

**PROCEDURES FOR REVIEW OF HUMAN SUBJECTS PROTOCOLS
BY
THE HOMEWOOD IRB**

I. INTRODUCTION

Review of human subjects research activities has been conducted at Johns Hopkins for decades. In 1967, a joint committee called the Joint Committee on Clinical Investigation (JCCI) was established that was designed to serve the review needs of both The Johns Hopkins School of Medicine and the Johns Hopkins Hospital. In the 1960s and 1970s, review of human subjects research protocols was governed by institutional standards for the design and conduct of the studies, and no national standard for review was available. Subsequently the University established IRBs at the Bloomberg School of Public Health and for the Homewood schools that reviews human subjects protocols for the schools not covered by the JCCI.

In 1978, the President's National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published a document entitled The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research (Appendix A). The Belmont Report was a benchmark in the movement to set forth federal regulations requiring institutional prior review and approval of human subjects research activities. In 1981 federal regulations were finalized, detailing the required review process to be followed by institutional review boards (IRBs) at all facilities conducting federally funded research or research under the jurisdiction of the Food and Drug Administration. The Johns Hopkins Institutions decided at that time that the regulations should be applicable to all projects, regardless of funding source or lack of funding source.

In 1991, a new "Federal Policy for the Protection of Human Subjects" became effective. This new policy, referred to as the "Common Rule" is applicable to 16 federal departments and agencies. The provisions basically copy the DHHS regulations, thus simplifying adherence to federal Human Subjects regulations regardless of the agency to which one submits a funding application. The only agency which did not adopt the "Common Rule" in its entirety is the FDA.

For over twenty years, the Homewood Review Board on the Use of Human Subjects (Homewood IRB) has been publishing guidelines to explain the Committee's institutional charge, outline the process by which it operates in compliance with federal regulations, and define the obligations of principal investigators and their staff who conduct human subjects research. At this time the Homewood IRB serves The Krieger School of Arts and Sciences, the Whiting School of Engineering, School of Professional Studies in Business and Education, the School of Advanced International Studies (SAIS), the

Peabody Institute and The Applied Physics Laboratory (APL) for its behavioral and social sciences research (The Schools). In addition, Homewood IRB works with the JCCI and Committee on Human Research in The School of Hygiene and Public Health. In particular, human subjects protocols involving clinical investigations are referred to the JCCI where expertise to appropriately evaluate clinical studies is resident.

II. AUTHORITY

The Johns Hopkins University Krieger School of Arts and Sciences, the Johns Hopkins University Whiting School of Engineering, School of Professional Studies in Business and Education, SAIS and the APL require all social science and behavioral research projects involving human subjects to be reviewed and approved, or declared exempt by the Homewood IRB before a project may be initiated.

The Homewood IRB is charged with the responsibility for review and approval of human subjects research conducted by faculty members (full or part time) and staff of The Schools.

The Homewood IRB reviews of all research involving employees or students of the School of Arts and Sciences, the School of Engineering, School of Professional Studies in Business and Education, Peabody, SAIS and APL. The requirement for review applies regardless of the source (or lack of source) of funding for a project and regardless of the site at which the research is performed.

The Homewood IRB operates in compliance with the U.S. Code of Federal Regulations, Department of Health and Human Services (DHHS) Title 45 Part 46, entitled "Protection of Human Subjects," as well as the Food and Drug Administration (FDA) regulations on human subjects research. A copy of the DHHS and FDA regulations may be obtained on line at the respective agency web sites and the JHUResearch web site. The Multiple Project Assurance (MPA) number issued to Homewood IRB by the DHHS is M1091. A five year renewal of the assurance was submitted on November 1, 1998.

The primary concerns of the IRB in all deliberations is to determine that:

1. the rights and welfare of the subjects are protected adequately,
2. the risks to subjects are outweighed by the potential benefits of the research,
3. the selection of subjects is equitable, and
4. informed consent will be obtained and, when appropriate, documented.

All applications submitted to the IRB must designate a faculty member, or senior staff member in the case of APL as the principal investigator. The Institutions require that responsibility for compliance with Institutional guidelines and policies rests with a faculty member of the department in which the project will be conducted. Therefore, postdoctoral fellows, staff or students may actively participate in human subjects research activities, but the principal investigator of record on a research project submitted to the

IRB must be a Johns Hopkins University faculty member, or a senior staff member at the APL.

The IRB has the authority to suspend or terminate approval of research at The Schools when it is determined that the research has been associated with unexpected serious harm to participants, or is not being conducted in compliance with the determinations of the IRB or the federal regulations on human subjects research. If the Homewood IRB determines that a research project should be suspended or terminated for cause, the action will be reported to appropriate institutional officials, the head of any supporting Federal Department or Agency (if applicable), and the Office of Human Research Protections at DHHS. If the project that is suspended or terminated involves a drug, device, or diagnostic regulated by the FDA, the FDA shall also be notified of the suspension/termination.

The responsibility for appointing and maintaining the Homewood IRB rests with the President of the University and the Deans of the Schools, in consultation with appropriate Department Chairs. Members are appointed to include faculty who represent the breadth of scientific and scholarly specialties, at least one member whose primary concerns are in a non-scientific area, and at least one member who is otherwise unaffiliated with The Schools. Appointments are for three years, are renewable, and continuity is fostered by staggered reappointment for subsequent years when possible. Faculty preparing an application for submission may wish to contact a Homewood IRB member prior to the submission.

III. REPORTING AND COMMUNICATION

The IRB shall report promptly to the Provost and the NIH Office of Human Research Protections any serious or continuing noncompliance by investigators with the requirements and determinations of the Homewood IRB: any suspension or termination of IRB approval for reasons of noncompliance or unexpected serious harm to subjects: and, any unanticipated problems involving risks to subjects or others encountered in the research.

Homewood IRB findings and actions taken on protocols are communicated with the University administration and the respective schools in a variety of ways. Periodic reports identify projects that are under consideration, have been approved, have been re-approved, or have been terminated. The JHUResearch web site is being updated to include a listing of protocols that are active and a listing of terminated protocols. The Assistant Dean for Research Administration and an Associate General Counsel sit on the IRB, and provide timely information to the to the Research Deans of the relevant schools, the Provost and the Vice Provost for Research on human subjects issues.. The chair of the IRB reports to the Provost through the Vice Provost for Research on all human subjects activity that is approved by the Homewood IRB in order that they are fully and timely informed.

IV. REVIEW CATEGORIES

A Human Subject Research form (Attachment A) is the application form to be used to submit a new human subjects research protocol for Homewood IRB review. The form contains preprinted instructions on submission requirements. Only one signed original new application must be submitted to the Homewood IRB Office to initiate the review process.

The following review categories are defined by regulation:

- A. FULL BOARD REVIEW.
- B. EXPEDITED REVIEW.
- C. HUMAN SUBJECTS RESEARCH PROJECTS EXEMPT FROM IRB REVIEW.

V. A FULL BOARD/COMMITTEE REVIEW

Review at a convened Homewood IRB meeting is required for those new applications and renewal applications not determined to be exempt or eligible for expedited review.

The Homewood IRB reviews all research involving human subjects not subject to exemptions with the exception of human subjects investigations involving clinical studies. ALL CLINICAL STUDIES should be submitted for review through the Homewood IRB to the JCCI at the School of Medicine. The Homewood IRB will maintain a file on the protocol throughout its existence.

The review process requires submission of an application in the Hopkins' format (Attachment A). The application form is structured to assist investigators in providing information required to allow the Homewood IRB to evaluate whether the research addresses the specific issues referenced in federal human subject regulations. Required attachments to the application include the following: a copy of the full protocol developed in accordance with Attachment B, the proposed consent document (Attachment C), a copy of the investigator-initiated Investigational New Drug Application submitted to the FDA (if applicable), a copy of proposed advertisement material for recruitment of subjects; and if funded by any federal agency, a copy of the complete grant application.

Copies of the full protocol, consent form(s), and proposed advertisement material are distributed to all Homewood IRB members for review and comment.

Members are asked to make several determinations. One is for an assessment of whether final approval of the project should be for the period of one year, or if the project should be reviewed more often than annually. In making this determination, members will consider the risks of the procedures, the novel nature of the protocol intervention(s), and the subject population to be studied. Members may recommend a variety of reporting periods. This could include reporting after enrollment of a limited number of subjects, or

reporting at a designated time period (quarterly or semi-annually). Applications listed on the agenda for consideration at convened meetings will list recommended interim reporting requirements if members suggest a period of review other than one year. When action is taken at the convened meeting, the investigator is informed of the required reporting period.

The Homewood IRB will make a judgment on the validity of the study as part of its assessment of the risk-benefit ratio, because no risk to subjects can be justified if the study design is flawed to the degree that no useful information is likely to be forthcoming. The composition of the population to be recruited will be reviewed to ensure that equitable selection of subjects based on gender, age, or ethnicity has been taken into account in the design of the study.

By regulation, final action on protocols that require full review may be taken ONLY at a legitimately convened meeting. A simple numerical majority of members must be present at a meeting, including a member whose primary concern is in a non-scientific area. In order for the protocol application to be approved, it must receive approval of a majority of members present at the meeting.

The range of actions that may be taken at a convened meeting are:

1. The application may be approved.
2. The application may be tabled for response to questions or required modifications. Discussion of the response must be conducted at a convened meeting.
3. The application may be approved with stipulations that are considered minor and require only simple concurrence by the investigator. The response to minor stipulations may be reviewed by the Chair, or the Chair's designee; and such cases do not require return to a convened meeting for final action.
4. The protocol application may be disapproved. In cases where a study is disapproved, the rationale for the action taken will be provided in written form. The investigator may request an appearance at a convened meeting to present arguments for reversal of a decision to disapprove, or the investigator may propose a change in the protocol based the advice and counsel of the Homewood IRB. Institutional officials cannot approve a protocol that has been disapproved by the Homewood IRB. Effectively, therefore, there is no possibility of appeal of a Homewood IRB approval to a higher University, Hospital, or Federal official.

An application approved by the Homewood IRB may be subject to further review and approval, or disapproval, by officials of the University, School of Arts and Sciences, School of Engineering, Peabody Institute, SAIS, SPSBE or APL.

When a project receives initial approval, no protocol changes, consent form changes, amendments, or addenda may be made without re-review and approval. Written notification of actions taken at convened meetings is mailed to the principal investigator after each meeting.

The approval notice reiterates the investigator's obligation to report any unanticipated problems or adverse events. Attached to the standard approval notice is the final approved version of the consent form(s) with the approval stamp affixed on the signature page. The consent form is valid only for the period noted in the approval box. If a consent form is revised in association with an amendment review, it is valid only until the annual review date for the project.

VI. CATEGORIES OF RESEARCH THAT MAY BE REVIEWED BY THE IRB THROUGH AN EXPEDITED REVIEW PROCEDURE

In 1998, the Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) regulations were revised with regard to categories of research that may be reviewed by an expedited review procedure. The list of research categories was expanded and clarified.

Please note that the term "expedited review" does not refer to the Webster's Dictionary definition of expedited. Only research projects which meet the regulatory definition of minimal risk qualify for the expedited review process.

The following two criteria must be met before a protocol may be considered for an expedited review process:

- (1) The activity must present no more than minimal risk to subjects AND
- (2) The protocol procedures must be listed as one of the categories in the regulations' list of procedures that qualify for an expedited review process.

In addition, DHHS and FDA regulations state that an 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.

The Research Categories listed below qualify for an expedited review process. The final decision on whether an expedited review process may be used rests with the IRB Chair or his/her designee.

- (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, non-pregnant 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 subject, 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.

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

Examples:

(a) hair and nail clippings in a non-disfiguring 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) cannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric acid 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.

(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. (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).
- (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 belief or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
- (8) Continuing review of research previously approved by the convened Homewood IRB as follows:
 - (a) where (i) the research 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; or
 - (b) where no subjects have been enrolled and no additional risks have been identified; or
 - (c) where the remaining research activities are limited to data analysis.
- (9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the Homewood IRB has determined and documented at a convened meeting, that the research involves no greater than minimal risk and no additional risks have been identified.

The expedited review process requires submission of an application in the Homewood IRB format. Required attachments to the application include the following: a copy of the full protocol, the proposed consent document (written in the Homewood IRB format), a copy of proposed advertisement material for recruitment of subjects; and if funded by any federal agency, a copy of the complete grant application. If a drug or device is part of the study, information is required for the IRB to make the determination in (1)(a) or (1)(b) above. The grant application will be reviewed by a member to determine that the protocol submitted and the activities described in the grant are consistent. Any discrepancies between the protocol application and the grant application must be resolved before final action can be taken to approve the project.

The expedited review process is conducted by the chair or his/her designee. If the protocol meets the regulatory criteria for an expedited review, it will be forwarded to a Homewood IRB reviewer.

The following actions may be taken on applications that qualify for an expedited review process:

- (1) The application may be approved as submitted.
- (2) The application may be approved with restrictions, conditions, stipulations, or required modifications including changes to the consent document. The investigator's response to approval with stipulations will be reviewed by the chair or his/her designee to determine if final approval may be granted.
- (3) The application may be referred for discussion at a convened meeting.

The agenda for convened meetings is the mechanism by which the Homewood IRB members are notified of actions taken using an expedited review process. Members at the convened meeting may challenge an action taken through the expedited review process. The reviewer conducting the expedited review does not have the authority to disapprove an application. Disapproval is an action that may be taken only at a convened meeting.

When a project receives approval through an expedited review process, written notification is provided to the principal investigator. The notice will state the period of approval. Attached to the standard approval notice is the final approved version of the consent form(s) with the approval stamp affixed on the signature page. No protocol changes, consent form changes, amendments, or addenda may be made to the application without re-review and approval.

VII. HUMAN SUBJECTS RESEARCH PROJECTS EXEMPT FROM IRB REVIEW

Broad categories of research which do not use living human subjects or which normally present little or no risk of harm to subjects may be exempt from formal review by the IRB. In general, most social, economic and educational research is exempt if the only involvement of human subjects is in one or more of the following categories: (a) the use of survey and interview procedures, (b) observation of public behavior or (c) the study of existing data, documents, records and specimens.

A request for an exemption should be submitted in the form of a letter addressed to the chair of the IRB explaining in detail why the project does indeed qualify for exemption. The letter should contain the title of the project and note the exemption category that the investigator believes is applicable. Requests should be submitted to the IRB office. For projects that are funded by a federal agency, a copy of the grant or contract must be appended to the exemption request letter. An investigator must receive a written

exemption from the IRB before he/she represents that a research activity is exempt from review and begins the research project.

More specifically, the DHHS regulations contain categories of social, education, and economic research activities that may be considered exempt. The categories are described below. By regulation, exemptions DO NOT apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization. A written response will be sent to the PI to indicate either: a) the proposed research activity is exempt and may be conducted without IRB review; or b) the project is not exempt, explain why, and note that submission of a human subjects application is required. Written confirmation of an exemption must be available for a grant application submitted with an exemption number in the human subjects section.

DHHS Exemption Categories include:

1. Research conducted in established or commonly accepted educational setting, involving normal education practices, such as:
 - a. research on regular and special education instructional strategies, or
 - b. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and
 - b. any disclosure of the human subjects responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

EXCEPTION: DHHS Regulations at 46.401 state that parts of Exemption #2 DO NOT apply to research with children. Therefore, projects involving educational tests and/or survey procedures involving children must be submitted for IRB review.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior that is not exempt under paragraph (2) of this section, if:
 - a. The human subjects are elected or appointed public officials or candidates for public office;
 - or
 - b. federal statute(s) requires(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. .
4. Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly

available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifies linked to the subjects.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - a. public benefit or service programs;
 - b. procedures for obtaining benefits or services under those programs;
 - c. possible changes in or alternatives to those programs or procedures; or
 - d. possible changes in methods or levels of payment for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies;
 - a. if wholesome foods without additives are consumed or
 - b. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

VIII. RENEWAL APPLICATIONS AND CONTINUING REVIEW REQUIREMENTS

All protocols approved by the IRB are subject to continuing review. Federal regulations (both DHHS and FDA) require conduct of continuing review of research "not less than once per year." Federal agencies have made it very clear that they expect IRB to review an application for continuing review before the approval date expires. Submission of a renewal application after approval has lapsed is not acceptable. Administrative extensions will not be granted. Projects for which the required reports or renewal application were not submitted in time to allow review within the designated approval period (one year or less) are considered terminated. New subjects may not be enrolled and subjects on study must be removed from a protocol for which approval has lapsed. The IRB will consider on a case-by-case basis whether removal of subjects from a lapsed protocol would adversely affect subjects already enrolled.

When initial approval is granted, the approval notice will indicate the period of approval. Approval may require continuing review based on numbers of subjects enrolled, quarterly reports, semi-annual reports, or annual reports. The investigator must acknowledge in writing that he/she understands the reporting requirements. Regardless of the required reporting period, investigators have a continuing responsibility to inform the IRB of any circumstances or new information that might change the perception of a favorable risk: benefit assessment. Adverse event reports or unanticipated problems should be submitted in accord with the Homewood IRB guidelines (See Adverse event reporting guidelines).

IRB renewal notices are mailed to principal investigators as a courtesy to prompt submission of renewal applications. There may, however, be problems with the database,

and a renewal notice may not be issued. Therefore, an investigator should not depend solely on renewal notifications as a prompt for submitting a request for renewal. Initial approval notices state clearly the dates for approval. Renewal notices sent to investigators indicate the precise date on which approval will expire and a precise date by which the renewal application must be submitted to the office to allow review within the time period required by regulations.

To initiate the continuing review process, a renewal application must be submitted to the Homewood IRB office. The principal investigator must provide responses to all items and questions noted on the renewal form. This includes the number of subjects accrued, information on whether any subjects were withdrawn from the project and the reasons for withdrawal, proposed amendments to the research plan or consent form, etc. The progress report must include a status report on the progress of the research study and any findings to date. An unstamped copy of the consent form must accompany the renewal form. Any new proposed changes in the consent form should be highlighted on a copy attached to the renewal application.

The Homewood IRB will determine if a renewal application qualifies for an expedited review procedure or requires review at a regularly convened meeting. The IRB will determine if a specific project needs verification from sources other than the investigator. In such instances, the Homewood IRB may request an independent assessment of information or data provided in the renewal application. The scope and extent of such an independent assessment will be determined on a case-by-case basis.

Applications that qualify for an expedited review procedure will be listed on the agenda with that designation, and copies of the applications will not be provided to each member. Applications that do not qualify for an expedited review process must be discussed at a convened meeting. A copy of each continuing review application that requires discussion at a convened meeting will be provided to each member as part of the agenda packet. At the convened meeting, the Homewood IRB will determine if re-approved is appropriate. The range of actions that may be taken is:

1. The renewal application may be approved.
2. The renewal application may be tabled for response to questions or required modifications.
3. The renewal application may be approved with minor stipulations that require only simple concurrence by the investigator. The response to minor stipulations may be reviewed by the Chair, or the Chair's designee; and such cases do not require return to a convened meeting for final action.
4. The renewal application may be disapproved. In cases where a renewal application is disapproved, the rationale for the action taken will be provided in written form. The investigator may request an appearance at a convened meeting

to present arguments for reversal of a decision to disapprove, or the investigator may propose a change in the protocol based on advice and counsel of the Homewood IRB.

Institutional officials cannot approve a protocol that has been disapproved by the Homewood IRB. Effectively, therefore, there is no possibility of appeal of a Homewood IRB disapproval to a higher University, or Federal official.

IX. IMPACT OF THE CONTINUING REVIEW PROCESS ON FEDERAL GRANT CONTINUATION APPLICATIONS:

On 8/2/91, the NIH instituted a policy for submission of continuation funding applications which affects investigators with approved protocols. As of that date, non-competing continuation grant applications may not be submitted with a pending human subjects approval date, nor may they be submitted with an approval date beyond one year from the initial review. This means that Homewood IRB review and approval of an application for continuing review must be completed before the NIH continuation funding application is submitted.

X. UNANTICIPATED PROBLEMS THAT AFFECT RISKS TO SUBJECTS.

In the case of clinical investigations submitted to the JCCI through the Homewood IRB, the JCCI procedures for reporting adverse or unanticipated events must be followed.

The standard IRB approval notice contains the following statement:

"If adverse consequences or unanticipated side effects are encountered in the course of the study, or new information becomes available which could change the perception of a favorable risk :benefit ratio, you are responsible for informing the Committee PROMPTLY."

There are two reporting forms, depending upon the location of the event:

A) Events at a Johns Hopkins site:

The principal investigator must complete JCCI Form A and submit it to the IRB.

A copy of every adverse event report, letter or form, submitted to an outside agency (e.g., sponsor, FDA or NIH) should also be forwarded to the appropriate Hopkins' IRB. Fatal or life- threatening events should be reported to the Homewood IRB (and if the Hopkins investigator holds the IND number, to the FDA as well), within 7 working days after discovery. All other unexpected serious adverse experiences should be reported to the Homewood IRB (and if a Hopkins Investigator held IND number is involved, to the FDA) within 15 working days after discovery. When an IND is held by a sponsor (other than Hopkins investigator), it is the sponsor's responsibility to report events to the FDA.

A serious adverse experience in a protocol enrolling subjects at a Johns Hopkins site is defined as any event that is fatal or life-threatening, that is permanently disabling, requires or extends hospitalization of the subject, or that represents a significant overdose or breach of protocol. In addition, any event that suggests that a drug, device, or procedure used in a research protocol has produced a congenital anomaly or cancer is also considered a serious adverse experience and must be reported.

The Schools and the Homewood IRB recognizes that assignment of cause and effect of an adverse experience may be difficult. In order to assure that review of all serious events is systematically undertaken, all studies that involve intervention with a diagnostic or therapeutic drug, biologic, device, or procedure should have all serious unexpected adverse experiences reported to the appropriate IRB regardless of the probability of cause. Minimal risk observational studies need only report adverse experiences that are believed to have an obvious direct causal relationship to the study.

The Homewood IRB will make the final determination regarding protocol changes required due to adverse event reports.

B) Adverse Event Report and Review for single or multiple reports from other sites.

Adverse events, or unanticipated problems involving risks to subjects, that occur at sites other than Hopkins must be reported using JCCI Form B. The form must be completed and signed by the principal investigator, and supporting documentation from the sponsor must be attached to the form. Unless the adverse event or unanticipated problem that occurred at a site other than Hopkins requires a change in the consent form, Homewood IRB will not routinely acknowledge receipt of the documentation. If a sponsor requires documentation of Homewood IRB receipt of these events, the IRB staff may supply a copy of the sheet that contains the date received by the Homewood IRB.

XII. Protocol file

The principal investigator **MUST** maintain a protocol file. The file must include the following items:

- a. A copy of the original protocol application submitted to Homewood IRB.
- b. A copy of the sponsor's protocol (if applicable).
- c. If the project involves an investigational drug or investigational device supplied by a sponsor of the study, a copy of the investigator's brochure should be kept. In the case of investigator-initiated IND or IDE studies, the file must contain a copy of the IND/IDE application submitted by the principal investigator to the FDA and any subsequent correspondence with the FDA.
- d. Copies of all correspondence with the IRB (and the sponsor, if applicable).
- e. A copy of the original approved consent document containing the Homewood IRB approval stamp
- f. The original of each consent form signed by subjects/patients enrolled in the research protocol. If the Committee has approved use of the oral consent procedure, the

principal investigator must keep a list of individuals who were approached to join the study and documentation on the list of a subject's decision to accept or decline participation.

It is the responsibility of the principal investigator to assure that a copy of the consent form is provided to each subject enrolled in a research study. For studies involving in-patients, the investigator should see that a copy of the signed consent form is inserted into each subject's medical record.

Additional requirements for investigators are as follows:

g. If the Homewood IRB approved a waiver from the requirement to use a written consent form and approves an oral consent procedure, the protocol file should contain a list of individuals who agreed to participate in the project.

h. Copies of all data derived from the study (case report forms, computer data, adverse event reports, drug/device accountability records, etc.).

PLEASE NOTE: The IRB, the FDA, and the sponsor/company/manufacture conduct periodic random audits of investigators' protocol records. Investigators are urged to keep their copies of signed consent forms readily accessible for review. If the FDA schedules an inspection of an approved protocol, the Homewood IRB should be informed so that a representative from Administration may attend the FDA audit sessions.

7/18/02