U.S. Army Medical Research and Development Command
Office of Research Protections
Human Research Protection Office

Guidance on HRPO Review Requirements for Research Involving the Secondary Use of Data/Specimens

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Background.

All United States Army Medical Research and Development Command (USAMRDC) supported research (hereafter referred to as Department of Defense (DoD) -funded) involving the secondary use of human data, records, human tissue, or human biospecimens (henceforth referred to as data/specimens) must undergo review for compliance with Federal and DoD human subjects protection requirements and receive written approval by the USAMRDC Office of Research Protections (ORP) Human Research Protection Office (HRPO) prior to implementation. The USAMRDC ORP HRPO review includes assessing the source of the data/specimens and whether the initial manner and consent for the data/specimen collection permits use in the DoD-funded research. Additionally, the ORP must review the use of all research uses of post-mortem specimens for compliance with the Army Cadaver Use Policy.

For the purpose of this guidance, the term human specimens refers to the research use of any human anatomical substances, cells, cell lines, or organoids obtained or derived from humans, either living or post-mortem.

The HRPO's review and approval of data/specimen research is based upon the nature of the research, the source and identifiability of the data/specimens, privacy and confidentiality protections, and whether the individuals providing the data/specimens allowed the use of their data/specimens for research. Additional HRPO submission instructions and guidance follow below.

IMPORTANT NOTE: The research protocol submitted for HRPO review MUST only include those activities funded by the DoD, as reflected in the approved Statement of Work (SOW). The HRPO will NOT accept protocols submitted for DoD funded activities for review if the DoD-funded work has been added to an ongoing/existing protocol. For the use of any data/specimens obtained from biorepositories, core facilities, or similar, the HRPO <u>requires</u> that investigators submit a stand-alone protocol that details ONLY the data/specimen use funded by the DoD.

HRPO Submission Form for Secondary Research Use.

For HRPO review of any DoD-funded research activities involving access, use, and analysis of data/specimens, investigators must complete and submit the HRPO Submission Form -- Secondary Research Involving the Use of Data/Specimens found here: https://mrdc.amedd.army.mil/index.cfm/collaborate/research_protections/hrpo. The Submission Form identifies the documents to include with the submission.

U.S. Food and Drug Administration (FDA)-regulated Research.

If data collected from the DoD-funded research uses human biospecimens (even those obtained without identifiers or purchased from a commercial vendor) and will be part of a submission to the FDA or held for later submission to the FDA, in support of an application for FDA clearance or approval, the FDA and HRPO require prospective Institutional Review Board (IRB) review and approval of the research. A regulatory determination of "research not involving human subjects" or "exempt human subjects research" will not suffice.

I. Specimen Research that <u>Does Not Require</u> HRPO Review Prior to Implementation.

- The exceptions described in Sections I.A., B., and C. of this guidance apply only to the specified commercially available human products, and not to other commercially available human anatomical

substances. The HRPO requires review of use of all other commercially available human anatomical substances per section II.B. below.

A. Commercially available CELL LINES.

When the research solely involves use of commercially available cell lines (please see additional information that follows), it does not require submission for HRPO review. HRPO has determined that the use of commercially available cell lines by investigators does not meet the regulatory definition of human subjects research. Investigators and DoD Program Management staff members (e.g., Science Officers) do not need to forward materials in support of this category of research to the HRPO for review.

- Use of commercially available human embryonic cell lines **DOES** require HRPO review, with the exception of commercially available HEK 293 cell lines. See Section II.I. for HRPO requirements for the use of human embryonic cell lines.

- If an investigator can purchase or obtain the cell lines from a vendor, the HRPO considers the cell lines commercially available. The vendor source can include a for-profit, not-for-profit, or academic entity that provides cell lines commercially.

- If the investigator obtained/will obtain the cell line(s) from a collaborator and the collaborator purchased the cell lines from a commercial vendor, the cell lines are considered commercially available.

- Commercially available cells line that have been modified (e.g., a gene not originally present in the cell line has been added via stable transfection, a gene has been mutated or knocked out via CRISPR, etc.) also do not require HRPO review.

- The following are examples commercial vendors:

American Type Culture Collection
National Center for Biotechnology Information
National Disease Research Interchange

- The use of commercially available *cadaveric* cell lines does <u>not</u> require HRPO review. See Section II.H. for HRPO requirements for use of other cadaveric and post-mortem specimens.

B. Commercially available ORGANOIDS.

When the research solely involves use of commercially available organoids, it does not require submission for HRPO review.

Use of commercially available organoids derived from human embryonic cell lines or fetal tissue **DOES** require HRPO review. See Section II.I. for HRPO requirements for the use of human embryonic cell lines.

C. Commercially procured POOLED human products.

When the research solely involves use of commercially procured **pooled** human products (e.g., serum, plasma, red blood cells, urine, cerebrospinal fluid), it does not require submission for HRPO review. This exception does not apply to use of commercially available single donor products.

D. Established, existing patient-derived xenograft (PDX) models.

The use of established, existing PDX models and/or the creation of cell lines from established, existing PDX models does not require HRPO review. A xenograft is a surgical graft of tissue from one species to another species (e.g., tissue from a patient's cancerous tumor implanted directly into a mouse).

- The research use of established, existing PDX models (e.g., mouse models) does require institutional animal use and USAMRDC ORP Animal Care and Use Review Office (ACURO) review (https://mrdc.amedd.army.mil/index.cfm/collaborate/research_protections/acuro).

E. Commercial services.

HRPO does not need to review when a DoD-funded organization receives samples to perform analyses as a commercial service to another organization. For example, Quest Diagnostic Laboratory providing routine serology diagnostic support to a DoD funded clinical trial does not require a separate HRPO review and determination.

II. Secondary Human Data/Specimens Research that Requires HRPO Review Prior to Implementation.

For the items listed in paragraphs 2.A. – 2.I. below, the HRPO requires submission of:

a. Completed HRPO Submission Form -- Secondary Research Involving the Use of Data/Specimens (and/or Cadaver Use Submission Form, if applicable);
b. A standalone protocol/protocol application limited to the sources and research analyses as described in the approved DoD SOW; and
c. Documentation of an institutional regulatory office determination or IRB approval of the DoD-funded research activities. Self-determination or self-certification by the Principal Investigator will not suffice for HRPO review.

- **For research with data/specimens that the researchers will collect prospectively and solely for research purposes:** Investigators should refer to the guidance *HRPO Information for Investigators* and complete the HRPO Submission Form for Human Subjects Research found on the HRPO website (https://mrdc.amedd.army.mil/index.cfm/collaborate/research_protections/hrpo).

A. Established cell lines that have been published and are otherwise freely available but cannot be purchased from a vendor.

These cell lines are NOT commercially available as defined by the HRPO. Therefore, the use of these cell lines requires review by the HRPO.

B. Commercially available human anatomical substances.

Commercially available non-pooled human biospecimens such as peripheral blood mononuclear cells, primary cells, blood, saliva, tissue, etc., are NOT included in the exemption from HRPO review for

commercially available human products. Therefore, the use of commercially available human anatomical substances requires review by HRPO.

C. Creating new PDX models.

HRPO submission and review is required when the researcher uses DoD funding to combine human specimens (e.g. cell lines, tissue) with non-human material to create a xenograft for research use.

D. Secondary use of data/specimens, e.g., from clinical trials/other research studies.

HRPO review is required for secondary research use of:

- Existing human data/specimens (to include publically available data/specimens)
- Data/specimens that *will* be collected and for which the institution has determined that the research is exempt under Category 4 of the Common Rule's exempt categories [.104(d)(4)]

E. Research involving excess clinical samples obtained/to be obtained from medical facility clinical departments/services (e.g., excess or surgical discarded materials obtained from clinical laboratories (including pathology) or clinical care areas, such as operating suites)

HRPO must review any DoD-funded research use of excess clinical samples, including pathology samples.

F. Research involving use of clinical data/specimens obtained from established institutional clinical repositories, biobanks, or tumor banks.

Consent forms for data/specimens obtained from established institutional repositories, registries, or tissue banks are NOT required to be included in the submission for HRPO review. These entities have institutional procedures in place to ensure that the samples were collected with the appropriate consent of subjects and permitted release of data/specimens for research. If necessary during review, HRPO will request institutional procedures or confirm the institution has oversight of the repository.

G. Secondary data/specimen research and collaborators.

Investigators must provide complete information on collaborative efforts to include the source of data/specimens, the role of collaborators, purposes of the collaboration, and the investigators' access to identifiable data/specimens. This includes all collaborators at the awardee institution or those at external sites.

- Multi-institutional research collaborations funded by the DoD: each institution conducting research will require a protocol approved by the reviewing IRB (single IRB requirements apply) or institutional regulatory office, and will receive separate HRPO review and approval. Each site must complete the HRPO Submission Form for Secondary Research and provide supporting documents.

- Awardee institution internal collaboration: describe the sources and types of data/specimens received from individuals or departments at your institution within the protocol, application, or project description submitted to the IRB or institutional regulatory office.

- Data/specimen source institutions: describe the sources and types of data/specimens received from external institutions within the protocol, application, or project description submitted to the IRB or institutional regulatory office. Provide a copy of the informed consent document used to obtain

the data/specimens at the source institution if the data/specimens were collected under a research protocol.

- When collaborators provide analyses of data/specimens for the awardee institution: describe the analysis of data/specimens by collaborators within the protocol, application, or project description submitted to the IRB or institutional regulatory office.

H. Research involving use of cadavers and post-mortem human specimens.

The ORP reviews all projects involving cadavers in accordance with the 2019 Army Policy for Use of Human Cadavers for Research, Development, Test and Evaluation, Education or Training found here: https://mrdc.amedd.army.mil/index.cfm/collaborate/research_protections. In this policy, the term "cadaver" includes organs, tissue, bones, or other specimens obtained from an individual upon or after death.

All research using cadaveric and post-mortem human specimens requires submission of the USAMRDC ORP Cadaver Use Submission Form found here: https://mrdc.amedd.army.mil/index.cfm/collaborate/research_protections/hrpo.

The ORP requires an institutional approval from the organization performing work with cadaveric specimens. A determination, such as an "exempt" or "research not involving human subjects" determination from the IRB or IRB Office, is not sufficient to document institutional approval.

- If there is no specific oversight committee at the performing institution for research with cadaveric specimens, a letter from the investigator's department leadership, dean, environmental health office, or similar satisfies the requirement for institutional approval when the letter states that the investigator has met all institutional requirements to conduct the proposed project.

The HRPO requires the investigator to identify the source of the cadaveric specimens and provide the template specimen donation form in use by that organization. This allows HRPO to confirm that the proposed research is reasonably consistent with donor intent.

The HRPO also requires that the investigator provide basic information related to the physical security, safe handling, transportation, and disposition of cadaveric specimens.

Activities meeting the Army policy definition of "sensitive uses" (i.e., exposure of cadavers to destructive forces) have additional requirements, as well as a 15-day staffing period to Army senior leaders.

Investigators whose DoD-funded research uses both cadaveric and non-cadaveric materials must provide both the ORP Cadaver Use Submission Form and the HRPO Submission Form -- Secondary Research Involving the Use of Data/Specimens, as the cadaver use activity will receive separate review.

I. Use of unique or regulated sample types: fetal tissue and human embryonic stem cell lines.

Fetal Tissue. HRPO submission and review is required for research using fetal tissue and cell lines derived from fetal tissue. Note that use of cord blood or materials derived from placenta are not considered fetal tissue. Due to state and federal laws that govern research use of fetal tissue, the HRPO will confirm that the institutional review determined: the written consent of the mother was obtained; the fetus can be used for research; the use of fetal material is required for the research and

other materials cannot be substituted; and the source of the materials is documented (institution, clinical providers, non-profit repositories, etc.). Additional approvals are required for research with fetal tissues in accordance with DoD Instruction 3216.02. The HRPO will coordinate these reviews; investigators should allow for additional time to receive HRPO approval.

Human embryonic stem cell lines. The HRPO adheres to the NIH policy requirements and requires submission and review of research on existing human embryonic stem cell lines and derivation of new human embryonic stem cell lines. Due to the ethical issues related to research use of embryonic stem cells, HRPO recommends investigators who plan to conduct research with embryonic stem cells consult the HRPO for input during the proposal process. As part of the HRPO submission, investigators should provide the NIH registration numbers for the use of human embryonic stem cell lines.

III. HRPO Review and Approval.

The HRPO will review the submission and request sufficient information and documents to approve non-exempt specimen/data research or concur with the institutional review of the DoD funded activities before the human subjects research activity can begin. As required by DoD Instruction 3216.02, Section 3, paragraph 3.6.b(6)(b), when the institution determines either the activity is not research involving human subjects or is exempt human subjects research, the HRPO must concur with the performing institution's determination. The HRPO will provide a written HRPO approval or concurrence memorandum to the Principal Investigator at the DoD-funded institution and provide copies to the Science Officer and Contract Specialist. Investigators who do not have a designated IRB or regulatory office at their institution (e.g., small business awardees) should consult HRPO for guidance.

- If data/specimens used in the DoD-funded study originate from outside the United States, additional requirements may apply. The HRPO will review the host nation's oversight/approval of the collection activities for prohibitions on transfer of data/specimens out of the country.