NATIONAL INSTITUTES OF HEALTH
NIH Ethics Program

Procedure for Review and Clearance of Clinical Research Protocols

Background

Clinical Research Protocols (protocols) are research studies conducted by NIH staff. The protocol may test something for a specified condition or purpose, e.g., a drug or medical device, or may review previous studies or record the history of a disease or condition. Staff on a protocol consist of a Principal Investigator (PI), possibly a Co-Principal Investigator (Co-PI), one or several Associate Investigators (AI), a Medical Advisory Investigator (MAI), and a Research Contact (RC). There may also be consultants to the protocol, e.g., statistical or scientific consultants. Some of the investigators or consultants may not be NIH employees. To protect the integrity of the protocol and therefore the NIH in general, the financial interests of the NIH employees named on a protocol must be reviewed to confirm that no conflict of interest exists between investigators' official duties on the protocol and their personal or imputed financial interests.

This procedure provides step-by-step guidance for staff in IC Ethics Offices to conduct the conflicts of interest analysis and document that no conflict exists, before the protocol receives final approval by the Institutional Review Board (IRB). Some of this review may have already been conducted during the review of investigator's financial disclosure report and this review will update that analysis. See also the NIH Office of Intramural Research notice to NIH regarding protocol submission and the updated "A Guide for Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH" located on the NIH Ethics Program web site, on the procedures page:
http://ethics.od.nih.gov/procedures.htm#protocol

This review will be accomplished in parallel with the review by the IRB. At any time, the ethics staff reviewer may request additional information from the employee with the expectation that the employee will provide a timely full and accurate response.

Conducting the Review

1. **Receipt of the protocol.** Upon receipt of the protocol, enter data about the protocol into EMIS, under the Principle Investigator's name. See the detailed procedure on the EMIS Help Menu.

   For an amendment for which the protocol was reviewed and cleared within the past six months, and the only change is the addition of NIH personnel, only the new personnel must be cleared. However, if the amendment adds a new drug or other device to be tested, all investigators must be cleared again, regardless of the date of a previous clearance.

2. **Obtain background information.** Read the summary (précis) to determine if any commercial drugs or devices are being studied. If a commercial drug or device is being studied or used in a new or novel way, determine the manufacturer of the product. If you have any questions about the protocol's research and/or the use of any drug or device, call the PI.

   It is useful to review the description of the company and to identify potential competitors to assist the PI in identifying potential conflicts. Using Hoovers or other available resources, look up the company providing the agent being tested and its top competitors. Identify other companies, if any, which are producing a product similar to the one being tested, and which could thus be a potential competitor (and therefore affected by the protocol). This information may help your discussion with the PI.

3. **Review financial interests of the PI, Co-PI, AI, MAI, RC and consultants who are NIH employees.** In EMIS, data from the original HHS-716 and subsequent HHS-717-1 are summarized under the form name **SAO Update**. Look at the date of the last entry for form HHS-717-1. If the last update is less than 6 months old, it is not necessary to ask the employee to submit another update. For employees within your own IC, request updated information from each investigator whose updated information is more than 6 months old. Electronic mail is acceptable; send a copy to the employee's DEC. For employees in other ICs, contact the Ethics Office in that IC and request that they obtain updated SAO information from their employee(s).

   When you have received the updated information from each investigator, enter their data into EMIS, The data for the employees in other ICs will be entered by staff in their Ethics Office. Data entry instructions for form HHS-717-1 are available on the EMIS Help Menu:
   http://ethics.od.nih.gov/emis2/emis2-help.htm

   Note: If an investigator has no SAO data in EMIS, i.e., has never filed either the HHS-716 or the HHS-717-1, the investigator must immediately submit the HHS-717-1 Confidential Report of Financial Interests in Substantially Affected Organizations for Employees of the NIH.

4. **Compare holdings to the protocol.** Compare the commercial interests and potential competitors against the list of SAOs reported by NIH employees on the study. Determine which of the following situations apply and proceed as directed.

   a. If no SAOs are reported by the PI and all other investigators, it is not necessary to contact the PI and the DEC can clear the protocol. Proceed to the next section, **Prepare Protocol Package for DEC Review**.

   b. If the aggregate amount of all SAOs for each individual investigator meets the *de minimis* designated in 5 CFR 2640 Subpart B (i.e., $15,000 for securities), the protocol can be cleared. Proceed to the next section, **Prepare Protocol Package for DEC Review**.

   c. If any investigator's aggregate SAO holdings are greater than the *de minimis*, prepare the list of SAOs for review by the PI, as directed in the next step.

5. **Prepare a list of SAO holdings for review by the protocol PI.** Submit the list of SAOs to the protocol PI for his/her determination of whether any of the reported SAOs post a conflict of interest. List only the holdings; do NOT indicate which investigator holds which interest, and do not include amounts. Ask the PI to indicate which interests are directly and which are indirectly affected so you can determine which are parties to the matter and which are affected non-parties.

   » **Directly affected** outside entities may include those organizations with which the employee has some official interaction, such as a partner in an official collaborative endeavor. These entities may be a 'party' to a particular matter, such as a CRADA partner.

   » **Indirectly affected** outside entities includes those organizations which could be affected by the results of a matter, even though the entity may not be involved in the matter. These entities would be considered 'non-parties' since they are not part of the particular matter, but could be affected by the outcome. For example, the outcome of a drug trial can affect not only the maker of the drug being tested, but also the maker of a competing drug.

6. **The PI returns the list of SAO holdings**. If any of the financial interests can be affected by the protocol, determine which investigator has that interest, look at his/her value of the holding, and

determine appropriate resolution. For investigators outside of your IC, contact the employee's DEC to resolve the conflict. Review the regulatory exemptions (5 CFR 2640 Subpart B) before requiring recusal or divestiture.

Because protocol review affects the initiation or continuation of a study, the review must be accomplished as quickly as possible. DECs or Ethics Specialists contacted for resolution of real or apparent conflict due to SAO holdings will respond as quickly as possible to obtain updated information and/or resolve a conflicting financial interest.

7. **Complete the Protocol Conflict of Interest Statement.** Once all updated information is obtained and conflicts resolved, indicate the outcome of the review and prepare the package for DEC review and signature.

Prepare Protocol Package for DEC Review

When the analysis has been completed and all actual conflicts resolved, the package can be submitted to the DEC for signature. In some cases, the DEC may already have been consulted to finalize resolution of a conflict. The package must contain a discussion of any conflicts found and how they were resolved, including the following:

- » Protocol Conflict of Interest Statement
- » Brief summary (précis) of the study. This can be found on the Protocol Query System (PQS) web site. See Appendix 1.
- » Updated SAO list from EMIS for each NIH employee listed on the Protocol COI Statement. This information is treated as confidential information and must stay in the Ethics Office of the DEC responsible for clearing the protocol.
- » Correspondence from the PI indicating that none of the SAOs reported present a conflict or a brief explanation of any conflicts reported and how such conflicts have been or will be resolved.

Finalizing the Clearance

1. **Finish data entry.** Finish any data entry in EMIS, i.e., date of protocol review.

2. **Return the signed Protocol Conflict of Interest Statement** to the person indicated as cc: below the PI's name. Return only the signed COI statement page; do not forward any of the other information used to conduct the review.

Using the NIH Research Protocol Database

The Clinical Center maintains a Research Protocol Database, which is searchable using the Protocol Query System (PQS). For additional information about a protocol, including investigator names, the lead IC, and type of protocol, use PQS. Instructions for using PQS are included in Appendix 1.

Appendix 1, NIH Protocol Query System (Active Intramural Research Protocols)

The content for the Protocol Query System (PQS) application is a subset of data from the database Protrak, maintained by the Office of Protocol Services (OPS), in the NIH Clinical Center. The site is updated nightly reflecting changes in the protocol actions submitted and approved by the Intramural Institutional Review Board (IRB) and processed by the OPS. The PQS permits ethics staff to identify any official participation in protocols which involve outside entities. The application is available on the NIH intranet (accessible only from NIH computers) at: http://pqs.cc.nih.gov

The application provides 3 search options:

1. Institute of the Principal Investigator
2. Investigator last name
3. Protocol number

Search Instructions

1. Open the web site and logon.

2. Select the type of search desired from the drop down box.

3. Enter the search criteria:

   a. To retrieve by the IC of the Principal Investigator (PI), enter the IC's PQS abbreviation, i.e.,:

CC	CC	NIAAA	AA	NIDCR	DC
NCI	C	NIAID	I	NIEHS	E
NHGRI	HG	NIAMS	AR	NIMH	M
NEI	EI	NICHD	CH	NINDS	N
NHLBI	H	NIDCD	DC	NINR	NR
NIA	AI	NIDDK	DK	NCCAM	AT

   b. To retrieve by PI last name, enter the last name, e.g., Smith.

   c. To retrieve by specific protocol, enter the full protocol number, e.g, 99-C-0058. The sections of the entire protocol number are defined as follows:
      - The first two digits of the protocol number represent the fiscal year during which the protocol was implemented.
      - The next one/two letter(s) represent the IC financially responsible for the protocol.
      - The remaining four digits provide a sequential number assigned to the protocol by the Office of Protocol Services (OPS) in the Clinical Center.

      Protocols in which patients are not seen at the Clinical Center will have either the fiscal year preceded by the letters "OH" (i.e., OH99-C-0083), or the letter "N" preceding the sequential number of the protocol number (i.e., 99-C-N083).

   d. To retrieve IC protocols by year, enter just year and IC, e.g., 05-CC.

4. Click on "Search."

Sort Order of Results

The results for each search will be ordered according to:

- Search by IC: results are sorted by protocol number, from newest to oldest.

- Search by Investigator: results are sorted alphabetically by investigators' last name, first name, and within by protocol number from newest to oldest.

Content of Results

Results of the search include the following information:

Protocol # NIH Intramural protocol number

Title Official title of the study

IRB The Institutional body responsible for the regulatory oversight of the protocol.

Investigator List

Contains the investigators associated with the protocol, identifying:

- Name
- Role: Association to the protocol
  - » PI: Principal Investigator
  - » AI: Associate Investigator
  - » MAI: Medical Advisory Investigator
  - » RC: Research Contact
- Start Date: Reflects the date on which the investigator was first identified in one of the four roles. Dates were retrospectively entered for investigators serving as PIs, using the earliest date in which s/he started. The date 11/1/05, point of implementation, is reflective as the start date for Investigators who are not PIs. The actual ate an investigator assumed responsibility in one of the 4 roles will be used from this point forward for any new investigators.
- IND/IDE List: Identifies investigational drugs/devices identified by the PI on the initial/continuing review protocol application.
- Commercial Entities: identifies commercial or other entities providing the IND/IDE as identified by the PI on the initial or continuing review protocol application.
- Precis: The scientific summary of the protocol.

Assistance

Questions may be addressed to and assistance obtained from:

Kim Jarema Office of Protocol Services 301-435-2401 kjarema@cc.nih.gov

NIH/NEO (DC/FP/TM); 6/11/2007; 2:17pm
Updated 5/16/08 to reflect new NIH procedure/policy documents FP
File Name: E:\NEO\Protocol Review\Protocol-Review-Instructions.wpd