HRP – 405 – SOP: Determining Human Subjects Research

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<th>Version Number</th>
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<td>HRP-405</td>
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**Purpose**

SOP-405 outlines the procedures for determining whether submissions meet the definition of human subjects research, including but not limited to, human in the loop (HITL) studies, quality improvements activities, engineering studies, or use of data/specimens that are not readily identifiable.

All activities that constitute **human subject research**— when NASA is **engaged** in the research - must be reviewed and approved by NASA IRB and in compliance with NASA NPR 7100_001B and NASA NPD 7100_008F and 14 CFR 1230. NASA may enter into a Reliance Acknowledgment with another IRB, where appropriate [as specified by NASA SOPs 100, 101, and 102].

Examples of activities that may or may not require NASA IRB are included in **Table 1**.

**Policy**

1. The final determination of Not Human Subjects Research (NHSR) is made by the NASA IRB. Once the determination is made, the NASA IRB will do either of the following:
   a. The NASA IRB may issue a letter of determination of ‘Not Human Research’, OR
   b. The NASA IRB may request that the PI complete a submission in the eIRB for Exempt or Expedited Review, or at the convened Full Board.

   **Note:** for projects involving astronaut subjects, the PI should contact a crew representative for feedback regardless of the NASA IRB determination.

2. Protocols involving international partner research, reviewed by an international ethics board, will be uniquely assessed for NHSR determinations and may deviate from this policy as determined by the NASA IRB Chair.

3. For protocols involving international partner research that intend to enroll US astronauts and have received an NHSR determination from the NASA IRB, the NASA IRB will request the following language be added to the Multinational Consent Form: **“NOTE FOR US CREW ONLY: The NASA IRB has determined the proposed**
project is not considered human subjects research per U.S. 14CFR1230. As such, 14CFR1230 regulations have not been applied and the project is not under the purview of the NASA IRB.”

4. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by NASA to allow the identification, monitoring, assessment, or investigation of potential public health signals, onsets of disease outbreaks, or conditions of public health importance are deemed not to be research per the Office of Human Research Protection and will be given an NHSR determination per NASA 14CFR1230.102(l)(2).
   a. It is recommended that public health surveillance activities be submitted to the NASA IRB for an NHSR determination prior to commencement.

5. An NHSR determination applies only to the activities described in the NASA IRB submission for which the determination was made and does not apply should any changes be made. If changes are being considered and there are questions about whether NASA IRB review is needed, the PI is to submit a study modification to the NASA IRB for a determination. Another NHSR determination may be made or the NASA IRB Office will require a protocol submission if deemed HSR.

Procedures

1. **Principal Investigators** (or Investigators) should review the definitions and examples in this SOP to determine whether an activity might be human subjects research. They may also contact the NASA IRB for assistance.

2. Investigators who are uncertain as to whether their proposed activities meet the definition of human subjects’ research should complete and submit **Appendix 1: ‘Not Human Subject Determination Questionnaire’** to the eIRB as a new submission.
   a. Note – for NHSR submissions, only the NHSR Determination Questionnaire (Appendix 1) must be uploaded to the eIRB. No other documents are required for the eIRB submission.
   b. Investigators who require documentation that an activity is Not Human Subject Research, must submit the **Not Human Subject Determination Questionnaire** (Appendix 1) to the eIRB as a new submission.

3. The NASA IRB Chair or their Designee will review the Human Subjects Research Determination Questionnaire submitted by the PI and confirm whether the research meets the definition of human subject research.
   a. NASA IRB Chair or their Designee will review **Appendix 1** and communicate a determination to the PI as soon as possible, but no later than 2 weeks after a
Not Human Subject Determination Questionnaire is submitted to the eIRB.

b. If it is determined that the study does not meet the definition of Human Subjects Research, the NASA IRB will issue a Not Human Research letter to the PI.

c. If it is determined that the study does meet the definition of Human Subjects Research, the PI will be informed and directed to submit a protocol and supporting documents to the eIRB for applicable review by the NASA IRB (Exempt, Expedited, or Full Board).

4. Human subjects research is any research or clinical investigation that involves human subjects as defined below:


See: NASA 14CFR1230.102(l)(1-4) and HHS 45CFR46(l)(1-4) for a list activities deemed not to be research by the regulations.

**RESEARCH:**

First, the protocol must meet the definition of research, defined by NASA and DHHS as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge [NASA 14CFR1230.102(l); HHS 45CFR46.102(l)].

**Systematic investigation:**

- A systematic investigation is an activity that involves a prospective plan that incorporates data collection (quantitative or qualitative) and data analysis to answer a question.
- Activities are not considered a systematic investigation if they do not involve an organized approach to studying a specific topic developed to answer a specific question, testing a specific hypothesis, or developing theory.
- Examples of activities that typically ARE systematic investigations:
  - Interviews and focus groups
  - Surveys and questionnaires
  - Analysis of data and specimens
  - Observational studies
  - Epidemiological studies
  - Cognitive and perceptual experiments
  - Medical chart reviews
  - Comparisons of methods, products, and/or treatments

- Examples of activities that typically ARE NOT systematic investigations:
Training activities provided the activities are not designed to develop or contribute to generalizable knowledge

Classroom activities where the objective of the activity is to teach proficiency in performing certain tasks or using specific tools or methods and the activity is not designed to develop or contribute to generalizable knowledge

Activities which individuals are completing tasks as part of an already established routine such as classroom exercises/assignments or the use of equipment/procedures previously deemed necessary for other purposes in the clinical or work setting

Instrument/product development

**Generalizable Knowledge:**

- Activities designed (with intent) to develop or contribute to generalizable knowledge are those designed to draw general conclusions, inform policy, or generalize findings beyond a single individual or an internal program.

    **NOTE:** The *intent* to develop or contribute to generalizable knowledge makes an activity research. Publication/dissemination is not a determining factor for whether an activity is human research requiring review and approval by the IRB. Results do not have to be published or presented to qualify the activity as research.

- Examples of qualities of activities that typically ARE designed to contribute to generalizable knowledge:
  - basis in a theoretical framework of established knowledge
  - identification of a gap in knowledge that the project plans to address
  - identification and description of one or more specific populations of interest
  - unbiased sampling methods (i.e. random or probability sampling), when feasible, that allow for the recruitment of samples representative of the population(s)
  - operationalization of variables and constructs
  - data collection plans employing measurement tools and techniques with established and satisfactory reliability and validity
  - data analysis plans using techniques consistent with those employed in the literature of the theoretical framework and considered appropriate for the type(s) of data collected
  - an ability and plan to use the collected and analyzed data to draw meaningful conclusions about the result and link those back to the theoretical framework and identified gap in knowledge

- Examples of activities that typically are NOT designed to develop or contribute to generalizable knowledge:
  - Biographies
o Oral histories that are designed solely to create a record of specific historical events
o Program evaluation, program development, quality assurance, or quality improvement activities, such as:
  ▪ Services, courses, or concepts where it is not the intention to share the results beyond the NASA community
  ▪ Classroom exercises solely to fulfill course requirements or to train users/students in the use of particular methods or devices
  ▪ Activities designed to continuously improve the quality or performance of a department or program where it is not the intention to share the results beyond the NASA community
  ▪ Specimens or hardware/software testing for the purposes of quality assurance or quality improvement
o Instrument/survey development
o Case reports
o Public health surveillance activities (see Policy 4 of this SOP)

FDA regulations define a clinical investigation as any experiment that involves a test article and one or more human subject, and that either subject to the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Act, or need not subject to 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 [FDA 21CFR50.3(c), 21CFR56.103(c), 21CFR312.3(b), and 21CFR812.3(h)].
- A test article is 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 FDA regulations.
- Examples of activities that are clinical investigations:
  o Clinical trials that involve investigational drugs or devices
  o Research testing the safety and effectiveness of a device
  o Medical outcome studies comparing approved drugs or devices

HUMAN SUBJECT:
Second, the protocol must meet the definition of a human subject, defined by NASA and DHHS regulations as a living individual about whom an investigator (whether professional or student) conducting research [NASA 14CFR1230.102(e)(1-7); HHS 45CFR46.102(e)(1-7)]

(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.

- **Intervention** includes both physical procedures by which data are gathered (e.g. venipuncture) and manipulations of the subject or by the subject’s environment that are performed for research purposes
- **Interaction** includes communication or interpersonal contact between investigator and subject
- **Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g. 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.

Common activities that are NOT involving a **human subject** per the NASA and DHHS definition:

- Activities involving information collected *from* individuals but not generalizable *about* individuals such as quality assurance, quality improvement, program evaluation, course evaluation, documentaries, case studies, etc.
  - Examples include pre-test/post-test data to evaluate a program, instrument, hardware, or software
- Activities using publicly available data or de-identified data in which the investigator cannot re-identify the individuals. If the researcher has access to a link or code, the data are identifiable and the activity is human subject research.
- Activities using de-identified pre-existing or archived data

FDA Regulations define **human subject** as an individual who becomes a participant in research, either as a recipient of the test article or as a control [21 CFR 50.3(g), 21CFR56.103(e), 21CFR312.3(b), and 21CFR812.3(p)].

- A subject may be either a healthy individual or a patient
- Clinical investigations that use human specimens (e.g. in vitro diagnostic devices, assays or culture media) involve “human subjects.”

5. **Recordkeeping when activities are determined to be Human Subjects Research**

**NASA IRB Responsibilities:**

- The NASA IRB maintains records of all studies, including those that are determined to be Not Human Subjects Research.
• Communications between the NASA IRB and the investigator and key personnel, specifically the Not Human Subjects Research Determination Questionnaire, will be maintained in the e-IRB system.
• Copies of study-related correspondence between the IRB and other entities, including regulatory authorities, other review committees and study subjects
• Any additional documents deemed appropriate on a case-by-case basis
• eIRB application and all accompanying documentation including, but not limited to appended recruitment and consent documents, data collection materials and instruments, and funding proposal, if applicable.
• Records of Not Human Research determinations are maintained in the NASA IRB eIRB for at least 3 years.

Investigator Responsibilities:
• Maintaining records of documents used for determining Not Human Subjects Research and correspondence which include at a minimum the eIRB letter of determination, as appropriate for your department policy(ies).
### Table 1: Examples of Activities that May or May Not Require NASA IRB Review

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>DESCRIPTION</th>
<th>NASA IRB REVIEW</th>
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<tbody>
<tr>
<td>Case Report Studies</td>
<td><strong>Retrospective</strong> review of a patient’s medical record with intent to</td>
<td>Refer to LSAH for identifiable data determination</td>
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<td></td>
<td>prepare for an eventual research study and/or to document a specific</td>
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<td></td>
<td>situation or the experience of an individual without intent to form a</td>
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<td></td>
<td>research hypothesis, draw conclusions, or generalize findings. The data</td>
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<td></td>
<td>will be de-identified.</td>
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<td></td>
<td><strong>Prospective</strong>: a single subject study without prior research intent,</td>
<td>YES</td>
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<td>before recruiting or interacting with the participant, to use data that</td>
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<td>would not ordinarily be collected in the course of treatment. The intent</td>
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<td>is to report and publish the case study.</td>
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<tr>
<td>Public Health Surveillance Activities</td>
<td><strong>Collection of data as part of a NASA specified health surveillance</strong></td>
<td>NO</td>
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<td>program to allow the identification, monitoring, assessment, or investigation</td>
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<td></td>
<td>of astronaut health signals, onsets of disease, or conditions of space</td>
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<td></td>
<td>travel.</td>
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<td>Analysis of Pre-existing or Archived</td>
<td>LSAH/LSDA data requests in which only de-identified information will be</td>
<td>NO</td>
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<tr>
<td>Data</td>
<td>analyzed. The researcher does not have the ability to identify participants</td>
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<tr>
<td></td>
<td>(link a participant with her or her data).</td>
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<tr>
<td>Research involving Astronaut</td>
<td>The use of astronauts for any research activity.</td>
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<td>Participants</td>
<td></td>
<td>Contact a crew representative For feedback regardless of the IRB determination</td>
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<td>Oral Histories</td>
<td>The activity is limited to investigations or interviews (structured or</td>
<td>NO</td>
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<td>open-ended) that focus on specific events (current or historical), views,</td>
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<td></td>
<td>etc.</td>
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<td>Pilot Studies</td>
<td>Pilot studies meet the definition of human research, regardless of the</td>
<td>YES</td>
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<tr>
<td></td>
<td>number of subjects enrolled or the duration of the studies</td>
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<td>Sizing Fit Checks</td>
<td>Process by which appropriate size suit components are selected and</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>evaluated by test subjects/crewmembers for future suited activities.</td>
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<td></td>
<td>Unless designed as research to meet the definition of HSR.</td>
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Quality Assurance or Quality Improvement | Projects which include evaluating the quality of an established method, instrument, procedure with the intent of improving upon the method, instrument, or procedure. | NO

Program Development or Program Evaluation | Projects designed with the purpose of developing a program or evaluating the effectiveness of a current program (often includes pre- and post-testing). | NO

Instrument Development | Projects designed to only solicit expert opinions in order to develop a survey or testing instrument. | NO

**Definitions**

**Engaged:** NASA is considered engaged in research when NASA’s employees or agents obtain:

1. data about the subjects of the research through intervention or interaction with them, or
2. identifiable private information about the subjects or research, or
3. the informed consent of human subjects for the research and parabolic flight and analog studies funded by NASA.

**FDA (Food and Drug Administration)-Regulated Research:** The US FDA regulates clinical studies conducted on drugs, biologics, devices, diagnostics, and in some cases dietary supplements and food additives. All such research studies must be conducted in accordance with FDA requirements for the protection of human subjects and IRBs, regardless of funding source [21CFR50 and 56]. When FDA regulated test articles are used in research at NASA and funded by another agency, more than one set of regulations may apply. For example, clinical trials involving FDA-regulated test articles that are supported by NASA (or the DHHS), may fall under the jurisdiction of both the FDA and the DHHS. Such trials must comply with the FDA and the DHHS Office for Human Research Protections (OHRP). Where regulations differ, NASA IRB will apply the stricter regulation.

**Key Personnel:** Those involved in the conduct of human subject research in which the persons engaged are in direct contact with research participants consenting and/or collecting data, and/or have access to private and identifiable research data.

**Minimal Risk [14CFR1230.102(j)]:** 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 or psychological examinations or tests.

**Minimal Risk for Prisoners:** 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. The regulations further state that the IRB must find that the risks involved in the research are commensurate with risks that would be accepted by non-prisoner.
volunteers [45 CFR 46.305(a)(3)]. If Subpart C does not apply, the IRB may use an equivalent definition of minimal risk for prisoners. [45 CFR 46.303(d)]

Minimal Risk for Research Involving the Department of Defense (funding, subjects, facilities, resources). Per DoD regulations, the phrase “ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” must not be interpreted to include the inherent risks certain categories of subjects face in their daily 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 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).

**NASA IRB Office:** Office staff to include the NORA Manager, the NASA IRB and HRPP Manager, IRB Coordinator(s), and the NASA IRB Chair.

**Principal Investigator (PI):** The NASA PI or PI that is responsible for coordination with the NASA IRB or the IRB of Record for all research sites.

**Public Health Authority:** an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate” (14CFR1230.102(k)).

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**References**

**NASA**
- 1. NASA 14 CFR 1230.102
- 2. NPR 7100_001B
- 3. NASA NPD 7100 _008F

**DHHS Regulations**
- 4. OHRP ‘Human Subject Regulations Decision Charts: 2018 Requirements, Chart 1
- 5. HHS 45CFR 46.102
- 7. Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements

**FDA Regulations**
- 8. 21CFR50.3(c)[g]
- 9. 21CFR56.103(c)(e)
- 10. 21CFR312.3(b)
- 11. 21CFR812.3(h)(p)

**AAHRPP**
- 12. AAHRPP Elements: I.1.A, III.1.A
- 13. AAHRPP Tip Sheet 2: Determining Whether an Activity is Research Involving Human Participant
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<td>Author</td>
<td>J. Christensen / J. Kisenwether</td>
<td>21Oct2020</td>
</tr>
<tr>
<td>Revised</td>
<td>J. Kisenwether</td>
<td>27Sept2021</td>
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<td>Reviewer</td>
<td>M. Covington</td>
<td>27Sept2021</td>
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<td>Approver</td>
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