

APPENDIX A: GLOSSARY OF DEFINITIONS

Adverse Event: Any untoward medical occurrence in a subject receiving a test article and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the test article, whether or not related to the product.

Agent (DHHS): Any individual performing institutionally designated activities or exercising institutionally delegated authority or responsibility.

Allegation of noncompliance: Non-compliance that is suspected and/or reported.

Amendment: A written description of a change(s) to, or formal clarification of, a protocol.

Analysis Set: A set of subjects whose data are to be included in the main analyses.

Approval (in relation to institutional review boards): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and applicable regulatory requirements.

Arm: A planned sequence of elements, typically equivalent to a treatment group.

Assent (DHHS): A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Assent (FDA): A child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

Assessment: A measurement, evaluation, or judgment for a study variable related to the status of a subject. Assessments are usually measured at a certain time, and may be derived by combining several simultaneous measurements to form an assessment (e.g., BMI).

Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit Report: A written evaluation (by the auditor) of the results of the audit.

Audit Trail: Documentation that allows reconstruction of the course of events. May be a secure, time-stamped record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic study record.

Baseline Assessment: Assessment of a subject as they enter a trial and before receiving any treatment.

Bias: Situation or condition that causes a result to depart from the true value in a consistent direction. Bias refers to defects in study design or measurement.

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

Bonus payments: Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment.

Case History: An adequate and accurate record prepared and maintained by an investigator that records all observations and other data pertinent to the investigation on each individual administered the investigational drug (device or other therapy) or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records, hospital charts, and nurse's notes.

Case report: A case report is a retrospective analysis of a clinical case.

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

Certified Copy: A copy of original information that has been verified with a dated signature as an exact copy with all the same attributes and information as the original.

Children (DHHS): Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In Minnesota a person must be 18 years of age or older to legally consent to treatments or procedures. There are certain exceptions allowing children to give consent for treatments involving emergency care, or care related to pregnancy, sexually transmitted diseases or contraceptives.

Children (FDA): Persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. In Minnesota a person must be 18 years of age or older to legally consent to treatments or procedures. There are certain exceptions allowing children to give consent for treatments involving emergency care, or care related to pregnancy, sexually transmitted diseases or contraceptives.

Clinical investigation (FDA): 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 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.

Clinical Trial/Study: 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.

Compliance: Adherence to all trial-related requirements, Good Clinical Practice (GCP) requirements, and applicable regulatory requirements.

Confidentiality: Maintenance of the investigator's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated (prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity and medical information).

Continuing non-compliance: An episode or episodes of repeated non-compliance.

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

Contract Research Organization (CRO): A person or organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Control Group: Subjects in a controlled study that receives no treatment, standard treatment, or placebo.

Curriculum Vitae: Document that outlines an individual's educational and professional history.

Data and Safety Monitoring Board (DSMB): See *data monitoring committee*.

Data Clarification: Answer supplied by the investigator in response to a query.

Data Integrity: An attribute of data pertaining to clinical trials depending on the quality of processes for data capture, correction, maintenance, transmission, and retention. Key dimensions of data integrity include that data be attributable, legible, contemporaneous, original, and accurate.

Data Monitoring: Process by which clinical data are examined for completeness, consistency, and accuracy.

Data Monitoring Committee (DMC): A group of individuals with pertinent expertise that reviews, on a regular basis, accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. A DMC can stop a trial if it finds toxicities or if treatment is proved beneficial.

Database Lock: Action taken to prevent further changes to a clinical trial database. Locking a database is done after review, query resolution, and a determination has been made that the database is ready for analysis.

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

Discontinuation: The act of concluding participation, prior to completion of all protocol-required elements, by an enrolled subject. Four categories of discontinuation are defined: A) dropout: active discontinuation by a subject; B) investigator-initiated discontinuation; C) loss to follow-up: cessation of participation without notice or action by a subject; D) sponsor-initiated discontinuation. Subject discontinuation does not necessarily mean the exclusion of subject data from analysis.

Discrepancy: The failure of a data point to pass a validation check.

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

Dosage: The amount of drug administered to a patient or test subject over the course of the clinical study; a regulated administration of individual doses.

Dosage Form: Physical characteristics of a drug product that contains a drug substance, possibly in association with one or more other ingredients.

Dosage Regimen: The number of doses per given time period; the elapsed time between doses, the time that the doses are to be given, and/or the amount of a medicine to be given at each specific dosing time.

Dosage strength: The proportion of active substance to inert substance, measured in units of volume or concentration. The strength of a drug product tells how much of the active ingredient is present in each dosage.

Dose: The amount of drug administered to a patient or test subject at one time or the total quantity administered.

Drug: An article other than food intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body. Not a device, component, part, or accessory of a device. Substance recognized by an official pharmacopeia or formulary.

Effect: An effect attributed to a treatment in a clinical trial. In most clinical trials, the treatment effect of interest is a comparison (or contrast) of two or more treatments.

Efficacy: The capacity of a drug or treatment to produce beneficial effects on the course or duration of a disease at the dose tested and against the illness and patient population for which it is designed.

Electronic Case Report Form (e-CRF): An auditable electronic record designed to record information required by the clinical trial protocol.

Electronic Record: Information that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

Electronic Signature: Any computer data collection of symbols or series of symbols that are authorized to be the legally binding equivalent of an individual's handwritten signature.

Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data.

Exclusion Criteria: List of characteristics in a protocol, any one of which may exclude a potential subject from participation in a study.

Emergency use (FDA): The 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 IRB approval.

Federalwide Assurance (FWA): The only type of new assurance of compliance accepted and approved by the Office for Human Research Protections (OHRP) for institutions engaged in non-exempt human subject's research conducted or supported by the Department of Health and Human Services (HHS).

Family member (FDA): Any one of the following legally competent persons: spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Finder's fees: Payments in exchange for referral of potential subjects.

Generalizability: The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings.

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

Guardian (DHHS): An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Minnesota, a guardian is most frequently appointed by a court, although they may also be appointed by will or by a spouse. Note: When a child is a ward of the State (parental right terminated—no adoptive parent—a guardian is required to consent

on the child's behalf). If you have questions concerning this determination of authority to consent on behalf of the child, please consult the HSRC.

Guardian (FDA): An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research. In Minnesota, generally either of the married parents of a child may give consent for medical care and for research. If the patient/subject is the child of a woman who was not married when the child was born, the woman is generally the sole legal custodian of the child and may consent on the child's behalf. If the parents of the child are divorced, then the divorce decree should establish legal custody of the child, upon which you may rely. If you have questions concerning this determination of authority to consent on behalf of the child, please consult the HSRC

HSRC: Human Subjects Research Committee

Human subject (DHHS): A living individual about whom an investigator (whether professional or student) conducting research obtains: (1) data through intervention or interaction with the individual, or (2) identifiable private information. *Intervention* includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Human subject (FDA): 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. This definition also includes an individual on whose specimen an investigational device is used.

Informed Consent: An ongoing process that provides the subject with explanations that will help in making educated decisions about whether to begin or continue participating in a trial. Informed consent is an ongoing, interactive process, rather than a one-time information session.

Institutional Official: The individual legally authorized to represent the institution.

Investigational Device Exemption (IDE): Allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to the Food and Drug Administration (FDA). Clinical studies are most often conducted to support a PMA. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Investigational New Drug Application (IND): A request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

Institutional Review Board (IRB): An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocols and the methods and materials to be used in obtaining and documenting informed consent of trial subjects. *Synonyms: Independent Review Board, Independent Ethics Committee, Committee for the Protection of Human Subjects.*

Inter-rater Reliability: The property of scales yielding equivalent results when used by different raters on different occasions.

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

Investigator: An individual responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator's Brochure: A collection of clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

Legally authorized representative (DHHS and FDA): An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. In Minnesota, a legally authorized representative of an incapacitated individual includes the following: a health care agent named in a duly executed Health Care Directive or a guardian of the prospective subject appointed by a parental or spousal appointment or by the court.

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

Non-compliance: Includes: (1) failure to follow the requirements of the HSRC and/or CRC, (2) failure to follow the HSRC policies and procedures, (3) failure to follow an OHSR/HSRC approved protocol and/or (4) failure to follow federal, state, and institutional regulations.

Objective: The reason for performing a trial in terms of the scientific questions to be answered by the data collected during the trial. The primary objective is the main question to be answered and drives the statistical planning for the trial. Secondary objectives are goals of a trial that will provide further information on the use of the treatment.

Patient Reported Outcome (PRO): Report coming directly from patients or subjects through interviews or self-completed questionnaires or other data capture tools such as diaries about their life, health condition(s), and treatment.

Primary Source Documents: Original documents, data, and records contained in, but not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm, or magnetic media, x-rays subject files, and records kept at the pharmacy, laboratories, and at medico-technical departments.

Prisoner (DHHS): Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Privacy: Refers to persons and their interest in controlling the access of others to themselves (e.g., based on their privacy interest people may want to control: (1) time and place where they give information, (2) the nature of the information they give, (3) the nature of the experiences that are given to them, and (4) who receives and can use the information).

Protected health information (PHI): Information about an individual in combination with health data that could identify the individual.

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Protocol Deviation: Failure to adhere to the pre-specified trial protocol.

Quality Assurance (QA): All planned and systematic actions that are established to ensure that a trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and applicable regulatory requirement(s).

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

Quality improvement activities: Quality improvement activities are projects that are completed to improve quality of programs, improve services, or improve the provision of medical care, customer service, etc. and are usually done for internal purposes only.

Query: A request for clarification on a data item collected for a clinical trial; specifically a request from a sponsor or sponsor's representative to an investigator to resolve an error or inconsistency discovered during data review.

Query Resolution: The closure of a query usually based on information contained in a data clarification.

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Redact: The act of selecting or adapting for publication. To prepare a document or report for inspection by an auditor by removing all identifying information the auditor is not legally entitled to see

Regulatory Authorities: Any federal, state, local, or tribal bodies having the power to regulate clinical research.

Reliability: Pertains to questions concerning whether an instrument is accurate, repeatable, and sensitive. Reliability is distinguished from validation, which answers whether the instrument actually measures the selected construct.

Research (DHHS): A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Research involving a human being as an experimental subject: An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria, and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

Research activities involving de-identified data and/or human biological specimens: Projects that involve data and/or human biological specimens where all direct personal identifiers are permanently removed from the data or specimens, no code or key exists to link the materials to the original source(s), and the remaining information cannot reasonably be used by anyone to identify the source(s).

Research activities involving non-living individuals: Projects that collect information on deceased subjects.

Risk: The probability of harm or discomfort for subjects in a clinical trial.

Screen Failure: A potential subject who did not meet one or more criteria required for participation in a trial.

Serious Adverse Event: An untoward medical occurrence that: (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability/incapacity, or (5) is a congenital anomaly/birth defect.

Serious Non-compliance: An action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risks to subjects, decreases potential benefits, or compromises the integrity or validity of the research.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

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

Source Document Verification: The process by which the information reported by an investigator is compared with the original records to ensure that it is complete, accurate, and valid.

Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. A corporation or agency whose employees conduct the investigation is considered a sponsor and the employees are considered investigators.

Sponsor-Investigator: An individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency.

Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

Stopping Rules: A statistical criterion that, when met by the accumulating data, indicates that the trial can or should be stopped early to avoid putting participants at risk unnecessarily or because the intervention effect is so great that further data collection is unnecessary.

Stratification: Grouping defined by important prognostic factors measured at baseline.

Sub-Investigator: Any member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

Subject/Trial Subject: An individual who participates in a clinical trial, either as recipient of the investigational product(s) or as a control.

Surveillance activities: Surveillance activities are projects that collect, analyze, and interpret health-related data essential to planning, implementing and evaluating health care practice.

Trial Monitoring: Oversight of quality of study conduct and statistical interim analysis.

Trial Site: The location(s) where trial-related activities are actually conducted.

Unanticipated Adverse Device Effect (FDA): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Problem Involving Risks to Subjects or Others: A problem that is unanticipated or unexpected, involves risks to subjects or others, and is reasonably believed to be related to research participation.

Unexpected Adverse Event: An untoward medical occurrence, the nature, severity, or frequency which is not consistent with the applicable production information.

Unexpected serious harm: Serious adverse event(s) that is/are not anticipated but is/are reasonably believed to be protocol related.

Validation: Process of establishing suitability to purpose.

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

Ward (FDA): A child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

Well-Being: The physical and mental integrity of the subjects participating in a clinical trial.