1. Purpose

To establish and describe the Office of Sponsor and Regulatory Oversight's (OSRO) Sponsor Determination of Expectedness 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, Investigational Device Exemption (IDE), or Non-Significant Risk Device (NSR) under OSRO oversight shall assist OSRO in following the policy.

2.3. Limitations

2.3.1. CCR personnel are not bound to this policy when working on non- IND, IDE or NSR 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 implementing a Sponsor Determination of Expectedness policy within OSRO and supporting its continual improvement.

3.2. OSRO personnel are responsible for understanding and using the Sponsor Determination of Expectedness policy.

3.3. OSRO Sponsor and Regulatory Oversight Support (SROS) Contractor staff assisting OSRO Functional Groups are responsible for understanding the Sponsor Determination of Expectedness policy.

3.4. The OSRO Director is responsible for establishing and maintaining the Sponsor Determination of Expectedness 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. 21 CFR Part 312.32 – Investigational New Drug Application – IND Safety Reporting

4.3. Safety Reporting Requirements for INDs and BA/BE Studies, Guidance for Industry and Investigators (FDA), December 2012

4.4. 301 Serious Adverse Events Reporting Policy

4.5. 305-S01 Reference Safety Information – Guidance for PIs

5. Definitions

Refer to the OSRO Lexicon.

6. Policy

6.1. The Office designation of OSRO shall refer both to the Office of Sponsor and Regulatory Oversight staff and the OSRO Sponsor and Regulatory Oversight Support contractor staff.

6.2. As sponsor of a clinical trial, OSRO is responsible for the ongoing safety evaluation of the investigational product(s) (IP).

6.2.1. OSRO Safety will assess all serious adverse events reported to the Sponsor that may adversely affect subject safety or impact the conduct of the trial.

6.2.1.1. OSRO will expedite the reporting of all adverse reactions that are both serious and unexpected to all concerned investigators, regulatory authority(ies) and collaborators per Reference 4.4.

6.3. OSRO as the Sponsor has the regulatory obligation to determine "expectedness" of all serious suspected adverse reactions, reported to the Sponsor, that occur in clinical trials.

6.3.1. Specified sources (see next step) are used by the Sponsor to determine expectedness of a suspected serious adverse reaction for purposes of expedited reporting to regulatory authorities. If the serious event is considered related to the study intervention and the serious adverse reaction is not included in the source to determine expectedness, then this event is a SUSAR and must be reported to the FDA.

6.3.2. Sources used by the Sponsor to determine expectedness include:

6.3.2.1. Investigator Brochure Reference Safety Information (RSI) list of serious adverse reactions.

6.3.2.2. Package insert sections: events listed in Warnings and Precautions section, and list of serious events in Adverse Reactions section.

6.3.2.3. Report of Prior Investigations for devices.

6.3.2.4. If there is no other source of the RSI information (e.g., the IND does not require an IB or an IB is not available), the protocol RSI table of expected SAEs for regulatory reporting purpose (with known severity and known frequency) that have been previously observed and considered or suspected to be related.

6.3.2.4.1. Refer to Reference 4.5 for guidance on RSI.

6.3.3. When no IB is available, no RSI section is included in the IB, or no RSI information is provided and no "expected" SAEs are identified in the protocol then all SAEs are considered "unexpected" events.

6.3.4. When increased severity and/or frequency is observed in an expected SAE identified in the source document (e.g., Step 6.3.2) then the event is considered "unexpected."

6.3.5. The following items are not used in sponsor determination of expectedness:

6.3.5.1. Informed Consent form,

6.3.5.2. Anticipation of the event or reaction due to the pharmacological properties of the IP, or

6.3.5.3. Published articles, peer reviewed papers, etc.

7. Change Summary

Revision Number	Effective Date	Description of Change
1	25JUL2023	New Document