

Title:	IRB Review Process		
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## 1 Purpose

The IRB will review and ensure that University of North Carolina at Chapel Hill (UNC-Chapel Hill) research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited Review
- Review by Convened IRB

The following describes the procedures required for the review of research by the on-site IRB. (See SOP 901 for a description of the procedures for review of research by the *off-site/external IRBs*.)

## 2 Procedure

### 2.1 Expedited Review

An IRB may use the expedited review procedure to review either or both of the following:

1. Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk.
2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Note: review of minor changes does not alter the end-date of study approval.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--used by the IRB.

#### 2.1.1 Categories of Research Eligible for Expedited Review

The UNC-Chapel Hill applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998.

The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

The categories in this list apply regardless of the age of subjects, except as noted in category 2.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may not be used for classified research involving human subjects.

Research Categories one (1) through seven (7) may be used for both initial and continuing IRB review:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. (Note: Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.)

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i)

mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization; (k) vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

(4) Collection of data through noninvasive procedures, not involving general anesthesia or sedation, routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Note: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(2) and b(3). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior); or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Categories 8 and 9 apply only to continuing review.

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research at the UNC-Chapel Hill is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects (Note: "Long-term follow-up" includes research interactions that involve no more than minimal risk to subjects (e.g., quality of life surveys); and collection of follow-up data from procedures or interventions that would

have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not interventions that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.); or

(b) Where no subjects have ever been enrolled at the UNC-Chapel Hill and no additional risks have been identified (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.); or

(c) Where the remaining research activities at the UNC-Chapel Hill are limited to data analysis. (Note: Simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subject research and thus does not require continuing review.

(9) Continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified. (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.)

### **2.1.2 Expedited Review Procedures**

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB

As warranted, the Chair, in collaboration with the Office of Human Research Ethics (OHRE) Director will designate a list of IRB members eligible to conduct expedited review of submissions. The designees must be experienced voting members or alternate members of the IRB. Selected reviewers will have the qualifications, experience and knowledge in types of research to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review (i.e., CIP certified members or non-CIP certified members who have completed training and demonstrated proficiency). IRB members with a conflict of interest in the research may not conduct the expedited review.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documentation that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer will determine and document the regulatory criteria allowing use of the expedited review procedure in IRBIS, the electronic application.

If the research meets the criteria allowing review using the expedited procedure, the reviewer(s) conducting initial or continuing review will document the regulatory criteria allowing use of the expedited review procedure in IRBIS. The same criteria of approval apply to reviews conducted via expedited review as to those conducted by the convened board. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB and the research study will be placed on the next available agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Section 2.3 (Criteria for IRB Approval of Research) and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the convened IRB. If modifications are required, the OHRE staff will inform the investigator in writing.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the IRB Chair may make a final determination or the study will be referred to the convened IRB for review.

### **2.1.3 Informing the IRB**

All members of the IRB will be apprised of all expedited review approvals by means of a list in the agenda for the next scheduled meeting. Any IRB member can request to review any study by contacting the OHRE.

## **2.2 Convened IRB Meetings**

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all non-exempt research at convened meetings at which a quorum (see below) of the members is present.

### **2.2.1 IRB Meeting Schedule**

The IRB meets on a regular basis throughout the year. Each IRB generally meets once a month on a regularly scheduled day (e.g., first Monday of each month). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings is posted on the IRB website ([ohre.unc.edu](http://ohre.unc.edu)). Special meetings may be called at any time by the Chair or OHRE Director.

### **2.2.2 Preliminary Review**

The IRB Analyst will perform a preliminary review of all submissions for determination of completeness and accuracy, including an informed consent checklist, when applicable. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed either by e-mail, phone or in person of missing materials and the necessary date of receipt for inclusion on the agenda. If an investigator is submitting for the first time or is not be well-versed in the submission procedures, consultations can be arranged with IRB staff.

The IRB defers to another meeting, IRB, or obtains consultation if there is not at least one person on the IRB with appropriate scientific or scholarly expertise or other expertise or knowledge to conduct an in-depth review of the protocol.

### **2.2.3 Primary and Secondary Reviewers**

After it has been determined that the submission is complete, the IRB Analyst with the assistance of the IRB Chair, as needed, will assign submissions for review paying close attention to the subject matter of the research, the potential reviewer's area/s of expertise and representation for any vulnerable populations involved in the research. The "primary reviewer" will be assigned to each submission and have access to and review the full submission materials. A reviewer may be assigned several submissions or other items for review. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (See SOP 401.7, Use of Consultants). Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

Primary and secondary reviewers are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research and leading the IRB through the regulatory criteria for approval (See Section 2.3, Criteria for IRB Approval of Research).
4. Making suggestions for changes to the proposed research, where applicable.
5. Performing an in-depth review of the proposed research, including review of any relevant grant applications and/or protocol.
6. Completing the applicable *IRB Reviewer Checklist*.

A "secondary" reviewer may be assigned in addition to the primary reviewer. A secondary reviewer will be assigned to review the full submission materials.

All IRB members have access to and are expected to review all studies, not just those assigned as primary or secondary reviewer.

When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer may be assigned, providing that they have sufficient time to review the materials in advance of the meeting. Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

#### **2.2.4 Materials received by the IRB**

All required materials need to be submitted to the OHRE approximately two weeks prior to the convened meeting for inclusion on the IRB agenda. The meeting agenda will be prepared by the IRB analyst in consultation, as needed, with the IRB Chair. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, and research submission materials approximately 10 business days before the scheduled meeting to allow sufficient time for the review process. Continuing education materials are emailed to all IRB members on the first day of each month.

Each IRB member reviews the following documentation, as applicable, for all studies on the agenda:

- A Protocol/Research Plan Summary or the complete Protocol
- The Study Application
- Proposed Consent / Parental Permission / Assent Form(s)
- Recruitment materials including advertisements intended to be seen or heard by potential subjects

The primary and secondary reviewers review, in addition to the above, (1) the full protocol/research plan, (2) any relevant grant applications; and, (3) the investigator's brochure (when one exists) and/or other risk information. Additionally, for DHHS-supported multicenter clinical trials, the primary reviewer should receive and review a copy of the DHHS-approved sample informed consent document(s) (when one exists) and the complete DHHS-approved protocol/research plan (when one exists). All members have access to all study materials described above.

If an IRB member requires additional information to complete the review, they are encouraged to contact the investigator directly or may contact the IRB Analyst to make the request of the investigator.

Primary and secondary reviewers will use the appropriate UNC-Chapel Hill *IRB Reviewer Checklist* as a guide to completing and documenting their review.

#### **2.2.5 Quorum**

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained

for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the IRB staff, will confirm that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the IRB staff, will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing all non-scientific members or another required member, the IRB cannot take further actions or vote on regulatory determinations until quorum is restored, even if half of the members are still present. The IRB Staff will monitor the arrival and departure for all IRB members and notify the IRB Chair if a quorum is not present. An attendance/vote card is completed by the IRB Staff to determine and document whether the IRB meeting is appropriately convened and quorum is maintained.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (i.e., the “non-scientist”) will be present at all IRB meetings. An individual may serve as both the unaffiliated and non-scientist member. The IRB may, on occasion, meet without representation of the unaffiliated member; however, this should be the exception.

If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or persons with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with those subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. Whether or not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

### **2.2.6 Meeting Procedures**

The IRB Chair will call the meeting to order, once it has been determined that a quorum is in place. The Chair will remind IRB members to recuse themselves from the discussion and votes by leaving the room when they have a conflict. The Chair will provide an opportunity for members to discuss the minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If major revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The Primary Reviewer will present an overview of the research and assist the

Chair in leading the IRB through the completion of the regulatory criteria for approval. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the IRB analyst to record the proceedings of the session. In addition, the IRB Office Assistant and IRB analyst are responsible for taking Minutes at each IRB meeting.

### **2.2.7 Guests**

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. Attendance is generally reserved for studies that are under reconsideration. The investigator/research staff may not be present for the deliberations or vote on the research.

All meeting guests will be listed on the Attendance/Vote Card and documented in the meeting minutes.

The OHRE Director and staff may attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless they have been appointed as an IRB committee member.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair. All guests will be asked to sign a confidentiality agreement and do not participate in discussion unless requested by the IRB, under no circumstances may they vote.

## **2.3 Criteria for IRB Approval of Research**

In order for the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must determine that the following requirements are satisfied. These criteria apply to all categories of IRB reviews including initial reviews, continuing reviews, and modifications of previously approved research.

- 1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- 2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- 3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally

disable persons, or economically or educationally disadvantaged persons.

- 4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.116].
- 5) Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.117].
- 6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- 7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- 8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

### **2.3.1 Risk/Benefit Assessment**

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves a series of steps:

1. Identify the risks associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive even if not participating in research;
2. Determine whether the risks will be minimized to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;
3. Identify the anticipated benefits to be derived from the research, both direct benefits to subjects and possible benefits to society, science and others;
4. Determine whether the risks are reasonable in relation to the benefits, if any, and assess the importance of the knowledge to be gained;

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research - as distinguished from risks and benefits subjects would receive even if not participating in the research.

In addition to evaluation of the risks in the research, the IRB determines, based on the materials submitted by the investigator, that research studies have the resources necessary to protect participants, such as adequate time for the researchers to conduct and complete the research, adequate number of qualified staff, adequate facilities, access to a population that will allow recruitment of the necessary number of participants, availability of medical or psychosocial resources that participants might need as a consequence of the research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

### **2.3.2 Scientific or Scholarly Review**

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to reasonably expect the research to answer its proposed question.

In making this determination, the IRB may draw on its own knowledge and expertise, and/or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, or departmental review. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation that the above questions were considered must be provided to the IRB for review and consideration.

Scientific or scholarly review is documented and provided to the IRB by the Scientific Review Committee for all biomedical research conducted at the University of North Carolina at Chapel Hill involving procedures that pose greater than minimal risk that have not received external independent scientific/scholarly review or multi-center industry-sponsored research.

Scientific or scholarly review of research not meeting the above criteria can be delegated to a departmental or other appropriate review committee.

### **2.3.3 Equitable Selection of Subjects**

The IRB determines by reviewing the application, protocol/research plan and other materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;

- Scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

At the time of the continuing review the IRB will determine that the investigator has followed the subject selection criteria that was originally set forth at the time of the initial IRB review and approval.

#### **2.3.4 Recruitment of Subjects**

The investigator will provide the IRB with a plan for recruitment of all potential subjects. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence). See Section 2.4.10 for a discussion of IRB review of advertisements and Section 2.4.11 for a discussion of IRB review of payments.

#### **2.3.5 Informed Consent**

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See SOP 1101 for detailed policies on informed consent.

#### **2.3.6 Data and Safety Monitoring**

For all research that is more than minimal risk, the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the monitoring results to the IRB. When applicable, the monitoring plan should include information regarding an independent Data and Safety Monitoring Board (DSMB).

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects and address problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether or not a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study.

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

1. Monitoring is commensurate with the nature, complexity, size and risk involved.
2. Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
4. A written Data and Safety Monitoring Plan (DSMP) prospectively identifies and documents monitoring activities intended to protect the safety of the subjects, the validity of the data and the integrity of the research study. The DSMP may also identify when to terminate a subject's participation (i.e. individual stopping rules) and/or the appropriate termination of a study (i.e. study stopping rules). The nature, size, risk, and complexity of the study will determine whether and how to address the following seven elements within the DSMP:
  - Subject Safety – monitoring is conducted to avoid or minimize risks (i.e. physical, psychological or social).
  - Data Integrity – monitoring is conducted to assure data is accurate and complete. Monitoring of data assures adherence to the approved clinical study.
  - Subject Privacy – monitoring is conducted to assure individual's rights are protected.
  - Data Confidentiality – monitoring is conducted to assure data is secured.
  - Product Accountability – monitoring is conducted to assure drug(s) or device(s) are tracked and accounted for.
  - Study Documentation – monitoring is conducted to assure that required documentation and reports are on file, accurate, and complete.
  - Study Coordination – monitoring is conducted to assure that investigator delegation and communication with the research team is planned and systematic.
5. For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should describe:
  - The composition of the board or committee. Generally, a DSMB should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.
  - Frequency and content of meeting reports

- The frequency and character of monitoring meetings (e.g., open or closed, public or private)
- The Charter should be provided, when one exists

In general, it is desirable for a DSMB or DMC to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB or DMC as a condition for approval of research where it determines that such monitoring is needed. When DSMBs or DMCs are used, IRBs conducting continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study wide interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

### **2.3.7 Privacy and Confidentiality**

The IRB will determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data.

#### **2.3.7.1 Definitions**

**Privacy.** Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

**Confidentiality.** Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

**Private information.** Information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

**Sensitive Information.** Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information (e.g., could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation).

**Identifiable information.** Information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

#### **2.3.7.2 Privacy**

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual subjects. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access subjects or subjects' private, identifiable information and the subjects' expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

In developing strategies for the protection of subjects' privacy, consideration is given to:

1. Methods used to identify and contact potential participants
2. Settings in which an individual will be interacting with an investigator
3. Appropriateness of all personnel present for research activities
4. Methods used to obtain information about participants, and the nature of the requested information including minimizing the information obtained to achieve the aims of the research
5. Information that is obtained about individuals other than the "target subjects," (e.g., a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of "human subject"

### **2.3.7.3 Confidentiality**

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects will be inappropriately divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate or unintentional disclosure.

At the time of initial review, continuing review and with any requests for modification, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. Additionally, the investigator will provide information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all information received from the investigator and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality (CoC) be obtained to additionally protect research data (See AOP 2001.9 for additional information about the use of a CoC.)

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and organizational requirements and policies regarding the use of information and information security.

Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of 21 CFR Part 11.

### **2.3.8 Vulnerable Populations**

Certain individuals, by nature of their age or mental, physical, economic, educational, or other situation, may be more vulnerable to coercion or undue influence than others. At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to SOP 1201.

## **2.4 Additional Considerations**

### **2.4.1 Determination of Risk**

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research plan. Risks associated with the research will generally be classified as either "minimal" or "greater than minimal" with additional classifications as required by the various subparts or FDA regulations. Risk determinations may vary over the life of a research plan depending on the procedures and risks that subjects will be exposed to as the research progresses. The level of risk associated with the research influences eligibility for expedited review. The meeting minutes will reflect the convened IRB's determination regarding risk levels; expedited reviewers will document the determination of risk level in IRBIS.

### **2.4.2 Period of Approval**

At the time of initial review and at continuing review, the IRB will make a determination regarding the period of approval. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the convened IRB's determination regarding review frequency; expedited reviewers will document the determination of risk level in IRBIS.

IRB approval is considered to have lapsed at midnight on the expiration date of the approval (i.e., the expiration date is the last day research can be conducted). For a new study reviewed by the IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or expedited reviewer approves the research or the date ("effective date") that it is verified that the requirements of the IRB have been satisfied following an action of "Conditions Required for Approval". The expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after the date of convened IRB approval (with or without conditions).

For subsequent continuing reviews of a research study subject to convened board review, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators should allow sufficient time for development and review of continuing review submissions.

IRB review of a proposed modification to research ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full research project, not simply a change to it.

The regulations 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 must occur by midnight of the date when IRB approval expires.

### **2.4.3 Review More Often Than Annually**

The following factors will be considered when determining which studies require review more frequently than on an annual basis:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The overall qualifications of the investigator and other members of the research team.
4. The specific experience of the investigator and other members of the research team in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events/unanticipated problems more likely.
7. The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (e.g., terminally ill)
8. A history of serious or continuing non-compliance on the part of the investigator.
9. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review must be documented in the

minutes.

#### **2.4.4 Independent Verification That No Material Changes Have Occurred**

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes occurred during the IRB-designated approval period.

The IRB will determine the need for verification from outside sources on a case-by-case basis. The following factors will be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
5. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
6. Research without a routine monitoring plan.
7. Any other factors the IRB deems verification from outside sources is relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may require such verification at the time of continuing review, review of modification requests and/or unanticipated problems.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see SOP 1402 on Non-compliance).

#### **2.4.5 Consent Monitoring**

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (e.g., consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

1. High risk studies;

2. Studies that involve particularly complicated procedures or interventions;
3. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
4. Studies involving study staff with minimal experience in administering consent to potential study participants; or
5. Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (e.g., prior investigator non-compliance, etc.).

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

The responsible party for conducting this activity will be the IRB monitor (i.e., an unbiased observer appointed by the Director of the Office of Human Research Ethics/IRB). The Principal Investigator if responsible for complying with this policy.

#### **2.4.5.1 Consent Monitoring Procedure**

1. The IRB monitor may or may not provide advance notice to the Principal investigator or other members of the research team. When research is being conducted in the Clinical and Translational Research Center (CTRC), the IRB monitor will review the CTRC schedule and select study visits during which informed consent is scheduled to occur.
2. If the Principal investigator is notified in advance, he/she must respond to the IRB's request in writing (i.e., email) within 10 working days
3. Prior to the consent monitoring process, the IRB monitor will introduce him/herself to the potential participant, explain the reason for his/her presence and obtain the participant's verbal permission for observing the consent process.
4. During the monitoring process:
  - a. The IRB monitor will monitor the process of informed consent conducted by the PI (or designee) with the prospective research participant and/or the participant's legally authorized representative/guardian.
  - b. The IRB monitor will collect data on the informed consent process by employing a variety of methods, including but not limited to, a physical presence (monitoring) during the consent process and/or employing the use of open-ended questions to evaluate the effectiveness of the consent process and the use of a monitoring checklist. The IRB monitor will determine whether:
    - c. The consent document includes all of the required and applicable additional elements (outlined in 21 CFR 50.25).
    - d. The information in the consent document and any other written information was clearly and accurately *explained* to the participant or the participant's legally authorized representative/guardian

- e. Adequate time was available to review the research with the participant and/or the participant's legally authorized representative/guardian.
  - f. The participant and/or legally authorized representative/guardian were given an opportunity to ask and have their questions answered.
  - g. The consent process was free of coercion or undue influence.
  - h. The participant and/or legally authorized representative/guardian comprehended the information that was presented to them. This may be accomplished by soliciting the participant's and/or participant's legally authorized representative's understanding by employing the use of open-ended questions.
  - i. The information that is given to the participant and/or legally authorized representative/guardian was in a language understandable to them.
  - j. The informed consent was free of exculpatory language.
  - k. The informed consent process was appropriately documented.
5. Following the monitoring process:
- a. The IRB monitor may discuss any initial observations privately with the individual who conducted the consent process. If the observation indicates that the consent process is not legally effective, the participant must be re-consented or may not be entered into the research, in which case the Principal Investigator will be promptly notified.
  - b. The IRB monitor will determine if additional education is required and/or if a second consent monitor visit should be scheduled.
  - c. Within 10 business days, the IRB monitor will prepare a written summary of the consent process and summarize his/her findings and if applicable, recommendations. The report will be shared with the OHRE Director and if applicable, the person(s) who requested the monitoring visit.
  - d. The IRB monitor will contact the Investigator (via e-mail) to set up a mutually convenient time to meet to review the findings of the monitoring visit. The written summary will be reviewed during the meeting which will be scheduled no later than 15 business days following the monitoring visit.

#### **2.4.6 Investigator Qualifications**

The IRB reviews credentials, curriculum vitae, resumes, or other relevant materials to determine whether investigators and members of the research team, who are external to UNC, are appropriately qualified to conduct the research. The IRB relies upon department approval and other UNC-Chapel Hill processes (e.g., credentialing) to inform this determination when investigators are UNC-Chapel Hill faculty or staff.

#### **2.4.7 Investigator Conflicts of Interest (COI)**

The IRB research application asks specific questions regarding the investigator and research team compliance with disclosure requirements and whether or not any COI management plans are in place. As part of its review process, the IRB will make a final determination as to whether any conflict of interest is adequately addressed and protects the human subjects in the research. The IRB has final authority to determine whether the declared COI and the management plan, if any, allow the study to be approved.

#### **2.4.8 Institutional Conflicts of Interest**

As with individual conflict of interest, the IRB has final authority to determine whether the Institutional Conflict, the Financial Interest, and the management plan, if any, allow the study to be approved.

#### **2.4.9 Significant New Findings**

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator must report any significant new findings to the IRB and the IRB will review them with regard to the impact on the subjects' rights and welfare. Because the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process, that the investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this requirement to the investigator. If the study is still enrolling subjects, the consent document should be updated. IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. The IRB may also require that former subjects be provided with the new information, e.g., if it impacts their rights or welfare.

#### **2.4.10 Advertisements and Recruitment Materials**

The IRB must review and approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of the UNC-Chapel Hill.

The IRB will review:

1. The information contained in the advertisement.
2. The mode/method of its communication.
3. The final copy of printed advertisements.
4. The proposed script and final audio/video recorded advertisements.

This information should be submitted to the IRB with the initial application or, if recruitment is proposed after study approval, as a modification request.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. This includes but is not limited to:

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the research plan.
2. Claims, either explicitly or implicitly, that the test article (drug, biologic or device) is safe or effective for the purposes under investigation.
3. Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device.
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational.
5. Promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation.
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
7. Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing.
8. The inclusion of exculpatory language.

Recruitment materials should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (e.g., no-cost health exam).

Once approved by the IRB, an advertisement cannot be altered or manipulated in any way without prior IRB approval.

The first contact prospective study subjects make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects.

#### **2.4.10.1 Advertising on clinical trial websites**

OHRP issued guidance on internet advertising on September 20, 2005. Clinical trial websites that provide only directory listings with basic descriptive information about clinical trials in general do not need to be reviewed by an IRB. Examples of clinical trial listing services that do not need IRB review and approval include the National Institutes of Health (NIH) ClinicalTrials.gov website, the NIH National Cancer Institute's cancer clinical trials listing (Physician Data Query [PDQ]), and the government-sponsored AIDS Clinical Trials Information Service (ACTIS).

In keeping with the DHHS and FDA guidance, the UNC IRB has determined that the IRB review/approval for brief internet advertisements (e.g., listing of studies on department or research website) is not necessary provided that the information is limited to:

- study title
- purpose of the study
- protocol summary
- basic eligibility criteria
- study site location(s), and
- contact information for the study site

When information posted on a clinical trial website goes beyond directory listings with the basic descriptive information given above, such information is considered part of the informed consent process and therefore requires IRB review and approval. *Information exceeding such basic listing information* includes:

- descriptions of clinical trial risks and potential benefits, or
- solicitation of identifiable information from potential research subjects.

#### **2.4.11 Payments to Research Subjects**

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid unduly influencing subjects. The amount of compensation must be proportional to the time and inconveniences posed by participation in the study.

Investigators who wish to pay research subjects must submit to the IRB the amount and schedule of all payments. Investigators should indicate in their research project application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither entails problems of coercion or undue influence.

Credit for payment should be prorated and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion of the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

The consent form must describe the terms of payment including the amount and schedule of payments and any conditions under which subjects would receive partial payment (e.g., if they withdraw from the study before their participation is completed) or no payment.

The UNC-Chapel Hill Office Disbursement Services requires identifying information to issue checks for payment. A separate Social Security Number collection form informs subjects that they are being asked to provide their Social Security Number for payments in excess of \$400/calendar year or for any amount when payment is being issued by the Office of Disbursement Services.

#### **2.4.11.1 Non-Monetary Gifts and Incentives**

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential subject's ability to fully and freely consider participation in research.

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the approximate retail value must be described to the IRB and the IRB will be provided with a description, photo, or sample product to review.

The IRB will review all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing to not participate will not adversely affect an individual's relationship with the organization or its staff or the provision of services in any way (e.g., loss of credits or access to programs).

Investigators should carefully structure incentives and methods of disbursement so that while the incentives may serve as a factor in a subject's decision to participate, that they have not served to unduly influence or coerce participation.

#### **2.4.11.2 Lotteries, raffles and door prizes**

Occasionally, investigators who are not in a position to offer equal compensation to each research subject propose to substitute a drawing as an incentive. For example, an investigator with only \$200 to compensate 100 subjects might propose a drawing for two \$100 prizes rather than paying each subject \$2.00. University research projects may not include distribution of prizes to the research subjects via chances purchased by the human subjects or obtained by them in exchange for something of value (e.g., money, human tissues or blood samples). The

terms used for these purchased chance distributions include “lottery” and “raffle.” The prohibition is pursuant to State law and University policy. A prize distributed by chance where the chance is obtained merely by attendance at an event (sometimes called a “door prize”) and not by the payment of any fee, donation or other consideration is not prohibited by law or University policy.

Regardless of the terminology used, University research should generally not include distribution of incentives to human subjects by chance. This method may represent coercion or undue influence if the incentive is sufficiently valuable. Additionally, the distribution of incentives via chance represents an unequal distribution of the incentive and may be unfair to subjects who will ultimately receive nothing. Generally, rather than conducting a drawing, researchers should provide equitable incentives to each subject, even if such a practice diminishes the value of the incentive. However, use of incentives structured as described above for “door prizes” may be considered by the IRB on a case-by-case basis for research studies of minimal risk and brief duration if the proposed incentives do not have potential for coercion or undue influence and clearly are not distributed in exchange for valuable consideration such as blood or tissue samples or significant time and effort in research participation. The IRB should consult with the Office of University Counsel prior to approval of any incentive distributed by chance. If such an incentive is approved for a given study, consent form language describing the incentive should avoid terms like “lottery” or “raffle.” Acceptable terminology might include a reference to a “drawing based on chance in which each subject has equal odds of receiving [the incentive].”

NCGS §14-309.15 Raffles

#### **2.4.12 State and Local Laws**

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on the UNC-Chapel Hill Counsel for the interpretation and application of North Carolina law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB will ensure that consent forms are consistent with applicable state and local laws.

## 2.5 Possible IRB Actions

**Approval.** The research, proposed modification to previously approved research, or other item is approved. The IRB has made all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). No further action is needed.

**Conditions Required for Approval.** (Also known as approval with stipulations or approval with contingencies.) The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

The IRB may approve research with conditions if, given scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

The IRB may require the following as conditions of approval of research:

1. Confirmation of specific assumptions or understanding on the part of the IRB regarding how the research will be conducted (e.g., confirmation that research excludes children);
2. Submission of additional documentation (e.g., certificate of training);
3. Precise language changes to the study, consent, or other study documents; or
4. Substantive changes to the study, consent, or other study documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, the conditions will be documented in the IRB minutes for research reviewed at a convened meeting or in IRBIS for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, the IRB Chair (and/or other qualified individual(s)) will review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the stipulation is resent to the investigator. No additional stipulations may be added by the expedited reviewer.

After verification, the following will be documented in IRB records and written communication to the investigator:

- The date when the IRB determined that the criteria for approval were satisfied (i.e., the "approval date");
- The date when verification was made that all IRB conditions have been satisfied (i.e., the "effective date"), and;
- For initial approval and continuing reviews, the date by which continuing review must occur.

**Partial Approval.** The IRB may stipulate that certain components of the research, which the IRB has determined to meet the criteria for approval, may commence or continue while other components of the research that require modification or clarification cannot begin or continue until the outstanding issues are resolved and approved by the convened IRB. For example, the IRB could determine that a study may begin but that children cannot be enrolled until the investigator submits, and the IRB approves, a plan for assent.

**Deferral.** This action is taken by the convened IRB when modifications are required (of the nature or amount that the full IRB cannot make or specify exact changes or parameters), or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed with the information provided).

The deferral and the basis for the deferral is documented in the IRB minutes and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting. When the full board defers approval, the original full board reviewer will review the response materials whenever possible. In the event that the original reviewer is unavailable at the meeting during which the submission is being reviewed, the response will be reviewed by the IRB Chair or other qualified IRB member who has been designated to conduct the review.

**Disapproved.** The IRB may determine that the proposed research cannot be conducted at the UNC-Chapel Hill or by employees or agents of UNC-Chapel Hill or otherwise under the auspices of the UNC-Chapel Hill.

Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

**Approval in Principle.** As per federal regulations, [45CFR46.118], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., certain training grants or grants in which the procedures involving human subjects are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant “approval in principle” without having reviewed the as yet undeveloped procedures or materials. The IRB Chair or designee will review the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, will provide certification of IRB approval in principal. The investigator must obtain IRB approval before conducting human subjects research.

## **2.6 Continuing Review**

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research plan, but not less than once per year. The date by which continuing review must occur will be recorded in the IRB minutes or other IRB records and communicated in writing to the investigator. Continuing review must occur as long as the

research remains active including when the remaining research activities are limited to the analysis of private identifiable information.

### **2.6.1 Continuing Review Process**

As a courtesy to investigators, the OHRE staff will send out renewal notices to investigators at 60 and 30 days in advance of the expiration date; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

1. The initial study application form updated with any changes;
2. The current protocol/research plan;
3. The current consent document;
4. The current Investigator's Brochure or other updated risk information (if applicable);
5. The most recent report from the DSMB or DMC (if applicable);
6. The most recent multi-center progress report (if applicable);
7. Any proposed modifications to the protocol/research plan, consent, or study; and
8. The progress report (for continuing review).

The complete renewal application can be accessed by all IRB members. Members can request the complete study file (i.e., previous submissions) or any additional materials from the IRB staff prior to the meeting.

In the case of expedited review, the reviewers will have access to the complete study files.

### **2.6.2 Approval Considerations**

In order to re-approve research at the time of continuing review, the IRB must determine that the regulatory criteria for approval continue to be satisfied. Because the research was previously found to satisfy the criteria for approval, the IRB focuses its considerations at the time of continuing review on whether any new information is available that would affect the IRB's prior determination that the criteria for approval are satisfied. The IRB pays particular attention to four aspects of the research:

1. Risk assessment and monitoring;
2. Adequacy of the informed consent process;
3. Local investigator and organizational issues; and
4. Research progress.

### **2.6.2.1 Convened Board Review**

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in Section 2.6.1 and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, multi-center study progress reports, and any proposed modifications to the protocol/research plan, or consent. The Primary Reviewer is responsible for reviewing the complete materials submitted for continuing review including the complete research plan. If requested, the reviewer is given access to the complete IRB file and relevant IRB meeting minutes. At the meeting, the Primary Reviewers assist the Chair in leading the IRB through the completion of the regulatory criteria for approval.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but consent documents should be reviewed whenever new information becomes available that may require modification of information in the consent document.

### **2.6.2.2 Review of PI Responses**

The IRB may use the expedited review procedure to approve an investigator's response to a convened board's request for minor changes following initial or continuing review of an IRB protocol.

Changes regarded as minor:

- Specific revisions stipulated by the IRB requiring only simple concurrence by the investigator
- Requests for additional information that is not relevant to the IRB's determination of whether the research meets the regulatory criteria for approval. If the investigator's response is concordant with the stipulations, or the additional information is provided as requested, the IRB Chair/designee may approve the revised protocol on behalf of the convened board using the expedited review procedure. This action is permitted when the IRB requires modifications (stipulated in the meeting) to secure approval.

Examples of board actions permitting review of the investigator's response using the expedited procedure:

- If the submission does not include an adequate plan for monitoring the data to ensure the safety of subjects, the board determines what level of monitoring is appropriate and requires the investigator to incorporate the stipulated plan into the protocol.
- Although there might be some ambiguity in the protocol regarding the age range of subjects to be enrolled, the board determines that one or more age ranges would meet the regulatory requirements for approval. The investigator is asked to specify which will be the criterion for eligibility, and if the choice fits within the IRB's predetermined acceptable range, the protocol may be approved using the expedited review procedure.

- Although it is unclear whether results of genetic testing will be returned to subjects, rather than asking the investigator to clarify, the board determines whether results should be returned and the investigator is asked to concur with the board's decision.
- To further minimize the risk to individual participants, the board requires that those with known history of a particular condition, for example known heart disease, be excluded from participation.
- To assist in the future review of a protocol, the IRB asks the investigator to add specific information from the sponsor's protocol to the IRB protocol summary.

Changes that are NOT minor and that may not be expedited by the Chair:

- When the IRB asks substantive questions about the protocol/consent form or requests additional information that is directly relevant to the IRB's determination of whether the research meets the regulatory criteria for approval (45 CFR 46.111 or 21 CFR 56.111), then approval of the proposed research must be deferred, pending subsequent review of the investigator's response by the IRB at a convened meeting.
- When the investigator refuses to make modifications stipulated by the convened board, the Chair cannot approve the protocol. The modifications proposed by the investigator, and his justification for not making the IRB's changes, must be reviewed by the convened IRB for approval or disapproval.

Other examples of board actions requiring review of the investigator's response by the convened board:

- Request for additional information on pre-clinical or clinical experience with the drug/device/biologic. This additional information is directly relevant to the board's determination of whether risks to subjects are reasonable in relation to anticipated benefits.
- Request for justification and rationale for doing research biopsies in healthy volunteers. The response has direct bearing on minimizing risks by using procedures that do not unnecessarily expose subjects to risk.

Review of Investigator responses:

- Investigator responses for studies that were reviewed via expedited review will be reviewed by an experienced IRB member; typically the same individual who completed the initial review.
- Investigator responses for studies that were reviewed by the convened IRB and received contingent approval, will be reviewed by the Chair or other experienced expedited reviewer or, upon request, by committee member reviewer(s).
- Investigator responses for studies that were reviewed by the convened IRB and were either deferred or disapproved, will be reviewed by the convened IRB.

### **2.6.2.3 Expedited Review**

In conducting continuing review under expedited procedures, the reviewers will have access to entire study file. The reviewer(s) determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 2.1.1). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

### **2.6.3 Possible IRB Actions after Continuing Review**

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 2.5 for a detailed description of these actions):

1. Approval
2. Conditions Required for Approval (i.e., Approval with stipulations)
3. Deferred

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See SOP 1402 for a detailed discussion of suspensions and terminations).

If a research study receives Approval with Conditions at the time of the Continuing Review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. 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. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition/s to be satisfied as long as the activity with conditions is not begun/restarted until approval is granted.

### **2.6.4 Lapses in Continuing Review**

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without

IRB approval. If re-approval does not occur within the time set by the IRB, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must submit their continuing review materials enough in advance of expiration to allow sufficient time for IRB review before the expiration date.

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes; however, the failure to meet continuing review obligations may be grounds for suspension or termination of the research. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to FDA/OHRP any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations.

The OHRE is responsible for notifying the investigator of the expiration of approval and that all research activities must stop.

However, the IRB recognizes that, while enrollment of new subjects cannot occur after the expiration of IRB approval, temporarily continuing participation of already enrolled subjects may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects, or when withholding those interventions or safety monitoring procedures, would place subjects at increased risk. In these instances, the investigator should, at the earliest opportunity, contact the OHRE and submit a written request to continue those research activities that are in the best interests of subjects. Such a request should specifically list the research activities that should continue, and provide justification, and indicate whether the request applies to all or only certain subjects. The IRB Chair or designee will review the request and provide a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

## **2.7 Modification of an Approved Protocol**

Investigators may wish to modify or amend their approved applications. Investigators must seek IRB approval before making any changes, no matter how minor, in approved research -

even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazards to the subject (in which case the IRB must then be notified at once). Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant should be reported to the IRB within 30 days. The changes are reviewed by the IRB to determine whether the changes(s) was consistent with ensuring the participants' continued welfare.

Modifications may be permanent (Protocol Modification) which make changes to the protocol for all remaining subjects or temporary (Protocol Exceptions) circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient(s)/subject(s) (examples: patient/subject is allergic to one of the medications provided as supportive care; patient/subject is not eligible in a direct benefit study). Usually an Exception is a change that is planned and has prior agreement from the sponsor. See Section 2.7.3 for details on Protocol Exceptions.

Note: Protocol Deviations [see SOP 1401] are unplanned and are reported to the IRB after the fact.

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

### **2.7.1 Modification Procedures**

Investigators must submit a modification request to inform the IRB about the proposed changes to the study, including, but necessarily limited to:

- For Protocol Modifications, a revised protocol/research plan, application, and/or study materials (with a detailed summary of changes and the locations of those changes);
- Revised consent/parental permission/assent documents (if applicable);
- When the proposed change(s) to the research might relate to current subjects' willingness to continue to participate in the study and they won't be asked to re-consent using the revised consent form, an information sheet, letter, script, or other mechanism of providing information; and
- Any other relevant documentation provided by the sponsor or coordinating center.

The IRB reviewer will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants convened board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.

### **2.7.1.1 Convened Board Review of Modifications**

When a proposed change in a research study is not minor, then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members are provided and review all documents provided by the investigator.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB will also determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to future/current/past participants.

### **2.7.1.2 Expedited review of Modifications**

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members.

The Chair or designee reviews the submission to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

The reviewer will also consider whether information about those modifications might relate to future/current/past participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

## **2.7.2 Possible IRB Actions after Modification Review**

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 2.5 for a detailed description of these actions):

1. Approval
2. Conditions required for Approval
3. Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the

proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See SOP 1402 for a detailed discussion of suspensions and terminations).

### **2.7.3 Protocol Exceptions**

A *Protocol Exception* is a type of planned change to the research. Unlike an amendment, a protocol exception is not a permanent revision to the research protocol. A *Protocol Exception* may be permitted:

- For an individual subject (i.e., Single Subject Protocol Exception) when it is in the best interest of that subject and the subject does not meet the current approved Inclusion/Exclusion (I/E) criteria.
- When IRB approval has lapsed (or is expected to lapse) and the investigator wishes to continue research interventions or interactions for some or all subjects when it is in the best interest of the subjects to continue.

A *Protocol Exception* must not adversely affect the safety of the subject(s) or integrity of the study data. Similar to an amendment or modification, the PI is responsible for submitting any protocol exceptions prior to initiation of the change to the IRB. Failure to submit all protocol exceptions represents non-compliance with the federal regulations and UNC policies.

#### **2.7.3.1 Single Subject Protocol Exception**

A *Single Subject Protocol Exception* should be rare, is limited to a single subject and justified in terms of serving the best interests of the potential study participant. The inclusion of additional participants who do not meet the eligibility criteria requires an amendment (i.e., modification) to the protocol.

If the research involves an investigational agent (drug, device, or biologic), prior approval by the sponsor is also required. Additionally, when the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required [21 CFR 812.150 (4)].

If the research is investigator-initiated, a colleague uninvolved in the care of the subject must provide a written endorsement for the inclusion of the ineligible person because alternatives are limited to less favorable options.

##### **2.7.3.1.1 Requesting a Protocol Exception**

The Investigator will submit a modification requesting a Protocol Exception. Protocol Exceptions should be submitted separately from other modification requests. A *Protocol Exception Request Form* must be completed and submitted along with any additional required documentation. The investigator must explain the underlying reasons for which the protocol exception is requested and where an over-riding safety concern or ethical issue indicates that it is in the best interest of the individual to continue participating.

If a protocol exception request cannot be submitted via IRBIS because a previous submission is under review, the investigator should call the IRB (919-966-3113) and inform the receptionist that you have a protocol exception that cannot be submitted via IRBIS due to a pending review. The receptionist will refer you to an IRB Analyst who will guide you through the submission process.

Investigators are encouraged to submit all single subject protocol exception *requests as soon as the potential subject is identified*. If the request is time-sensitive, the investigator should be sure to indicate this when calling the IRB office, or, if applicable, handle as Emergency Use (described below.)

#### **2.7.3.1.2 Alternatives to a Single Subject Protocol Exception**

A Single Subject Protocol Exception should be rare, and is generally limited to a single subject. Subsequent requests may be denied. The following alternatives should be considered.

Off protocol – If the treatment being studied under this protocol is FDA-approved, the patient may be treated off protocol.

Protocol Amendment -- Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, inclusion/exclusion criteria, study design, sample sizes, study procedures, or significant administrative aspects.

Expanded Access to Investigational Drugs for Treatment Use (Compassionate Use) --The purpose of an expanded access protocol is to make investigational drugs available to patients who do not qualify for participation in a clinical trial. Expanded access protocols allow a larger group of people to be treated with the drug.

Emergency Use is defined as the use of an investigational drug, biologic or device with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. The emergency use exemption is permitted only if each of the following conditions exists as outlined in 21 CFR 56.102(d). 1) A life-threatening or severely debilitating situation exists necessitating the use of the investigational drug, biologic or device; 2) No standard acceptable alternative treatment is available; and 3) Because of the immediate need to use the drug, biologic or device, there is not sufficient time to use existing procedures to obtain IRB approval for the use.

#### **2.7.3.2 Protocol Exception to Conduct Research During Approval Lapse**

Request for approval during approval lapse should be rare. The expectation is that researchers will submit renewal applications well in advance of the expiration date however; there may be circumstances that result in an unexpected IRB approval lapse. In these cases, the investigator may submit a request for a protocol exception to conduct research during approval lapse when it is in the best interest of the subjects to continue.

### **2.7.3.2.1 Requesting a Protocol Exception to Conduct Research during Approval Lapse**

Interventions are allowed to continue only when it is in the best interest of the subjects and when approved by the IRB. To request the continuation of certain aspects of the research, the investigator must submit a *Protocol Exception Request Form* describing the activities. The investigator must also explain the underlying reasons for which the protocol exception is requested for each activity and each subject. A protocol exception must be requested even if a continuing review application has been submitted. Approval of a protocol exception does not replace or represent continuing IRB review of the research.

The Investigator should first call the OHRE and request to speak with an IRB Analyst. The *Protocol Exception Request Form* should be completed and emailed directly to the IRB Analyst. Once the protocol exception has been reviewed, the IRB will return the form, which has been completed by the IRB, to the Investigator (or designee) via e-mail. Following continuing review and approval of the study, the Investigator will submit a modification via IRBIS. The modification should include a completed copy of the *Protocol Exception Request Form* on which the IRB decision has been documented. Doing so will document the protocol exception approval in IRBIS.

### **2.7.3.3 IRB Review of Protocol Exceptions**

1. The *Protocol Exception Form* will be reviewed to determine if the request represents no greater than minimal risk and is limited to minor changes in previously approved research. The Chair (or designee) will review the request and evaluate the impact of the protocol exception with regards to:

- a. The safety of the research participant
- b. The potential benefits to the subject
- c. Affect to the rights or welfare of the subject
- d. Integrity of the data

2. If the protocol exception represents changes that are no greater than minimal risk and is limited to minor changes, the Chair or designee may review the request via Expedited Review as described in §46.110(b). A summary of the review will be documented in the study submission notes.

3. If the reviewer determines that the Protocol Exception request represents changes that are greater than minimal risk and/or more than minor changes, or is otherwise not approvable, the Protocol Exception should be placed on the next available Full Board agenda. A summary of the review will be documented in the Internal Meeting Notes.

Lapse in IRB approval represents non-compliance. If the Chair or designee determines that the lapse represents possible continuing noncompliance, it is referred to the Safety Committee for a final determination.

<b>Examples of Single Subject Protocol Exceptions that <i>require Full Board Review</i></b>
A dose increase of the investigational drug dose that is not allowed by the current approved protocol.
Request to enroll a potential subject who is currently taking an excluded medication.
<b>Examples of Single Subject Protocol Exceptions that <i>may be reviewed by Expedited Review</i></b>
The protocol requires PET scan for tumor imaging within 28 days of being enrolled into the study. The potential subject's last PET scan was completed 32 days ago (i.e., 4 days out of window). The Investigator does not believe that a repeat CT scan is in the best interest of the subject.
Subject ID 003 experienced an infusion rate reaction during the third dose of the investigational drug. The patient was re-challenged at a slower rate of infusion and successfully completed treatment without further reaction. The Investigator is requesting that use of a slower infusion rate for this subject for all subsequent doses.
Subject ID 024 requires a 60 day (+/- 7 days) follow-up visit. The subject will be traveling during this time and is not available to come in for the visit until January 5 <sup>th</sup> which is 7 days out of window. (Note: The IRB will consider the number of days outside of window and potential risk to the subject.)
<b>Examples of Requests that should not be submitted as Protocol Exceptions</b>
Request for approval to complete screening visits during lapse of approval because subjects have already been scheduled.

## 2.8 Closure of Research Studies

The completion or early termination of the study, is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete). Studies may be closed when the only remaining research activity involves the analysis of unidentifiable individual level data, or aggregate data sets.

For multi-center research, the study may be closed once all research activities (as above) are complete at the UNC-Chapel Hill and any sites for which the IRB is the "IRB of record". If the investigator is serving as the lead investigator or the UNC-Chapel Hill is the coordinating center, please note that the study must remain open as long as the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

Investigators may submit study closures to the IRB via IRBIS. With closure submissions, the investigator must also complete the progress report questions.

The IRB reviewer will confirm the disposition of the data and/or specimens that they collected, including identifiable private data, is consistent with the IRB-approved research plan. Investigators may not conduct any additional analysis of identified data without re-applying for IRB approval. Investigators must continue to protect the confidentiality of the data as

described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The IRB will review study closure reports, typically by expedited review, and either approve the closure of the study or request additional information or confirmation of facts from the investigator.

## **2.9 Reporting IRB Actions**

All IRB actions are communicated to the investigator, and/or designated contact person(s) for the research study, in writing via an electronic template letter. For an approval, along with written notification of approval, access to the approved consent/assent/permission form/s (if applicable) will be provided to the investigator. For approval with conditions, the notification will include a listing of the conditions that must be satisfied. For a deferral, the notification will include the modifications and/or clarifications required along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision and give the investigator an opportunity to respond in person or in writing.

All research documents are maintained by the IRB for a period of up to three years following closure of the study.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the UNC-Chapel Hill Institutional Official.

## **2.10 Failure to Respond**

Failure to submit a response to IRB requirements within 90 days of the IRB date of determination may result in administrative closure of the IRB file (for new study submissions). When research has IRB approval, and an investigator fails to respond to requirements related to a subsequent submission (e.g., a request for modification), the IRB reviewer will review the circumstances, including any potential impact on human subjects, and will contact the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and may be reviewed in accordance with the procedures in SOP 1402. The investigator will receive notification, including an explanation. An extension beyond 90 days may be granted by the IRB if sufficient cause is provided by the investigator.

## **2.11 Appeal of IRB Decisions**

When an IRB research study is disapproved or deferred, the IRB will notify the investigator in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. Similarly, when research is suspended in part or in full, or terminated, the IRB will notify the investigator in writing of the suspension or termination and the reasons for its decision. The investigator

may ask that the decision be reconsidered by submitting a request in writing to the IRB. The request must contain the basis for the appeal, including any substantive new information that the Board did not have the opportunity to consider previously. The request is scheduled for review at a convened IRB meeting; at the discretion of the Chair, the Investigator may invited to attend the meeting.

## **2.12 Research Previously Approved By Another IRB**

When an investigator transfers research to the UNC-Chapel Hill that was previously approved by another IRB, the investigator must submit the research for review under the procedures covered by this section. No research activity may take place under the UNC-Chapel Hill auspices without the appropriate review and approval.

Research approved as exempt at the previous institution will be reviewed according to the procedures in SOP 601. All other research must be submitted as if it were undergoing initial review and will be reviewed under expedited review or by the convened IRB. Research that solely involves the analysis of existing identifiable data may be considered under Expedited Review Category 5.

For research transfers where stopping research interventions might harm subjects, the investigator can request permission from the IRB to continue research interventions under the oversight of the prior organization's IRB until final the UNC-Chapel Hill approval is obtained.

## **3 Definitions**

**Minimal Risk.** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

**Minor Change.** A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

1. The acceptability of the risk-to-benefit analysis or increases the level of risks to subjects
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 2.1) would be considered more than a minor change
3. The number of subjects enrolled in the research (usually not greater than 10% of the total requested locally)
4. The qualifications of the research team
5. The facilities available to support safe conduct of the research
6. Any other factor which would warrant review of the proposed changes by the convened IRB

**Quorum.** A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum.

**Suspension of IRB approval.** A suspension of IRB approval is a directive of the IRB to temporarily stop some or all previously approved research activities. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period). If a suspension is lifted and IRB approval of the suspended research study has expired, a continuing review is required before the study may resume.

**Termination of IRB approval.** A termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously IRB approved research study. Terminated research studies are closed and no longer require continuing review.