NIH Policy Manual

3014-001 - Introduction to NIH Human Research Protection Program (HRPP) Policy Development

Issuing Office: OD/OIR/OHSRP **Phone:** (301) 402-3713

Release Date: 6/03/2020 ? **Technical Revision Date:** 7/17/2023 ?

Transmittal Notice

1. **Explanation of Material Transmitted:** NIH Human Research Protection Program (HRPP) policies have been revised to comport with the revised DHHS Common Rule (45 CFR 46) and to reflect the newly consolidated IRB structure within the NIH Intramural Research Program. This Manual Chapter describes the policy development and structure for the NIH Human Research Protection Program (HRPP) policies of the NIH Intramural Research Program (IRP). This manual chapter will partially supersedes the Introduction to the NIH Human Research Protection Program.

2. **Filing Instructions:**

    - **Insert:** NIH Manual Chapter 3014-100, dated 06/03/2020
    - **Implentation Date:** 07/28/2020

3. **PLEASE NOTE**

    - The current policies can also be found at: https://irbo.nih.gov/confluence/display/ohsrp/Policy.
    - Content of this chapter, contact the issuing office listed above.
    - NIH Policy Manual, contact the Division of Compliance Management, OMA, on (301) 496-4606, or enter this URL: https://oma.od.nih.gov/DMS/Pages/Manual-Chapters.aspx

A. Purpose

1. The purpose of this policy is to establish the requirements for the development, maintenance, and accessioning of Intramural Research Program (IRP) policies for the conduct of human subjects research.

B. Scope

1. This policy applies to:

a. The Deputy Director for Intramural Research (DDIR);
b. The NIH Office of Human Subjects Research Protections (OHSRP) and its offices;
c. The Office of Management Assessment (OMA); and
d. All NIH Institutes and Centers (ICs) that conduct human subjects research under the IRP.

C. Policy

1. NIH HRPP policy will:

   a. Be issued by the NIH Office of the Director (OD), Office of Intramural Research (OIR), OHSRP, which has the primary authority at NIH for writing and implementing NIH Human Research Protection Program (HRPP) policies.
   b. Be subject to oversight by the NIH Deputy Director for Intramural Research (DDIR).
   c. Be approved by the Deputy Director for Intramural Research (DDIR), as head of the NIH IRP.
   d. Be applied uniformly by OHSRP to all NIH ICs that operate under the NIH IRP.
   e. Be developed and revised by the OHSRP office of Policy and Accreditation, as appropriate and necessary, in accordance with the needs of the NIH HRPP, and consistent with federal law, regulation and policy, including NIH policy, and accreditation standards. Such policies will describe:

      I. The policy requirements for the NIH HRPP; and
      II. The required organizational and staff responsibilities.

   f. Be submitted to the NIH Office of Management Assessment (OMA) by the OHSRP office of Policy and Accreditation, for publication in the NIH Policy Manual System. In order to be published and maintained by OMA in the NIH Policy Manual System, HRPP policies will be:

      I. Drafted in the format established between OMA and OHSRP;
      II. Prepared in accordance with NIH Policy Manual #1710 - Publishing and Maintaining Policies;
      III. Compliant with 29 U.S.C § 794 (d), Section 508 of the Rehabilitation Act of 1973, prior to posting on an NIH website, to a shared document directory or distributed in electronic format; and
      IV. Accessible from the NIH Policy Manual website (https://policymanual.nih.gov/chapter/browse/byfunctionalseries/8).

   g. Be published and retained by the NIH Office of Management Assessment (OMA). The HRPP policies and the manual chapter will be developed by OHSRP in accordance with:

I. The NIH Policy Manual #1710 - Publishing and Maintaining Policies;
II. 29 U.S.C § 794 (d), Section 508 of the Rehabilitation Act of 1973; and
III. The NIH Records Management Schedule.

h. Be communicated by the OHSRP to the NIH IRP community, upon implementation, and be available on the OHSRP Office of IRB Operations website (https://irbo.nih.gov/confluence/display/IRBO/OHSRP), both internally and externally to the NIH.

2. The authority for development of IRP HRPP policy: IRP HRPP policy may only be authorized by the DDIR through the OHSRP Director. No IC-level HRPP policies are authorized to apply to the broader IRP HRPP.

    a. As such, the NIH ICs do not have the authority to write, amend, or supersede NIH HRPP policy.

3. When there are any policy conflicts between HRPP policy and NIH policy, the OHSRP Director will inform the NIH DDIR of the policy conflict, the reason(s), and the proposed course of action.

    a. The DDIR must concur with the proposed course of action, prior to approving the final policy.

4. The organization of the HRPP policies will be grouped as follows:

    a. 3014-100 Series – Institutional Authorities and Requirements
    b. 3014-200 Series – IRB Authorities and Requirements
    c. 3014-300 Series – Investigator Responsibilities
    d. 3014-400 Series – Regulatory Protections for Vulnerable Populations
    e. 3014-500 Series – FDA Requirements for Human Subjects Research and Data and Safety Monitoring
    f. 3014-600 Series – Reserved
    g. 3014-700 Series – International Research Requirements
    h. 3014-800 Series – Compliance and Research Event Reporting Requirements

5. The HRPP policies will undergo formal review by the OHSRP office of Policy and Accreditation at a minimum of every three (3) years for compliance with law, regulation and policy, including NIH policy, accreditation standards and operational needs. The HRPP policies will be updated at that time, as applicable.

    a. However, these policies may be reviewed and revised more frequently at the discretion of the OHSRP Director.

6. Agency-wide policy documents are considered permanent records. Therefore, HRPP policies will be retained and disposed by of OMA and OHSRP under the authority of the NIH Records Management Schedule.

7. Access to HRPP records will be determined by the OHSRP Director. This determination will be based on documentation of a legitimate need and made in accordance with applicable federal law, regulation, and policy, including NIH policy. For more information, see *Policy 3014-206 Maintenance of Records*.

D. Definitions

1. The NIH HRPP Glossary which contains definitions of all HRPP terms is located at NIH IRP HRPP Policy Glossary.

E. Responsibilities and Requirements

1. **OHSRP Director responsibilities**

    a. The OHSRP Director is responsible for:

        I. Acting as the primary authority at NIH for developing, and implementing NIH HRPP policies;
        II. Ensuring that NIH HRPP policies comply and conform with federal law, regulation and policy, including NIH policy, and accreditation standards;
        III. Ensuring that NIH HRPP policy drafts are disseminated for review and comment by HHS and NIH policy offices, as applicable;
        IV. Ensuring that final approved NIH HRPP policy is disseminated to the appropriate IC communities upon implementation;
        V. Determining when new NIH HRPP policies should be developed.

2. **The OHSRP office of Policy and Accreditation Responsibilities**

    a. The OHSRP office of Policy and Accreditation is responsible for:

        I. Ensuring that HRPP policies and the corresponding manual chapter are developed consistent with the agreed upon format established between the OHSRP and OMA. (NIH Policy Manual #1710 - Publishing and Maintaining Policies)
        II. Ensuring that approved policies are processed through OMA for publication in the NIH Manual System. Such policies must meet the following criteria:

            i. The policy is not targeted solely toward a restricted audience (e.g., only NIH federal employees);
            ii. The policy does not contain sensitive information that should not be publicly accessible; and
            iii. The policy is understandable by a majority of the general NIH population, e.g., not overly technical.

III. Consulting and vetting NIH HRPP policies with NIH policy offices (e.g. the NIH Senior Official for Privacy, the Office of Human Resources (OHR)), as appropriate.
IV. Advising the OHSRP Director of any conflicts which require adjudication by the DDIR.
V. Clearing HRPP policies with the HHS Office of General Counsel to ensure that they are legally sufficient.
VI. Informing the NIH IRP community when approved policies are implemented.
VII. Coordinating with the OHSRP office of Compliance and Training, for any educational materials or sessions needed to educate the NIH IRP community about new policy requirements.
VIII. Ensuring that all published policies are in compliance with HHS 508 requirements.
IX. Ensuring that all links to implemented HRPP policies on the IRBO website must directly link to the NIH Policy Manual System.

i. All policy versions developed for this series of policies (see *C.2.* above) must be archived by OMA and accessible according to *Policy 3014-206 Maintenance of Records*.
ii. All HRPP Standard Operating Procedure (SOPs) previously developed by OHSRP must be maintained by OHSRP and made accessible according to *Policy 3014-206 Maintenance of Records*.

X. Reviewing internal controls relative to this policy.
XI. Conducting a formal review of HRPP policies not less than once every three (3) years. Such a review must identify needed policy revisions, if any. This does not preclude an earlier review and revision of HRPP policies as needed, and when directed by the OHSRP Director.

3. **Deputy Director for Intramural Research Responsibilities**

a. The DDIR must:

I. Provide oversight and approve NIH HRPP policies; and
II. Adjudicate disagreements on access to NIH HRPP policy records.

b. When there is an identified policy conflict, the DDIR must concur with the proposed course of action, prior to approving the final policy.

4. **Institute and Center Responsibilities**

a. Institutes and Centers must comply with NIH HRPP policy in the conduct of human subjects research.
b. Institutes and Centers may not write, amend or supersede NIH HRPP policy.

5. **Office of Management Assessment Responsibilities**

a. The NIH Office of Management Assessment (OMA) must publish and retain HRPP policies and the manual chapter developed by OHSRP in accordance with:

I. The NIH Policy Manual #1710 - Publishing and Maintaining Policies;
II. 29 U.S.C § 794 (d), Section 508 of the Rehabilitation Act of 1973; and
III. The NIH Records Management Schedule.

b. OMA must make implemented policies available internally and externally to the NIH.

I. OMA must provide for determination by the OHSRP Director, any request to access draft NIH HRPP policies.

c. The formal review of NIH HRPP policies by the OHSRP office of Policy and Accreditation must be monitored and tracked by the OMA (see *E.2.a.XI.* above).

F. References

1.**Federal Laws and Regulation:**

29 U.S.C § 794 (d), Section 508 of the Rehabilitation Act of 1973, as amended

2.NIH Policy:

Policy 3014-206 Maintenance of Records

NIH Policy Manual
NIH Policy Manual #1710 - Publishing and Maintaining Policies
NIH Human Research Protection Program (HRPP) Policies
NIH Records Management Schedule

APPENDIX 1: NIH IRP Human Research Protection Program (HRPP) Policy Glossary

Printer Friendly Version

NIH IRP HUMAN RESEARCH PROTECTION PROGRAM (HRPP) POLICY GLOSSARY

OHSRP has developed a comprehensive glossary of terms that are utilized in the NIH HRPP Policies and are defined below. The HRPP Policies are part of the Intramural Research Program policy series under Manual Chapter 3014.

Note: *There may be more than one definition per term*, so please review terms in the source policy carefully, to make sure they match the terms listed below. Qualified terms are indicated with a parenthetical qualification. When reviewing a definition, be sure that you are reviewing the appropriate definition that links to this policy. To further assist the reader, each term in the glossary cites the relevant policy number(s) indicating where the term is utilized.

Definitions demarcated with (***Pre-2018 Common Rule***) apply to research approved by an IRB (or deemed to be exempt, or for which no Institutional Review Board (IRB) review was required under the regulations) prior to the effective date of the 2018 Common Rule (January 21, 2019).

Definitions demarcated with (***2018 Common Rule***) apply to all research approved by an IRB (or deemed to be exempt, or for which no IRB review was required under the regulations) on or after January 21, 2019 and to research transitioned to the 2018 requirements in accordance with NIH Human Research Protection Program (HRPP) policy.

A B C D E F G H I L M N O P Q R S T U V W

Ability to Consent Assessment Team (ACAT) – A group of NIH healthcare staff, including members from Psychiatry (the National Institute of Mental Health (NIMH) Human Subjects Protection Unit (HSPU)) and Bioethics, which is trained to conduct assessments of prospective or current human subjects at the Clinical Center (CC) to determine if the prospective subject has the capacity to consent to research participation, the capacity to assign a Durable Power of Attorney (DPA), and, when needed, to assess and determine if a Legally Authorized Representative (LAR) is appropriate. (This definition is cited in Policy 3014-403)

Accountable Investigator (For the purposes of HRPP policy) – A tenured or tenure-track investigator, senior clinician or Staff Clinician who is responsible and accountable for the expenditure of resources for clinical research protocols. They are not engaged in human subjects research in all cases. (This definition is cited in Policy 3014-300)

Adjunct Principal Investigator (Adjunct PI) – An individual who shares some responsibilities with the NIH PI at the NIH, or for multisite studies also conducted at the NIH Clinical Center. However, the NIH PI retains the ultimate oversight and responsibility for the research. (This definition is cited in Policies 3014-102 and 3014-300)

Adult – A person who has 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. For purposes of providing consent at the NIH Clinical Center, an adult is anyone 18 years of age or older, or a minor who is married or a parent. (This definition is cited in Policy 3014-403)

Adverse Event (AE) – Any untoward 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 research, whether or not considered related to the subject's participation in the research. (This definition is cited in Policies 3014-500 and 3014-801)

Adverse Event *(In the context of Food and Drug Administration (FDA)-required reporting)* - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (21 CFR 312.32 (a)) (This definition is cited in Policy 3014-500)

Affiliated Institutional Review Board (IRB) Member – Affiliated IRB member includes, but is not limited to, an NIH Federal employee, a Special Government Employee (SGE) (except for those in which the SGE status is only due to their membership on an NIH IRB), personnel appointed at NIH through an Intergovernmental Personnel Act (IPA) agreement, a current NIH trainee, a paid or unpaid consultant to the NIH, a healthcare provider holding credentials to practice at NIH sites, a contractor, a Guest Researcher, and also a Special Volunteer (SV). (This definition is cited in Policy 3014-201)

Allegation of Non-Compliance (also "Allegation") – A disclosure of possible non-compliance through any means of communication (e.g., by written or oral statement) to an NIH official. This may include concerns from research participants, investigators, staff, Institutional Review Board (IRB) members, reports from audits, and discoveries made during review of other human subjects issues, such as protocol deviations. It does not include self-reporting by the PI/designee to the IRB, using a reportable event form submitted in the electronic IRB system. (This definition is cited in Policy 3014-802)

Alternate Institutional Review Board (IRB) Member – A member formally appointed and listed in the membership roster who may substitute for a primary member. (This definition is cited in Policy 3014-201)

Amendment (See Modification) – A proposed modification of previously approved exempt research, previously exempt research for which Limited Institutional Review Board (IRB) review is required, or previously approved non-exempt human subjects research. (This definition is cited in Policies 3014-204 and 3014-205)

Appearance of Conflict of Interest – Occurs when an individual's impartiality in clinical research, particularly clinical research involving commercial interests, might reasonably be questioned because the interests of a member of the individual's household would be affected by the matter, or because certain persons or entities (i.e. those with whom the individual has a "covered relationship") are involved in or will be affected by the research, including close relatives or household members of the individual or others with whom the individual has or recently had (within the past year) certain personal or business relationships, or with whom the individual's spouse, parent or dependent child has certain personal or business relationships. (5 C.F.R. § 2635.502) (This definition is cited in Policies 3014-102 and 3014-202)

Assent – The affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (See 45 CFR 46.402(b) of the 2018 Common Rule) (This definition is cited in Policies 3014-402 and 3014-403)

Associate Investigator - Individuals, other than the PI, who make substantial contributions to the conception, design, and/or execution of the study, including, but not limited to: obtaining informed consent; interacting or intervening with living human subjects to obtain, use, or analyze identifiable private information or specimens; or obtains, uses, studies, analyzes, or generates identifiable private information or specimens. Also referred to as "sub-

investigator" by FDA regulation. There may be several AIs on a protocol. NIH employees, contractors, NIH trainees and non-NIH collaborators may, when appropriate, serve as AIs. (This definition is cited in Policy 3014-300)

Asynchronous (store-and-forward) – Acquiring medical information and transmitting this data to a qualified healthcare provider at a convenient time for assessment offline. (This definition is cited in Policy 3014-303)

Back to top

Biological Product – (1) a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. (2) The term "biosimilar" or "biosimilarity", in reference to a biological product that is the subject of an application under subsection (k) (of 42 USC 262), means (A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. (3) The term "interchangeable" or "interchangeability", in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.(4) The term "reference product" means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k). (42 USC 262(i)(1)) (This definition is cited in Policy 3014-500)

Biomedical Research – Basic, clinical, and translational medical research conducted to investigate the causes, treatments, and cures for both common and rare diseases. (This definition is cited in Policy 3014-103)

Board Chair or Chair – An individual with relevant scientific/clinical background and expertise in research methods who is appointed to lead convened meetings and conduct administrative duties required for a successful operation of the Board. (This definition is cited in Policy 3014-201)

Back to top

Certificate of Confidentiality – A Certificate of Confidentiality (Certificate or CoC) (Section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)) is issued by the National Institutes of Health to protect research participants' privacy. Certificates prohibit the investigator and others who have authorized access to research records from disclosing names, information, documents, or biospecimens containing identifiable, sensitive information about research subjects, including in response to any civil, criminal, administrative, legislative or other proceeding, whether at the federal, state or local level. Identifiable, sensitive information may only be disclosed for certain statutory exceptions, including when required by federal law (e.g., for mandatory public health reporting, but not in response to a legal proceeding as described above), for any purposes participants have consented to, and for other research that is in compliance with applicable federal human subjects regulations. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping to assure confidentiality and privacy to research participants. (This definition is cited in Policy 3014-107)

Children – Are 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. (See 45 CFR 46.402(a).) (This definition is cited in Policies 3014-400 and 3014-402)

Clinical Investigation – 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 (*21 CFR*), regarding nonclinical laboratory studies. (21 CFR 50.3(c))

1. **Clinical Investigation *(involving drugs)*** - Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. (21 CFR 312.3(b)

(This definition is cited in Policies 3014-500 and 3014-502)

Clinical Protocol – A document outlining human subjects studies requiring IRB approval. Clinical protocols may include clinical trials, non-interventional observational (natural history) studies, screening protocols, repository protocols and teaching and training protocols, in accordance with the *Policy for Scientific Review of Clinical Protocols Utilizing the NIH Intramural Program*. (This definition is cited in Policy 3014-106)

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 the interventions on biomedical or behavioral health-related outcomes. (45 CFR 46.102(b)) (This definition is cited in Policies 3014-301 and 3014-503)

Coercion - An overt or implicit threat of harm that is intentionally presented by one person to another in order to obtain a certain outcome. (This definition is cited in Policies 3014-200, 3014-301 and 3014-404)

Collaboration – Non-exempt human subjects research conducted by at least one NIH employee and a non-NIH institution/individual who is not otherwise covered by the NIH Federalwide Assurance (FWA). (This definition is cited in Policy 3014-105)

Collaborative Institutional Training Initiative (CITI) – A subscription service that provides research ethics education to the members of the research community. (This definition is cited in Policy 3014-103)

Color Additive – A material which (A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other

source, and (B) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. (2) The term ''color'' includes black, white, and intermediate grays. (3) Nothing in subparagraph (1) of this paragraph shall be construed to apply to any pesticide chemical, soil or plant nutrient, or other agricultural chemical solely because of its effect in aiding, retarding, or otherwise affecting, directly or indirectly, the growth or other natural physiological processes of produce of the soil and thereby affecting its color, whether before or after harvest. (Federal Food Drug and Cosmetic Act at 21 USC 301(t)) (This definition is cited in Policy 3014-500)

Complainant – A person who makes an allegation of non-compliance. (This definition is cited in Policy 3014-802)

Complaint ***(For the purposes of Policy 3014-104)*** – An expression of concern, dissatisfaction or grievance, related to participation in research. (This definition is cited in Policy 3014-104)

Confidentiality – The protection of research participants' privacy from disclosure of their personal, sensitive or private information to unauthorized persons, this includes methods used to ensure that information obtained by researchers about their research participants is not improperly divulged. (This definition is cited in Policy 3014-107)

Conflict of Interest (CoI) – When a government matter, including clinical research, will have a direct and predictable effect on the financial interests of an individual or the individual's spouse, minor children, general partner(s), or certain other organizations in which the individual serves as an officer, director, trustee, general partner or employee, and any entities with which the individual is negotiating for, or has an agreement regarding, prospective employment. (18 U.S.C. § 208) (This definition is cited in Policies 3014-102 and 3014-202)

Consent Monitor - An impartial observer who ensures the approved consent process is being followed properly. (This definition is cited in Policies 3014-301 and 3014-404)

Consultant – An individual who may be requested to provide additional scientific and/or specialty expertise to the Institutional Review Board (IRB) as necessary. Consultants are not IRB members and may not vote. (This definition is cited in Policy 3014-201)

Continuing Review *(2018 Common Rule)* – The ongoing, scheduled Institutional Review Board (IRB) review of a previously approved non-exempt human subjects research study, at intervals appropriate to the degree of risk, but not less than once per year, except as described in 45 CFR 46.109(f) for research that is subject to the 2018 Common Rule. (This definition is cited in Policies 3014-204 and 3014-205)

Continuing Review *(Pre-2018 Common Rule)* – The ongoing, scheduled IRB review of a previously approved non-exempt human subjects research study, at intervals appropriate to the degree of risk, but not less than once per year. (This definition is cited in Policies 3014-204 and 3014-205)

Convened Institutional Review Board (IRB) – Committee review of human subjects research by an IRB that meets the membership requirements specified in federal regulations at 45 CFR 46.108(b) and 21 CFR 56.108(c), and as described in *Policy 3014-201 IRB Membership and Composition*. (This definition is cited in Policy 3014-204)

Cooperative Research – See **Multi-site Research**. (This definition is cited in Policy 3014-105)

Cooperative Research and Development Agreement (CRADA) Review Subcommittee – The Subcommittee that reviews CRADAs containing exclusive licensing-related clauses. (This definition is cited in Policy 3014-106)

Cooperative Research and Development Agreements (CRADAs) – Agreements authorized by 15 U.S.C. 3710a to formalize scientific collaborations. It is not a federal contract, grant or cooperative agreement (as defined in 31 USC § 6303 *et seq.*). CRADAs allow NIH Investigators to use NIH personnel, services, facilities, equipment or other resources to conduct CRADA research, and the non-Federal collaborator can provide funds, personnel, services, facilities, equipment or other material and/or technical resources to the NIH. Importantly, the CRADA provides the non-Federal party the option to negotiate an exclusive license to the resultant CRADA Subject Invention(s). (This definition is cited in Policy

3014-106)

Covered Research Protocol – Covered research protocols (and covered substudies) include: (1) studies of investigational drugs and devices, (2) studies with a research question about a commercially available drug or device, and (3) studies involving collaborations with a substantially affected organization (SAO) or another for-profit entity when the entity is receiving data or specimens from the NIH for the purpose of developing a product. Most interventional protocols will be Covered Research Protocols unless the intervention does not involve the criteria listed above.

- **Non-covered research protocol** – For the purposes of Policy 3014-102, non-covered research protocols include NIH research protocols that are categorized as Natural History studies, unless these studies meet the criteria for *covered research protocols* listed above.

(This definition is cited in Policies 3014-102 and 3014-106)

Back to top

Data and Safety Monitoring – A formalized process for reviewing accumulated outcome data from an ongoing research study to ensure the continuing safety and welfare of current research subjects and those yet to be enrolled, as well as the continuing validity and scientific merit of the study. (This definition is cited in Policy 3014-503)

Data and Safety Monitoring Board (DSMB*)* – A formal committee made up of independent experts, which reviews accumulating data and critical efficacy endpoints from one or more ongoing clinical trials, including multi-site research. For purposes of Policy 503, the terms DSMB, independent Data and Safety Monitoring Committee (DSMC), and Data Monitoring Committee (DMC), will be considered synonymous and will be referred to herein as "DSMB". (This definition is cited in Policy 3014-503)

Data and Safety Monitoring Entity – The identified individual or group (e.g., the investigator, a coordinating or statistical center, a medical monitor, an Institute or Center (IC)

monitor, independent Data and Safety Monitoring Board (DSMB), Data and Safety Monitoring Committee (DSMC), Data Monitoring Committee (DMC), or other entity) assigned to conduct interim monitoring of data from research activities. (This definition is cited in Policy 3014-503)

Data and Safety Monitoring Plan (DSMP) – A written description that prospectively identifies and documents monitoring activities, or that are none are needed, to protect the safety and welfare of the subjects, the validity of the data, and the integrity of the research study. The DSMP may also identify when to terminate a subject's participation (i.e. individual stopping rules) and/or the appropriate termination of a study (i.e. study stopping rules). (This definition is cited in Policy 3014-503)

Dead Fetus – A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord. (45 CFR 46.202(a)) (This definition is cited in Policy 3014-400)

Delivery – Complete separation of the fetus from the woman by expulsion or extraction or any other means. (45 CFR 46.202(b)) (This definition is cited in Policy 3014-400)

Deputy Ethics Counselor (DEC) – The DEC of each of the Institutes and Centers (ICs), and within the Office of the Director (OD), manages and administers the government ethics program for employees within their component, and has delegated authority to make government ethics determinations related to employee involvement in human subjects research. (This definition is cited in Policy 3014-106)

Device – The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

1. recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
2. 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
3. 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 its primary intended purposes.(21 USC 321(h))

(This definition is cited in Policy 3014-501)

Dietary Supplement – (1) Means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E); (2) means a product that— (A)(i) is intended for ingestion in a form described in section 350(c)(1)(B)(i) of this title; or (ii) complies with section 350(c)(1)(B)(ii) of this title; (B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and (C) is labeled as a dietary supplement; and (3) does— (A) include an article that is approved as a new drug under section 355 of this title or licensed as a biologic under section 262 of title 42 and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 342(f) of this title; and (B) not include— (i) an article that is approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title, or licensed as a biologic under section 262 of title 42, or (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter. Except for purposes of paragraph (g) and section 350f of this title, a dietary supplement shall be deemed to be a food within the meaning of this chapter. (21 USC 321(ff)) (This definition is cited in Policy 3014-501)

Disqualifying Financial Interests for Federal Employees –These include:

1. Ownership and other financial interests in publicly traded SAOs involved in or that will be affected by the research unless the values are within regulatory de minimis levels (see 5 C.F.R. Part 2640). At present, the de minimis exemptions provide there is no conflict where:

    1. The aggregate value of the interest of an investigator and his/her spouse and minor child(ren) in the SAO(s) whose products are being/may be evaluated in the research does not exceed $15,000;
    2. The aggregate value of the interests of an investigator and his/her spouse and minor child(ren) in all SAOs that may be directly or indirectly affected by the research (including those whose products are being/may be evaluated) does not exceed $25,000;

3. The aggregate value of the interest of an investigator and his/her spouse and minor child(ren) in health-related sector funds does not exceed $50,000; and/or
4. The otherwise disqualifying financial interest arises from ownership of shares in a widely-diversified mutual fund.

2. Ownership and other financial interests, regardless of value, in privately-held companies whose products are/may be evaluated by the research and/or that might be indirectly affected by the research.
3. Proprietary interests and royalty sharing rights derived from work done outside of the federal government that are related to or may be affected by research performed at/by the NIH including, but not limited to, a patent, trademark, copyright or licensing agreement. (Note: under federal law, neither royalty payments received nor the right to receive such payments from the Federal Government based on work done as a federal employee constitutes a disqualifying financial interest.
4. A Board or other fiduciary relationship to a commercial sponsor of the research, regardless of compensation. (Note: NIH employees are subject to legal and policy limitations on such activities and need prior approval consistent with NIH and IC procedure(s); such activities with commercial entities generally are prohibited.)

(This definition is cited in Policy 3014-102)

Drug – (A) articles recognized in the official United States Pharmacopœia, official Homeopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of [The Food Drug & Cosmetic Act] or sections 343(r)(1)(B) and 343(r)(5)(D) of [the Food, Drug & Cosmetic Act], is made in accordance with the requirements of section 343(r) of [the Food Drug & Cosmetic Act] is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of [the Food, Drug & Cosmetic Act] is not a drug under clause (C) solely because the label or the labeling contains such a statement. (2) The term "counterfeit drug" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor. (21 USC 321(g)(1))

Note: Biological products are generally included within this definition and are covered by some of the same laws and regulations, but differences exist regarding their manufacturing

processes (chemical process versus biological process; see definition for "*biological product*"). (This definition is cited in Policy 3014-500)

Dual Use Research of Concern (DURC) – Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, material, or national security. DURC review is built into and initiated on all biological registration submissions with the NIH Institutional Biosafety Committee (IBC). (This definition is cited in Policy 3014-106)

Durable Power of Attorney (DPA) for Health Care – An advance directive in which individuals appoint another individual to make health care decisions for them in the event that they become incapable of doing so. (This definition is cited in Policy 3014-403)

Back to top

Emergency Use – 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 Institutional Review Board (IRB) approval. (21 CFR 56.102(d)) (This definition is cited in Policy 3014-502)

Engaged in Human Subjects Research – An individual is engaged in human subjects research if that individual, for research purposes, either:

1. Obtains information or biospecimens through intervention or interaction with a living individual, and uses, studies, or analyzes the information or biospecimens; or
2. Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens from a living individual; or
3. Obtains informed consent from a prospective subject for the purposes of research participation.

(This definition is cited in Policies 3014-102 and 3014-300)

(The) Ethical and Regulatory Aspects of Clinical Research - A seven (7) week course offered by the Clinical Center (CC) Bioethics Department each fall that provides a comprehensive overview of the ethical issues in human subjects research in the United States. For more information, see References in Policy 3014-103. (This definition is cited in Policy 3014-103)

Exempt Investigational Device Study –This part [21 CFR part 812], with the exception of §812.119, does not apply to investigations of the following categories of devices:

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the Food and Drug Administration (FDA) has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
3. A diagnostic device, if the sponsor complies with applicable requirements in §809.10(c) and if the testing:

    1. Is noninvasive,
    2. Does not require an invasive sampling procedure that presents significant risk,
    3. Does not by design or intention introduce energy into a subject, and
    4. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. A device intended solely for veterinary use.
6. A device shipped solely for research on or with laboratory animals and labeled in accordance with §812.5(c).
7. A custom device as defined in §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution . (21 CFR 812.2(c)

(This definition is cited in Policy 3014-501)

Exempt Research – Research exempt from compliance with the full requirements of 45 CFR 46:

1. For research subject to the pre-2018 Common Rule, the exempt categories are described at 45 CFR 46.101(b).
2. For research subject to the 2018 Common Rule, the exempt categories are described at 45 CFR 46.104.

(This definition is cited in Policy 3014-205)

Expanded Access (Sometimes referred to as "compassionate use") – 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. (See Expanded Access Keywords, Definitions and Resources.) (This definition is cited in Policy 3014-502)

Experienced Institutional Review Board (IRB) Member – An IRB member, as determined by the Chair, who has demonstrated during a period of active participation a broad understanding and competency in human subjects protection ethics, board operations, and regulatory requirements, including expedited review procedures. (This definition is cited in Policies 3014-201 and 3014-204)

Expiration Date – The last date research activities can be performed under the auspices of Institutional Review Board (IRB) approval. (This definition is cited in Policy 3014-204)

Back to top

Federal Employee ***(For the purposes of Federal Ethics Requirements)*** – An individual who is appointed by and is subject to the supervision of an individual named by paragraph (a)(1) in 5 U.S.C. § 2105 (e.g. the President) while engaged in the performance of the duties of his position. For the purposes of Policy 3014-102, this includes Special Government Employees (SGEs) and Intergovernmental Personnel Act (IPA) appointees, including trainees, who are federal employees. However, Guest Researchers, Special Volunteers, contractors and Intramural Research and Cancer Research Training Awardees are not federal employees.

(This definition in cited in Policy 3014-102)

Federal Employee ***(For the purposes of Human Research Protection Program Policies)*** – An individual who is engaged in the performance of a Federal function under authority of law or an Executive act and subject to the supervision of an individual named by paragraph (1) in 5 U.S.C. § 2105 while engaged in the performance of the duties of his position. This includes Special Government Employees (SGE) and Intergovernmental Personnel Act (IPA) appointees for the purpose of the NIH Human Research Protection Program (HRPP) policies. (This definition is cited in Policies 3014-100, 3014-103, 3014-105, 3014-202, and 3014-300.)

Federalwide Assurance (FWA) – A written commitment that human subjects research conducted on behalf of an institution will comply with the protections for human subjects specified in the Common Rule regulation (e.g., 45 CFR 46). The FWA is filed with the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP). (This definition is cited in Policies 3014-105, 3014-109, 3014-207 and 3014-700)

Fetus – The product of conception from implantation until delivery. (45 CFR 46.202(c)) (This definition is cited in Policy 3014-400)

Back to top

Generalizable Knowledge (in the context of human subjects research) – Conclusions, results or findings from the research that can be generalized to a broader population, class, or applicability than the study population or sample size. (This definition is the official NIH IRP HRPP definition.)

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. (This definition is cited in Policy 3014-103)

Guardian –An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. (45 CFR 46.402(e)) (This definition is cited in Policy 3014-402)

Guest Researcher (GR) – A scientist, engineer, or student who is permitted to engage in scientific studies and investigations using NIH facilities. Under this program, these individuals further their own research by using equipment and resources that are otherwise unavailable to them. They provide no direct services to NIH. They may not have any patient contact. (See NIH Manual Chapter "2300-308-1 – Guest Researcher/Special Volunteer Programs.) (This definition is cited in Policy 3014-102)

Back to top

HIPAA Privacy Rule (45 CFR 164.508(c)) – HIPAA establishes national standards to protect individuals' medical records and other personal health information and apply to health plans, healthcare clearinghouses, and those healthcare providers that conduct certain health care transactions electronically. Section 45 CFR 164.508(c) covers the subpart applicable to this policy. **Note** that the NIH is not subject to the HIPAA Privacy Rule. (This definition is cited in Policy 3014-107)

Human Subject *(2018 Common Rule)* –

1. A living individual about whom an investigator (whether professional or student) conducting research:

    1. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
    2. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

2. *Identifiable biospecimen – A* biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

3. *Identifiable private information* – Private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
4. *Interaction* –Communication or interpersonal contact between investigator and subject.
5. *Intervention* – 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.
6. *Private information* –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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g. a medical record). (45 CFR 46.102(e) 2018 Common Rule)

(This definition is cited in Policies 3014-100, 3014-103, 3014-106, 3014-200, 3014-204, 3014-300, 3014-500, and 3014-501)

Human Subject *(FDA Regulations)* – 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 human or a patient. (21 CFR 50.3(g)) (This definition is cited in Policy 3014-200)

Human Subject *(Pre-2018 Common Rule)* – 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.

1. *Intervention* - includes both physical procedures by which data are gathered (for example, 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.
2. *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 (for example, 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. (45 CFR 46.102(f) pre-2018 Common Rule .)

(*See also the FDA definitions of Subject below.*) (This definition is cited in Policies 3014-100, 3014-103, 3014-106, 3014-200, 3014-204, 3014-300, 3014-500, and 3014-501)

Human Subject (For FDA regulated *In Vitro* Devices) – Is any human specimen that will be used to test a FDA regulated *in vitro* device, if it is individually identifiable or coded**[1]** such that an investigator or any other individual associated with the investigation, or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through a coding system. (See also "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.") (This definition is cited in Policy 3014-501).

Human Subjects Research (HSR) – Any activity that:

1. Meets the US Department of Health and Human Services (HHS) definition of research and involves human subjects as defined in the HHS regulations; and/or
2. Meets the Food and Drug Administration (FDA) definition of research and involves human subjects as defined in FDA regulations.

(This definition is cited in Policies 3014-200 and 3014-300)

Humanitarian Device Exemption (HDE) – A premarket approval application submitted pursuant to this subpart [21 CFR 814] seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the act as authorized by section 520(m)(2) of the act [FD&C Act]. (21 CFR 814.3(m)) (This definition is cited in Policy 3014-501)

Humanitarian Use Device (HUD) –A medical device intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in not more than 8,000 people in the United States per year. (21st Century Cures Act, Public Law 114-255, 130 Stat. 1033 (2016) and 21 CFR 814.3(n)) (This definition is cited in Policy 3014-501)

Back to top

Identifiable Biospecimen *(2018 Common Rule)* – A biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the

biospecimen [45 CFR 46.102(e)(6)]. (This definition is cited in Policy 3014-107)

Identifiable Private Information *(2018 Common Rule)* – Private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information [45 CFR 46.102(e)(5)]. (This definition is cited in Policy 3014-107)

Identifiable Sensitive Information (ISI) – Information that is about an individual and that is gathered or used during the course of research and (A) through which an individual is identified; or (B) for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual. Identifiable, sensitive information includes but is not limited to name, address, social security or other identifying number; and fingerprints, voiceprints, photographs, genetic information, tissue samples, or data fields that when used in combination with other information may lead to identification of an individual who is the subject of the research. (This definition is cited in Policy 3014-107)

Immediate Family Member (*For the purposes of Policy 3014-404 only)* – *G*enerally, a group of relatives that includes parents, siblings, spouse, and children. (This definition is cited in Policy 3014-404)

Immediately life-threatening disease or condition – A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. (21 CFR 312.300(b)) (This definition is cited in Policy 3014-502)

Implant – A device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. The Food and Drug Administration (FDA) may, in order to protect public health, determine that devices placed in subjects for shorter periods are also "implants" for purposes of this part. (21 CFR 812.3(d)) (This definition is cited in Policy 3014-501)

Investigator – An individual who is involved in the conduct of human subjects research. Such involvement would include:

1. obtaining information about living individuals by intervening or interacting with them for research purposes;
2. obtaining identifiable private information or identifiable biospecimens about living individuals for research purposes;
3. obtaining the voluntary informed consent of individuals to be subjects in research; and
4. studying, interpreting, or analyzing identifiable private information, biospecimens, or data for research purposes.

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. For more information see the OHRP Investigator Responsibilities FAQs (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/investigator-responsibilities/index.html). At the NIH, this term also includes study coordinators and may also include other individuals as determined by the NIH PI. (This definition is cited in Policy 3014-300)

In vitro diagnostic (IVD) products –Those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act. (21 CFR 809.3(a)) (This definition is cited in Policy 3014-501)

IND (Application) - An investigational new drug application for purposes of this part. "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." (21 CFR 312.3(b)) (This definition is cited in Policy 3014-500)

Individual or Institutional Investigator Agreement (IIA) – An agreement between the NIH and a non-NIH investigator that extends the NIH Federalwide Assurance (FWA) to either an individual investigator or to institutional investigators who are not covered by an FWA (e.g., physicians in private practice or individuals who work at an institution that does not have an FWA). (This definition is cited in Policy 3014-207)

Individually Identifiable *(Pre-2018 Common Rule)* – When the identity of the subject is or may be readily ascertained by the investigator or associated with the information (45 CFR 46.102). (This definition is cited in Policy 3014-107)

Informed Consent - The agreement by a subject (or their Legally Authorized Representative) to participate, or continue participation, in human subjects research. Informed consent may be written or oral. It includes the ongoing process of information exchange that takes place between the subject and the investigator throughout research participation. The purpose of informed consent is to provide the subject information about the research (e.g., the purpose, a description of the research interventions, risks and benefits, if any) in a manner that facilitates the subject's comprehension, such that the subject can make an informed and voluntary decision whether to participate or continue participation in the research, or to withdraw from the research. (This definition is cited in Policy 3014-301)

Informed Consent Document – The IRB-approved written record that is in compliance with 45 CFR 46 and as applicable, 21 CFR 50 Subparts B and D, and is used to demonstrate the consent by a subject/Legally Authorized Representative to participate in research. (This definition is cited in Policy 3014-301)

Initial Review – The first submission of a research protocol for review of exempt or non-exempt human subjects research. (This definition is cited in Policies 3014-204 and 3014-205)

Institutional Biosafety Committee (IBC) – An advisory body to the Division of Occupational Health and Safety (DOHS), Office of Research Services (ORS). This committee reviews basic and clinical research involving recombinant Deoxyribonucleic Acid (DNA), including human gene transfer, or potentially infectious/toxic materials to ensure that proper containment and biosafety practices are employed. This Committee provides recommendations to the Director of the NIH or his designee, and the Deputy Director of Intramural Research (DDIR), in matters pertaining to the control of hazards associated with the intramural use of microbiological agents, their vectors, and associated recombinant and synthetic molecular technologies. (NIH Policy Manual Chapter 1340). (This definition is cited in Policy 3014-106)

Institutional Official (IO) – The individual who is legally authorized to act for the institution and can obligate the institution to the terms of the Federalwide Assurance (FWA). The Institutional Official (IO) is the signatory on the FWA which is on file with the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP). (This definition is cited in Policies 3014-101 and 3014-207)

Institutional Review Board (IRB) – Any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. However, for the purposes of NIH Human Research Protection Policy (HRPP) policy, IRB review includes additional types of human subjects research (e.g. socio-behavioral) and is not limited to biomedical research. (This definition is cited in Policy 3014-200)

Investigation *(Clinical Investigation of a Device)* – A clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (21 CFR 812.3(h)) (This definition is cited in Policy 3014-501)

Investigational Device – A device, including a transitional device, that is the object of an investigation. (21 CFR 812.3(g)) (This definition is cited in Policy 3014-501)

Investigational New Drug – A new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used *in vitro* for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part. (21 CFR 312.3(b)) (This definition is cited in Policies 3014-500 and 3014-502)

Investigator *(FDA)* – 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. (21 CFR 312.3(b)) (This definition is cited in Policy 3014-300)

Investigator *(For Research Involving Investigational Drugs)* – 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. (21 CFR.312.3(b)) (This definition is cited in Policy 3014-500)

Investigator *(Office of Human Research Protections and NIH)* – An individual who is involved in the conduct of human subjects research. Such involvement would include:

1. obtaining information about living individuals by intervening or interacting with them for research purposes;
2. obtaining identifiable private information about living individuals for research purposes;
3. obtaining the voluntary informed consent of individuals to be subjects in research; and
4. studying, interpreting, or analyzing identifiable private information or data for research purposes.

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. (For more information see the OHRP Investigator Responsibilities FAQs.)

At the NIH, this term also includes study coordinators and may also include other individuals as determined by the NIH Principal Investigator (PI). (This definition is cited in Policy 3014-300)

Back to top

Lead Associate Investigator (LAI) – An individual who plays a leading role in the formulation, writing, and implementation of a clinical research protocol under the mentorship and supervision of the protocol's Principal Investigator (PI). (This definition is cited in Policy 3014-300)

Lead Site Investigator – The lead investigator responsible for the conduct of research at a participating site on a multi-site protocol. If at the NIH, this investigator will be referred to as the NIH PI and will have responsibilities of a PI under NIH policy. (This definition is cited in Policy 3014-300)

Legally Authorized Representative ***(LAR) (2018 Common Rule)*** **-** 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. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in

the research. (45 CFR 46.102(i)) (This definition is cited in Policies 3014-301, 3014-403 and 3014-502)

Legally Authorized Representative *(LAR) (FDA Definition)* - An individual or judicial or other body authorized under applicable law to consent on behalf of a subject to the subject's participation in the procedure(s) involved in the research. (21 CFR part 50.3(l)) (This definition is cited in Policy 3014-502)

Legally Authorized Representative *(LAR)* (Pre-2018 Common Rule) – 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. (45 CFR 46.102(c)) (This definition is cited in Policies 3014-301 and 3014-403)

Legally Effective - Informed consent is legally effective if it is both obtained from the subject (or the subject's legally authorized representative) and documented in a manner that is consistent with the US Department of Health and Human Services (HHS) protection of human subjects regulations, FDA regulations, and with applicable laws of the jurisdiction in which the research is conducted. (This definition is cited in Policy 3014-301)

Letter of Authorization (LOA) – A letter permitting FDA to refer to the company's Investigation New Drug (IND) or Investigational Device Exemption (IDE) file to provide certain necessary information about the investigational medical product (e.g., chemistry, manufacturing, controls) for the individual patient expanded access IND or IDE submitted by the applying licensed physician. The company should include the IND or IDE number for its investigational medical product in the LOA. (See Expanded Access Keywords, Definitions and Resources.) (This definition is cited in Policy 3014-502)

Limited Institutional Review Board (IRB) Review (*2018 Common Rule*) – Review by limited IRB procedures to ensure exempt research meets the requirements referenced at 45 CFR 46.104 and 46.111(a)(7) or 46.111(a)(8). (This definition is cited in Policy 3014-204)

Local Context – The unique institutional (or site-specific) requirements and information, including protocol-specific information, to be considered by the IRB in its review of research. For example, local context attests to the adequacy of research team training and qualifications, the resources available to the Principal Investigator to conduct the study, and any other relevant information to be considered by the IRB. (This definition is cited in Policy

3014-105)

Back to top

Medical Advisory Investigator (MAI) – The "Medical Advisory Investigator" (MAI) is the person appointed to assist the PI in the development of clinical aspects of the protocol and is responsible for ensuring that the provision of any clinical interventions mandated by the protocol are conducted appropriately and safely. (This definition is cited in Policy 3014-300)

Medical Monitor (also known as Safety Monitor) – A health care professional capable of overseeing the progress of the research protocol, especially individual subject management and safety. Depending on the level of risk, the IRB may require that the medical monitor be independent of the investigative team. The medical monitor must possess sufficient educational and professional experience to serve as the subject advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more phases of a research project. (This definition is cited in Policy 3014-503)

Minimal Risk – The probability and magnitude of harm or discomfort anticipated in the 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(i) (pre-2018 Common Rule), 45 CFR 46.102(j) (2018 Common Rule) and 21 CFR 50.3(k) (FDA regulations). (This definition is cited in Policies 3014-204, 3014-303, 3014-402 and 3014-403)

Minimal Risk *(for Prisoner Research under Subpart C)* - The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. (45 CFR 46.303(d)). At NIH, this is interpreted to mean healthy persons who are not incarcerated.

Note: The definition of "minimal risk" for research under Subpart C differs from the definition of minimal risk for other human subjects research; compare 45 CFR 46.102(j) (Subpart A) with 45 CFR 46.303 (Subpart C). (This definition is cited in Policies 3014-204 and 3014-401)

Minor Changes – Changes to the research that do not have the potential to adversely impact the risk/benefit assessment and does not substantially alter the research aims. (This definition is cited in Policy 3014-204)

Modification (previously referred to as an Amendment) – A proposed modification of previously approved exempt research, previously exempt research for which Limited Institutional Review Board (IRB) review is required, or previously approved non-exempt human subjects research. (This definition is cited in Policies Policy 3014-204 and 3014-205)

Multi-site Research - Use of the same protocol to conduct non-exempt human subjects research at more than one site. (NIH Single IRB Policy) (This definition is cited in Policy 3014-105)

Back to top

Neonate – A newborn. (45 CFR 46.202(d)) (This definition is cited in Policy 3014-400)

NIH Executive Institutional Review Board (IRB) Chair – The individual in the NIH Office of Human Subjects Research Protections (OHSRP) who oversees the IRB Chairs. This individual assists the Director of the OHSRP Office of IRB Operations and the OHSRP Director in supporting the mission of the NIH Human Research Protection Program (HRPP). (This definition is cited in Policy 3014-101)

NIH Federal Employee – NIH Federal employees include those NIH staff with an appointment to the federal government pursuant to, for example, Title 5, 38 or 42, or the Commissioned Corps, and may include some fellows. Personnel appointed at NIH through an Intergovernmental Personnel Act (IPA) agreement and Special Governmental Employees (SGEs) working at NIH are considered NIH federal employees for the purposes of this policy.

(This definition is cited in Policies 3014-202 and 3014-300)

NIH Human Research Protection Program (HRPP) - The NIH HRPP is made up of certain NIH Institutes' and Centers' (ICs) intramural programs, NIH officials, the NIH Institutional Review Board (IRB), NIH Investigators who conduct exempt and non-exempt human subjects research, and those who provide support for research protocols involving human subjects. (This definition is cited in Policies 3014-100 and 3014-101).

NIH Institutional Review Board (IRB) - A system of IRB panels within the NIH Human Research Protection Program (HRPP) overseen by the Director of the Office of Human Subjects Research Protections (OHSRP) and the Executive IRB Chair. (This definition is cited in Policy 3014-101)

NIH Institutional Review Board (IRB) Executive Chair - The individual in Office of Human Subjects Research Protections (OHSRP) who oversees the IRB Chairs. This individual assists the Office of IRB Operations (IRBO) Director and the OHSRP Director in supporting the mission of the NIH Human Research Protection Program (HRPP). (This definition is cited in Policy 3014-101)

NIH Intramural Research Program (IRP) - The IRP consists of separately funded programs within the Institutes and Centers (ICs) of the NIH. The IRP is the internal research program of the NIH whose investigators conduct exempt and non-exempt human subjects research. (This definition is cited in Policies 3014-100 and 3014-101)

NIH Investigator – An NIH federal employee (intramural or extramural), Special Volunteer, Intramural Research Training Awardee (IRTA), Cancer Research Training Awardee (CRTA) or Visiting Fellow (VF) who is conducting NIH human subjects research on behalf of the NIH. This may include a contractor in accordance with Policy 3014-100. (This definition is cited in Policies 3014-100, 3014-103, 3014-104, 3014-105, 3014-106, 3014-107, 3014-109, 3014-200, 3014-203, 3014-206, 3014-207, 3014-300, 3014-301, 3014-303, 3014-404, 3014-500, 3014-501, 3014-700, 3014-801, and 3014-802)

NIH Senior Employee (Institutional leader) – The Director and the Deputy Director of the National Institutes of Health; members of the senior staff within the Office of the Director who report directly to the NIH Director; the Directors, the Deputy Directors, Scientific Directors, and Clinical Directors of each Institute and Center within NIH, and any employee

of equivalent levels of decision-making responsibility who is designated as a senior employee by the designated agency ethics official or the NIH Director, in consultation with the designated agency ethics official. (This definition is cited in Policy 3014-102)

NIH Single Institutional Review Board (sIRB) Policy – The NIH policy that mandates the use of a single IRB (sIRB) by all domestic sites participating in multi-site studies funded by the NIH, where each site will conduct the same protocol involving non-exempt human subjects research. This policy applies whether the research is supported through NIH grants, cooperative agreements, contracts, or the NIH Intramural Research Program. It does not apply to NIH career development, research training or fellowship awards. (NIH Single IRB Policy) (This definition is cited in Policy 3014-105)

NIH Staff ***(For purposes of Policy 3014-404 only)*** – An employee defined by 5 USC §2105, an NIH contractor, a Special Volunteer, a Guest Researcher, or a trainee. (This definition is cited in Policy 3014-404)

Non-Compliance – Failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.

1. *Continuing non-compliance* - A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different non-compliant events. Such non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).
2. *Serious non-compliance* - Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

(This definition is cited in Policies 3014-500, 3014-801 and 3014-802)

Non-federal IRB Members – Any IRB member who is not employed by the federal government. For example, contractors and Intramural Research Training Awardees (IRTAs),

Special Volunteers, or certain unaffiliated IRB members. (This definition is cited in Policy 3014-202)

Non-NIH Employee *(for NIH Institutional Review Board (IRB) Membership)* – A Non-NIH employee includes a Co-Principal Investigator, a Guest Researcher, a Special Volunteer, a contractor, an Intramural Research and Cancer Research Training Awardee, a collaborator from academia and industry when not an Intergovernmental Personnel Act appointee and, for purposes of *Policy 3014-202*, those who are retired, or another non-employed person in addition to those employed by private industry. (This definition is cited in Policy 3014-202)

Non-NIH Federal Employees – Individuals who are employed by a federal agency other than the NIH. This includes individuals employed at other components of DHHS as well as other Executive Branch agencies. (This definition is cited in Policy 3014-202)

Non-NIH Investigator *(For the purposes of Policy 3014-103)* - An individual who is not an NIH employee, who is conducting Human Subjects Research (HSR) at a non-NIH site when the NIH Institutional Review Board (IRB) is the Reviewing IRB. (This definition is cited in Policy 3014-103)

Non-Significant Risk (NSR) Device – An investigational device that is not a significant risk device as defined at 21 CFR 812.3(m). (This definition is cited in Policy 3014-501)

Nonviable Neonate – A neonate after delivery that, although living, is not viable. (45 CFR 46.202(e)) (This definition is cited in Policy 3014-400)

Back to top

Office of Human Subjects Research Protections (OHSRP) – An Office within the NIH Office of the Director (OD) that reports to the NIH Institutional Official (IO) who is the

Deputy Director for Intramural Research (DDIR). The OHSRP carries out the day-to-day operations and regulatory oversight of human research activities within the Human Research Protection Program (HRPP) via a delegation from the DDIR to the Director of OHSRP. (The organizational structure of the OHSRP is depicted in Policy 3014-101, Appendix 1, *Organizational Structure of the NIH OHSRP.)* (This definition is cited in Policy 3014-101)

Office of Compliance and Training – The Office of Human Subjects Research Protections (OHSRP) office responsible for review and management of reportable events that occur during the conduct of Intramural Research Program (IRP) human subjects research (HSR) activities. This office conducts: (a) noncompliance investigations, and (b) Quality Assurance (QA)/Quality Improvement (QI) reviews of NIH Institutional Review Board (IRB) activities. This office also provides education and training related to human subjects protections policies and procedures. (This definition is cited in Policies 3014-101 and 3014-802)

Office of IRB Operations (IRBO) – The Office of Human Subjects Research Protections (OHSRP) office that manages the NIH Institutional Review Board (IRB) for the NIH Intramural Research Program (IRP). (This definition is cited in Policy 3014-101)

Office of Policy – The Office of Human Subjects Research Protections (OHSRP) office that writes Human Research Protection Program (HRPP) policies and manages accreditation activities for the NIH HRPP. (This definition is cited in Policy 3014-101)

Office of Research Support and Compliance (ORSC) – The office, located within the NIH Clinical Center (CC) and which reports to the Chief Executive Officer (CEO) of the NIH CC, that ensures the quality and integrity of clinical research and product manufacturing/compounding conducted at the NIH by providing regulatory and compliance support and guidance for all NIH researchers in the areas of protocol navigation and coordination, quality assurance auditing and monitoring, support for FDA regulated studies and centralized facility oversight. (This definition is cited in Policy 3014-101)

Office of Technology Transfer (Tech Transfer or OTT) – The Office, within the Office of Intramural Research (OIR), that dockets new inventions made by the NIH (and, as requested, the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC)), asserts patent rights against infringers, monitors and enforces the terms of technology licenses, pursues and administers royalties received from licensees, and encourages commercial development of new products and services that will benefit public health. (This definition is cited in Policy 3014-106)

Back to top

Parent – A child's biological or adoptive parent. (45 CFR 46.402(d)) (This definition is cited in Policy 3014-402)

Participating Site – A research site in a multi-site study that is conducting human subjects research on the same project. (This definition is cited in Policy 3014-105)

Permission - The agreement of parent(s) or a guardian to the participation of their child or ward in research. (45 CFR 46.402(c)) Permission and assent are ongoing and should be assessed throughout the study. (This definition is cited in Policy 3014-402)

Personally Identifiable Information (PII) – Information about an individual maintained by an agency, including, but not limited to, education, financial transactions, medical history, and criminal or employment history and information which can be used to distinguish or trace an individual's identity, such as their name, social security number, date and place of birth, mother's maiden name, biometric records, etc., including any other personal information which is linked or linkable to an individual. (This definition is cited in Policy 3014-107)

Pregnancy – The period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery. (45 CFR 46.202(f)) (This definition is cited in Policy 3014-400)

Principal Investigator (PI) – The investigator with the overall responsibility for the design, conduct, and reporting of the research, and must assure both the protocol and the research team's actions are compliant with law, regulation, and NIH policy, even when certain aspects of the research are delegated to other investigators. (This definition is cited in Policies

3014-102, 3014-106, and 3014-300)

Prisoner – Includes any individual who is:

1. Involuntarily confined or detained (ability to leave the institution is restricted) in a penal institution (e.g., prison) having been sentenced to such an institution under a criminal or civil statute;
2. Detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution; or
3. Detained pending arraignment, trial or sentencing. (45 CFR 46.303(c))

(This definition is cited in Policy 3014-401)

Prisoner Representative – An IRB member formally appointed and listed in the Institutional Review Board (IRB) membership roster who has the appropriate background, experience and working knowledge to provide an understanding and appreciation of prison conditions from the prisoner's perspective. (This definition is cited in Policies 3014-201 and 3014-401)

Private Information *(2018 Common Rule)* – 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) [45 CFR 46.102(e)(4)]*. (This definition is cited in Policy 3014-107)

Private Information *(Pre-2018 Common Rule)* – 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 (for example, 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 (45 CFR 46.102(f)(2)). (This definition is cited in Policy 3014-107)

Protocol Deviation (PD) – Any change, divergence, or departure from the IRB-approved research protocol.

1. Major Deviation – Deviation from the IRB-approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to

substantially negatively impact the scientific integrity or validity of the study.
2. Minor Deviation – A Deviation that does not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

(This definition is cited in Policies 3014-500 and 3014-801)

Back to top

Quality Assurance (QA) - A systematic evaluation of program functions to maximize the probability that quality standards are being attained. In the context of *Policy 108 Quality Assurance and Quality Improvement Program for the NIH IRB*, this means auditing the NIH IRB to determine whether they are effectively meeting established NIH policies and regulatory requirements. QA includes a systematic and independent examination of IRB related activities and documents, including IRB operations. (This definition is cited in Policy 3014-108)

Quality Assurance/Quality Improvement Review (QA/QI Review) – A comprehensive, systematic, and independent assessment of the NIH IRB regarding protocol review and approval as well as review of documentation of IRB activities. Such reviews may result in identification of measures that need to be taken to improve IRB compliance, performance, and quality. The types of QA/QI reviews established by the QA/QI program are defined below:

1. *Routine*: A planned periodic QA/QI review to provide a regulatory assessment of the activities of the IRB. The selection of studies uses a random or risk-based approach and may include such factors as study risk, enrollment of vulnerable populations, and degree of external oversight. These reviews may also include attendance by the QA/QI reviewer at a convened IRB meeting(s).
2. *Directed*: A comprehensive or targeted QA/QI review requested by NIH HRPP leadership to provide an assessment of IRB compliance. The review may be focused on one aspect of the IRB review or a broader review of the IRB.

(This definition is cited in Policy 3014-108)

Quality Assurance/Quality Improvement Review (QA/QI Review) of the NIH IRB – A comprehensive, systematic, and independent assessment of the NIH IRB and IRB office (IRBO) actions. (This definition is cited in Policy 3014-101)

Quality Improvement (QI) – The effort to take measures to improve the level of performance of a program, process, or institution. (This definition is cited in Policy 3014-108)

Back to top

(The) Radiation Safety Committee (RSC) – The Committee that provides oversight of the NIH Radiation Safety Program to ensure the safe use of radioactive materials and all sources of ionizing radiation throughout NIH and those NIH-occupied buildings included in the NIH Radiation Safety Program. (This definition is cited in Policy 3014-106)

Radioactive Drug – Any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product" as defined in 21 CFR 600.3(ee). (See 21 CFR 310.3(n)). (This definition is cited in Policy 3014-106)

(The) Radioactive Drug Research Committee (RDRC) – A subcommittee of the Radiation Safety Committee which is authorized by the Food and Drug Administration (FDA) to review and approve the use of certain “non-approved” radioactive drugs for research purposes in humans that would otherwise require review by the FDA in the form of an Investigational New Drug (IND). (This definition is cited in Policy 3014-106)

Recruitment Materials – Information potential subjects will see or hear that is used as part of the research recruitment process, including but not limited to websites, flyers, posters, newspaper ads, television or radio ads, brochures, doctor-to-patient or Investigator-to-subject letters, and social media ads. (This definition is cited in Policy 3014-302)

Recruitment Methods – Methods used to identify potential research subjects, or to draw a potential research subject's attention to participation in research, including but not limited to identification through records review, in-person discussion, and use of recruitment materials. (This definition is cited in Policy 3014-302)

Reliance *(Authorization) Agreement* – An agreement between institutions involved in the same multi-site research that provides a mechanism to delegate IRB review, and that sets forth the authorities, roles, and responsibilities of the IRB and participating institutions. The agreement may apply to a single study or to certain categories of studies. (This definition is cited in Policies 3014-105, 3014-207 and 3014-802)

Relying Institution – An institution participating in multi-site research that cedes Institutional Review Board (IRB) review to an external Reviewing IRB for human subjects research consistent with the terms of a reliance agreement. (This definition is cited in Policies 3014-105 and 3014-107)

Reportable Event – An event that occurs during the course of human subjects research that requires notification to the IRB. For the purposes of this policy, reportable events include non-compliance, unanticipated problems involving risks to subjects or others (also referred to as UPs), major deviations, deaths related or possibly related to research activities, and new information that might affect the willingness of subjects to enroll or continue participation in the study. (This definition is cited in Policy 3014-801)

Required NIH Language – Language included in the NIH informed consent document that is reserved for use by the NIH to describe certain important information to research subjects (e.g., confidentiality protections, research related injury, who to contact for problems or questions, etc.) (This definition is cited in Policy 3014-107)

Research *(2018 Common Rule)* – 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 (45 CFR 46), 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. For purposes of this part, the following activities are deemed not to be research:

1. Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
2. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions. (45 CFR 46.102(l) of the 2018 Common Rule)

(This definition is cited in Policies 3014-100, 3014-200, 3014-204 and 3014-300)

Research (Clinical investigation) ***(For FDA-Regulated Research)*** - 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 FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. For research involving drugs, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. The term does not include experiments that are subject to the provisions of part 58 of this chapter (*21 CFR*), regarding nonclinical laboratory studies. (21 CFR 50.3(c)). (This definition is cited in Policy 3014-200)

Research ***(Pre-2018 Common Rule)*** – A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for the purposes of this policy (45 CFR 46), whether or not they are conducted or supported under a program which is

considered research for other purposes. For example, some demonstration and service programs may include research activities. 45 CFR 46.102(d) (This definition is cited in Policies 3014-100, 3014-200, 3014-204 and 3014-300)

Research Compliance Review Committee (RCRC) – A duly established NIH Institutional Review Board (IRB) that adheres to the membership and committee requirements described in *Policy 3014-201-IRB Membership and Composition*. The RCRC primarily reviews allegations of non-compliance that have been deemed by the office of Compliance and Training to be both credible and potentially serious and/or continuing. As a duly convened committee, the RCRC may exercise the full authority of an IRB including suspension or termination of IRB approval of research. (This definition is cited in Policy 3014-802)

Respondent – The investigator or entity, if any, against whom an allegation of non-compliance is made. (This definition is cited in Policy 3014-802)

Review Finding – A noted deficiency during a Quality Assurance/Quality Improvement QA/QI review. (This definition is cited in Policy 3014-108)

Reviewing Institutional Review Board (IRB) – The IRB responsible for reviewing human subjects research and determining that the research meets the required criteria for approval under the US Department of Health and Human Services (HHS) regulatory requirements at 45 CFR 46 and, as applicable, the pertinent Subparts of 21 CFR. (This definition is cited in Policies 3014-105, 3014-107, 3014-204, 3014-205, 3014-300 and 3014-801)

Back to top

Scientific Review (SR) – The process for reviewing the scientific merit of NIH Intramural Research Program (IRP) protocols before they are submitted for review to an NIH Institutional Review Board (IRB). The scientific review process includes, but is not limited to, evaluation of:

1. The soundness of the research design; and
2. The ability of the research to answer the proposed questions.

(This definition is cited in Policy 3014-106)

Scientist/Non-scientist members – Scientist members are members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline.

1. Non-scientist members are members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline.

(This definition is cited in Policy 3014-201)

Secretary – The Secretary of Health and Human Services (HHS) and any other officer or employee of HHS to whom authority has been delegated. (45 CFR 46.202(g)) (This definition is cited in Policies 3014-400 and 3014-401)

Sector Fund – A mutual fund whose objective is to invest in a particular industry or sector of the economy to capitalize on returns. The fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States (5 C.F.R. § 2640.102(q)). (This definition is cited in Policy 3014-202)

Select Agent Program (SAP) – Located within the Office of Research Services (ORS) Division of Occupational Health and Safety (DOHS) the Biorisk Management branch is the NIH program that manages a range of functions to facilitate research with select agents. (This definition is cited in Policy 3014-106)

Select Agents – Biological agents and toxins that the Federal Select Agent Program (US Department of Health and Human Services (HHS) and US Department of Agriculture (USDA)) has determined pose a severe threat to both human and animal health, to plant health, or to animal and plant products. Any microorganism or toxin capable of harming living organisms or the environment, regardless of its origin (naturally occurring, engineered or synthesized) can be classified as a select agent. (This definition is cited in Policy 3014-106)

Serious Adverse Event (SAE) – Any Adverse Event that:

1. Results in death;
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity;
5. Results in a congenital anomaly/birth defect; OR
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

See Office For Human Research Protection (OHRP) Guidance: Unanticipated Problems Involving Risks & Adverse Events Guidance (2007).

In terms of IND safety reporting, this term is used synonymously with *serious suspected adverse reaction.* (See 21 CFR 312.32(a) for the FDA definition.) (This definition is cited in Policy 3014-801)

Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction (SUSAR) ***(For FDA-Regulated Research)*** – An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (21 CFR 312.32(a)) (This definition is cited in Policy 3014-500)

Serious disease or condition – A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or

recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. (21 CFR 312.300(b)) (This definition is cited in Policy 3014-502)

Significant Risk (SR) Device –An investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. 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
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

(This definition is cited in Policy 3014-501)

Social Behavioral Research – The study of the interactions of biological factors with behavioral or social variables and how they affect each other. This includes, but is not limited to, individual or group characteristics or behavior (e.g., research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior). Methodologies may include basic and applied research; research employing survey, interview, focus group, human factors evaluation. (This definition is cited in Policy 3014-103)

Special Government Employee (SGE) - Individuals that provide temporary service to the Government. SGEs are often recruited because they provide outside expertise or perspectives that might be unavailable among an agency's regular employees. (This definition is cited in Policy 3014-201)

Special Volunteer – An individual who provides research services, direct patient care, clerical support, technical assistance, or any other necessary services for the NIH. Intramural Scientist Emeriti may be Special Volunteers, upon approval by the Board of Scientific Directors and the Deputy Director for Intramural Research, provided that they meet the provisions of this policy. https://oir.nih.gov/sourcebook/personnel/ipds-appointment-mechanisms/scientist-emeritus

(See NIH Manual Chapter "2300-308-1 – Guest Researcher/Special Volunteer Programs.") (This definition is cited in Policies 3014-102, 3014-201, and 3014-202)

Sponsor – A person (or other entity) who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. An entity other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct a clinical investigation that it has initiated is considered to be a sponsor, and the employees are considered to be investigators. (21 CFR 50.3(e)) (This definition is cited in Policy 3014-503)

Sponsor *(for devices)* – A person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. (21 CFR 812.3(n)) (This definition is cited in Policy 3014-501)

Sponsor *(for drugs and biologics)* – A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. (21 CFR 312.3(b)) (This definition is cited in Policy 3014-500)

Sponsor *(For FDA-Regulated Research)* – A person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators. (21 CFR 50.3(e)) (This definition is cited in Policy 3014-502)

Sponsor-Investigator *(for devices)* – An individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any

person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor. (21 CFR 812.3(o)) (This definition is cited in Policy 3014-501)

Sponsor-Investigator *(for drugs and biologics)* – An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor. (21 CFR 312.3(b)) (This definition is cited in Policy 3014-500)

Sponsor-Investigator *(for FDA regulated research)* – 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., corporation or agency. (21 CFR 50.3(f)) (This definition is cited in Policy 3014-502)

Stopping rules – Predetermined guidelines as to when enrollment or study interventions in one or more study arms should be altered or stopped. (This definition is cited in Policy 3014-503)

Study Closure – Closure of a non-exempt human subjects research protocol for which all human subjects activities are complete, and for which access to identifiable private information or identifiable biospecimens, consistent with the purposes described in the IRB-approved protocol has ceased. This includes premature closure with IRB approval that takes into consideration the rights, safety and welfare of any enrolled subjects. (This definition is cited in Policies 3014-204 and 3014-205)

Study Monitor (also known as a Clinical Monitor or Clinical Research Associate) – A qualified and objective individual who reviews the research records and processes to look at the timeliness of accrual and ensure that the trial is being conducted as planned. A study monitor is someone with no direct involvement in the design and conduct of a study. Study monitors inspect regulatory binders (including informed consents and eligibility criteria) and study data (including source documents and case report forms (CRFs)). (This definition is cited in Policy 3014-503)

Subject ***(For the purposes of FDA research for the study of investigational devices)*** – A human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease. (21 CFR 812(p))

1. Biospecimens that are used as part of a clinical investigation of an *in vitro* diagnostic (IVD) device are considered to meet the definition of a human subject, even if they are deidentified. (See Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable for more information.)

(This definition is cited in Policy 3014-501)

Subject ***(For the purposes of FDA research for the study of investigational drugs)*** – A human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease. (21 CFR 312.3(b)) (This definition is cited in Policy 3014-500)

Subordinate – An individual who reports directly to another person in the same section, unit or branch who has authority over the individual. (e.g., team lead/employee relationship) (This definition is cited in Policy 3014-404)

Substantially Affected Organization (SAO) – A biotechnology or pharmaceutical company, a medical device manufacturer; or a corporation, partnership, or other enterprise or entity significantly involved, directly or through subsidiaries, in the research, development, or manufacture of biotechnological, biostatistical, pharmaceutical, or medical devices, equipment, preparations, treatments, or products (5 C.F.R. § 5501.109(b)(10)). (This definition is cited in Policies 3014-102 and 3014-202)

Substantially Affected Organization (SAO) Sector Fund – A sector fund that states in its prospectus the objective of concentrating its investments in the securities of substantially affected organizations. (This definition is cited in Policy 3014-202)

Supervisor – An individual with the authority to evaluate performance, give job assignments, allocate resources, recommend pay raises or promotions, or to hire or fire. (This definition is cited in Policy 3014-404)

Suspension - A directive by the convened IRB to temporarily stop some or all previously IRB-approved research activities (or future enrollment) conducted under an IRB-approved research study.

Synchronous (real-time interactive services) – Using live interactive technologies to provide for real-time information exchange and interactions between the patient and a qualified healthcare provider. The information exchange and interaction provides the potential for continuous, live, audio and visual connectivity between the patient and provider for the entirety of the encounter. (This definition is cited in Policy 3014-303)

Systematic Investigation - A planned investigation that uses standardized methods and/or procedures to study a scientific hypothesis. (This is the official NIH IRP HRPP definition.)

Back to top

Telehealth (for the purposes of Policy 3014-303) – The use of electronic information and telecommunication technologies to support long-distance clinical healthcare, research encounters, patient and professional health-related education, public health preparedness, public health and health education.

- **Telemedicine** (a subset of Telehealth) - the remote delivery of healthcare services and clinical information using telecommunications technology. For the purposes of this policy, this includes a wide array of research and clinical services using internet, wireless, and satellite media.2 This would include teleconsultations, telemonitoring, teleradiology, etc.

(These definitions are cited in Policy 3014-303)

Termination - A directive by the convened IRB to permanently stop all activities in a previously NIH IRB-approved research study. When IRB approval has been withdrawn the

study is closed.

Test Article - Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). (21 CFR 50.3.(j)) (This definition is cited in Policy 3014-200)

Test Article (for FDA Regulated Research) – Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). (21 CFR 50.3(j)) (This definition is cited in Policies 3014-500 and 3014-502)

Transitional Device – A device subject to section 520(l) of the Food, Drug & Cosmetic Act, that is, a device that the Food & Drug Administration (FDA) considered to be a new drug or an antibiotic drug before May 28, 1976. (21 CFR 812.3(r)) (This definition is cited in Policy 3014-501)

Back to top

Unaffiliated Member – An IRB member (whether paid or unpaid), who does not meet the definition of an "Affiliated member". In addition, this member is not an immediate family member of an individual who is affiliated with the NIH. (This definition is cited in Policy 3014-201)

Unanticipated (Unexpected) – An experience that was not expected or previously observed, or is not consistent in nature, severity, or frequency with existing risk information, such as in the investigator's brochure, device manual, research protocol, consent form, or other available information (e.g., Investigation New Drug (IND) application for an investigational drug or Investigational Device Exemption (IDE) application for an investigational device).

Interchangeable with "unexpected". This includes an event or problem occurring in one or more subjects in a research study that is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the event/problem. (This definition is cited in Policy 3014-801)

Unanticipated Adverse Device Effect (UADE) – 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. (21 CFR 812.3(s)) (This definition is cited in Policies 3014-501 and 3014-801).

Unanticipated Problem Involving Risks to Subjects or Others (UP) – Any incident, experience, or outcome that meets **all** 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; and
2. Related or possibly related to participation in the research (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 (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected. (*Policy 3014-801 Reporting Research Events*)

(This definition is cited in Policies 3014-500 and 3014-801)

Undue Influence – An offer of an excessive or inappropriate reward or other overture in order to obtain a certain outcome. (This definition is cited in Policies 3014-200 and 3014-301)

Back to top

Viable – As it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart.

If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of 45 CFR 46 Subpart A and Subpart D of this part. (45 CFR 46.202(h)) (This definition is cited in Policy 3014-400)

Back to top

Ward – A child who is placed under the protection of, and in the legal custody of, the State or other agency, institution, or entity (including guardians), consistent with applicable State or local law. (This definition is cited in Policy 3014-402)

– The team, laboratory, branch, department, group, or office in which staff work. (This definition is cited in Policy 3014-404)

Written, or In Writing *(2018 Common Rule)* – Writing on a tangible medium (e.g., paper) or in an electronic format. (45 CFR 46.102(m)) (This definition is cited in Policy 3014-301)

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[1] Coded means that: 1) a number, letter, symbol, or combination thereof (i.e., the code) has replaced identifying information (such as name or medical record number) that would enable the investigator or any other individuals associated with the investigation, including the sponsor to readily ascertain the identity of the individual to whom the specimen pertains; and

2) a key to decipher the code exists, enabling linkage of the identifying information to the specimen.