1. Purpose

To define the process for reviewing a clinical study protocol amendment to determine if the amendment must be submitted to the Food and Drug Administration (FDA) at least 25 days prior to implementation for an Investigational New Drug application (IND) or within 5 days of the Sponsor's knowledge for an Investigational Device Exemption (IDE).

2. Scope

2.1. This standard operating procedure applies to protocols conducted under Center for Cancer Research (CCR)-held IND, IDE, or Non-Significant Risk Device Study (NSR) and overseen by Office of Sponsor and Regulatory Oversight (OSRO).

3. Responsibilities

3.1. OSRO Safety evaluates protocol amendments for impact on subject safety, study objectives and determines if the FDA must be notified.

3.2. OSRO Regulatory evaluates protocol amendments for changes to the investigational agents/device and communicates with the FDA regarding protocol amendments.

3.3. OSRO Sponsor and Regulatory Oversight Support (SROS) Contractor staff assists OSRO Functional Groups as needed.

3.4. The Protocol Support Office (PSO) and/or Principal Investigators (PIs) notify OSRO of protocol amendments.

4. References

4.1. 202 Protocol Development Policy

4.2. 21 CFR §312.30: Investigational New Drug Application – Protocol Amendments

4.3. 21 CFR §812.35: Investigational Device Exemptions – Supplemental Applications

4.4. Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies, FDA, 2006

5. Definitions

Refer to the OSRO Lexicon.

6. Procedure

6.1. The amendment review process targets specific items in order to determine whether the amendment requires FDA review within specified FDA time limits.

6.1.1. For legacy protocols, the review process does not constitute a review of the entire amendment, nor does it constitute Sponsor approval of the amendment.

6.1.1.1. Legacy protocols are those that the initial version was not accepted by OSRO.

6.2. Submission of amendments to OSRO

6.2.1. A draft amendment to a protocol, informed consent and the supporting documents are submitted to the OSRO SROS Request for Service System.

6.2.2. The supporting documents are, as applicable:

- Cover memo
- Investigator's Brochure, Product Label, or Instructions for Use
- A summary of manufacturing information for products that CCR manufactures
- A Manual of Procedures
- Response or change memo to the FDA and/or the Institutional Review Board (IRB)

6.3. OSRO Procedure for Reviewing Protocol Amendments Under an IND

6.3.1. OSRO Regulatory and OSRO Safety independently assess the protocol amendment.

6.3.1.1. OSRO Regulatory evaluates for possible changes to the investigational agents/device.

6.3.1.2. OSRO Safety evaluates for changes in the subject risk/benefit ratio.

6.3.2. All members of OSRO review the protocol for critical issues raised by the amendment.

6.3.3. If the proposed protocol change requires FDA submission at least 25 days prior to implementation, then the PI is notified that the protocol amendment must be submitted to the FDA for a 25-day review.

6.3.3.1. Note: Amendments that include changes to product manufacturing or the addition of a new study agent are submitted to the FDA 30 days prior to implementation.

6.3.4. In all cases, the protocol amendment must be submitted to the IRB for review.

6.4. OSRO Procedure for Reviewing Protocol Amendments Under an IDE

6.4.1. When a protocol amendment is received, OSRO assesses the changes using the same procedure outlined in Step 6.3 with the following exception:

6.4.1.1. FDA notification must occur within 5 working days of the Sponsor's knowledge of a change.

6.4.2. In all cases, the protocol amendment must be submitted to the IRB for review.

6.5. OSRO Procedure for Reviewing Changes in Protocol Using an NSR Device (not conducted under a CCR IND)

6.5.1. When a protocol amendment is received, OSRO assesses the changes using the same procedure outlined in Step 6.3 with the following exception:

6.5.1.1. FDA notification is not required.

6.5.2. In all cases, the protocol amendment must be submitted to the IRB for review.

6.6. OSRO Regulatory submits IND and IDE, legacy, and current protocol amendments to the FDA.

7. Associated Documents

7.1. 202-S01-W01 Reviewing Protocols

8. Change Summary

Revision Number	Effective Date	Description of Change
1	13NOV2019	New Document
2	07JUL2020	Changed the 30-day prior to implementation submission to FDA to 25 days. Added Step 6.3, IDE submission process.
3	03JUN2022	Step 2.2 – added Step 3.4 – added to include assistance by SROS contractor staff Section 4 – added hyperlinks Step 4.4 – added reference Section 6.1 – added Section 6.2 – added Section 6.6 – added NSR-using protocols Step 7.2 – added General updates to procedure and flow
4	08FEB2023	Step 1 – identified that time limits are 25 days for INDs and 5 days for IDEs Step 3.4 – added Step 6.2.1 & 6.2.2 – condensed into one step. All protocol amendments are submitted via the web based OSRO SROS Request for Service System (https://ncirfs.powerappsportals.com/add-rfs-information/). Step 6.2.2 – updated list of supporting documents Steps 6.3.1.3 & 6.3.1.4 – promoted to 6.3.3 & 6.3.4 respectively Step 6.3.1.3.1 – removed Step 6.3.2 – added Step 7.1 – removed
5	07MAR2023	Step 6.3.3.1 – added Step 6.4.1.1 – removed “minor” Step 6.5 – added “(not conducted under a CCR IND)”