protections (SACHRP), which advises the HHS Secretary on issues related to protecting human subjects in research.

Open-Label Study

A type of study in which both the health providers and the patients are aware of the drug or treatment being given.

Patient-oriented outcomes

Patient-oriented outcomes are those that affect patients' well-being. They involve one or more of the following:

- Prolongation of life
- Improved function (eg, prevention of disability)
- Relief of symptoms

PharmacoDynamic (PD) or PharmacoKinetic (PK) Study

Pharmacokinetics (PK) refers to the movement of drugs through the body, whereas pharmacodynamics (PD) refers to the body's biological response to drugs. PK describes a drug's exposure by characterizing absorption, distribution, bioavailability, metabolism, and excretion as a function of time.

Pharmacology/Toxicology

The science of drugs and poisonous materials (respectively) and their effects on the body. Studies in these areas include: diet and nutrition; overdoses; and vitamin deficiencies.

Phase I Study

A phase of research to describe clinical trials that focus on the safety of a drug. They are usually conducted with healthy volunteers, and the goal is to determine the drug's most frequent and serious adverse events and, often, how the drug is broken down and excreted by the body. These trials usually involve a small number of participants.

Phase II Study

A phase of research to describe clinical trials that gather preliminary data on whether a drug works in people who have a certain condition/disease (that is, the drug's effectiveness). For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied..

Phase III Study

A phase of research to describe clinical trials that gather more information about a drug's safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. These studies typically involve more participants

Phase IV Study

A phase of research to describe clinical trials occurring after FDA has approved a drug for marketing. They include postmarket requirement and commitment studies that are required of or agreed to by the study sponsor. These trials gather additional information about a drug's safety, efficacy, or optimal use.

PHI (Protected Health Information)

Protected health information is the term given to health data created, received, stored, or transmitted by HIPAA-covered entities and their business associates in relation to the provision of healthcare, healthcare operations and payment for healthcare services. Protected health information is often shortened to PHI. Protected refers to the fact that the information is protected under the HIPAA privacy rule.

There are 18 identifiers that can be used to identify, contact, or locate a person. If health information is used with any of these identifiers it is considered identifiable. If PHI has all of these identifiers removed, it is no longer considered to be protected health information.

1. Names (Full or last name and initial)

2. All geographical identifiers smaller than a state, except for the initial three digits of a zip code if, according to the current publicly available data from the U.S. Bureau of the Census: the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000
3. Dates (other than year) directly related to an individual
4. Phone Numbers
5. Fax numbers
6. Email addresses
7. Social Security numbers
8. Medical record numbers
9. Health insurance beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers (including serial numbers and license plate numbers)
13. Device identifiers and serial numbers;
14. Web Uniform Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger, retinal and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code except the unique code assigned by the investigator to code the data

Pilot Study

A pilot study is defined as "A small-scale test of the methods and procedures to be used on a larger scale" (Porta, *Dictionary of Epidemiology*, 5th edition, 2008). The goal of pilot work is not to test hypotheses about the effects of an intervention, but rather, to assess the feasibility/acceptability of an approach to be used in a larger scale study.

Placebo

An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.

Placebo-Controlled Trial

In undertaking a clinical trial, researchers don't want to leave anything to chance. They want to be as certain as possible that the results of the testing show whether or not a treatment is safe and effective. The "gold standard" for testing interventions in people is the "randomized, placebo-controlled" clinical trial. That means volunteers are randomly assigned—that is, selected by chance—to either a test group receiving the experimental intervention or a control group receiving a placebo or standard care. A placebo is an inactive substance that looks like the drug or treatment being tested.

Comparing results from the two groups suggests whether changes in the test group result from the treatment or occur by chance. In many trials, no one—not even the research team—knows who gets the treatment, the placebo, or another intervention. When participants, family members, and staff all are "blind" to the treatment while the study is underway, the study is called a "double-blind, placebo-controlled" clinical trial.

Placebo Effect

The placebo effect is a beneficial health outcome resulting from a person's anticipation that an intervention will help. How a health care provider interacts with a patient also may bring about a positive response that's independent of any specific treatment.

Pre-Clinical Testing

FDA: Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are In Vitro and In Vivo. Other source: Deciding whether a drug is ready for clinical trials (the so-called move from bench to bedside) involves extensive preclinical studies that yield preliminary efficacy, toxicity, pharmacokinetic and safety information. Wide doses of the drug are tested using in vitro (test tube or cell culture) and in vivo (animal) experiments, and it is also possible to perform in silico profiling using computer models of the drug–target interactions..

Prevention Trials

Refers to 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, vaccines, vitamins, minerals, or lifestyle changes.

Principal Investigator (PI)

Some research studies are conducted by more than one investigator, and usually one investigator is designated the "principal investigator" with overall responsibilities for the study. The Children's Wisconsin HRPP requires that only one individual be named Principal Investigator who has ultimate responsibility for assuring compliance with applicable Children's Wisconsin, policies and procedures, Federal Regulations and for the oversight of the research study and the informed consent process.

Privacy

Privacy refers to the subject and his/her control over the extent, timing, and circumstances of sharing oneself (physically, emotionally, behaviorally, or intellectually) with others.

Protection of Pupil Rights Amendment (PPRA)

Department of Education regulation that states that surveys, questionnaires and instructional materials for school children must be inspected by parents/guardians. PPRA requires schools to notify parents/guardians and obtain consent or allow the parent/guardian to opt his/her child out of participating in the activity. It is the researcher's responsibility to communicate with the institutions where research will be conducted to ensure that there are PPRA-compliant policies in place and design a consent process that complies with both the school's PPRA policy.

Protocol

A document that describes the objectives(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..

Quality Improvement

A process that measures compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance.

Randomization

The process of assigning trial subjects to investigational treatment or control groups (may use a comparator) using an element of chance to determine the assignments in order to reduce bias.
https://www.fda.gov/media/108378/download

Recruitment

Recruitment involves identifying or seeking individuals to enroll or participate in a research study..

Relying Institution

In the context of single IRB review, the entity that agrees to rely upon the reviewing IRB

Registry

Databases, registries (data banks), and repositories (tissue banks) all involve the collection and storage of information and/or biological specimens over time. Some registry/repositories serve diagnostic or clinical purposes, while others are solely for research. Many serve more than one purpose.

Research

A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102(l).

Research Personnel

Individuals, other than the PI, who are responsible for the conduct and/or reporting of research. Such individuals may include, among others: individuals making critical decisions regarding eligibility of subjects; Individuals obtaining consent; Individuals listed on Form FDA 1572 or the investigator agreement.

Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. (The Belmont Report – Part B1)

Retrospective studies

A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). Researchers study the medical and lifestyle histories of the people in each group to learn what factors may be associated with the disease or condition. For example, one group may have been exposed to a particular substance that the other was not. Also called case-control study. A retrospective chart review is another type of retrospective study in which no direct contact with people is conducted, just their electronic health record and is actually quite common.

Reviewing IRB (cIRB or sIRB)

An **Overall IRB of Record**, if there is one, (also known as a "Central IRB", "Reviewing IRB", "Designated IRB" or "Single IRB") is the reviewing IRB that assumes responsibilities for IRB determinations and oversight on behalf of another institution. This designation is established through a reliance agreement (also known as a "deferral" or "IRB Authorization Agreement" (IAA)). For federally-funded research, all centers engaged in research must have a current FederalWide Assurance (FWA) with OHRP (Office for Human Research Protections).

Risk

A possibility that harm may occur, are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm. .

Risk-Benefit Assessment

Risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

Screening Failure

Subjects who are actively screened (which may include actual testing) to determine eligibility for a study and fail by not meeting the inclusion criteria or by determining an exclusion.

Serious Adverse Event (SAE)

Defined by the FDA as any adverse event (AE) that is fatal, life-threatening, permanently disabling, or which results in hospitalization, initial or prolonged.

Serious Noncompliance

Non-compliance becomes **serious or continuing** when it results in harm, increases risk of harm, adversely affects the rights or welfare of participants, may affect the subject willingness to participate in the study, or undermines the scientific integrity of the data. This includes allegations of suspected non-compliance.

1. **Continuing:** repeated occurrences of non-compliance by the same investigator/study team or by the institution. This repetition may occur in the same **or different** protocols by the same investigator/study team. This repetition, if unaddressed may affect the protection of human subjects. Non-compliance does not need to be continuing to be serious.

2. **Serious:** there is an actual or potential increased risk to the safety, rights, or welfare of subjects. The event may have only occurred once, but still be considered serious depending of the effect on risk.

Side Effects

Any undesired actions or effects of a drug or treatment.

Significant Risk Device

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

https://www.fda.gov/media/75459/download

Source Data

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.[6] Access to source data is critical to the review and inspections of clinical investigations. The review of source data by both the FDA and sponsor is important to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the clinical investigation data. Source data should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.[7]

Source Documentation

When original observations are entered directly into a computerized system, the electronic record is the source document. Under 21 CFR 312.62, 511.1(b)(7)(ii) and 812.140, the clinical investigator must retain records required to be maintained under part 312, § 511.1(b), and part 812, for a period of time specified in these regulations. This requirement applies to the retention of the original source document, or a copy of the source document..

Sponsor

Individual, company, institution or organization taking responsibility for initiation, management and financing of study.

Standard Operating Procedure (SOP)

Official, detailed, written instructions for the management of research. SOPs ensure that all the functions and activities of a research are carried out in a consistent and efficient manner.

Standard Treatment

See Routine Care.

Standard of Care

Treatment that experts agree is appropriate, accepted, and widely used. Also called best practice, standard medical care, routine care and standard therapy.

Statement of Investigator (FDA Form 1572)

The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The 1572 has two purposes: 1) to provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the clinical investigation, and 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations. (FDA Guidance https://www.fda.gov/media/78830/download)

Subject Identification Code (Study ID number)

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.

Translational Research

Translation is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioral changes.

Translational Research Unit (TRU)

The Pediatric TRU provides nursing care and coordination for research subjects and their families. Care, from infancy through adulthood, is individualized to meet a variety of research needs. The TRU provides the infrastructural support for the conduct of clinical and translational research projects by providing access to space, resources and the expertise of research support personnel. They are commonly specific as Pediatric and Adult separately.

Treatment Use of an Investigational New Drug (IND)

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment available; 3) the drug is already under investigation, or trials have been completed; and 4) the trial sponsor is actively pursuing marketing approval.

Twenty First (21st) Century Cures Act

The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

UPIRSO (Unanticipated Problems Involving Risk to Subjects or Others)

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This is a specific type of adverse event that must be reported externally to OHRP because it meets the three criteria above. HHS defines "adverse event" as *Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research* (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Unexpected adverse event or suspected adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application

Vulnerable Subjects

Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests. (The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects)

HHS regulations at 45 CFR 46 calls out specific groups for which additional regulatory protections apply:

- Subpart B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D—Additional Protections for Children Involved as Subjects in Research