SOP: Definitions				
NUMBER	DATE	AUTHOR	APPROVED BY	PAGE
HRP-001.1	01/10/2020	B. DeCausey	L.M. Lee	1 of 8

1 PURPOSE

1.1 This policy establishes the definitions followed by the human research protection program (HRPP). This is a non-exhaustive list and documents from respective regulatory agencies should be referenced for complete definitions where applicable.

2 REVISIONS FROM PREVIOUS VERSION

2.1 None

3 POLICY

3.1 Adverse Event (AE): An adverse event is any untoward or unfavorable physical or psychological harm that occurs in a human research subject that is temporally associated with the subject's participation in the research, regardless if it is related to the research.

3.2 Allegation of Non-Compliance: Allegation of non-compliance refers to an unproved assertion of non-compliance with human subjects policies or regulations.

3.3 Assurance of Compliance (Human Subjects) or Federalwide Assurance (FWA): Assurance of compliance (Human Subjects) or Federalwide Assurance (FWA) refers to a written commitment made by an institution to federal regulators to protect human research subjects and comply with the requirements of the Common Rule.

3.4 Authorization Agreement or Reliance Agreement: An authorization agreement is a document that outlines respective authorities, roles, responsibilities, and communication between an institution/organization providing the ethical review and an institution relying on the ethical review.

3.5 Certificate of Confidentiality: A certificate of confidentiality is a document issued by the Secretary of the U.S. Department of Health & Human Services (HHS) to investigators or institutions engaged in biomedical, behavioral, clinical, or other research during which identifiable, sensitive information is collected. It protects the privacy of individuals who are subjects of such research when the research is funded wholly or in part by the federal government. The authority (Section 2012 of the 21st Century Cures Act, enacted December 13, 2016) specifies the prohibitions on disclosure of names of research participants or any information, documents, or biospecimens that contain identifiable, sensitive information collected or used in research by an investigator or institution with a certificate. If the research is not federally funded, the secretary may issue a certificate to an investigator or institution engaged in such research, upon application. The National Institutes of Health (NIH) automatically provides a certificate to NIH-funded research and recipients no longer need to apply.

3.6 Certification: Certification refers to official notification by the institution to the supporting federal department or agency that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

3.7 Clinical Trial: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more behavioral or biomedical interventions (including placebo or other control arm) to evaluate the effects of the interventions on health-related outcomes.

3.8 Coercion: Coercion refers to an overt threat of harm that is intentionally presented by one person to another in order to obtain compliance.

3.9 Collaborative Study: A collaborative study is a study in which two or more institutions coordinate, with each institution completing a portion of the research activities outlined in a specific protocol.

3.9.1 For Veterans Administration (VA) research, collaborative research includes human subjects research activities involving VA investigators and at least one non-VA institution.

3.10 Conflicting Interest: An individual involved in research review is automatically considered to have a conflicting interest when the individual, their spouse, or their dependent children have any of the following relationships or interests in the sponsor or product/service being tested, or competitor of the sponsor held by the individual or the individual's immediate family:

3.10.1 Involvement in the design, conduct, or reporting of the research

3.10.2 Stock, stock options, or other ownership interest of any value, including in investment vehicles if you directly control the investment decisions made through these vehicles

3.10.3 Compensation of any amount in the past year or of any amount expected in the next year, excluding compensation for costs directly related to conducting research

3.10.4 Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement

3.10.5 Board or executive relationship, regardless of compensation

3.10.6 Any other reason for which the individual believes that it is not possible to be independent and objective

3.11 Continuing Non-Compliance: Continuing non-compliance refers to a pattern of non-compliance that suggests the likelihood that, without intervention, instances of non-compliance will recur; a repeated unwillingness to comply, or a persistent lack of knowledge of how to comply.

3.12 Designated Reviewer: Designated reviewer refers to the IRB chair or an experienced IRB member designated by the IRB chair to conduct non-committee reviews.

3.13 Experienced IRB Member: An IRB member is considered experienced if the IRB chair or HRPP director considers the IRB member to have sufficient experience in and knowledge of conducting IRB reviews.

3.14 Expiration Date: The expiration date refers to the first date after which the protocol is no longer approved. It is the date after the end date of the approval period.

3.15 Finding of Non-Compliance: A finding of non-compliance is a determination (or conclusion) that is reached when a claim of alleged or suspected non-compliance is deemed factual by an investigation that includes a review of the data and information related to the claim.

3.16 Human Research: Human research refers to any activity that either:[1]

3.16.1 Meets the HHS definitions of research and human subjects; or

3.16.2 Meets the Food and Drug Administration (FDA) definitions of research and human subjects.

3.17 Human Subject:

3.17.1 As defined by HHS: A human subject, as defined by HHS, is a living individual about whom an investigator (whether professional or student) conducting research (1) obtains information about a person 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. For the purpose of this definition:

3.17.1.1 Intervention: Intervention refers to procedures by which information or biospecimens are gathered (for example, questionnaire or venipuncture)

[1] The terms "Human Subject Research," "Research Involving Human Subjects," "Clinical Research," "Clinical Investigation," "Clinical Study" and similar phrases are considered to be synonyms for the term Human Research.

and manipulations of the subject or the subject's environment that are performed for research purposes.

3.17.1.2 Interaction: Interaction refers to communication or interpersonal contact between investigator and subject.

3.17.1.3 Private Information: Private information refers to 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 that the individual can reasonably expect will not be made public (for example, a medical record).

3.17.1.4 Identifiable Private Information: Identifiable private information refers to private information for which the identity of the subject is known, either through identifiers associated with the record or when the identity of the subject can be readily ascertained by the investigator.

3.17.1.5 Identifiable Biospecimen: Identifiable biospecimen refers to a biospecimen for which the identity of the subject is known, either through identifiers associated with the record or when the identity of the subject can be readily ascertained by the investigator.

3.17.2 As Defined by FDA: A human subject, as defined by FDA, is an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject can be either a healthy human or a patient. A human subject includes an individual on whose specimen a medical device is used.

3.18 Immediate Family: Immediate family refers to spouse, domestic partner, and dependent children.

3.19 Institutional Official/Organizational Official (IO/OO):

3.19.1 Institutional official (IO) is the term used by HHS to refer the individual who is legally authorized to act for the institution and, on behalf of the institution, obligates the institution to the terms of the assurance. The IO is responsible for ensuring that the HRPP functions effectively and that the institution provides the resources and support necessary to comply with all requirements applicable to research involving human subjects. The IO represents the institution named in the Federalwide Assurance (FWA)2. The Virginia Tech IO is the vice president for research and innovation.

3.19.2 Organizational official (OO) is the term used by AAHRPP to refer to an identified, knowledgeable leader of the HRPP who is responsible for the program and has the authority to implement the program. This individual may rely on others for the interpretation of laws, regulations, codes, and guidance related to the day-to-day operations of the HRPP. The OO should have a basic understanding of the relevant laws, codes, regulations, and guidance that govern research involving human participants. They should understand the responsibilities of an organizational official, and the responsibilities of the IRB, researchers, and research staff in protecting research participants. This individual should be directly involved in the allocation of

[2] https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2008-september-18-letter-attachment/index.html

resources to the HRPP. In some circumstances, more than one individual serves in this capacity3.

3.20 Institutional Profile: An institutional profile is a record of information that an institution keeps about collaborating institutions/organizations for collaborative studies or multi-site studies.

3.21 Investigation: Investigation refers to a searching inquiry for facts; detailed or careful examination.

3.22 Legally Authorized Representative (LAR): Legally authorized representative (LAR) refers to an individual or organization authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research.

3.22.1 If there is no applicable law addressing this issue, then the LAR is the person recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject.

3.22.2 See HRP-013.1 - SOP - LARs, Children, and Guardians for who may serve as a LAR at this institution.

3.23 Minimal Risk: Minimal risk refers to the probability and magnitude of harm or discomfort anticipated in the research that 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.[4]

3.23.1 For research involving prisoners, minimal risk is 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.

3.23.2 For projects under the Department of Defense (DOD) human subjects protections regulations, the definition of minimal risk based on the phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests" shall not be interpreted to include the inherent risks certain categories of human participants face in their everyday life. For example, the risks imposed in research involving human participants focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

3.24 Multi-Site Study: A multi-site study is a study in which two or more institutions coordinate or collaborate, with each institution completing all research activities outlined in a common protocol.

3.25 Non-Committee Review: Non-Committee Review refers to any of the following:

3.25.1 Determination of whether an activity is human subjects research

3.25.2 Determination of whether human subjects research is exempt from regulation

3.25.3 Review of non-exempt research using the expedited procedure

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[3] AAHRPP Evaluation Instrument (2018-10-15); http://www.aahrpp.org/apply/web-document-library/domain-i-organization

[4] The phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" should not be interpreted to include the inherent risks certain categories of subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

3.25.4 Determination of which subjects can continue in expired research

3.25.5 Concurrence of IRB chair or designee, in lieu of obtaining IRB approval at a convened IRB meeting, for non-emergency individual patient/small group expanded access for an unapproved medical device (commonly known as “compassionate use”) or non-emergency individual patient expanded access to investigational drugs

3.26 Non-Compliance: Non-compliance refers to failure to follow the regulations, or the requirements or determinations of the IRB.

3.26.1 In the case of research funded or conducted by the DOD, non-compliance includes failure of a person, group, or institution to act in accordance with DOD instruction 3216.02, its references, or applicable requirements.

3.26.2 In the case of VA research, non-compliance is any failure to adhere to the requirements for conducting VA research covered by the Veteran’s Health Administration Directive.

3.27 Participating Site (pSite): Participating site (pSite) refers to an institution that participates in a multi-site study that uses a single IRB (sIRB) review.

3.28 Prisoner: Prisoner refers to any individual involuntarily confined or detained in a penal institution, including prisons, jails, and detention centers. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes, or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

3.28.1 Inmates and parolees who are detained in a treatment center are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.

3.28.2 For DOD funded research, the term includes military personnel in either civilian or military custody.

3.29 Related to the Research: Related to the research refers to a financial interest in:

3.29.1 A sponsor of the research;

3.29.2 A competitor of the sponsor of the research;

3.29.3 A product or service being tested; or

3.29.4 A competitor of the product or service being tested.

3.30 Research as Defined by HHS:

3.30.1 Research, as defined by HHS, refers to systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

3.30.2 The following activities are not considered research as defined by HHS:

3.30.2.1 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

3.30.2.2 Public health surveillance activities conducted by a public health authority, 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. Public health surveillance includes:

3.30.2.2.1 The collection and testing of information or biospecimens that is conducted, supported, requested, ordered, required, or authorized by a public health authority

3.30.2.2.2 The collection of data related to trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products

3.30.2.2.3 The collection of data associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or human generated disasters)

3.30.2.3 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

3.30.2.4 Authorized operational activities (as determined by the relevant federal agency) in support of intelligence, homeland security, defense, or other national security missions

3.30.2.5 Secondary research involving non-identifiable newborn screening blood spots

3.31 Research as Defined by FDA: Research, as defined by FDA, refers to any experiment that involves a test article and one or more human subjects, and that meets any one of the following:

3.31.1 Must meet the requirements for prior submission to the FDA under section 505(i) of the Federal Food, Drug, and Cosmetic Act meaning any use of a drug other than the use of an approved drug in the course of medical practice;

3.31.2 Must meet the requirements for prior submission to the FDA under section 520(g) of the Federal Food, Drug, and Cosmetic Act meaning any activity that evaluates the safety or effectiveness of a device; or

3.31.3 Any activity, 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.

3.32 Restricted Investigator: A restricted investigator is a researcher who is delinquent in meeting IRB requirements.

3.33 Serious Non-Compliance: Serious non-compliance refers to non-compliance such that the failure to comply could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of research data.

3.33.1 For DOD research serious non-compliance includes failure of a person, group, or institution to act in accordance with DOD Instruction 3216.02 and its references such that the failure could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of research data.

3.33.2 For VA research serious non-compliance is any failure to adhere to requirements for conducting human subjects research that may reasonably be regarded as:

3.33.2.1 Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or

3.33.2.2 Substantively compromising a VA facility's HRPP.

3.34 Single IRB (sIRB) Study: Single IRB (sIRB) study refers to a study in which two or more institutions (participating sites, or pSites) coordinate or collaborate to complete the research

activities, but all institutions rely on a single institution's/organization's IRB for ethical review. The reviewing IRB might or might not be affiliated with any of the pSites.

3.35 Suspension of IRB Approval: Suspension of IRB approval refers to an action of the IRB, IRB designee, IO/OO (or designee) to temporarily or permanently withdraw IRB approval of some or all research procedures short of a termination of IRB approval. Suspended studies remain open and are subject to continuing review.

3.35.1 For VA research, suspension of IRB approval refers to a temporary interruption in selected research activities (e.g., new enrollments or specific interventions) due to concerns about the safety, rights, or welfare of human subjects, research personnel, or others, regardless of whether the action was taken by an investigator, facility official, research review committee, or external entity. It does not refer to interruptions in research for other reasons, including the expiration of project approval periods.

3.36 Systematic: Systematic refers to having or involving a system, consistent method, or plan.

3.37 Termination of IRB Approval: Termination of IRB approval is an action of the IRB, IRB designee, IO/OO (or designee) to permanently withdraw IRB approval of all research procedures. Terminated studies are permanently closed, thus no longer require continuing review.

3.37.1 For VA research, termination of IRB approval refers to a permanent halt in all research activities due to concerns about the safety, rights, or welfare of human subjects, research personnel, or others, regardless of whether the action was taken by an investigator, facility official, research review committee, or external entity. It does not refer to interruptions in research for other reasons, including the expiration of project approval periods.

3.38 Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO): Unanticipated problem involving risks to subjects or others (UPIRTSO) refers to any incident, experience, or outcome that meets the three following conditions:

3.38.1 Is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied;

3.38.2 Is related or possibly related to participation in the research

3.38.2.1 "Possibly related" means there is a reasonable possibility that the incident, experience, or outcome could have been caused by the procedures involved in the research); and

3.38.3 Suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm actually occurred.

3.38.4 For VA sponsored research:

3.38.4.1 Unanticipated problem involving risks to subjects or others includes any serious problem or local serious adverse event (SAE) that is both unanticipated and related to the research.

3.38.4.2 The term "serious problem" includes a problem in human research or research information security that may reasonably be regarded as:

3.38.4.2.1 Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or

3.38.4.2.2 Substantively compromising a VA facility's HRPP or research information security program.

3.38.4.3 A “serious adverse event” (SAE) is an untoward occurrence in human research that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability or incapacity, congenital abnormality, or birth defect, or that requires medical, surgical, behavioral, social, or other intervention to prevent such outcome.

3.38.4.4 The terms “unanticipated” and “unexpected” refer to an event or problem that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol documents and the characteristics of the study population.

3.38.4.5 The term “related” means the problem could reasonably be regarded as caused by, or probably caused by, the research.

3.39 Undue influence: Undue influence refers to an offer of excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance.

4 RESPONSIBILITIES

4.1 Individuals writing policies and procedures are to indicate terms defined in this policy with a double underline.

4.2 Individuals using policies and procedures are to consult this policy for the definitions of double underlined terms.

5 PROCEDURE

5.1 None

6 MATERIALS

6.1 HRP-013.1 - SOP - LARs, Children, and Guardians

7 REFERENCES

7.1 45 CFR §46.102.

7.2 21 CFR §50.3, 21 CFR §56.102, 21 CFR §312.3, 21 CFR §812.2(a), 21 CFR §812.3(p)

7.3 VHA Handbook 1058.01 dated June 15, 2015; VHA Directive 1058, dated March 28, 2017; VHA Directive 1200.05 dated January 7, 2019