

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &  
IMPLEMENTATION**

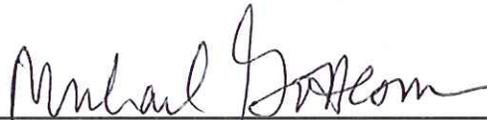
**OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS**

**SOP Number: 9**

**SOP Title: CONTINUING REVIEW BY THE CONVENEED IRB**

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB  
Chairs, IRB Administrators, Protocol Navigators**

**Approval:**

  
\_\_\_\_\_  
**Deputy Director for Intramural Research**

6/27/13  
**Date**

**Date of Implementation:** 6/27/13

## SOP 9. CONTINUING REVIEW BY THE CONVENEED IRB

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## **SOP 9. CONTINUING REVIEW BY THE CONVENED IRB**

### **9.1 PURPOSE**

This SOP describes the policies and procedures for continuing review by the convened IRB. See SOP 7A “Requirements for Expedited Review of Research by NIH Institutional Review Boards” for policies and procedures for continuing review by the expedited process.

### **9.2 POLICY**

Consistent with 45 CFR 46.109(e), and OHRP “Guidance on IRB Continuing Review of Research”, dated November 10, 2010, (see References), NIH IRBs shall conduct continuing review of human subjects research at intervals appropriate to the degree of risk, but not less than once per year.

When conducting continuing review, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the regulatory criteria. The IRB should focus on whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB’s prior determinations, particularly with respect to the IRB’s prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document.

### **9.3 REGULATORY REQUIREMENTS FOR CONTINUING REVIEW**

- A. NIH IRBs conduct continuing review for each research study to ensure the continued protection of the rights and welfare of research subjects in accordance with 45 CFR 46.109(e) and, as applicable, 21 CFR 56.109(e). The IRB applies the same criteria for approval at the time of continuing review as it does for review of initial studies (see 45 CFR 46.111, SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)”, and 21 CFR 56.111).

- B. Continuing review occurs at intervals appropriate to the degree of risk, but not less frequently than once a year. The IRB must set the frequency for continuing review based on its analysis of risk at the time of initial (see SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)”) and continuing review and may increase the frequency of review, i.e., if new information negatively impacts the risk/discomforts and benefits ratio, if the IRB is notified of a complaint or alleged non-compliance or for any other appropriate reason.
- C. Continuing review of research must be substantive and meaningful. At continuing review, the IRB will decide whether the research continues to meet the criteria for IRB approval as set forth in 45 CFR § 46.111.
- D. NIH IRBs will review information provided by the PI about the number and types of vulnerable subjects enrolled and determine whether the protections for vulnerable subjects continue to be adequate (see SOP 14A “Research Involving Vulnerable Subjects (General Considerations)”).

#### **9.4 RESEARCH STUDIES WHICH REQUIRE CONTINUING REVIEW**

- A. Continuing review and re-approval of all non-exempt research studies, including those approved by expedited review (See SOP 7A “Requirements for Expedited Review of Research by NIH Institutional Review Boards”), is required at least annually as long as the study remains active, e.g., human subjects are engaged. Active studies include all non-exempt IRB approved research when, for example:
  - 1. Recruitment of subjects has not yet begun.
  - 2. There is active recruitment and enrollment of subjects.
  - 3. The study is no longer recruiting, but research remains active for long-term follow-up.
  - 4. Subjects have completed all research-related activities and data analysis of private identifiable information is ongoing; or

5. Research is under suspension or administrative hold (e.g., recruitment or enrollment of subjects is suspended see SOP 11 “Suspensions and Terminations of IRB Approval and Administrative Holds”).

B. Federal regulations and NIH policy do not provide for exceptions to the requirement for continuing review; therefore, failure by the Principal Investigator to ensure timely IRB review and approval is a serious matter that could lead to suspension and possibly termination of the study (see Sections 9.12 and 9.13 below) regarding what may occur when IRB approval expires. Continuing research activity on an expired study is considered non-compliant with HRPP policies and regulations and must be reported as described in SOP 16A “Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP)”.

## **9.5 TIMING OF THE CONTINUING REVIEW SUBMISSION**

- A. Continuing review and approval must be completed by midnight on the date on which IRB approval of the research study would expire (the “expiration date”). See Section 9.10 below, for the explanation of how the expiration date is determined.
- B. It is the PI’s responsibility to ensure that the review and IRB re-approval of ongoing research is conducted before the expiration date.
- C. As a courtesy, the IRB office sends at least two separate reminders to the PI of the expiration date.

## **9.6 CONTINUING REVIEW SUBMISSION MATERIALS**

An IRB staff member, or a designee, will review each IRB submission package to determine that each of the required items has been submitted.

- A. Timing: Investigators should not submit continuing review materials too far in advance of the continuing review expiration date but close enough to the expiration date to ensure time to respond, if needed, to any stipulations/conditions.

B. Materials: The PI must submit the following materials for continuing review:

1. A completed NIH Intramural Clinical Research Protocol Continuing Review Application (see Attachment 1 “Intramural Clinical Protocol Continuing Review Application Form”).
2. A dated protocol, if changed from the previous year, with version number, page numbers, and all amendments incorporated.
3. The current IRB-approved informed consent/assent document(s), unless enrollment is complete.
4. If the PI intends to close the study, an Intramural Clinical Protocol Study Closure Application (see Attachment 2 “Intramural Clinical Protocol Study Closure Application”).
5. Amendments to the protocol may accompany the continuing review submission but must be reviewed and approved separately.
6. Aggregated summary reports, as follows (numbers 1-5, below, are also referenced in SOP 16 “Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations” regarding event reporting duties):
  - a. All Unanticipated Problems (UPs).
  - b. All Protocol Deviations (except those expected Protocol Deviations granted a waiver in the protocol - unless it is also a UP).
  - c. All Unanticipated Adverse Device Effects (UADE)
  - d. All Adverse Events (AEs) (including expected AEs, except those specified in the protocol and approved by the IRB as not reportable, i.e., granted a waiver, unless it has been determined by the PI or IRB that they are also UPs).

- e. While preparing the continuing review application, the PI must assess whether expected AEs are occurring at greater frequency or severity than previously expected. If this occurs, the aggregate information may also qualify as a UP and must be reported as such (See SOP 16 “Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations”).
  - b. Any information in the literature, or evolved from similar research, that might affect the IRB’s analysis of risk/benefit for the protocol. If such information is obtained before the time of continuing review, it should be reported to the IRB at the time that it becomes known, and summarized at the time of continuing review.
- C. Any additional requirements of the NIH Human Research Protection Program.

## **9.7 PROCEDURES FOR CONTINUING REVIEW BY THE CONVENEED IRB**

- A. An IRB staff member, or a designee, will review each IRB submission package to determine that each of the required items has been submitted.
- B. NIH IRBs may elect to assign primary (and possibly secondary) reviewer(s) to conduct an initial review of the continuing review materials and present the findings at the convened IRB meeting (See SOP 7B for details). However, all IRB members are provided with and are expected to review the materials described in Section 9.6 above prior to the convened IRB meeting. At the convened IRB meeting, the primary and, if applicable, the secondary reviewer leads the IRB through the criteria for approval, using the IRB’s continuing review checklist, as applicable.
- C. The complete IRB file for the particular protocol will be available to IRB members before, during, and after the IRB meeting.

D. IRB members or the primary and if applicable secondary reviewer, if applicable (see SOP 7B “Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting”), will:

1. Confirm that the current consent/assent is still accurate and complete.
2. Consider if new or additional risks have been identified (e.g. unanticipated problems) that would require changes to the research study protocol, consent form, review frequency, etc.
3. Consider if any new information may impact subjects’ willingness to continue participation.
4. Review the cumulative number of subjects accrued by gender and ethnic/racial category(ies) (see SOP 13 “Recruitment, Selection and Compensation of Research Subjects”).
5. Verify that no material changes have been made since the previous IRB review or determine that independent verification is needed. In making this determination, the IRB takes into account the risk level of the research study; whether the PI has previously failed to comply with IRB requirements; when materials submitted for continuing review include unapproved modifications or inconsistent information, or when the IRB has been informed of non-compliance by other sources.
6. Determine if new NIH policies necessitate changes in the study and/or consent. Changes that do not impact subject safety or welfare may be stipulated for completion prior to the next continuing review or within a stipulated timeframe.
7. Determine that each of the elements of 45 CFR 46.111 is satisfied.
8. If applicable, determine that the requirements of Subpart B (Pregnant Women, Fetuses, Neonates), C (Prisoners), D (Children) are met.

- E. Each study that is scheduled for continuing review at a convened meeting is discussed and voted upon at the meeting (See SOP 7B “Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting”). These votes may be by show of hands or by written ballot, which may be secret and the vote of a simple majority (more than half) of the voting members who are present is required. Additional voting requirements include the following:
1. Each regular member, including the Chair and Vice Chair, and each alternate who is substituting for a regular member, has one vote, unless recused.
  2. The Chair and Vice Chair count towards the quorum, unless recused, and either vote or abstain from voting on all actions for which votes are taken. Chairs and Vice Chairs will recuse themselves, as appropriate, when conflicts of interest exist.
  3. Consultants do not vote (see SOP 2 “IRB Membership and Structure” for use and selection of consultants).
  4. A vote that is cast by an individual on behalf of an IRB member is permitted only when that individual is an appointed alternate for an IRB member or category of members (see SOP 2 “IRB Membership and Structure”).
  5. If circumstances require members’ participation by telephone or video conference, approval of the IRB Chair must be obtained in advance. Members attending by telephone- or video-conference count towards the quorum and may vote only if (1) they have received all pertinent material prior to the meeting and (2) they can participate actively and equally in the discussion of the research study. The IRB minutes must document that these two conditions are met (see SOP 4 “Human Research Protection Program (HRPP) Documentation and Records”).
  6. Members with a real or perceived conflict of interest may not participate in IRB deliberations and will be required to leave the room during the IRB discussion and vote. They may be asked to

provide information prior to deliberations but cannot be included in the quorum. (See SOPs 7B “Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting” and 21 “Conflict of Interest Requirements for Researchers and Research Staff”, for definitions and examples of conflict of interest).

- F. The IRB votes separately on new amendments that accompany continuing reviews.

## **9.8 IRB ACTIONS ON CONTINUING REVIEWS**

The types of action possible at continuing review are the same as for initial reviews (see SOP 7B “Requirements for the Conduct of Research Review at a Convened NIH Institutional Review Board (IRB) Meeting”).

## **9.9 NOTIFYING THE PRINCIPAL INVESTIGATOR ABOUT IRB ACTIONS**

The IRB will notify the PI in writing of the IRB’s determination. See SOP 7B “Requirements for Expedited Review of Research by NIH Institutional Review Boards” which provides additional detail regarding the possible IRB determinations including the following:

- A. Unconditional Approval
- B. Approval with Stipulations – The IRB may approve research with stipulations (conditions).
  - 1. The IRB should be careful to specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies

that the protocol includes the new screening procedure. Suspension of subject enrollment at the time of continuing review would not be considered suspension of IRB approval.

2. After the PI has submitted a response to the IRB-stipulated changes, the IRB Chair or another IRB member or group of IRB members with appropriate subject matter expertise or experience designated by the Chair may approve the PI's response to the stipulations.
- C. Deferred-The protocol is not approved and the PI's responses to stipulations/conditions require review by the convened IRBs
  - D. Tabled-The IRB determines the protocol is not approved because the IRB does not have sufficient information
  - E. Disapproval-The IRB determines that it cannot re-approve a study as submitted.

The IRB communication to the PI will also indicate the next expiration date. The correspondence also reminds the investigator that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

## **9.10 SETTING THE CONTINUING REVIEW (EXPIRATION) DATE**

- A. To determine the date of initial approval, see SOP 7B "Requirements for Expedited Review of Research by NIH Institutional Review Boards".
- B. To determine the date of continuing review:
  1. Setting the date of the first continuing review:
    - a. For a study approved at initial review by the convened IRB without stipulations/conditions, the approval period starts on the date the convened IRB approved the research.

- b. For a study approved at initial review with stipulations/conditions, the approval period starts on the date the Chair or designee approves and signs off on the stipulations/conditions.
    - c. For a study initially approved by expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gave final approval to the study.
  - 2. Setting the date of the second and subsequent continuing reviews:
    - a. No Fixed Anniversary Date: The date of the last IRB approval (with or without stipulations/conditions) determines the latest permissible date of the next continuing review (see Section 9.12, below), **OR**
    - b. Fixed Anniversary Date: If the IRB conducts its continuing review and approves the study for a year-long time period and approves the study (with or without stipulations/conditions) within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.
- C. At the time of initial and continuing review, the IRB will make a determination regarding the frequency of review of the research studies. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but not less than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required (see SOP 7 “Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards (IRBs)”). The meeting minutes will reflect the IRB’s determination regarding the frequency of review (see SOP 4 “Human Research Protection Program (HRPP) Documentation and Records”).

## **9.11 CC OFFICE OF PROTOCOL SERVICES (OPS) ACTIONS FOLLOWING RECEIPT OF THE CONTINUING REVIEW APPLICATION FROM THE IRB**

The OPS will extract required data from the continuing review application and enter it into the NIH Intramural Research Program database. Missing or incomplete information is resolved with the IRB office or the package is returned to the IRB.

For research conducted at the NIH CC, the IRB-approved consent/assent document(s) are posted on the NIH Clinical Research Studies web page. OPS will apply the IRB approval date to the first page of the approved consent document. The period of approval for use of the consent document will be indicated on the last page of the form and will read “THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM “X DATE” (IRB approval date) through “Y DATE” (IRB approval expiration date)

Upon completion of these activities, OPS will provide a signed copy of the NIH Continuing Review Application and the updated watermarked consent/assent document(s) to the IRB office and the PI.

## **9.12 LAPSES: WHEN THE IRB DOES NOT RE-APPROVE RESEARCH BY THE EXPIRATION DATE**

### **9.12.1 NO PROVISION FOR A GRACE PERIOD**

The regulations and NIH policy make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research with or without stipulations/conditions must occur by midnight of the date when IRB approval expires. The IRB Chair and staff do not have the authority to extend the continuing review date of the research. Note that when the IRB re-approves research with stipulations/conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse even if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB’s stipulations/conditions.

### **9.12.2 LAPSE IN IRB APPROVAL**

A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted a continuing review and re-approved the research - with or without stipulations/conditions - by the expiration date of IRB approval. For instance, if a IRB has conducted continuing review but tabled or deferred the research and the expiration date passes, the research has lapsed. However, if the IRB conducted continuing review and approved the research subject to stipulations prior to the date of expiration, the research has not lapsed. In such circumstances, all research activities (including recruitment, enrollment, consent, interventions, interactions, and data collection) must stop unless one of the following IRB actions is taken and documented in the minutes:

The IRB may allow all or a subgroup of already-enrolled subjects to continue in a research project during the period when IRB approval has lapsed if the IRB finds that continuation is in the best interest of the subjects. For example, the IRB may find that research interventions hold prospect of direct benefit to subjects or, alternatively, withholding study interventions may pose increased risk for subjects. The IRB must document its approval for the continuation of research for these subjects.

### **9.12.3 REPORTING LAPSES TO OHRP**

A lapse in IRB approval is not required to be reported to OHRP as a protocol suspension or termination so long as no human subjects research occurs during this time period (aside from possible research performed in accordance with this policy in order to further a subject's best interest).

### **9.12.4 LAPSES AS NONCOMPLIANCE**

If the IRB notes a pattern of non-compliance with the requirements for continuing review, the IRB should determine whether this represents serious or continuing non-compliance that needs to be reported within NIH as described in SOP 16A "Allegations of Non-compliance with Requirements of the NIH Human Research Protection Program (HRPP)".

### **9.13 ACTIONS WHEN IRB APPROVAL LAPSES AND RESEARCH EXPIRES**

When the IRB Office has not received the Continuing Review Application or if the protocol has not been re-approved (with or without stipulations/conditions) by its expiration date, the IRB will notify the PI that all human subjects research under that protocol must stop and notify the OPS, ICD and OHSRP that IRB approval has expired.

#### **9.13.1 ACTIONS AT THE CLINICAL CENTER**

For protocols conducted at the NIH Clinical Center, the OPS will deactivate the research study from the NIH Clinical Research Information System (CRIS) and remove the consent/assent documents from the CC website.

In the event that the IRB has received the application, but not approved the action by the expiration date, the OPS will deactivate the research study from the NIH Clinical Research Information System (CRIS) and remove the consent/assent document(s) from the CC website for studies conducted at the NIH Clinical Center.

#### **9.13.2 ACTIONS AT OTHER SITES OTHER THAN THE CC WHEN AN NIH IRB IS THE IRB OF RECORD**

For expired protocols conducted at sites other than/or in addition to the Clinical Center, the IRB office:

- A. Notifies the PI that human subjects research, consistent with the requirements outlined in Section 9.12.1 above, must cease, and
- B. Notifies OHSRP and the IC Clinical Director that the protocol has expired.

## REFERENCES

- A. 45 CFR 46:  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- B. 21 CFR 56:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56>
- C. OHRP “Guidance on IRB Continuing Review of Research”, dated 11/10/10: <http://www.hhs.gov/ohrp/policy/continuingreview2010.html>
- D. FDA “Guidance for IRBs, Clinical Investigators and Sponsors: IRB Continuing Review After Clinical Investigation Approval, February 2012: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>

## LIST OF ATTACHMENTS

Attachment 1: Intramural Clinical Protocol Continuing Review Application Form

Attachment 2: Intramural Clinical Protocol Study Closure Application

## ATTACHMENT 1: INTRAMURAL CLINICAL PROTOCOL CONTINUING REVIEW APPLICATION FORM

National Institutes of Health

### Intramural Clinical Protocol Continuing Review Application

This application is for human subject research that requires IRB continuing review and approval. NOTE: If also submitting an amendment, complete the Amendment Application)

#### I. Protocol Information

1. Protocol Number
2. Principal Investigator's (PI) name, address and contact information
3. Protocol Title
4. Précis
5. Accrual/Recruitment Status *(select one)*
  - No Recruitment Planned
  - Not Yet Recruiting
  - Recruiting
  - Enrolling by Invitation
  - Suspended
  - No Longer Recruiting, subject follow-up only

- Open for Data Analysis** ~~subjects have completed follow-up and the data is being analyzed, or there is ongoing use of samples/data.~~
- If Expanded Access Study Update Status:** Status indicating availability of an experimental drug or device outside any clinical trial protocol.

This data element is only applicable for Expanded Access records (see Expanded Access under Study Type). Select one.

- Available:** expanded access is currently available for this treatment.
- No longer available:** expanded access was available for this treatment previously but is not currently available and will not be available in the future.
- Temporarily not available:** expanded access is not currently available for this treatment, but is expected to be available in the future.
- Approved for marketing:** this treatment has been approved for sale to the public.

**6. Anticipated date that the protocol will complete data analysis:**  
\_\_/\_\_/\_\_\_\_ (update as necessary–If an observational study zeros may be entered if there is no foreseeable end-date or is open-ended) ~~(populated by the system)~~

**7. Primary Completion Date** (update as necessary) (the date that the final subject will be examined or an intervention received for the purposes of final collection of data for the primary outcome): \_\_/\_\_/\_\_\_\_ ~~(populated by the system)~~

## II. Study Population

- 1. Are you currently recruiting:** (check all that apply) ~~(populated by the system)~~
- Patients
  - Healthy Volunteers
  - Other Volunteers (i.e. Environmental studies, surveys, swabs)
  - NIH Employees <http://oma.od.nih.gov/manualchapters/person/2300-630-3>
  - Non-English Speaking

**2. Does this research involve vulnerable or other special populations?** (check all that apply) ~~(populated by the system)~~

- Children
- Children who are wards of the state
- Prisoners
- Pregnant Women, Fetuses, or Neonates
- Adults who are or may be unable to consent
- N/A

**III. Enrollment Information**

**1. Summary of Protocol Enrollment:** ~~(Also complete Supplement Q)~~

**NIH/CC column:** only subjects seen at NIH/CC

**Other Sites column:** all NIH offsite and non-NIH clinical sites

**Total column:** only total for multi-site studies that include both NIH/CC and other sites, i.e. NIH/CC site + All other sites = Total Accrual

NIH/CC	Other Sites	Total
_____	_____	_____ Accrual Ceiling
_____	_____	_____ New Subjects since Last CR
_____	_____	_____ Aggregate Total Accrued

**2. If the protocol is open to accrual but there has been no subject accrual, or accrual was lower than expected during this past year:** (if applicable)

Explain the reason; summarize the plans for resuming or increasing subject recruitment and enrollment. Comment on whether the lack of accrual affects the overall objectives and scientific validity of the study.

**3. Has analysis by Sex/Gender, Racial, and/or Ethnic Subgroups for Phase III clinical trials been conducted and have significant differences been found?**

- No  Yes (answer a and b)  N/A
- a. Have analyses been reported?  Yes  No (explain\_\_\_\_\_)
- b. Have significant differences been found?  Yes  No

If yes, please describe any differences found.

**IV. Ionizing Radiation Use** (check all that apply) ~~(populated by the system)~~  
([http://www.ors.od.nih.gov/sr/drs/rsc/Pages/forms\\_index.aspx](http://www.ors.od.nih.gov/sr/drs/rsc/Pages/forms_index.aspx))

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- None
- Ionizing radiation exposure – medically indicated
- Ionizing radiation exposure – research indicated
  - Research usage HAS NOT changed
  - Research usage HAS changed (explain)

**V. Investigational New Drug/Device/Biologic/Tobacco Product**

Is the protocol subject to US Food and Drug Administration regulations, or under an Investigational New Drug (IND) Application, Investigational New Biologic (BB IND) Application, Investigational Device Exemption (IDE) or Investigational Tobacco Product (ITP)?

Yes ~~(populated by the system)~~  N/A

Product Name	Manufacturer	Type,select IND BB IND IDE ITP	IND BB IND IDE ITP Number	Sponsor Name	Monitoring Entity

List commercially approved products used to test the research hypothesis ~~(if applicable, populated by the system)~~

Product Name	Manufacturer(s)*	Used as indicated	Off Label

*\*If a generic product with multiple manufacturers, enter "generic" in this column.*

Does the protocol involve a drug/device/product that may lead you or the NIH to receive payment or royalties?  Yes  No

~~(If yes, provide the "Statement of Disclosure" that is in the consent(s).)~~

**VI. Does the protocol involve any Tech Transfer Agreements?**

<http://www.ott.nih.gov/index.aspx>

Yes  No

If yes, select all that apply:

- CDA - Confidential Disclosure Agreement
- CTA - Clinical Trial Agreement
- CRADA - Cooperative Research and Development Agreement
- MTA - Material Transfer Agreement/Human Material Transfer Agreement
- MOU – Memorandum of Understanding
- Other, specify \_\_\_\_\_

**VII. Conflict of Interest**

**Has the Personal Financial Clearance Form (PFCF) form been completed and submitted to the Deputy Ethics Counselor?**

- Yes     No ~~(If no, complete the PFCF form, supplement E, <http://ethics.od.nih.gov/forms.htm>)~~

Date submitted to DEC: \_\_\_\_\_ Date cleared by DEC: \_\_\_\_\_

**Has the Conflict of Interest Certification document been distributed to new Non-NIH Investigators? <http://ethics.od.nih.gov/forms.htm>**

- Yes ~~(If yes, the PI must maintain the Certification documentation in the regulatory files.)~~

- No ~~(If no, complete IRB Supplement F for each non-NIH investigator.)~~

- N/A

**VIII. Progress Information**

- 1. Provide the multi-site data in the aggregate reports and the IRB/Ethics Committee annual review approvals. (if applicable)**
- 2. Provide a description of protocol progress/findings from this research (include interim analysis, if applicable)**

3. **Have any amendments been approved since the last continuing review?**  
 Yes (explain, include changes to investigators, sites, informed consent, study population, etc.)  
 No
4. **Have any unanticipated problems (UPs) (unexpected, related to research, and increases risks to subjects or others) occurred since the Initial Review (IR) or last CR?**  
 Yes  
 No
5. **Summarize unanticipated problems (UPs), reportable adverse events and deviations/violations as defined in the protocol since the last CR and in aggregate since the start of study.**
6. **Have any subjects withdrawn from the study?**  No  Yes  
*If yes, provide aggregate totals for withdrawals and reasons for withdrawal.*
7. **Is this study monitored by a DSMB/SMC?**  No  Yes  
If yes, date of the last DSMB/SMC review \_\_\_/\_\_\_/\_\_\_\_  
*(If not previously submitted, upload the most recent DSMB/SMC outcome letter.)*
8. **Has any information appeared in the literature, or evolved from this or similar research (published/unpublished), that might affect the IRB's evaluation of the risk/benefit analysis of human subjects involved in this protocol?**  
 Yes (explain)  
 No
9. **Risk/benefit assessment:** *(carry over from initial application; indicate if there has been a change)*
10. **Provide an updated list of publications for this protocol for this reporting period (manuscripts and abstracts)**
11. **Provide a justification for continuation of the protocol**

**Authority** – Section 3501 of Title 44 of the U.S. Code authorizes collection of this information. The collection, maintenance & use of personally identifiable information at the NIH are governed under provisions of the Privacy Act of 1974. The information you have been asked to provide on this form is necessary for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural clinical research protocols and will be used solely for those purposes.

## ATTACHMENT 2: INTRAMURAL CLINICAL PROTOCOL STUDY CLOSURE APPLICATION

### National Institutes of Health

#### Intramural Clinical Protocol Study Closure Application

This application is for human subject research that is being closed. Study Closure occurs when research-related interventions or interactions with human subjects have been completed *and* all data or specimen collection and analysis as described in the IRB-approved research plan have ceased.

#### IX. Protocol Information

8. Protocol Number (populated by the system)

9. Principal Investigator's (PI) name, address and contact information  
(populated by the system)

10. Protocol Title populated by the system

11. Précis populated by the system

12. Type of Study Closure *(select one)*

- Completed** – *the study has concluded as described in the protocol.*
- Premature Closure** – *the study has permanently stopped (i.e., recruiting and enrolling participants has ended, participants are no longer being examined or treated; and all data or specimen collection and analysis has ceased) earlier than anticipated by the protocol.*
- Withdrawn** – *the study is stopped prior to enrollment of the first participant.*

13. Reason for study closure *(select all that apply)*

- Primary endpoint reached

- Unanticipated toxicity/risks to subjects
- Slow/Insufficient accrual
- Investigator left NIH
- Closed by the Sponsor/Data Safety Monitoring Board/Institutional Review Board
- Other
- If other, explain:

Provide a brief narrative explaining the reason for closing the protocol.

## II. Enrollment Information

### 1. Summary of Protocol Enrollment: ~~Complete Inclusion Enrollment Report Supplement Q~~

**NIH/CC column:** *only subjects seen at NIH/CC*

**Other Sites column:** *all NIH offsite and non-NIH clinical sites*

**Total column:** *only total for multi-site studies that include both NIH/CC and other sites, i.e. NIH/CC site + All other sites = Total Accrual*

NIH/CC	Other Sites	Total
_____	_____	_____ Accrual Ceiling
_____	_____	_____ New Subjects since Last CR
_____	_____	_____ Aggregate Total Accrued

### 2. Has analysis by Sex/Gender, Racial, and/or Ethnic Subgroups for Phase III clinical trials been conducted and have significant differences been found?

- Yes (*answer a and b*)     No     N/A
- c. Have analyses been conducted?  Yes  No explain: \_\_\_\_\_
- d. Have significant differences been found?  Yes  No  
If yes, please describe any differences found.

## III. Investigational New Drug/Device/Biologic/Tobacco Product

Is the protocol subject to US Food and Drug Administration regulations, and under an Investigational New Drug (IND) Application, Investigational New Biologic (BB IND) Application, Investigational Device Exemption (IDE) or Investigational Tobacco Product (ITP)?

Yes **(populated by the system)**  N/A

Product Name	Manufacturer	Type, select IND BB IND IDE ITP	IND BB IND IDE ITP Number	Sponsor Name	Monitoring Entity

List commercially approved products used to test the research hypothesis (if applicable)

**(populated by the system)**

Product Name	Manufacturer(s)	Used as indicated	Off Label

**IV. Description of the research results**

1. Describe the research results of the protocol.
2. Provide a summary of Unanticipated Problems and reportable adverse events, as defined in the protocol, in aggregate.
3. Have any subjects withdrawn?  Yes  No  
If yes, provide aggregate totals for withdrawals and reasons for withdrawal.

**V. Disposition of collected samples**

- Samples have been used up or destroyed
- Samples have retained identifiers or have been coded and have been transferred to another IRB-approved protocol and/or stored for future use. Identify protocol

number:

- Samples have been de-identified and have been transferred to another IRB-approved protocol and/or stored for use in a NIH-controlled freezer.
- Samples have been transferred to a repository for future use
- Other, specify \_\_\_\_\_

**VI. Disposition of collected data**

- Data with codes/identifiers has be transferred for use by another IRB-approved protocol and/or stored for future use. Identify protocol number:
- Data has be de-identified and transferred for another protocol and/or stored for future use.
- Other, specify \_\_\_\_\_

**VII. Total list of abstracts/publications that resulted from this study:**