# Section 7. **IRB Review Process**

The medical school IRB reviews and ensures that research involving human subjects meets all required ethical and regulatory criteria for initial review, continuing review, and any modifications of approved research. The IRB may conduct their review using expedited review, or review by convened IRB.

The following describes the procedures required for the review of research by the medical school IRB. (See Section 9 for a description of medical school procedures for research reviewed by external IRBs.)

## 7.1 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:
    - The acceptability of the risk-to-benefit analysis (changes that increase the level of risks to subjects generally are considered major changes unless the overall risk of the study remains minimal or the increase in risks is so minor that it does not negatively impact overall risks-to-benefits).
    - The research design or methods. Adding procedures that are not eligible for expedited review would be considered more than a minor change (see Section 7.2.2).
    - The number of local subjects to be enrolled in greater than minimal risk research (usually not greater than 10% of the total requested locally).
    - The qualifications of the investigators and research staff.
    - The facilities available to support safe conduct of the research.
    - Any other factor which would warrant review of the proposed changes by the convened IRB.

- **Suspension of IRB approval**: Suspension of IRB approval is a directive of the convened IRB to temporarily stop some or all research activities that have been previously approved by the IRB. Suspended research studies remain open and require continuing review by the IRB.

- **Termination of IRB approval** Termination of IRB approval is a directive of the convened IRB to permanently stop all activities that have been previously approved by the IRB. Terminated research studies are closed and no longer require continuing review by the IRB.

## 7.2 Expedited Review

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

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

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

### *7.2.1 Categories of Research Eligible for Expedited Review*

The medical school IRB 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 categories of research listed in this section 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 if 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 if 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 are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal risk.

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 () is not required. Research on marketed drugs is not eligible for expedited

review if the research significantly increases the risks or decreases the acceptability of the risks associated with the use of the product.

(b) Research on medical devices for which (i) an investigational device exemption application () 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 meeting one or both of the following conditions:

(a) Collection 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) Collection 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. 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 include:

(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) Supragingival 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 approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of approved medical devices for new indications. Examples include:

(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 (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. Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and (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 meeting one or more of the following conditions:
(a) Where (i) the research at 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. "Long-term follow-up" includes research interactions that involve no more than minimal risk to subjects (eg, 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.

(b) Where no subjects have ever been enrolled, and no additional risks have been identified, which 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.

(c) Where the remaining research activities are limited to data analysis. 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.

For a multicenter research project, an expedited review procedure may be used by the IRB for a particular institution whenever the conditions of category (8)(a), (b), or (c) are satisfied for that institution.

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

(a) The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE).

(b) Expedited review categories (2) through (8) do not apply to the research.

(c) 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.

(d) No additional risks of the research have been identified. "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.

### *7.2.2 Expedited Review Procedure*

Under an expedited review procedure, the review may be carried out by the IRB chair or by one or more reviewers designated by the IRB chair from among members of the IRB. On at least an annual basis, the IRB chair will designate a list of IRB members eligible to conduct expedited reviews. The designees must be members or alternate members of the IRB who are experienced, meaning having served on an IRB for at least one year.

HRPP/IRB staff select expedited reviewers from the list of designated reviewers. Selected reviewers must have the qualifications, experience, and knowledge in types of research to be reviewed unless specific expertise is not needed to conduct the review (eg, minor administrative changes), as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest or commitment with the research (see Section 21.2) may not be selected to perform the expedited review.

When reviewing research under an expedited review procedure, the IRB chair, or designated IRB member, receives and reviews all documentation that would normally

be submitted for convened 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 by using the *Initial Study Review Form*.

If the research meets the criteria allowing review using the expedited procedure, the reviewer conducting initial or continuing review completes the appropriate review form checklist (*Initial Study Review Checklist* or *Continuing Review Checklist*) to determine whether the research meets the regulatory criteria for expedited review and approval. 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 indicates that the research requires convened board review and the research study is placed on the next available agenda for an IRB meeting.

In reviewing the research, the reviewers must follow the review procedures described in Sections 7.2 and 7.4 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 (see Section 7.3).

Reviewers will indicate approval, required modifications, or requirement for convened board review on the *Initial Study Review Checklist*. The HRPP/IRB staff informs the investigator of the review outcome in writing or by email.

In the event that expedited review is performed by more than one IRB member and the expedited reviewers disagree, the IRB chair may make a final determination or refer the study to the convened IRB for review.

#### *7.2.3 Informing the IRB*

All members of the IRB shall be apprised of all expedited review approvals by means of a list in the agenda for the next scheduled IRB meeting. Any IRB member may request to review any study by contacting the HRPP/IRB staff.

### 7.3 Convened IRB Meetings

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

#### *7.3.1 IRB Meeting Schedule*

The IRB meets on a regular basis throughout the year, usually once per month. The schedule for the IRB may vary because of holidays, workload, or lack of quorum for scheduled meetings. The schedule for IRB meetings is posted on the IRB website. Special meetings may be called at any time by the IRB chair or HRPP director.

### *7.3.2 Preliminary Review*

HRPP/IRB staff perform a preliminary review of all submissions for determination of completeness and accuracy. Only complete submissions are placed on the IRB agenda for review. The Principal Investigator is informed either by e-mail, phone, or in person of missing materials and the necessary date of receipt for receipt of materials to permit inclusion on the IRB agenda. The Principal Investigator may request consultation with HRPP/IRB staff at any step in the review process.

### *7.3.3 Primary and Secondary Reviewers*

After it has been determined that the submission is complete, HRPP/IRB staff, with the assistance of the IRB chair as needed, assigns submissions for review paying close attention to the subject matter of the research, potential reviewer's areas of expertise and, representation of any vulnerable populations involved in the research. One "primary reviewer" is assigned to each submission and conducts an in-depth review of all submission materials. A single reviewer may be assigned several submissions or other items for review. When the IRB is presented with a research study that may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (see Section 4.5). Research studies for which appropriate expertise cannot be obtained for a given IRB meeting will be deferred to another IRB meeting when appropriate expertise is available.

Primary reviewers are responsible for:

- Having a thorough knowledge of all of the details of the proposed research.
- Performing an in-depth review of the proposed research.
- 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 7.4).
- Making suggestions for changes to the proposed research, where applicable.
- Completing all applicable IRB reviewer forms.

One or more "secondary reviewers" may be assigned in addition to the primary reviewer. A secondary reviewer may be assigned to review the full submission materials or may be asked to review specified components of the submission (eg, the consent/assent/permission forms).

All IRB members receive and are expected to review all studies, not just those assigned to them 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 provided that they have sufficient time to review the materials in advance of the meeting. Alternatively, an absent reviewer may submit their written comments for presentation at the convened meeting. If an absent reviewer

submits comments, the comments may indicate a recommendation regarding approval or nonapproval, but such recommendation will not be counted as a vote.

### *7.3.4 Materials received by the IRB*

All required materials must be submitted to the IRB 15 business days prior to the convened meeting for inclusion on the IRB meeting agenda. The meeting agenda is prepared by HRPP/IRB staff in consultation as needed with the IRB chair. All IRB members must receive the IRB agenda, prior meeting minutes, applicable business items, continuing education materials, and research submission materials no less than 7 business days before the scheduled IRB meeting to allow sufficient time for the review process.

Each IRB member receives and is expected to review, at minimum, the following:

- A Protocol Summary or the complete protocol/research plan.
- The study application.
- Proposed consent/parental permission/assent form(s), if applicable.
- Recruitment materials including advertisements intended to be seen or heard by potential subjects, if applicable.

The primary and secondary reviewers receive and review, in addition to the above: (1) the complete protocol/research plan; (2) the grant application when the organization is the prime awardee of a HHS grant; (3) the investigator's brochure, when one exists, and/or other risk information; (4) questionnaires, diaries, and other materials intended for use with or completion by subjects; and (5) any other relevant research materials. For DHHS-supported multicenter clinical trials, this should include 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.

The materials provided to the primary reviewer are available to all IRB members.

If an IRB member requires additional information to complete the review, they may contact the investigator directly or may contact HRPP/IRB staff to make the request of the investigator.

Primary reviewers use the *Initial Study Review Checklist* as a guide to completing their review.

### *7.3.5 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 drug is on the agenda for review, a physician should be included in the quorum. When nursing research from a facility with Magnet designation by the American Nurses Credentialing Center is on the agenda for review, a

nurse 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 HRPP/IRB staff, confirms that quorum is present before calling the meeting to order. The IRB chair, with the assistance of HRPP/IRB staff, is responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, or losing all non-scientific members or another required member, the IRB cannot take further actions or vote on regulatory determinations until quorum is restored.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants will be present at all IRB meetings. A single individual may serve in both capacities simultaneously. The IRB may, on occasion, meet without this representation; however, this should be the exception and not routine.

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 (eg, 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 means such as teleconferencing and videoconferencing 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.

Members who are recused from voting on a specific study because of conflicting interests may not be counted toward the quorum.

### *7.3.6 Meeting Procedures*

The IRB chair calls the IRB meetings to order once it has been determined that a quorum is in place. The IRB chair reminds IRB members to recuse themselves from discussion and votes by leaving the room when they have a conflict of interest or commitment. The IRB reviews and discusses the minutes from the prior meeting and determines whether there are any revisions or corrections to be made. If there are no changes to be made, the minutes are accepted as presented and considered final. If substantive revisions or corrections are necessary, the minutes are amended and presented at the following IRB meeting. Minor revisions and corrections may be verified

by the IRB chair or vice chair after the meeting to meet the intent of the revisions or corrections that were discussed at the meeting.

The IRB reviews all submissions for initial review and continuing review, as well as requests for modifications. The primary reviewer presents an overview of the research and assists the IRB chair in leading the IRB through the evaluation 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.

HRPP/IRB staff are responsible for recording minutes at each IRB meeting.

#### *7.3.7 Guests*

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB chair, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator and research staff may not be present for the deliberations or vote on the research.

The HRPP director and HRPP/IRB staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless they are attending as members or as alternates in place of members.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB chair and the HRPP director. Guests may be asked to sign a confidentiality agreement and will not participate in discussion unless requested by the IRB chair or vice chair, and under no circumstances may they vote on any action of the IRB.

### 7.4 Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited review or by convened IRB, the IRB 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.

- 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.
- 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.

- 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.
- 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 [, ].
- Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [, ].
- When appropriate, the protocol/research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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.

### *7.4.1 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:

- 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.
- 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.
- Identify the anticipated benefits to be derived from the research, both direct benefits to subjects and possible benefits to society, science, and others,
- 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.

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

When research subjects are assigned to different arms or otherwise undergo differing interventions, procedures, or exposures, the evaluation of risk and benefit should be made for each subject group (ie, "component analysis").

#### *7.4.1.1 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 yield the expected knowledge.

In making this determination, the IRB may draw on its own knowledge and expertise, or the IRB may draw on the knowledge and expertise of others, such as reviews by an external reviewer, funding agency, departmental review, or research committee. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation of the scientific review should be included in the submission to the IRB.

### *7.4.2 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, and other characteristics. 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.
- The inclusion/exclusion criteria, and the procedures and materials intended for use for the identification and recruitment of potential subjects.

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

#### *7.4.2.1 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 and do not present undue influence. See Section 7.5.10 for a discussion of IRB review of advertisements and Section 7.5.11 for a discussion of IRB review of payments.

### *7.4.3 Informed Consent*

The IRB must ensure that informed consent is sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by,  and . In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by  . The IRB must ensure, as part of its review, that the information in the consent document and process is consistent with the protocol/research plan, and, if applicable, the HIPAA authorization. See Section 11 for detailed policies on informed consent.

### *7.4.4 Data and Safety Monitoring*

For all research that is greater than minimal risk, the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe what data will be collected and monitored for safety, how and to whom the data will be reported, descriptions of interim reviews, if any, and the actions that may be taken as a result of the monitoring.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision to monitor 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:

- Monitoring is commensurate with the nature, complexity, size and risk involved.
- Monitoring is timely. Frequency should be commensurate with risk.

- Conclusions are reported to investigators, sponsors, regulatory authorities, and the IRB, as applicable.
- For lower 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 authorities as appropriate.
- Data and Safety Monitoring plans should specify:
    - The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
    - The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
    - The frequency or periodicity of review of safety data
    - The procedures for analysis and interpretation of the data
    - The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
    - The conditions that trigger a suspension or termination of the research (ie, stopping rules), if applicable
    - The procedures for reporting to the IRB and others, including a summary description of what information, or the types of information, will be provided, when, and to whom
- For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also describe:
    - The composition of the board or committee. Generally, a DSMB or DMC 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.
    - The frequency and character of monitoring meetings (eg, open or closed, public or private)
    - The DSMB or DMC charter should be provided, if available.

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. A DSMB is required for some studies sponsored by the National Institutes of Health (NIH). The IRB has the authority also to require a DSMB or DMC as a condition for approval of research if the IRB determines that such monitoring is necessary and appropriate. When a DSMB or DMC is used, the IRB conducting the continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC that 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.

### *7.4.5 Privacy and Confidentiality*

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

#### *7.4.5.1 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**: Information, on any storage media or in any form or format, which requires protection because of the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information; information that 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.

#### *7.4.5.2 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:

- Methods used to identify and contact potential participants.
- Settings in which an individual will be interacting with an investigator.

- Appropriateness of all personnel present for research activities.
- Methods used to obtain information about participants.
- Information that is obtained about individuals other than the "target subjects," (eg, a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of "human subject."

#### *7.4.5.3 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 that may affect confidentiality, 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 Principal Investigator provides 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 (eg, audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB reviews 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 be obtained to additionally protect research data (see Section 25.8).

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 .

### *7.4.6 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. When research that includes vulnerable populations is proposed, the IRB must consider the scientific and ethical reasons for including vulnerable subjects in the research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects.

Section 12 provides additional information about the IRB review and approval process for specific populations of vulnerable subjects.

## 7.5 Additional Considerations

### *7.5.1 Determination of Risk*

At the time of initial and continuing review, the IRB makes a determination regarding the risks associated with the protocol/research plan. Risks associated with the research are generally classified as either "minimal risk" or "greater than minimal risk" with additional classifications as required by the various subparts or FDA regulations. When modifications are proposed, the IRB evaluates whether the modification changes the risk determination. Risk determinations may vary over the life of a protocol/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 IRB meeting minutes must reflect the convened IRB determination regarding risk levels. Expedited reviewers must document the determination of risk level on the *Initial Study Review Checklist*.

### *7.5.2 Period of Approval*

At the time of initial review and at continuing review, the IRB makes a determination regarding the period of approval. All studies are reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year (12 months). In some circumstances, a shorter review interval (eg, semi-annually, quarterly, or after accrual of a specific number of participants) may be required. The IRB meeting minutes must reflect the convened IRB determination regarding review frequency. Expedited reviewers must document the determination of risk level on the *Initial Study Review Checklist*.

IRB approval is considered to have lapsed at midnight on the expiration date of the approval. The expiration date is the last day research may 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 effective date of initial IRB approval.

The use of the effective date of IRB approval to determine the latest permissible date for continuing review only applies to the first continuing review. For all 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 review of the proposed change.

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. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

### *7.5.3 Review More Often Than Annually*

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

- The probability and magnitude of anticipated risks to subjects.
- The likely medical/psychological/social/legal/educational condition of the proposed subjects.
- The overall qualifications of the Principal Investigator, other investigators, and research staff.
- The specific experience of the Principal Investigator, other investigators, and research staff in conducting similar research.
- The nature and frequency of adverse events observed in similar research.
- The novelty of the research making unanticipated adverse events/unanticipated problems more likely.
- For clinical trials, the phase of the research, and whether the research is first-in-humans.
- The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (eg, the terminally ill).
- A history of serious or continuing non-compliance on the part of the Principal Investigator, other investigators, and research staff.
- 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 that may be 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 should be documented in the IRB minutes and also the *Initial Study Review Checklist*.

### *7.5.4 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 submission of monitoring, audit, and inspection reports serves as one source of independent verification. Beyond this, the IRB determines the need for verification from outside sources on a case-by-case basis. The following factors may be considered when determining which studies require independent verification:

- The probability and magnitude of anticipated risks to subjects.
- The likely medical/psychological/social/legal/educational condition of the proposed subjects.
- The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
- Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
- Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
- Research without a routine monitoring plan.
- 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 a single point in time. The IRB may request that HRPP QA staff perform the independent verification, may form a subcommittee for this purpose, or may rely on a consultant reviewer or other source to perform the review.

If any material changes have occurred without IRB review and approval, the IRB will evaluate the issue in accordance with the procedures described in Section 16 (Non-compliance).

### *7.5.5 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 (eg, 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:

- High-risk studies.
- Studies that involve particularly complicated procedures or interventions.
- Studies involving vulnerable populations (eg, persons with impaired decision-making capacity, children who are wards).
- Studies involving research staff with minimal experience in administering consent to potential study participants.
- Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (eg, prior investigator non-compliance).

If the IRB determines that consent monitoring is required, the IRB develops a monitoring plan. The consent monitoring may be conducted by HRPP/IRB staff, IRB members, or another individual designated by the IRB, either affiliated or not with the medical school. Arrangements are made with the Principal Investigator for the monitoring of the consent process, typically for a specified number of subjects. When observing the consent process, the monitor evaluates:

- Whether the informed consent process was appropriately conducted and documented.
- Whether the participant had sufficient time to consider study participation.
- Whether the consent process involved coercion or undue influence.
- Whether the information was accurate and conveyed in understandable language.
- Whether the subject appeared to understand the information and gave their voluntary consent.

Following the monitoring, a report of the findings is submitted to the IRB, which will determine the appropriate action to be taken, if any.

### *7.5.6 Investigator Qualifications*

The IRB may review credentials, curricula vitae, resumes, and other relevant materials to determine whether investigators and research staff are appropriately qualified to conduct the research. The IRB may rely upon other processes and entities (eg, a statement from a hospital, facility, or department chair that the investigators have the necessary expertise and credentials) to inform this determination.

### *7.5.7 Investigator Conflicts of Interest*

The IRB research application asks specific questions regarding the investigator and research staff compliance with disclosure requirements and whether or not any conflict management plans are in place. As part of the review process, the IRB makes a final determination as to whether any conflict of interest or commitment is adequately addressed and protects the human subjects in the research. Section 21 provides additional discussion of conflicts of interest and commitment.

### *7.5.8 Institutional Conflicts of Interest*

As with individual conflict of interest, the IRB has final authority to determine whether institutional conflicts, financial interests, and the management plan, if any, allow the study to be approved. Section 21.3 provides additional discussion of institutional conflicts of interest.

### *7.5.9 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 Principal Investigator must report any significant new findings to the IRB. The IRB will review the findings with regard to the impact on the subjects' rights and welfare. Because the new knowledge and 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 Principal Investigator or research staff contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this requirement to the Principal Investigator. If the study is still enrolling subjects, the consent document should be updated. The 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, such as when it affects their rights or welfare.

### *7.5.10 Advertisements and Recruitment Materials*

The IRB must review and approve any and all advertisements prior to posting or distribution for studies. The IRB reviews:

- The information contained in the advertisement.
- The mode/method of its communication.
- The final copy of printed advertisements.
- The proposed script and final audio/video taped 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:

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

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

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

Directory listings of research such as ClinicalTrials.Gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic study information: title, purpose of the study, protocol/research plan summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

### *7.5.11 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 raises concerns 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 permit the entire payment to be contingent upon completion of the entire study. Any amount paid as incentive 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 (eg, if they withdraw from the study before their participation is completed) or no payment.

If applicable, the consent must disclose when identifying information (eg, name, address, Social Security Number) may be provided to a component within an organization such as Accounts Payable to issue checks, cash, or gift certificates to subjects, and also that an IRS Form 1099 may be issued if payments to an individual exceed $600 in a calendar year.

### *7.5.12 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 potential impact on potential subjects' decision to participate and on existing subjects' decision to continue or withdraw participation.

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.

### *7.5.13 State and Local Laws*

The HRPP and 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 medical school counsel for the interpretation and application of Michigan 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.

## 7.6 Possible IRB Actions

### *7.6.1 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, meeting approval criteria and any applicable special determinations such as required waivers, alterations, or accommodations for vulnerable population determinations. No further action is needed.

### *7.6.2 Conditions Required for Approval*

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, meeting approval criteria and any applicable special determinations such as required waivers, alterations, or accommodations for vulnerable population determinations. 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:

- Confirmation of specific assumptions or understanding on the part of the IRB regarding how the research will be conducted (eg, confirmation that research excludes children).
- Submission of additional documentation (eg, certificate of training).

- Precise language changes to the study, consent, or other study documents.
- 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 the *Initial Study Review Checklist* for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, the IRB may designate the IRB chair and/or other qualified individual(s) to 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 responsive materials must be referred to the convened IRB for review. If the conditions have been satisfied and the expedited reviewer approves research with conditions, the original expedited reviewer and/or other qualified individual(s) will receive the response materials. HRPP/IRB staff can be designated by the convened IRB or expedited reviewer to review non-substantive conditions when they are appropriately qualified to do so.

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

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

The IRB will be informed of the outcome of the review of the investigator’s response as part of the agenda of the next meeting.

### *7.6.3 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. The IRB may also stipulate that an approval is limited to certain components of the research (eg, phase 1 of a proposed research project) or populations (eg, approved for adults but not children).

### *7.6.4 Deferred*

This action is taken by the 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 (eg, 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 (for convened review) or *Initial Study Review Checklist* (for expedited review) and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator are provided to the convened IRB for review at a subsequent meeting. When an expedited reviewer defers approval, the original expedited reviewer reviews the response materials whenever possible. In the event that the original expedited reviewer is unavailable, the response is reviewed by the IRB chair or other qualified IRB member who has been designated to conduct expedited reviews.

### *7.6.5 Disapproved*

The IRB may determine that the proposed research cannot be conducted at the site or sites included in the IRB submission. Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

### *7.6.6 Approval in Principle*

As per federal regulations [], 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 (eg, 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 reviews the available information (ie, the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, provides certification of IRB approval in principle. If the proposal is funded, the investigator must submit the materials required for initial submissions for review and approval before beginning any human subject activities, including recruitment or pilots.

## 7.7 Continuing Review

The IRB conducts a continuing review of ongoing research at intervals that are appropriate to the level of risk for each protocol/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.

### *7.7.1 Continuing Review Process*

As a courtesy to investigators, HRPP/IRB staff send out renewal notices to investigators three months, two months, and again one month 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:

- The initial study application form updated with any changes approved by the IRB since the initial or last continuing review (this serves as the protocol/research plan summary).
- The current protocol/research plan.
- The current consent document and the most recent signed consent document with the subject name redacted.
- The current Investigator's Brochure (if applicable).
- The most recent report from the DSMB or DMC (if applicable).
- The most recent multi-center progress report (if applicable).
- The *Continuing Review Request Form* (progress report).

IRB members have access to the full study file. Archived records can be requested by contacting HRPP/IRB staff.

### *7.7.2 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:

- Risk assessment and monitoring.
- Adequacy of the informed consent process.
- Local investigator and organizational issues.
- Research progress.

### *7.7.3 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 7.7.2 and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report and multi-center study progress reports. The primary reviewer is responsible for conducting an in depth review of all materials. At the meeting, the primary reviewer provides a summary

of the research and the progress report and assists the IRB Chair in leading the IRB through the evaluation of the regulatory criteria for approval.

### *7.7.4 Expedited Review*

In conducting continuing review under expedited procedures, the reviewers receive all of the previously noted materials. The reviewer(s) complete the *Continuing Review Checklist* to 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) of Expedited Review Categories in Section 7.2.1. 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.

### *7.7.5 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 7.6 for a detailed description of IRB actions.

- Approval.
- Conditions Required for Approval.
- Deferred.
- Partial Approval.

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 Section 8 for a detailed discussion of suspensions and terminations.

If a research study receives "Conditions Required for Approval" 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 restricted activity is not begun or restarted until approval is granted.

### *7.7.6 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 occurs 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 (eg, an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), 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.

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB's conditions. However, the investigator and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

HRPP/IRB staff are responsible for notifying the investigator of the expiration of approval and that all research activities must cease.

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 HRPP/IRB staff and submit a 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 subjects already enrolled in the study 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.

When there is insufficient time to obtain an IRB determination (eg, the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination, in consultation with the subjects' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact HRPP/IRB staff and submit a request for confirmation that the IRB agrees with the determination. The IRB chair or designee will review the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or agrees only in part (eg, agrees that some but not all of the activities are in the best interests of subjects), the IRB will notify the investigator who must then comply with the IRB requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

## 7.8 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** unless the change is necessary to eliminate apparent immediate hazards to the subject (in which case the IRB must then be notified at once).

Modifications may be permanent (protocol modification) which make changes to the protocol for all remaining subjects or one-time changes for a specific subject (protocol exception). See Section 7.8.5 for details on protocol exceptions.

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 protocol/research plan.

### *7.8.1 Procedures*

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

- Completed *Modification Request Form*.
- A revised protocol/research plan, application, and/or study materials (in tracked changes or with a detailed summary of changes and the locations of those changes), as applicable.
- 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.
- Any other relevant documentation such as cover letters provided by the sponsor or coordinating center.

HRPP/IRB staff 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 IRB 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.

### *7.8.2 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 with 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 assessment of 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.

### *7.8.3 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 performed by the IRB chair and/or experienced designee(s) among the IRB members.

The reviewer(s) completes the *Initial Study Review Checklist* 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 also considers 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 and how to provide that information to participants.

### *7.8.4 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 7.6 for a detailed description of IRB actions.

- Approval.
- Partial approval.
- Conditions required for approval.
- 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 Section 8 for a detailed discussion of suspensions and terminations.

### *7.8.5 Protocol/Research Plan Exceptions*

Protocol/research plan exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a protocol/research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

**Exceptions are planned, and the investigator must get approval from the sponsor and the IRB ahead of time.** For sponsored research, prior approval from the sponsor is generally required in addition to IRB approval. Depending on the nature of the exception, an expedited IRB review may be possible. In order to be approved under expedited review the proposed exception must not adversely affect the risk/benefit analysis, participant's rights, safety, welfare, or the overall integrity of the study data. Review of exceptions that represent more than minor changes are reviewed at a convened meeting of the IRB.

Procedures for exceptions are the same as for a protocol modification. The investigator must submit a *Modification Request Form* along with any revised documentation to be presented to the subject(s) and documentation of sponsor approval, if applicable.

The only time a protocol/Research Plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an immediate hazard to the participant. In such cases, the exception must be submitted to the IRB as soon as possible as a deviation.

## 7.9 Closure of Research Studies

The completion or early termination of the study, is a change in study activity and as such 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 medical school and any sites for which the medical school IRB is the "IRB of record". If the investigator is serving as the lead investigator or the site reviewed by the medical school IRB is the coordinating center, the study must remain open as long as the lead investigator or coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites even if local site interventions, interactions, observations, and data gathering is complete.

Investigators may submit study closures to the IRB on a *Study Completion or Closure Form*. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time via the *Study Completion or Closure Form*.

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved protocol/research plan. However, investigators may not conduct any additional analysis of identified data without 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 reviews study closure reports, typically by expedited review, and either acknowledges the closure of the study or request additional information, actions, or confirmation of facts from the investigator.

## 7.10 Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, in writing within ten (10) working days via a letter prepared by the HRPP/IRB staff. For an approval, written notification of approval and the approved consent/assent/permission form(s), if applicable, containing the IRB stamp with the dates approval became effective and the study expiration date are sent 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 includes the basis for deferral and a listing of the required modifications and/or clarifications. For a disapproval, termination or suspension, the notification includes the basis for making that decision.

IRB letters are maintained in the IRB study file.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by HRPP/IRB staff to the assistant dean for Research Compliance and Institutional Official.

## 7.11 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 (eg, a request for modification), the IRB chair or IRB director reviews the circumstances, including any potential impact on human subjects, and contacts 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 will be reviewed in accordance with the procedures in Section 16. Notice, including an explanation, is sent by HRPP/IRB staff to the investigator. An extension beyond 90 days may be granted by the IRB if the investigator provides sufficient cause.

## 7.12 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.

In cases where there is disagreement between the IRB and the investigator regarding the nature and extent of requested changes or the necessity of or basis for a suspension or termination, the investigator may submit an appeal to the IRB to request reconsideration. In the event a disagreement cannot be resolved, the investigator and/or the IRB may make an appeal to the assistant dean for Research Compliance or

Institutional Official, either of whom may organize a meeting to help facilitate discussion between the IRB and the investigator. While the Institutional Official may provide input and make recommendations to the investigator and IRB for resolution of the matter, final determinations for approval/required modifications/disapproval remain under the purview of the IRB.

## 7.13 Research Previously Approved by Another IRB

When an investigator transfers research to the medical school that was previously approved by another IRB, the investigator must notify both IRBs and submit the research for review under the procedures covered by this section. The IRBs work together to determine the effective date of transfer and any steps necessary to avoid a lapse in IRB oversight during the transfer process.