1. Purpose

To establish and describe the Office of Sponsor and Regulatory Oversight's (OSRO) Implementing Sponsor-Initiated Temporary Clinical Holds policy.

2. Scope

2.1. OSRO in the Center for Cancer Research (CCR), National Cancer Institute (NCI) shall establish and control the policy.

2.2. Investigators, research team members, other departmental personnel, and external NIH collaborators and contractors when they are working on studies conducted under a CCR-held Investigational New Drug (IND) application or Investigational Device Exemption (IDE) or participating in a CCR-supported Non-Significant Risk Device Study (NSR) under OSRO oversight shall comply with the policy.

2.3. Limitations

2.3.1. Personnel are not bound to this policy when working on non- IND or IDE studies and/or no interdepartmental collaboration with OSRO as Sponsor is required.

2.3.2. Nothing in this policy will supersede NCI, National Institutes of Health (NIH) or Health and Human Services (HHS) requirements.

3. Responsibilities

3.1. CCR Management is committed to providing resources to meet the requirements for an Implementing Sponsor-Initiated Temporary Clinical Holds policy within OSRO and supporting its continual improvement.

3.2. OSRO personnel are responsible for understanding and using the Implementing Sponsor-Initiated Temporary Clinical Holds policy.

3.3. The OSRO Director is responsible for establishing and maintaining the Implementing Sponsor-Initiated Temporary Clinical Holds policy.

3.4. OSRO Sponsor and Regulatory Oversight Support (SROS) Contractor staff assisting OSRO Functional Groups are responsible for understanding the Implementing Sponsor-Initiated Temporary Clinical Holds policy.

4. References

4.1. ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry (FDA), March 2018

4.2. 45 CFR Part 46: Protection of Human Subjects

4.3. HHS, Office for Human Research Protections, Reviewing and Reporting Unanticipated Problems Involving Risks and Adverse Events Guidance (January 2007)

4.4. HHS, Office for Human Research Protections, Reporting Incidents to OHRP (September 2022)

4.5. 412 Responding to FDA Clinical Holds

5. Definitions

Refer to the OSRO Lexicon.

6. Policy

6.1. This policy pertains to actions taken by OSRO when determining the need to place a clinical study on hold temporarily.

6.1.1. OSRO's response to a Food and Drug Administration (FDA) clinical hold is covered in Reference 4.5.

6.2. Events occurring during a clinical study which can be classified as one of the categories listed below must be reported promptly (within 24 hours of awareness) to OSRO.

6.2.1. A serious adverse event.

6.2.2. An unanticipated problem involving risks to subjects or others as defined in Section 8.

6.2.3. A serious and/or continuing noncompliance with 45 CFR part 46 (Reference 4.2) or the requirements or determinations of the Institutional Review Board (IRB) that significantly affects or has the potential to significantly affect human subject protection or reliability of clinical study results.

6.2.4. A suspension or termination of IRB approval.

6.3. OSRO will assess the risk of the event to determine the recommended course of action. Examples of corrective actions or substantive changes that may be considered include:

6.3.1. Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;

6.3.2. Modification of inclusion or exclusion criteria to mitigate the newly identified risks;

6.3.3. Implementation of additional procedures for monitoring subjects;

6.3.4. Suspension of enrollment of new subjects;

6.3.5. Suspension of research procedures in currently enrolled subjects;

6.3.6. Modification of informed consent documents to include a description of newly recognized risks; and

6.3.7. Provision of additional information about newly recognized risks to previously enrolled subjects.

6.4. The recommended corrective action(s) may require that the clinical study be placed on hold.

6.4.1. The hold decision will specify if the study should not enroll new participants, or if the study should not enroll new participants and hold administration of product for currently enrolled participants.

6.5. All OSRO decisions will be provided to the CCR Protocol Support Office, the study Principal Investigator (PI), and collaborators (as applicable).

6.6. OSRO Regulatory will notify the FDA if OSRO decides to place the clinical study on hold.

6.7. Incidents which meet the criteria of Steps 6.2.2 – 6.2.4 are reportable to the Health and Human Services (HHS) Office of Human Research Protection (OHRP).

6.7.1. OSRO Operations will request a copy of the OHRP notification.

7. Change Summary

Revision Number	Effective Date	Description of Change
1	31AUG2023	New Document

8. Appendix 1. Definition of unanticipated problems (Reference 4.3).

8.1. The Federal Office of Human Research Protections (OHRP) considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all the following criteria:

8.1.1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

8.1.2. Related or possibly related to participation in the research (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); and

8.1.3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.4. Examples include, but are not limited to:

8.1.4.1. A problem resulting in harm or posed a significant or substantive risk of harm to the research subject.

8.1.4.2. A compromise to the scientific integrity of the data collected for the study.

8.1.4.3. A breach of human subject protection regulations, or NIH policies or procedures on the part of the investigator(s).

8.1.4.4. Non-compliance with federal, state, local or institutional human subject protection regulations, policies or procedures.