PURPOSE: To establish the process for submitting research documents to the Duke University Health System Institutional Review Board (DUHS IRB), to the Division of Allergy and Infectious Diseases (DAIDS) Regulatory Compliance Center (RCC) and to pharmaceutical company sponsors in order for receipt of approvals to conduct research from these authorities.

POLICY: The clinical research coordinators assigned to the Protocol Office will assemble and oversee the submission of research documents to the IRB, the DAIDS RCC and pharmaceutical company sponsors and receipt of approvals and ensure that the Protocol Office functions within applicable guidelines and regulations of Good Clinical Practice, Code of Federal Regulations, HIPAA Regulations, sponsor requirements and the Duke University Health System (DUHS).

RESPONSIBILITY:
Each Clinical Research Coordinator (CRC) is educated and trained to prepare and compile research documents for submission to the IRB, the DAIDS RCC and pharmaceutical company sponsors, recognize and make changes necessary for those documents, and systematically complete each step of this SOP.

PROCEDURE:

1. BACKGROUND

A) DUMC IRB Panels

Duke University Health System has six Institutional Review Board panels. Panels 1, 2, 3, and 4 meet to discuss routine protocols submitted by Duke University Medical Center (DUMC) staff. Panel 5 is convened to discuss research at Durham Regional Hospital (DRH). Panel 6 is convened as needed for rapid response to discuss extraordinary protocols deemed academically or financially important to the institution. Each panel of the IRB has one assigned Chair and one Vice-Chair.

B) IRB Office Structure

The IRB Administrative Offices include an IRB Executive Director, IRB Administrative Director, Board Specialists and Medical Writers. Each Board Specialist is assigned to an IRB panel to assist the Chair and Vice-Chair to prepare for the meetings. Each Board Specialist also is assigned to a selection of departments to process the paperwork received for research protocols and interact with departmental staff regarding their research. However, simply because the Division of Infectious Diseases (ID) is assigned to one Board Specialist, the research for ID does not automatically go only to the IRB panel to which that Board Specialist is assigned. Organizational charts for the IRB panels and administration are attached to this SOP.

C) IRB Meetings

The current IRB meeting dates for the first four panels are scheduled for the 1st Thursday for panel 1, the 2nd Thursday for panel 2, the 3rd Wednesday for panel 3 and the 4th Wednesday for panel 4 of each month. Panel 5 meets the 4th Wednesday of each month. Panel 6 meets as needed. There are no deadlines for submitting research protocols to the IRB prior to a particular meeting.

The current roster of IRB panels, IRB personnel and IRB meeting schedules are posted on the Internet at http://irb.mc.duke.edu/.

D) IRB Numbers

IRB# xxxx – xx - x(Rx)(ER)
(a) (b) (c)

Where:

(a) is a number assigned by the IRB sequentially in order of submission and will be retained throughout the lifetime of the study. Note that prior to 2000, the assigned sequential number changed annually at the time of the renewal.
(b) represents the year of initial approval or renewal approval
(c) represents the month of approval; the "R" number is the number of times the study has been renewed; ER indicates expedited review. A new protocol will not have an "R" number but may have an "ER" designation. For an initial approval the number 0 is placed after "R" or "ER".

Examples: (1) IRB# 4347-02-12R0
The study was the 4347th study approved by the IRB. It was initially approved in December of 2002.

(2) IRB# 2495-03-3R2
This study was re-approved for the second time. Therefore, original approval was in March of 2001.

IRB SUBMISSIONS

A) Initial Submission

1) **IRB New Research Study Protocol Submission Form**
This submission form is posted on the website at http://irb.mc.duke.edu/forms.htm. Complete the first two pages of this form. Attach a summary of the protocol (summarize the protocol in 1-4 pages) including the following elements:
- Purpose of the study
- Background and significance
- Design and procedures
- Risk/benefit assessment
- Subject identification, recruitment and compensation
- Subject competency
- Costs to the subject
- Data analysis and monitoring
- Data storage and confidentiality

2) **Consent Form**
(See the DART SOP for consent forms.)

3) **Obtain Signatures**

Submit the DUHS IRB New Research Study Protocol Submission Form, consent form(s), study protocol and other documents (such as Investigator's Drug Brochures, patient education sheets, advertisements, grant or funding source information) to the following individuals (in order listed) for review and signature:

- Principal Investigator
- Department of Medicine (or OB/GYN) representative to the IRB ("first reviewer")
- Other reviewers such as Radiation Safety Officer, CRU Reviewer, as needed
- Division of ID Chair (not necessary for Division of Maternal/Fetal Medicine)
- Department of Medicine (or OB/GYN) Chairman

The signatories may make suggestions for changes to the protocol summary, consent form(s) and/or other documents for clarification. Any requested changes must be made before the protocol is submitted to the IRB.

4) **Deliver submission packet** to the IRB drop-box in the lobby of Seeley G. Mudd Library (keep one copy of each document for ID Protocol Office):
   - IRB New Research Study Protocol Submission Form and consent form(s) (original and two copies)
   - Three copies of sponsor's protocol
   - Three copies of grant renewal documents for federally sponsored protocols
   - Three copies of associated documents (Investigator's Drug Brochures, patient education sheets, advertisements, questionnaires, certificates of confidentiality, etc.)
   - Three copies of both the IRB reviewer and the Principal Investigator checklists
   - A copy of either a Review Preparatory to Research (for studies where no private health information is required prior to consent) or a Waiver or Alteration of Consent and HIPAA Authorization (which gives the research

team the ability to search for potential subjects and therefore have access to private health information prior to consent)

B) Amended Protocols

Amendments to IRB-approved research are submitted on a Request for Review of an Amendment to an IRB Approved Protocol with the Principal Investigator's signature.

When to Amend a Protocol

The file for each protocol maintained by the IRB must be an accurate record of how the study is being conducted. Thus, changes must be recorded in the file and in most cases (see below), receive prior written approval.

The federal regulations governing research with human subjects have this to say about the prior review of minor changes:

> "An IRB may use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized."

This directive leaves the IRB with the task of defining which changes are "minor," which are "major," and which fall below the threshold altogether, for example, a change in contact information. Given the complexity of the research enterprise, it is not possible to offer finite descriptions of categories of change, but only general guidelines. When in doubt, please contact the IRB staff.

Classification of Changes

As a general guideline, major changes would affect the experience of the subjects in some way, for example:

1. Introducing a new procedure or instrument
2. Revising the consent process

3. Changing the risk/benefit analysis
4. Adding a new subject population
5. Changing the investigator
6. Changing the target accrual number to reflect an increase in the original projection.

Examples of minor changes would include:

1. Adding questions to an approved instrument (providing the questions don't change the experience or risk to the subjects)
2. Revising a consent form to improve readability without changing the content
3. Adding one more iteration of a previously approved interview procedure to a longitudinal study
4. Adding HIPPA language to a consent form
5. Deleting an instrument

Examples of changes that are less than "minor" and that would not require IRB approval might include:

1. Changing contact information
2. Including an example to clarify a question

Although IRB approval is not required for less than "minor" changes, investigators should forward documentation of the changes to the IRB so that the protocol file can be made current.

Type of Review

As noted above, minor amendments to approved protocols may always be approved using the expedited review process. Determining the type of review required for major changes is more complex. Major changes may be reviewed through the expedited review procedures or may need review by the full IRB, depending upon the type of initial review and the level of risk. Please consult the IRB staff.

Other items in the submission packet may include an amended protocol (new version), letter of amendment , clarification letter, the consent form(s) revised in accordance with the amendment (if the amendment includes changes to the consent document), and any other items that need to be submitted with the protocol.

C) Safety Materials
(See DART SOP for submitting product safety documents to the IRB.)

D) Annual Review
A renewal application for IRB periodic review must be submitted by the first day of the month prior to the expiry month. For example, if the approval date is 8/2/03, approval expires on 8/1/04 and the renewal application is due by July 1, 2004. The renewal application includes the DUHS IRB Research Protocol Renewal Research Study Protocol Submission form, an updated summary of the protocol, copy of the most recently approved consent form(s), revised consent form(s), copies of all IRB-approved advertisements and patient education sheets and an annual report. The same review process, signature requirements and submission documents are required for this submission as with the original submission.

The basic requirements for the annual report are:

- Description of any SAEs or unanticipated problems involving risks to human subjects
- Complaints about the research
- Substantive or proposed substantive changes in the research
- New information or literature on possible risks to human subjects associated with this study

- Any internal audits
- Any available preliminary results
- The number of subjects enrolled/participating during the past year and cumulatively
- The number of subjects who refused to participate, terminated early or completed the study in the last year and cumulatively
- Study enrollment status (open or closed to accrual)
- Information regarding receipt of study drug
- Information regarding any potential risk related follow-up procedures
- The cumulative number, gender, and race of enrolled subjects enrolled to date

2) IRB REVIEW

A) Pre-Review

When the submission packet is received by the IRB administrative office, the Board Specialist enters it into the IRB database and the protocol is assigned a bar-coded IRB number for tracking purposes. A Chair or Vice-Chair reviews the packet to determine whether it is exempt from full board review. If it is exempt, then the Chair/Vice-Chair may review it at that time. If it is not exempt, then an IRB reviewer is assigned to make an initial review of the protocol. The Board Specialist

sends a copy of the submissions packet to the IRB reviewer for their pre-review. The IRB reviewer may contact the Protocol Office for changes to/clarifications of the submissions packet any time up to the day of the IRB panel meeting. The changes/clarifications must be completed before the research is discussed at the IRB panel meeting. This Pre-Review process is the reason there is no set deadline for submission of a packet for a particular IRB meeting date (the pre-review takes an indeterminate amount of time). The IRB Medical Writers may review the consent form(s) before the IRB meeting and may request 1) modifications via facsimile, or 2) an electronic copy of the consent form(s) to make needed modifications. If the Medical Writer makes changes electronically, request a copy of the changes before

the consent form(s) goes to the IRB panel meeting. It is possible the Writer will make changes unacceptable to the DAIDS RCC. Refer questionable changes to the AACTG Operations Center Clinical Trials Specialist listed in the protocol.

B) Approval notice

Initial IRB review may lead to 1) approval, or 2) approval with modifications. Notices are faxed to the site by the IRB Board Specialist.

1) Documentation of IRB approval without modifications is indicated by the signature of the IRB chair or another authorized official on the original submission form. The approval box is checked. A Notification of Approval letter that is also faxed with pertinent study related information (study title, PI, sponsor, date of approval, expiration date, type of review, etc) with the signature of the IRB chair or another authorized official.

2) Documentation of IRB approval with modifications is indicated by the signature of the IRB chair or another authorized official on the submission form. Both the approved and modifications boxes are checked. A Modifications Form will also be faxed which includes the requirements for final IRB approval. Other parts of the submission may also be faxed with needed changes noted.

   Modifications may include:

   - address questions regarding the research study
   - make additions or changes to the consent form(s)
   - need other approvals, such as CRU Committee or Radiation Safety (for research related x-rays, etc.)

   Final IRB approval is granted only after <u>all</u> modification issues are completed and authorized by the IRB office. The Notification of Approval letter will be faxed with the signature of the IRB Chair or another authorized official. In addition, the IRB stamps the final page of the consent form(s) with the date of approval and the expiration date (one year following initial approval or annual renewal). Once the approval

letter and final stamped consent form(s) page are received, the protocol is approved by the DUHS IRB.

3) FINAL REVIEW

A) Submission to RCC (DAIDS only)

Follow the DAIDS ACTG SOP for submission of site registration packets. The current site registration checklist is located at http://rcc.tech-res-intl.com/forms.htm. Packets are faxed to the RCC. Completed Forms FDA 1572 may be faxed to the RCC, but the original must be submitted also.

B) Approval notice from RCC (DAIDS only)

The RCC sends email notices to document receipt of packet, request changes necessary prior to approval and final approval for the protocol version.

C) Pharmaceutical Company Sponsors

Each pharmaceutical company has its own requirements for final approval. This information should have been given by them to the Protocol Office prior to the original submission.

History

Version	Effective Date	Supersedes	Review Date	Change
S007.1		NA		*Initial Release version S007.1*

Approval

Janet Mueller

Signature Date

Regulatory Coordinator

Charles B. Hicks, MD

Signature Date

Principal Investigator