1. PURPOSE
   1. This policy establishes the definitions followed by the human research protection program
   2. This is a non-exhaustive list and regulatory agencies should be referenced for complete definitions..
2. REVISIONS FROM PREVIOUS VERSION
   1. None
3. POLICY
   1. Adverse Event (AE): For Veterans Administration (VA) research any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research, whether or not considered related to the subject’s participation in research.
      1. Adverse events are untoward incidents, diagnostic or therapeutic incidents iatrogenic injuries, or other occurrences of harm or potential harm directly associated with care or services provided within the jurisdiction of the Veterans Healthcare System.
   2. Allegation of Non-Compliance: An unproved assertion of Non-Compliance.
   3. Assurance of compliance: (Human Subjects) or Federal Wide Assurance: A legally binding written document that commits an institution to complying with the Federal Policy (Common Rule) and other applicable Federal and VA standards for the protection of human subjects.
   4. Authorization agreement: Also called a Reliance Agreement, is the agreement that documents respective authorities, roles and responsibilities, and communication between an institution/organization providing the ethical review and a participating institution relying on the ethical review.
   5. Certificate of Confidentiality. A Certificate of Confidentiality is a document issued by a component of HHS pursuant to The Public Health Service Act Section 301(d), 42 U.S.C. 241(d) amended by Section 2012 of the 21st Century Cures Act, Public Law 114-255, to protect the privacy of individuals who are subjects of certain specified research activities by authorizing investigators to withhold from all persons not connected with the conduct of such research the names or other identifying characteristics of such subjects. Persons so authorized to protect the privacy of such individuals may not disclose information in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.
   6. Certification: the official notification by the institution to the supporting federal department or agency component that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance
   7. Children: 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.

3.7.1 See HRP-013 - SOP - LARs, Children, and Guardians for applicable law at this institution.

* 1. Clinical Trial: A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or another control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Clinical trials are used to determine whether new therapeutic interventions are safe, efficacious, and effective.
  2. Collaborative study: A Study in which two or more institutions coordinate, with each institution completing a portion of the research activities outlined in a specific protocol.
     1. For Veterans Administration (VA) research, Collaborative (Study) Research involves human subjects research activities involving investigators from VA and at least one non-VA institution. Collaborative Research includes VA and non-VA institutions.
  3. Conflicting Interest: An individual involved in research review is automatically considered to have a conflicting interest when the individual or the individual’s Immediate Family have any of the following:
     1. Involvement in the design, conduct, or reporting of the research.
     2. Ownership interest, stock options, or other ownership interest Related to the Research of any value exclusive of interests in publicly-traded, diversified mutual funds.
     3. Compensation Related to the Research of any amount in the past year or of any amount expected in the next year, including compensation for costs directly related to conducting research.
     4. Proprietary interest Related to the Research including, but not limited to, a patent, trademark, copyright or licensing agreement.
     5. Board or executive relationship, regardless of compensation.
     6. Any other reason for which the individual believes that he or she cannot be independent.
  4. Continuing Non-Compliance: A pattern of Non-Compliance that indicates a deficiency likely to result in further Non-Compliance or a circumstance in which an investigator fails to cooperate with investigating or correcting Non-Compliance.
     1. For Veterans Administration (VA) research Continuing Non-Compliance means repeated instances of noncompliance with applicable laws, regulations, policies, agreements, or determinations of a research review committee or the prolonged persistence of noncompliance occurring after its identification, awareness, or implementation of a corrective action intended to effectively resolve the noncompliance.
  5. Designated Reviewer: The IRB chair or an Experienced IRB Member designated by the IRB chair to conduct Non-Committee Reviews.
  6. Experienced IRB Member: An IRB member is considered experienced if the IRB chair considers the IRB member to have sufficient experience in and knowledge of conducting IRB reviews.
  7. Experimental Subject: For Department of Defense (DOD) research, research involving an “experimental subject” is an activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving “experimental subjects” is a subset of research involving human participants.
  8. Expiration Date: The first date that the protocol is no longer approved. The date after the end date of the approval period.
  9. Finding of Non-Compliance: Non-Compliance in fact.
  10. Guardian: an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.
      1. See HRP-013 - SOP - LARs, Children, and Guardians for applicable law at this institution.
  11. Human Research: Any activity that either:[[1]](#footnote-1)
      1. Is Research as Defined by DHHS and involves Human Subjects as Defined by DHHS; or
      2. Is Research as Defined by FDA and involves Human Subjects as Defined by FDA.
  12. Human Subject as Defined by DHHS: 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. For the purpose of this definition:
      1. Intervention: 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.
      2. Interaction: Communication or interpersonal contact between investigator and subject.
      3. 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 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).
      4. 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.
      5. 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.

The following activities are not considered Research as Defined by DHHS:

* 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.
* 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.
  + Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
  + Including trends, signals, risk factors patterns in diseases, or increases in injuries from usingconsumer products.
  + Including 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).
* 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.
* Authorized operational activities (as determined by the relevant federal agency) in support of intelligence, homeland security, defense, or other national security missions.
* Secondary research involving non-identifiable newborn screening blood spots
  1. Human Subject as Defined by FDA: An individual who is or becomes a subject 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. A human subject includes an individual on whose specimen a medical device is used.
  2. Immediate Family: Spouse, domestic partner; parent, and dependent children.
  3. Institutional Official/ Organizational Official (IO/OO):
     1. Institutional Official (IO): Term utilized by DHHS.
        1. The Institutional Official (IO) is 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 Human Research Protection Program (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]](#footnote-2). The IO at UMB is the Executive Vice President & Provost.
        2. For Veteran’s Administration (VA) research, the Institutional Official (IO) is the individual legally authorized as Signatory Official to commit an institution to an FWA. The Signatory Official assures that human subjects’ research to which the FWA applies is conducted in accordance with the terms of the assurance (see VHA Handbook 1058.03). The Principal Deputy Under Secretary for Health or designee is the IO for VHA Central Office, and VA facility Directors are the IOs for local VA facilities.
     2. Organizational Official (OO): Term utilized by AAHRPP.
        1. 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 and the day-to-day operations of the HRPP, and should have a basic understanding of the relevant laws, codes, regulations and guidance that govern research involving human participants, the responsibilities of an organizational official, and the responsibilities of the IRB or EC and researchers and research staff in protecting research participants. This individual should be directly involved in the allocation of resources to the HRPP. In some circumstances, more than one individual serves in this capacity[[3]](#footnote-3).
  4. Institutional Profile: A record of information an institution keeps about another collaborating institution/organization for one or more Collaborative Studies or Multi-Site Studies.
  5. Investigation: A searching inquiry for facts; detailed or careful examination.
  6. Legally Authorized Representative (LAR): 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 procedures(s) involved in the research.
     1. See “SOP: LARs, Children, and Guardians (HRP-013)” for who may serve as a Legally Authorized Representative at this institution.
  7. Minimal Risk: 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.
     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.
     2. When following Department of Defense regulations, the definition of minimal risk in 32 CFR 219 does not include the inherent occupational risks that certain participants face in their everyday life, such as those:
        1. Encountered by Service members, law enforcement, or first responders while on duty.
        2. Resulting from or associated with high-risk behaviors or pursuits.
        3. Experienced by individuals whose medical conditions involve frequent tests or constant pain.
  8. Multi-Site Study: A study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol.
  9. Non-Committee Review: Any of the following:
     1. Determination of whether an activity is Human Research.
     2. Determination of whether Human Research is exempt from regulation.
     3. Reviews of non-exempt research using the expedited procedure.
     4. Verification that modifications required to secure approval have been made.
     5. Determinations of which subjects can continue in expired research (IRB chair or Vice-Chair only)
     6. Concurrence of IRB Chair or designee 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 IND with request for authorization to use alternative IRB review procedures.
  10. Non-Compliance: Failure to follow the regulations, or the requirements or determinations of the IRB.
      1. In the case of research funded or conducted by the Department of Defense (DOD), Non-Compliance includes failure of a person, group, or institution to act in accordance with Department of Defense (DOD) instruction 3216.02, its references, or applicable requirements
      2. In the case of Veterans Administration (VA) research, Non-Compliance is any failure to adhere to the requirements for overseeing, reviewing, approving, or conducting VA research set forth in law, regulation, policy, or study agreements (such as reliance agreements, memoranda of understanding, data use agreements), including any failure to conduct research in accordance with a VA study protocol approved by a research review committee.
  11. Participating Site (pSite) An institution that participates in a Single IRB (sIRB) Study.
  12. Prisoner: Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentences to such an institution under a criminal or civil statue, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing.
      1. For Department of Defense (DOD) research the term includes military personnel in either civilian or military custody.
  13. Related to the Research: A financial interests is Related to the Research when the interest is in:
      1. A sponsor of the research;
      2. A competitor of the sponsor of the research;
      3. A product or service being tested; or
      4. A competitor of the product or service being tested.
  14. Research as Defined by DHHS: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
  15. Research as Defined by FDA: Any experiment that involves a test article and one or more Human Subjects, and that meets any one of the following:
      1. Must meet the requirements for prior submission to the Food and Drug Administration 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;
      2. Must meet the requirements for prior submission to the Food and Drug Administration 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. Any activity the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.
  16. Restricted: Applies to investigators or research staff members who are delinquent in meeting IRB requirements, including when educational requirements are not fulfilled.
  17. Serious Adverse Event (SAE): An untoward occurrence, whether or not considered related to a subject’s participation in Human Research, that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or that requires medical, surgical, behavioral, social or other intervention to prevent such an outcome.
  18. Serious Non-Compliance: Non-Compliance that adversely affects the rights or welfare of subjects.
      1. For Department of Defense (DOD) research Serious Non-Compliance includes failure of a person, group, or institution to act in accordance with Department of Defense (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.
      2. For Veterans Administration (VA) research Serious Non-Compliance includes any failure to adhere to requirements for conducting Human Research that might reasonably be regarded as:
         1. Presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, or others, including their rights to privacy and confidentiality of identifiable private information; or
         2. Presenting a genuine risk of substantive harm to the safety, rights, or welfare of research personnel who conduct research.
         3. Presenting a genuine risk of substantive reputational harm to the veterans Administration (VA)
         4. Substantively compromising the effectiveness of a Veterans Administration (VA) facility’s human research protection program (HRPP).
  19. Single IRB (sIRB) Study: A study in which two or more institutions (participating sites, or pSites) coordinate to complete the research activities, but all institutions rely on a single institution’s/organization’s IRB for ethical review. The reviewing IRB may or may not be affiliated with any of the pSites
  20. Suspension of IRB Approval: An action of the IRB, IRB designee, Institutional Official/Organizational Official, or designee of the Institutional Official/Organizational Official 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, as applicable.
      1. For Veterans Administration (VA) Research Suspension of IRB Approval:
         1. Refers to a temporary interruption in the enrollment of new subjects, activities involving previously enrolled subjects, or other research activities.
         2. Applies to interruptions related to concerns regarding the safety, rights, or welfare of human subjects, research investigators, research staff, or others.
         3. Do not include interruptions in research resulting solely from the expiration of a project approval period, and voluntary interruption of research enrollments, and ongoing research activities by an appropriate VA facility official, research investigator, or sponsor (including the Office of Research and Development (ORD) when ORD is the sponsor).

3.37 Systematic:

* 1. Termination of IRB Approval: An action of the IRB, IRB designee, Institutional Official /Organizational Official, or designee of the Institutional Official /Organizational Official to permanently withdraw IRB approval of all research procedures. Terminated studies are permanently closed and no longer require continuing review.
     1. For Veterans Administration (VA) research, Termination of IRB approval:
        1. Refers to a permanent halt in all 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.
        2. Does not refer to interruptions in research for other reasons, including the expiration of project approval periods.
  2. Unanticipated Problem Involving Risks to Subjects or Others: Any information that is (1) unanticipated and (2)related to the research , and (3) indicates that subjects or others are at increased risk of harm.
     1. For Department of Defense (DOD) research the term Unanticipated Problem Involving Risks to Subjects or Others includes any incident, experience, or outcome that meets ALL three of the following conditions:
        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.
        2. Is related or possibly related to participation in the research (in this Instruction, 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).
        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 has actually occurred.
     2. For Veterans Administration (VA) research:
        1. Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) is an incident, experience or outcome that is: unexpected; related or possibly related to participation in the research; and indicative of the research placing subjects or others at substantively greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.
        2. The term “unexpected” refers to an incident, experience, or outcome that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.
        3. The phrase “related to participation in the research” means a logical sequence of cause and effect shows that the study procedures were the reason for the incident, experience, or outcome. The phrase “possibly related to participation in the research” implies a lesser degree of certainty about causality and refers to an incident, experience, or outcome for which there is some evidence to reasonably suggest a causal relationship between study procedures and the incident, experience, or outcome.
        4. An unexpected SAE that is related or possibly related to participation in human subjects research constitutes a UPIRTSO.

1. RESPONSIBILITIES
   1. Individuals writing policies and procedures are to indicate terms defined in this policy with a double underline.
   2. Individuals using policies and procedures are to consult this policy for the definitions of double underlined terms.
2. PROCEDURE
   1. None
3. MATERIALS
   1. SOP: LARs, Children, and Guardians (HRP-013)
4. REFERENCES
   1. 45 CFR §46.102.
   2. 21 CFR §50.3, 21 CFR §56.102, 21 CFR §312.3, 21 CFR §812.2(a), 21 CFR §812.3(p)
   3. VHA Handbook 1058.01 dated October 22, 2020; VHA Directive 1004.08 dated October 31, 2018; VHA Directive 1200.05 dated January 7, 2019, amended January 8, 2021; VHA Directive 1058.03 dated September 17, 2020.
   4. AAHRPP elements I.1.A, I.1.E, I.5.D, I.6.B, I.7.C, I-9, II.1.D, II.2.A, II.2.B, II.2.G, II.2.H, II.2.E-II.2.E.2, II.2.F-II.2.F.3, II.2.I, II.3.A, II.4.A, III.1.B, III.2.D

1. The terms “Human Subject Research,” “Research Involving Human Subjects,” “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. [↑](#footnote-ref-1)
2. https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2008-september-18-letter-attachment/index.html [↑](#footnote-ref-2)
3. AAHRPP Evaluation Instrument (2018-10-15); http://www.aahrpp.org/apply/web-document-library/domain-i-organization [↑](#footnote-ref-3)