



## HRP – 470 – SOP: Suspension or Termination of IRB Approval

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HRP-470	8April2021	v.1	n/a

### Purpose

HRP 470 outlines NASA IRB’s authority to suspend or terminate NASA IRB-approved human subjects research that is not being conducted in accordance with NASA IRB’s requirements or that has been associated with a detrimental change in the risk-benefit ratio. The procedures for suspension or termination of a NASA IRB-approved protocol are detailed.

### Policy

1. NASA 14 CFR 1230.113, HHS 45 CFR 46.113, and FDA 21 CFR 56.113 state that an IRB shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB’s action and shall be reported promptly to the investigator, appropriate institutional officials, and OHRP or FDA (as appropriate).
2. NASA 14 CFR 1230.108 (4) and (ii) and HHS regulations 45 CFR 46.108 (4) and (ii) require the NASA IRB have written procedures to ensure that any suspension or termination of IRB approval are promptly reported to OHRP.
3. The NASA IRB and the NASA IRB Chair/designee have the authority to suspend or terminate IRB-approved human subjects research that is not being conducted in accordance with NASA IRB requirements or IRB-approved human subjects research that has been associated with unexpected serious harm to subjects.
4. The NASA IRB has the authority to suspend or terminate any human subjects research activity that has not been reviewed and approved or determined exempt by the NASA IRB.

5. The NASA IRB has the authority to suspend or terminate approval of single site research relying upon NASA IRB as the IRB of record.
6. The NASA IRB has the authority to suspend or terminate its approval of the research either at one institution because of a unique problem regarding the conduct of the research at that institution or at all institutions because of a study-wide problem when engaged in multicenter research relying upon the NASA IRB as the single IRB for review of the project.
7. It is the policy of the NASA IRB that a research project may be **suspended or terminated** for a variety of reasons in accordance with 14 CFR 1230.113, FDA 21 CFR 56.113, and HHS 45 CFR 46.113, including but not limited to:
  - a. *Human subjects research conducted outside of NASA IRB approval*
  - b. *Violation of the rights or welfare of human subjects or others*
  - c. *Detrimental change in the risk-benefit ratio of the study*
  - d. *Serious or continuing noncompliance with Federal regulations, NASA IRB policies, or*
  - e. *New information regarding increased risk to human subjects or others, including but not limited to serious adverse events and unanticipated problems*
8. It is the policy of the NASA IRB that suspension or termination of IRB approval may occur at any time during the period of IRB approval.
  - a. After suspension of an IRB-approved protocol, the NASA IRB has the authority to terminate the research if the events prompting the suspension of IRB-approval cannot be corrected in a way that serves the best interests of research participants.
9. It is the policy of the NASA IRB that the determination to **suspend** IRB approval is made:
  - a. At a convened IRB meeting either:
    - i. At the next scheduled convened IRB meeting, or
    - ii. The IRB Chair/designee may convene a Rapid Response meeting prior to the next scheduled IRB meeting if he or she feels it is warranted for the safety, rights, and welfare of research participants.
  - b. By the IRB Chair/designee if an emergent situation arises and review by a convened IRB is not possible. If the IRB Chair/designee determines a suspension of research is warranted, the IRB members will be notified of and review the circumstances surrounding the suspension at the next scheduled or rapid response convened meeting.
10. It is the policy of the NASA IRB that the determination to **terminate** IRB approval is made:
  - a. Only at a convened IRB meeting.
    - i. At the next scheduled convened IRB meeting, or

- ii. The IRB Chair/designee may convene a Rapid Response meeting prior to the next scheduled IRB meeting if he or she feels it is warranted for the safety, rights, and welfare of research participants.
11. The Investigator or study sponsor may initiate a suspension or termination of a study approved by the NASA IRB due to various reasons including, but not limited to those listed in **Policy** 7.a-e.
  - a. The Investigator or sponsor must notify the IRB in writing within 3 business days of initiating the suspension or termination. The Investigator must describe the steps that are or will be in place to protect the welfare of currently enrolled participants and any corrective actions that will be taken to address the cause for the research suspension or termination.
  - b. The report must include, at a minimum, the information listed in ‘Investigator Responsibilities’ in 3b(1) – (4) below, as applicable.
  - c. The report will be reviewed at a convened IRB meeting according to the procedures in this the document. The NASA IRB will determine whether or not to **suspend IRB approval, terminate IRB approval**, or take no action.

**Important Note:** *The cessation or hold of a single aspect of the research (i.e. new participant enrollment, procedures, dosing, or data analysis) is not a suspension of IRB approval unless it is found to be associated with an unanticipated problem involving risks to human subjects or others (UPIRSO), serious noncompliance, and/or continuing noncompliance and the NASA IRB finds that the event requires suspension or termination or IRB approval.*

## Procedures

1. NASA IRB Procedures for review of Suspension or Termination of NASA IRB-approved research
  - a. If the suspension or termination is related to a UPIRSO, serious adverse event (SAE), or research noncompliance, the IRB reviewer must complete the tasks as spelled out in the corresponding SOPs (*as of April 2021 SOPs are in draft form*).
  - b. If the suspension or termination is not related to an UPIRSO, SAE, or research noncompliance, the IRB reviews the written report submitted by the investigator as outlined in this SOP, “Investigator Responsibilities, 3b(i)-(iv).”
  - c. When cause for further **investigation** is determined by the NASA IRB Chair/delegate, NASA IRB office, and/or convened NASA IRB, the following applies:
    - i. Investigations or requests for more information may be initiated by the NASA IRB Chair/designee in cooperation with the NASA IRB Office Staff and the NASA Director to suspend or terminate protocols in emergent situations,

when it has been determined that the rights, safety, or welfare of subjects are in immediate jeopardy.

- ii. Investigations or requests for more information may be initiated in preparation for a Convened IRB meeting when deemed necessary to review the suspension or termination. IRB Reviewers shall have the opportunity to initiate *investigations* to obtain information necessary to determine that the NASA IRB approved protocol must be suspended or terminated and/or to propose **stipulations** during the Convened IRB Meeting.
  - a. Requests for more information may include, but are not limited to:
    - i. requests for additional documentation or study records,
    - ii. interviews with the investigator(s) or others involved in the research process,
    - iii. correspondence with the investigator, site(s), sponsor or oversight committees (DSMB, etc.), other IRB members, or any other fact-finding procedures the NASA IRB deems necessary.
  - b. The NASA IRB will use diligent efforts to ensure the investigation is thorough and examines all records and evidence relevant to reaching a conclusion and/or to make **stipulations**, conducts interviews as necessary, and communicates with the investigator and research staff as necessary throughout the process.
  - c. The NASA IRB may inform the Investigator(s) of the investigation or contact them for a response during the investigation.
  - d. Any NASA IRB members with a potential conflict of interest will be recused from fact finding and preparation of the investigation summary report.
  - e. The investigation, and subsequent report of findings, should be completed within two weeks, but no longer than 30 days from commencement, unless reasons for the delay are documented.
  - f. The process and outcomes of the investigation will be thoroughly documented and electronically stored in the NASA IRB Office.
- iii. The NASA IRB may require **stipulations** to protect research participants when NASA IRB approval is Suspended or Terminated, including but not limited to the following:
  - a. Continued safety follow-up of currently enrolled participants, which may include continued reporting of any additional adverse events, UPIRSOs, or outcomes to the NASA IRB and study sponsor for a specified amount of time.
  - b. Cessation of all subject accrual, study procedures, data analysis or other research activities associated with the research protocol (note: if only accrual is suspended, enrolled participants should continue per the protocol).

- c. Continued study treatment / intervention by the same or different investigator which may include a safe and monitored dose withdrawal plan from current study medication and/or a final study visit during which a physical exam or other tests will be performed.
  - d. In certain circumstances, research activities may continue if stopping study procedures/treatment will adversely affect the welfare of a subject. This will be determined by the NASA IRB Chair or his/her designee.
  - e. Procedures for withdrawal from the research that protects the rights, safety, and welfare of participants, which may include, but is not limited to, withdrawal and transition of participants from research to clinical care.
  - f. Notification to all current and/or former participants of the suspension or termination of the research
  - g. Require that participants re-consent to study participation
  - h. Notification by the Investigator or sponsor to editors if affected data has been submitted for publication or has been published.
  - i. Notification by the Investigator to funding agencies.
  - j. Dependent upon the status of ongoing study procedures at the time of termination, continuing review of the research may still be required or occur more frequently, as determined by the convened IRB.
  - k. Additional actions deemed necessary by NASA IRB to protect the rights and welfare of enrolled participants and/or to protect the integrity of the research protocol.
- iv. For ***Suspensions of IRB approval only***, the IRB may also require the following **stipulations** (but not limited to):
- a. Additional training and education of investigators and key personnel
  - b. More frequent review of the study or other studies under the purview of the investigator
  - c. Initiate audits of the affected or all active protocols under the purview of the investigator
  - d. Disallow the use of study data collected
  - e. Cessation of subject accrual, study procedures, data analysis or other actions associated with the research protocol deemed necessary by NASA IRB
- v. Corrective actions and stipulations necessary for the NASA IRB to consider reinstatement of IRB approval of the research will be described in the written correspondence to the Investigator.
- a. The investigator has satisfactorily resolved any pending issues as required by NASA IRB. This is determined by a quorum vote of the convened NASA IRB.
  - b. The letter to NASA IRB from the Investigator or sponsor for reinstatement of a suspended study should address the following:

- i. reason for requesting reinstatement
  - ii. description of how the study has changed since approval, and submission a modification, when applicable
  - iii. how many subjects were enrolled prior to suspension, and at what point in the treatment/procedures the subjects were at the time of suspension
  - iv. any adverse events or amendments since the last continuing review including a description of each, and any additional relevant information (e.g. corrective action plan)
  - v. a documented plan to ensure the reason(s) for suspension will not happen again and that the study will be in compliance with all applicable laws and regulations
  - vi. anticipated enrollment, if the study is reactivated
- c. When IRB-approval is reinstated, the IRB may require that subjects who were previously enrolled be re-consented.
  - d. During suspension of IRB approval, the protocol remains subject to continuing review requirements and deadlines.
- vi. For ***Terminations of IRB approval only***, the study may be reinstated with appropriate modifications to address the reason(s) for termination. Investigators must submit a completely new application if they wish to resume a terminated study.

## IRB Responsibilities

1. When a research protocol is suspended or terminated from IRB approval, a member of the NASA IRB Office will note whether any other submissions (modifications, continuing reviews, etc.) are currently under review and the NASA IRB Office will ensure that no approvals are issued after termination or until the suspension is lifted.
  - a. If, after one year of suspension or the expiration date of the study (whichever comes first), progress has not been made on the pending issues, the NASA IRB Office will administratively close the study protocol.
2. Reporting Suspensions and Terminations of IRB approval
  - a. Within 15 business days of the determination to suspend or terminate IRB approval of research, the NASA IRB will prepare, send, and file the final report as necessary.
  - b. For Reporting and Distribution Requirements, see Appendix A.
  - c. The Investigator will be provided an opportunity to respond in writing or in person to the IRB about the suspension or termination prior to finalization and external reporting. The Investigator will be provided 5 days to respond.
  - d. *Internal Reporting*

- a. Reports of Suspensions and Terminations and all accompanying documents, determinations by the NASA IRB, including follow up, etc. shall be retained by NASA IRB for 7 years.
- b. NASA IRB approved research that has been suspended or terminated will be reported to the NASA Office of Research Assurance at the Office of the Chief Health and Medical Officer and the Institutional Official.
- e. *External Reporting*
  - a. When applicable, the NASA IRB will report the study suspension or termination to the Office of Human Research Protections or the Food and Drug Administration as per the requirements set forth in 14CFR1230.108(a)(4), 45 CFR 46.108(a)(4) and 21 CFR 56.108(a)(4), respectively.
  - b. When an agency or individual other than the NASA IRB submits the report to an external agency, the NASA IRB need not report in duplicate but requests a copy of the report with verification of delivery within 30 days.

## Investigator Responsibilities

1. The Investigator is responsible for reporting violations of research compliance and identification of additional risks to participants to the NASA IRB, including, but not limited to, those listed in **Policy 7.a-e**.
2. When a protocol is suspended or terminated, the investigator must stop all research activities related to the protocol, including subject recruitment and enrollment, procedures, and analysis and/or publication of existing data, as determined by the IRB.
3. The Investigator must notify the NASA IRB in writing within 3 days of any investigator or sponsor initiated suspension or termination and describe the reason for the suspension or termination and the measures in place and those that will be taken to ensure the safety, rights and welfare of subjects.
  - a. If the suspension or termination is related to a UPIRSO, SAE, or research noncompliance, the Investigator must submit a reportable new information (RNI) form within the e-IRB.
  - b. If the suspension or termination is not related to an UPIRSO, SAE, or research noncompliance, the Investigator must submit a modification within the e-IRB system containing the following information (but not limited to):
    - i. A statement that the study is suspended or terminated.
    - ii. Reason for the suspension or termination
    - iii. Number of subjects currently enrolled
    - iv. The date that the suspension or termination went (will go) in to effect
    - v. When the suspension or termination involves the withdrawal or current participants from the research, the Investigator will be required to:

- (a) Inform enrolled participants that the study has been suspended or terminated
- (b) Develop procedures for withdrawal that protect the rights, safety, and welfare of participants, and develop methods of informing those procedures to participants including, but not limited to:
  - careful and safe titration off of study drug, as recommended by the Sponsor and/or the investigator(s)
  - transfer of care to another investigator
  - arrangements for clinical care outside the research environment including details and time points for follow-up, if necessary
  - safety outcomes reports which may include adverse event reports from sites at specific time intervals, and/or DSMB reports from the sponsor
  - Data analysis stipulations (restrictions on data inclusions, publication restrictions, etc.)
4. The Investigator is responsible for notifying, in a timely manner, all co-investigators, key personnel, and other research staff associated with the protocol as well as any subcontract grantees when a request to suspend or terminate has been submitted to the NASA IRB.
5. The Investigator must promptly respond to any NASA IRB terms and conditions as outlined in the NASA IRB correspondence related to suspension or termination of IRB-approved research.
6. The Investigator may submit concerns in writing to the NASA IRB within 14 days of receipt of the NASA IRB report detailing the Findings and stipulation. The Investigator may request a meeting to discuss the concerns. NASA IRB will inform the investigator of the outcome after further review.

## Definitions

**Investigator:** the individual responsible for personally conducting or supervising the conduct of research and for protecting the rights, safety, and welfare of subjects enrolled in the research. The investigator ensures all human subjects research is ethically conducted and in accordance with all applicable federal (including HIPAA if applicable), state/provincial, and local laws and regulations, the IRB's requirements/ determinations, and Good Clinical Practice, as appropriate.

- In this document, 'Investigator' refers to the Site Investigator, Overall/Study Investigator, or both; whichever is most appropriate.

**Suspension of IRB Approval:** NASA IRB approval is suspended and all project activities must cease until any pending issues can be resolved satisfactorily. Suspended studies are still approved, but the research team may not perform research activities associated with the NASA IRB approved protocol.

- A sponsor-imposed suspension alone does not constitute a suspension of IRB approval, as it is not an action by the IRB to withdraw approval of a previously IRB approved protocol.



**Termination of IRB Approval:** Termination is a permanent withdrawal of NASA IRB approval. All project activities must cease immediately, including enrollment, treatment and/or intervention, data analysis and any resulting data or analysis is null and void. Terminated studies are not considered complete.

**Closure:** An administrative status whereby a previously NASA IRB-approved protocol’s expiration date has passed and an investigator has not submitted a renewal. Or, the investigator has submitted a study closure request. The NASA IRB assumes no human subject research activities are ongoing and, for administrative record keeping, the study record is closed.

## References

### NASA

1. 14 CFR 1230.108 (a)(4)
2. 14 CFR 1230.113

### FDA

3. 21 CFR 56.113
4. 21 CFT 56.108(a)(4)

### HHS and OHRP

5. 45 CFR 46.108(b)(5)
6. 45 CFR 46.108(a)(4)
7. 45 CFR 46.113
8. Guidance on Reporting Incidents to OHRP (2011) <https://www.hhs.gov/ohrp/compliance-and-reporting/guidance-on-reporting-incident/index.html>

### AAHRPP

9. Association for the Accreditation of Human Research Protection Programs (AAHRPP) Tip Sheet 15: Reporting Unanticipated Problems Involving Risks to Participants or Others, Terminations or Suspensions of IRB or EC Approval, and Serious or Continuing Noncompliance <http://www.aahrpp.org/apply/resources/tip-sheets>
10. AAHRPP Tip Sheet 21: Suspensions and Terminations of IRB or EC Approval <http://www.aahrpp.org/apply/resources/tip-sheets>

SOP Role	Name	Date
Author	J. Christensen	1March2021
Reviewer	M. Covington	8April2021
Approver	J. Christensen	8April2021

Appendix A

***The following Section is to be completed by NASA IRB Office with the IRB Chair/designee***

### **NASA IRB Reporting Requirements**

*The report will be sent within 15 business days of NASA IRB's final determination assuming full resolution has been achieved.*

OHRP reporting requirements apply to all nonexempt research that is:

1. Conducted or supported by HHS, OR
2. Conducted or supported by any non-HHS federal department or agency that has adopted the Common rule and is covered by a FWA determined to be appropriate for such research, OR
3. Covered by an FWA, regardless of funding source

#### **Report Contents** *(all must be checked)*

*The reports will be sent within 15 business days of the IRB's final determination assuming full resolution has been achieved.*

<input type="checkbox"/>	The person or entity drafting the report.
<input type="checkbox"/>	The person or entity who approves the report
<input type="checkbox"/>	The recipient(s) of the report (See 'Report Distribution' below)
<input type="checkbox"/>	Title of research protocol/ grant
<input type="checkbox"/>	Name of the institution conducting the research (e.g. NASA Center, University, hospital, foundation, school, etc.)
<input type="checkbox"/>	Name of the Investigator on the protocol (and the names of all other clinical investigators, as applicable)
<input type="checkbox"/>	IND or IDE number, <b>OR</b> <input type="checkbox"/> N/A
<input type="checkbox"/>	NASA eIRB number
<input type="checkbox"/>	The project identifier of any applicable Federal awards (grant, contract, etc.), <b>OR</b> <input type="checkbox"/> N/A
<input type="checkbox"/>	A detailed description of the event
<input type="checkbox"/>	The findings of NASA IRB
<input type="checkbox"/>	Actions taken by the Investigator, NASA IRB, and/or the Sponsor/Funding Agency to address the issue (e.g. corrective actions, research staff education, protocol or consent documents revisions, audit(s) and audit reporting timelines, temporary cessation of subject enrollment during investigation, etc.)

	<p>If suspension or termination of NASA IRB approval is recommended [see NASA SOP 470 <a href="#">Suspension or Termination of IRB Approval</a>], note that the following must also be included in the report: number of subjects enrolled to date; the plan for notifying currently enrolled subjects and/or future (suspensions only) subjects, if necessary; the procedures that will be undertaken to ensure the orderly and safe withdrawal that protect the rights, safety, and welfare of currently enrolled subjects.</p> <p><i>Note: a final copy of the audit or the progress on the audit shall be submitted to the NASA IRB at the time of completion or at the next scheduled <b>Continuing Review</b>, whichever is first.</i></p>
<input type="checkbox"/>	Plans for continued investigation or action
<input type="checkbox"/>	Specify any follow-up requested by the Investigator, Site(s), or sponsor prior to the next scheduled Continuing Review. (e.g. verification of corrective action implementation, documentation of education, audit follow-up, hold procedures, monitoring reports, etc.).
<input type="checkbox"/>	When the site, investigator, or Sponsor reports directly to external agencies, NASA IRB requests a copy with verification of delivery within 30 days.
<input type="checkbox"/>	Request that the researcher, sponsor, or organization provide any <u>responses</u> or communication that stemmed from report submission to the appropriate agencies in a timely manner [within 10 business days of receipt].
<b>Report Distribution</b>	
<p><b>External Reporting Required for the following:</b></p> <ul style="list-style-type: none"> <li>• <b>Serious or Continuing Noncompliance</b></li> <li>• <b>UPIRSOs</b></li> <li>• <b>Suspension or Termination of IRB Approved Research</b></li> </ul> <ol style="list-style-type: none"> <li>1. <u>FDA regulated research</u>: NASA IRB requires that the Investigator sends the report to → <b>Sponsor/Funding Agency</b>, who must then report to → <b>FDA</b> with a copy to <b>NASA IRB</b>.</li> <li>2. <u>NASA as an Agency that is subject to the “Common Rule”</u>: NASA conducts or funds the research: NASA IRB sends the report → the <b>Agency</b> as required AND to → <b>OHRP</b>.</li> <li>3. <u>FDA regulated research</u>: NASA IRB requires that the Investigator sends the report to → <b>Sponsor/Funding Agency</b>, who must then report to → <b>FDA</b> with a copy to <b>NASA IRB</b>. <ul style="list-style-type: none"> <li>• If the PI is funded by NASA, NASA IRB requires the PI report → <b>FDA</b>. NASA IRB may choose to prepare and send the report directly to the FDA.</li> </ul> </li> </ol>	
<p><b>Internal Reporting:</b></p> <ol style="list-style-type: none"> <li>1. The Investigator involved in the reporting of the event</li> <li>2. Other site(s) or NASA Centers involved in the research, and/or the sponsor/funding agency, or others, as deemed necessary by the NASA IRB.</li> </ol>	
<input type="checkbox"/>	<p>Specific organizational officials including the organizational official responsible for the Human Research Protection Program (NASA IRB, the Site, other participating sites covered by the Reliance Agreement as deemed necessary by the NASA IRB, the Sponsor, etc.):</p> <p>List the recipients of the report:</p>
<input type="checkbox"/>	OHRP (all NASA IRB approved research is covered by an FWA)
<input type="checkbox"/>	FDA, when the research is FDA-regulated

<input type="checkbox"/>	Other government agencies when the research is overseen by those agencies, and they require reporting separate from that to OHRP. List the recipients of the report:
<b>OR</b>	
<input type="checkbox"/>	NASA IRB need not report to regulatory agencies already made aware of the event. The investigator, sponsor, or other organization has already reported the incident. Provide details of communication from the investigator verifying submission of the report: .
<input type="checkbox"/>	NASA IRB requests copies of the final report.
<p><b>When working under a <u>Reliance Acknowledgement</u>:</b></p> <ol style="list-style-type: none"> <li>1. It is the responsibility of NASA IRB to inform the PI, other Investigators, and any relevant contact involved when Serious or Continuing Noncompliance is suspected, even if the NASA IRB continues to gather data regarding the event.</li> <li>2. If the Serious or Continuing Noncompliance has a study-wide impact, all participating NASA Centers and institutions covered by the Reliance Acknowledgement will be informed, as deemed necessary by NASA IRB.</li> <li>3. NASA IRB will provide the Relying Institution the opportunity to review and provide input on the report of Serious and/or Continuing Noncompliance (no fewer than 5 business days) prior to sending.</li> </ol>	

### **Guidance**

NASA 14 CFR 1230.108(3)(iii), DHHS regulations at 45 CFR 46.108(3)(iii) and FDA regulations at 21 CFR 56.108(a)(4) require prompt reporting to the NASA IRB of proposed changes in a research activity, and for ensuring that investigators will conduct the research activity in accordance with the terms of the NASA IRB approval until any proposed changes have been reviewed and approved by the NASA IRB, except when necessary to eliminate apparent immediate hazards to the subject.

NASA 14 CFR 1230.108(4)(i), DHHS regulations at 45 CFR 46.108(4)(i) and FDA regulations at 21 CFR 56.108 require that Serious or Continuing Noncompliance be promptly reported to the OHRP, to any Federal Agency supporting research and/or to the FDA and to the sponsor.

NASA IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRBs requirements or that has been associated with unexpected serious harm to subjects (45 CFR 46.113)

**Investigator Reporting Responsibilities:** Investigators are required to self-report to the IRB any instances of noncompliance that involve potential risk to subjects or others, or involves failure to comply with federal regulations, state laws, and/or IRB requirements, determinations or provisions of the approved research study.

- Allegations of noncompliance may originate from a lead investigator, site investigator, monitoring staff, site staff, other Organization staff or offices, sponsors/funding agency, or collaborators, study participants, or those associated with study participants.
- Investigators are encouraged to seek the assistance of the NASA IRB staff in order to develop a corrective action plan to accompany any reports of noncompliance submitted to the NASA IRB.

- Investigators are required to respond promptly to any inquiries, correspondence or directives from the NASA IRB with respect to any allegations or actual noncompliance. They are also expected to cooperate with any requests for information or any investigations.

**Allegation of Noncompliance:** an unproven assertion of noncompliance that has not yet been supported by evidence. Allegations of noncompliance may originate from a lead investigator, site investigator, monitoring staff, site staff, other Organization staff or offices, sponsors/funding agency, or collaborators, study participants, or those associated with study participants. Persons other than the Investigator and research staff should report any actual or suspected noncompliance to NASA IRB on the Subject Complaint / Anonymous Report of Noncompliance.

**Noncompliance:** Conducting research involving human subjects in manner that intentionally or unintentionally disregards federal (or other applicable) regulations, ethical standards, or the policies, procedures, or determinations of the NASA IRB. Even in the absence of intent, an unapproved or otherwise noncompliant research activity may place a research participant at unnecessary risk.

Noncompliance with NASA IRB and/or federal requirements may involve a range of issues from relatively minor or technical violations which result from inadvertent errors, inattention to detail, or failure to follow operational procedures to more serious violations which pose risk to subjects and/or violations of their rights and welfare.

***Examples of Noncompliance that require reporting to NASA IRB using the Noncompliance Reporting Form:***

- Non-exempt human subjects research conducted without IRB review and approval [particularly when greater than minimal risk]
  - For example: before approval, after expiration of approval, in the absence of a continuation application submitted to the IRB, during a suspension of IRB approval, or after termination of IRB approval.
    - Note: OHRP does not consider an expiration of IRB approval via untimely submission of CR to be a suspension or termination of IRB approval (and, therefore, does not need to be reported to OHRP). However, if the IRB notes a pattern of noncompliance with CR requirements, the IRB should determine whether the pattern represents serious or continuing noncompliance that needs to be reported
- Human subjects research conducted without appropriate informed consent or re-consent, when consent could not be waived
  - Lack of documentation of informed consent
  - Obtaining consent after initiation of study procedures
  - Disregarding or otherwise violating NASA IRB-approved informed consent procedures
- Substantive changes to IRB-approved research without IRB approval
- Failure to follow the safety monitoring plan
- Failing to disclose conflicts of interest and/or failing to manage the conflicts as stipulated /approved by NASA IRB
- Failing to report or tardily reporting UPIRSOs, SAEs, or Noncompliance
- Failing to maintain adequate records
- Failing to train research team members in the proper procedures

- Failing to follow recommendations by the NASA IRB to ensure the safety of research participants
- Drug dispensing or dosing error
  - Missing or unreturned investigational product
- Bringing harm to research participants
- Exposing research participants to a significant risk of substantive harm
  - Performing a study procedure that is not outlined in the IRB-approved protocol
  - Study visit conducted outside of required timeframe that, in the opinion of the investigator, may affect subject safety
- Compromising the privacy and confidentiality of research participants
- Causing damage to scientific integrity of the research data that has been collected
- Engaging in willful or knowing noncompliance
- Impacting ethical principles adversely
- Other serious failure to comply with requirements for safeguarding the safety, rights, or privacy of human subjects
- Other incidents determined to be serious by the IRB

*The degree of noncompliance is evaluated on a case-by-case basis by NASA IRB Office, NASA Legal IRB representative, Chair or designee, and/or a Convened IRB meeting, when applicable.*

**Serious Non-compliance:** any action or omission during the conduct of human subjects research that reflects a failure to adhere to the laws, regulations, or policies governing human research that:

1. Significantly increases risk to participants or significantly decreases potential benefits, AND/OR
2. Affects the rights and welfare of participants, AND/OR
3. Compromises the scientific integrity or validity of human subjects research (which may include compromising the effectiveness of a facility's human research protection or research oversight program).
  - The IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance.
  - Multiple instances of noncompliance that are deemed not-serious individually may constitute serious noncompliance when considered collectively.

*NASA IRB Board may consider mitigating factors, such as a corrective action, that play a role in the determination of whether the event increased risk, decreased potential benefits, or negatively affected the integrity of the human subjects research. But if, despite these factors, the event's occurrence meets the definition of serious noncompliance, then the event should be categorized as such.*

**Continuing Non-compliance:** A pattern or persistent failure to adhere to the laws, regulations, or policies governing human research that:

- Significantly increases risk to participants or significantly decreases potential benefits, AND/OR
- Affects the rights and welfare of participants, AND/OR
- Compromises the scientific integrity or validity of human subjects research (which may include compromising the effectiveness of a facility's human research protection or research oversight program).

*This repetition may be in the same or in different protocols by a single investigator; such repetition, if not addressed, may affect the protection of human research subjects. NASA IRB may deem noncompliance “continuing” if not “serious”, particularly after NASA IRB has informed the Investigator(s) of problems.*

Examples of Continuing Noncompliance: [include, *but not limited to*]

- Compromises the scientific integrity of a study such that important conclusions can no longer be reached
- Suggests a likelihood that noncompliance will continue without intervention
- Involves frequent instances of minor non-compliance
- Failure to respond to a request from the IRB to resolve an episode of noncompliance
- OHRP has advised that it considers noncompliance to be continuing if it persists after the investigator knows or should have known about it
  - NASA IRB holds a presumption of continuing noncompliance, placing the burden on the investigator to present compelling, mitigating circumstances.
- The period in which the continuing noncompliance occurred could be days or weeks – depending on the seriousness of the matter – and NASA IRB does not need to call an issue noncompliance BEFORE being able to call it continuing noncompliance.

**Administrative Hold:** a voluntary action by the Investigator, Sponsor/Funding Agency, or NASA IRB to temporarily or permanently stop some or all research activities on approved research. This is not a suspension or termination of NASA IRB approval of the research protocol.

- An administrative hold may be used to correct a study-wide or site-specific issue that has potential for resulting in harm to subjects.
- An administrative hold must not be used to avoid reporting deficiencies or circumstances that otherwise require suspension or termination of IRB approval or reporting to regulatory agencies.
- Activities placed under administrative hold remain subject to continuing review and all NASA IRB policies.
- If a permanent change to the protocol results from the Hold, an **MOD** must be submitted to the eIRB.

Examples when Voluntary Suspensions/Administrative Holds are appropriate include, but not limited to:

- During the timeframe of UPIRSOs, SAEs, or Noncompliance investigation or while a corrective action plan is put in place.
- Investigator or essential staff turnover

## References

1. NASA 14 CFR 1230.103 (compliance assurance)
2. NASA 14 CFR 1230.108(3)(iii) (prompt reporting of changes in research)
3. NASA 14 CFR 1230.108(4) and (4)(i) (reporting of noncompliance)
4. NASA 14 CFR 1230.113 (suspension or termination)
5. DHHS 45 CFR 46.103 (compliance assurance)
6. DHHS 45 CFR 46.108(3)(iii) (prompt reporting of changes in research)
7. DHHS 45 CFR 46.108(4) and (4)(i) (reporting of noncompliance)
8. DHHS 45 CFR 46.113 (suspension or termination)

9. FDA 21 CFR 56.108(a)(3) and (4) (prompt reporting of changes in research); and 56.108(b)(2) (reporting of noncompliance)  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=56.108>
10. FDA 21 CFR 812.150 (device)  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=812.150>
11. Secretary's Advisory Committee on Human Research Protections (SACHRP) Attachment C: Recommendations on Protocol Deviations. March 30, 2012 SACRHP Letter to the HHS Secretary.  
<https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-c/index.html>
12. Association for the Accreditation of Human Research Protection Programs (AAHRPP) Tip Sheet 14: Non-compliance  
[https://admin.aahrpp.org/Website%20Documents/Tip\\_Sheet\\_14\\_Non-compliance.PDF](https://admin.aahrpp.org/Website%20Documents/Tip_Sheet_14_Non-compliance.PDF)
13. AAHRPP Tip Sheet 15: Reporting Unanticipated Problems Involving Risks to Participants or Others, Terminations or Suspensions of IRB or EC Approval, and Serious or Continuing Non-compliance  
<http://www.aahrpp.org/apply/resources/tip-sheets>