



INVESTIGATOR HANDBOOK

Human Research Protections Program

3/30/2009

INVESTIGATOR HANDBOOK

<u>MISSION.....</u>	<u>4</u>
<u>WEBSITE.....</u>	<u>4</u>
<u>FIRST TIME SUBMISSION.....</u>	<u>4</u>
<u>EDUCATIONAL REQUIREMENTS.....</u>	<u>5</u>
<u>NEW SUBMISSIONS.....</u>	<u>5</u>
<u>FOR SINGLE SUBMISSIONS.....</u>	<u>5</u>
<u>FOR MULTICENTER SUBMISSIONS Submitted by Sponsor/CRO:</u>	<u>6</u>
<u>MULTICENTER SUBMISSION Packet for Principal Investigator:</u>	<u>6</u>
<u>VULNERABLE POPULATIONS.....</u>	<u>6</u>
<u>STATE REQUIREMENTS FOR RESEARCH.....</u>	<u>7</u>
<u>INVESTIGATIONAL NEW DRUG STUDY (IND).....</u>	<u>7</u>
FDA Exemptions	8
<u>INVESTIGATIONAL DEVICE STUDY (IDE).....</u>	<u>8</u>
Exempted IDE Investigations:.....	9
<u>PRINCIPAL INESTIGATOR RESPONSIBILITIES.....</u>	<u>10</u>
<u>INFORMED CONSENT.....</u>	<u>11</u>
Informed Consent Process:.....	12
Nine Basic elements of informed consent:.....	13
Additional elements of informed consent to be applied, as appropriate:.....	13
Informed consent documentation:.....	14
Consent monitoring.....	14
Parental Permission and Assent	15
<u>Parental Permission</u>	<u>15</u>
<u>Assent from Children</u>	<u>16</u>
The Assent Form	16
<u>REPORTABLE EVENT REQUIREMENTS.....</u>	<u>17</u>
<u>Definitions:.....</u>	<u>18</u>
<u>AMENDMENTS.....</u>	<u>20</u>
<u>CONTINUING REVIEW.....</u>	<u>20</u>

Lapse in Continuing Review (Policy).....21

STUDY CLOSURE.....21

SITE VISITS.....21

SPECIAL DISCUSSION.....22

 Allowable Categories.....22

 Children Who are Wards23

HIPAA.....23

Waiver of Authorization.....23

MISSION

The mission of the HRPP is to:

- Protect the rights, welfare and privacy of human research participants. The IRB is guided by ethical principle mandates as outlined in the Belmont Report (1979) and legal mandates outlined in the Code of Federal Regulations Title 45 Part 46. To achieve these goals, the IRB will:
 1. Review all submitted research protocols thoroughly to ensure research subject's rights and welfare are not violated.
 2. Apply highest level of ethical standards in reviewing research protocols
 3. Adhere to federal and local guidelines in human rights protection.
 4. Require IRB staff, board members and investigators to complete periodic education in human subject protection.

The HRPP includes mechanisms to:

- Establish a formal process to monitor, evaluate and continually improve the protection of human research participants.
- Dedicate resources sufficient to do so.
- Exercise oversight of research protection.
- Educate investigators and research staff about their ethical responsibility to protect research participants.
- When appropriate, intervene in research and respond directly to concerns of research participants.

WEBSITE

Visit our easy to navigate website located at <http://www.irbco.com> to:

- View our meeting calendar (detailing schedules for weekly meetings and deadlines for submissions).
- Find links to obtain online training for investigators and staff members who work in research.
- Find links to Ethical Codes and Regulations of Human Subjects in Research.
- Download forms
- Submit online

IRBCo uses a secure and encrypted web submission system. Our electronic system reduces errors and processing time while enhancing communication between investigators/ sponsors, IRB coordinators and reviewers. Our new, secured web-based electronic submission and tracking program provides step-by-step protocol creation for single-site and multi-center clinical trials.

FIRST TIME SUBMISSION

Submissions to IRBCO as an investigator or sponsor are required to fill out the IRBCO authorization

form, and eProtocol access form, which are available in the "Forms" section of our website (www.irbco.com). Once these forms are filled out, the IRB Manager will ask you to write an Indemnification agreement and will provide you with a sample letter. From here, our workflow is web-based and 100% automated with step by step directions to develop and submit your research protocol, Informed consent and other documents. IRBCO also provides consultation to Investigators and Sponsors in developing informed consent and help design research with appropriate measures in human research subject protection.

EDUCATIONAL REQUIREMENTS

IRBCO requires that the PI and key investigators complete the IRBCO Required Core Modules in CITI Course in the Protection of Human Research Subjects. If PI or key investigators have other training in Human Research Subjects protection, please submit it with your application for board's approval. IRBCO provides CITI training to investigators at no cost, and it could be accessed through our website www.irbco.com under "Training" section. We also accept other equivalent training in human research subject protection and there are some links provided in the training section of our website.

New research protocols and applications for continuing review will not be accepted from principal investigators who have not completed the initial education requirement. All investigators and members of their research team must complete the requirements of Continuing Education (Renewal of CITI or equivalent training every two years).

NEW SUBMISSIONS

IRBCO's reviews submissions for single-site studies as well as multi-center studies.

In general, new submission documents include:

1. Sponsor Protocol
2. Informed Consent Document
3. Assent, if applicable
4. HIPAA Information
5. Investigator CV / Investigator license
6. Sub-Investigator CV / Sub-investigator license
7. Advertisements, Interviews, Surveys, Questionnaires
8. Investigator Brochures / Package Insert(s) for each FDA-approved drug being used off-label or specifically being used in the study protocol
9. Form FDA 1572 (IND Studies)
10. Investigator Agreement (IDE Studies)

SINGLE SITE TRIALS

FOR SINGLE SUBMISSIONS

- 1) Investigator initial application
- 2) Copy of completed and signed Form FDA 1572 - Maintain the original at your site. (Please ensure that all sections (1-11) are completed as any blank sections will result in review delay.)
- 3) Principal Investigator Site Questionnaire (Complete the Principal Investigator Site Questionnaire for Satellite Sites for each site listed in Section 3 of Form FDA 1572.)
- 4) Current curriculum vitae (CV) of PI. CVs must verify affiliation to at least one study site and must

- be current within 2 years.
- 5) Current professional license of PI. If PI is licensed in Massachusetts, a copy of the research license must also be included.
- 6) Proposed advertisement/recruitment material and requirements for the subject information and consent form (including any state and/or local requirements that are stricter than the Federal requirements).
- 7) Any additional study-related documentation to be provided to the subject (diaries, logging equipment).
- 8) Letter of Indemnification

Incomplete packets or packets received after the submission deadline will be placed on a later meeting agenda.

MULTI-CENTER CLINICAL TRIALS

Below is a list of information to be included in the IRBCO Independent Institutional Review Board submission packet from the sponsor/contract research organization (CRO), institution, or the principal investigator (PI). Please check with your sponsor contact to determine what you need to submit directly to IRBCO.

FOR MULTICENTER SUBMISSIONS Submitted by Sponsor/CRO:

- 1) Sponsor initial application for model protocol
- 2) Model Subject Information and Consent Form and Authorization to Use and Disclose Personal Health Information for Research Template
- 3) Clinical Investigator's Brochure (CIB) or Package Insert
- 4) Model proposed advertisement/recruitment material
- 5) Model Study Informational Sheets, Case Report Forms (CRF)
- 6) Study Protocol (final version)
- 7) Letter of Indemnification

MULTICENTER SUBMISSION Packet for Principal Investigator:

- 1) Investigator initial application
- 2) Site-specific information for consent document (including patient compensation), **IRBCo will incorporate any changes for PI site-specific consent. PI will be asked to complete an *Additional Site Worksheet* for each additional site.**
- 3) Proposed site-specific advertisement/recruitment material and site-specific requirements for the subject information and consent form (including any state and/or local requirements that are stricter than the Federal requirements).
- 4) Form FDA 1572 (IND, if applicable)
- 5) Investigator Agreement (IDE, if applicable)
- 6) Principal Investigator, Sub-Investigator, other study personnel CV(s) and current copy of medical license(s)

VULNERABLE POPULATIONS

When some or all of the participants in a research conducted under the oversight of IRBCO are likely

to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The PI is responsible for identifying patients who are at risk for impaired decisional capacity as a consequence of psychiatric illness, and who are being asked to participate in a research study with greater than minimal risk.

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

- 1) Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- 2) Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- 3) Subpart D - Additional Protections for Children Involved as Subjects in Research

DHHS-funded research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

The PI should provide appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent. Examples of studies that warrant independent monitoring include those involving schizophrenic patients who will be exposed to placebo, and/or drug washout, and/or treatment with agents that are not approved by the Food and Drug Administration (FDA). Populations requiring independent monitoring would include individuals with schizophrenia, other psychotic disorders or conditions characterized by lack of reality testing (i.e., psychosis). Populations not usually requiring independent monitoring would include those with substance use disorders. At IRBCO, we do not review research involving prisoners.

At Continuing review the PI should identify the number of vulnerable subjects enrolled and any that needed an independent monitor in the progress report.

STATE REQUIREMENTS FOR RESEARCH

California Experimental Subject's Bill of Rights: California Assembly Bill 1752: Human Experimentation became effective in January 1979, provides that all investigators doing a "medical experiment" must offer their subjects a copy of the "Experimental Subject's Bill of Rights." Failure to do so may result in civil or criminal penalties. (Sample forms in English and Spanish languages are available in "Forms" section of our website: www.irbco.com)

IRBCO has affiliation with commonwealth of Massachusetts to review research and IRBCO can review research in all 50 States.

INVESTIGATIONAL NEW DRUG STUDY (IND)

An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312) or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

- 1) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]

Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or 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. [21 CFR §56.104(d)].

The PI must indicate on the IRB application whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND/IDE could be a:

- 1) Industry sponsored protocol with IND/IDE.
- 2) Letter from FDA.
- 3) Letter from industry sponsor.
- 4) Other document and/or communication verifying the IND/IDE.

INVESTIGATIONAL DEVICE STUDY (IDE)

Investigational Device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

IDE means an investigational device exemption in accordance with 21 CFR 812.

Significant Risk (SR). Significant risk device means an investigational device that:

- 1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- 2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- 3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- 4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk (NSR). A non-significant risk device is an investigational device other than a significant risk device.

Humanitarian Use Device (HUD). Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year.

The Principal Investigator/ Sponsor must indicate on the IRB application whether the research involves investigational devices. If so, the PI/ Sponsor must indicate if there is an IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IDE could be a:

- 1) Industry sponsored protocol with IDE.
- 2) Letter from FDA.
- 3) Letter from industry sponsor.
- 4) Other document and/or communication verifying the IDE.

For investigational devices, NSR (Non-Significant Risk) device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves devices and there is no IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine whether there is an IDE and if so, whether there is appropriate supporting documentation.

Exempted IDE Investigations:

For devices, an IDE is not necessary if:

- 1) The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
- 2) The research involves a device that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
- 3) The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - a) Is noninvasive,
 - b) Does not require an invasive sampling procedure that presents significant risk,
 - c) Does not by design or intention introduce energy into a subject, and
 - d) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
- 4) The research involves a device undergoing consumer preference testing, testing of a

modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;

- 5) The research involves a device intended solely for veterinary use;
- 6) The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);

The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

PRINCIPAL INVESTIGATOR RESPONSIBILITIES

1. The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines and IRBCO policies and procedures.
2. The PI must obtain approval from the IRB before initiating any research activities.
3. The PI proposing the drug/device research will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the drug/biologics/device.
4. The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.
5. All investigational drugs will be stored under lock and key and dispensed by the Investigator or assigned Pharmacy Service.
6. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI's control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
7. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 8.
8. For research involving investigational new drugs:
 - a. The PI is required to inform Pharmacy Service that IRB have approved the protocol through submission of the IRB approval letters.
 - b. The PI must inform the IRB and Pharmacy Service when a study involving investigational drugs has been terminated by the sponsor.
 - c. The PI will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.
 - d. The PI will maintain the following:
 - i. Current curriculum vitae (CV)
 - ii. Protocol
 - iii. Records of receipt and disposition of drugs
 - iv. List of any co-investigators with their curriculum vitae
 - v. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and
 - vi. Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the investigator considers that the event

is not related to the drug. All unexpected adverse effects shall be reported immediately to Pharmacy Service and the IRB in the manner defined by the protocol.

- vii. IRB letters of approval.
- viii. Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.

9. For research involving investigational devices:

- a) If a device is considered NSR by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
- b) If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining.
- c) The PI will maintain the following:
 - i. Current curriculum vitae (CV)
 - ii. Protocol of the study,
 - iii. Records of animal study reports
 - iv. Records of receipt and disposition of devices
 - v. List of any co-investigators with their curriculum vitae,
 - vi. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation,
 - vii. Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All Unanticipated adverse device effects are reportable.
 - viii. IRB letters of approval and the EOC Committee approval letter if applicable.
 - ix. Device training.
 - x. Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.
- d) Following completion of the study the termination procedure for investigational drugs must be applied if pharmacy control, or if the devices are kept by the investigator the log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
- e) If, after use, the PI keeps the devices, he/she must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
- f) The PI will submit to the sponsor and to the IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. In this situation where Investigator is also sponsor, Investigator will be required to comply with the regulatory responsibilities of a sponsor and IRBCO will request Investigator to submit study monitoring plan and data safety monitoring plan (if applicable).

INFORMED CONSENT

Basic requirements:

Investigators must obtain consent prior to entering a subject into a study and/or conducting any

procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent from a patient, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

Informed Consent Process:

Legally effective informed consent is more than a document which demonstrates respect for the research subject. Consent process is ongoing and comprehensive and should not be passive.

Informed consent should be explained to research subject in a simple manner and in language he/she could understand. Risks should not be underestimated and benefits should not be overestimated. Informed consent must be obtained under the following circumstances:

- 1) Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, consent must be obtained from a legal guardian or a legally authorized representative.
- 2) The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to consider whether or not to participate.
- 3) The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
- 4) The informed consent information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research.
- 5) For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent.
- 6) The informed consent process may not include any exculpatory language through which the subject is made to waive, or appear to waive any of the subject's legal rights or through which the investigator, the sponsor, the IRBCO and IRBCO employees or agents are released from liability for negligence, or appear to be so released.

The PI is responsible for insuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

Nine Basic elements of informed consent:

- 1) A statement that the **study involves research**, an explanation of the **purposes** of the research and the expected duration of the subject's participation, a description of the **procedures** to be followed, and identification of any procedures which are experimental; a description of any reasonably foreseeable **risks** or discomforts to the subject.
- 2) A description of any **benefits** to the subject or to others, which may reasonably be expected from the research.
- 3) A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject.
- 4) A statement describing the extent, if any, to which **confidentiality** of records identifying the subject must be maintained.
- 5) For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury**, including who will pay for the treatment and whether other financial compensation is available.
- 6) An **explanation of whom to contact** on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject.
- 7) **Contact information for the IRB** to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff.
- 8) A statement that participation is **voluntary**, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- 9) For **FDA-regulated studies**, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.

Additional elements of informed consent to be applied, as appropriate:

- 1) A statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to subjects is not well known.)
- 2) A statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
- 3) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (For example: Include when there are

- anticipated circumstances under which the investigator may terminate participation of a subject.)
- 4) Any additional costs to the subject that may result from participation in the research. (For example: Include when it is anticipated that subjects may have additional costs.)
 - 5) The consequences of a subject's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences.)
 - 6) Procedures for orderly termination of participation by the subject. (For example: Include when the protocol describes such procedures.)
 - 7) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)
 - 8) The approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)

Informed consent documentation:

Informed consent must be documented by the use of a written consent form approved by the IRB.

- 1) Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent.
- 2) A copy of the signed and dated consent form must be given to the person signing the form.
- 3) The consent form may be either of the following:
 - a) A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed; or
 - b) A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used:
 - i) there must be a witness to the oral presentation; and
 - ii) the IRB must approve a written summary of what is to be signed by the subject or representative; and
 - iii) the witness must sign both the short form and a copy of the summary; and
 - iv) the person actually obtaining consent must sign a copy of the summary; and a copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

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 (consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

- 1) High risk studies

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

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

If the IRB determines that consent monitoring is required, the IRB Chair and the Director will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with the institution. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of subjects. When observing the consent process, the monitor will determine:

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

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

Parental Permission and Assent

Parental Permission

The IRBCO determines that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described.

The IRBCO may find that the permission of one parent is sufficient for research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., **minimal risk**).

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject, and the risk is justified by the anticipated benefit to the subjects; the IRB may find that the permission of one parent is sufficient; but IRB will require assent of the child. Any research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition, the risk represents a minor increase over minimal risk; and the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations, IRB will require consent from both parents **unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child** and assent from the child. The IRB's determination of whether consent must be

obtained from one or both parents will be documented in the consent checklist when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Assent from Children

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parent permission and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of this manual.

The Assent Form

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

- 1) tell why the research is being conducted;
- 2) describe what will happen and for how long or how often;
- 3) say it's up to the child to participate and that it's okay to say no;
- 4) explain if it will hurt and if so for how long and how often;
- 5) say what the child's other choices are;
- 6) describe any good things that might happen;
- 7) say whether there is any compensation for participating; and
- 8) ask for questions.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, **only if such research** is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

REPORTABLE EVENT REQUIREMENTS

IRBCO complies with DHHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others to the IRB, institutional officials and relevant federal agencies and departments. The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the oversight of IRBCO.

Unanticipated problems involving risk to participants or others.

Unanticipated problems involving risks to participants or others refer to any problem, event, or new information that:

- 1) Is unexpected (in terms of nature, severity, or frequency) given
 - a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent documents; and
 - b) the characteristics of the subject population being studied; and
- 2) Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Definitions:

- **Adverse Event.** An Adverse Event (AE) is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.
- **Serious Adverse Event.** A Serious Adverse Event (SAE) is defined as death; a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.
- **Unexpected Adverse Event.** An Unexpected Adverse Event (UAE) is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.
- **Adverse Device Effect.** An Adverse Device Effect (ADE) is any adverse event/effect caused by or associated with the use of a device that is unanticipated and has not been included in the protocol or the Investigator's Brochure.
- **Related.** An event is "related" if it is likely to have been caused by the research procedures.
- **Unexpected Death.** The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of these procedures.

TIMELINE

Investigators must report possible unanticipated problems to the IRB within ten (10) days of receiving notice of the event, if the event requires immediate intervention to prevent serious harm to participants or others. Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

Investigators must promptly report (according to the above schedule) the following events to the IRB if the events occur within thirty (30) days of participants' active participation or treatment:

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- 1) Adverse events which in the opinion of the principal investigator are both unexpected and related.
- 2) An unanticipated event related to the research that exposes participants to potential risk.
- 3) An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk
- 4) Information that indicates a change to the risks or potential benefits of the research. For example:
 - a) An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
 - b) A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.
- 5) A breach of confidentiality.
- 6) Incarceration of a participant in a protocol not approved to enroll prisoners.
- 7) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- 8) Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- 9) Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- 10) Event that requires prompt reporting to the sponsor.
- 11) Sponsor imposed suspension for risk.
- 12) Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

NON-REPORTABLE EVENTS

Adverse events are non-reportable if they are listed in the approved consent document and are unrelated to the study agent.

DEVIATIONS/VIOLATIONS

It is the responsibility of the Investigator not to deviate from the protocol approved by the IRB, except to avoid an immediate hazard to the participant. The Investigator must submit an amendment request to the IRB and receive written approval prior to implementation of any change to the protocol. When a sponsor requests that the IRB be notified of a deviation, the completed form will be forwarded to the IRB chair or designate for review of the "Protocol Deviation/Exception Report" form submitted by the Investigator. Repetitive deviations may be ruled by the IRB to constitute non-compliance resulting in suspension of IRB approval.

There are two forms to report deviation on our website.

- 1) Deviation Report Form (DRF): Fill out this form if an unplanned deviation occurred, and in your opinion, it may adversely affect the rights, safety or welfare of the subjects or significantly impact the integrity of research data.)
- 2) Deviation Log: Fill out this log to report minor deviations or violations, which doesn't affect the rights, safety or welfare of the subjects or significantly impact the integrity of research data.) Please contact us if you have questions about which deviation should be reported on this log.

The following procedures describe how protocol exceptions and deviations are reported to the IRB.

- 1) The Principal Investigator provides protocol deviations by submitting a detailed report of the

- event within 10 working days.
- 2) Upon receipt of the deviation report, an IRB administrator reviews and evaluates the deviation. If further information is needed, IRB will request clarification, correction or revision to the report from the PI including activity status of the study participant.
 - 3) A determination will be made whether the event had a significant effect on the participant's rights, safety, or welfare, or corrupted the integrity of the resultant scientific data. The IRB Medical Director may be consulted at any time during this process.
 - 4) The Principal Investigator will provide IRB with steps taken to implement a serious, viable plan for assuring the safety of research participants and the oversight of data integrity.
 - 5) After review and evaluation of the incident, the protocol deviation is acknowledged.

AMENDMENTS

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes in approved research** - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once).

Modifications may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, a modification request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. If, however, the researcher wishes to add a population and revise study procedures, he or she will need to submit a new application for human subjects approval.

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

- Revised Investigator's protocol application or sponsor's protocol (if applicable)
- Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study
- Revised or additional recruitment materials
- Any other relevant documents provided by the investigator
- Adding investigators or other staff members to multi-center studies
- Addition of sites

IRB Office staff will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants full board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the protocol for full board review.

CONTINUING REVIEW

To assist investigators the IRB Office staff will send out renewal notices to investigators up to two months 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:

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- the initial review application updated with any changes;
- the current consent document;
- any newly proposed consent document; and
- the protocol renewal form.

Lapse in Continuing Review (Policy)

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 the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. **This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.**

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval the PI must immediately submit to the IRB Office a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects should only continue when the IRB finds that it is in the best interest of the individual subjects to do so.

Failure to submit continuing review information on time is non-compliance and will be handled according to the non-compliance policy (See Section 10). Conduct of research after a lapse is serious non-compliance and must be reported to FDA and sponsor. Repeated lapse in coverage is considered continuing non-compliance and the IRB may lead to termination of the PI.

If the study approval has lapsed more than 30 days and the PI has not provided the required continuing review information, the PI must submit a new application and explanation of any research activities conducted during lapse of coverage to the IRB for review.

STUDY CLOSURE

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

IRB staff will review the closure application for completeness and will determine how to notify the IRB.

SITE VISITS

As part of our quality improvement program IRBCO conducts site visits. These visits are two types, a) for-cause and b) random, not-for-cause. Purpose of site visits is to evaluate that sites are compliant with regulations and to provide education to Investigators and other research staff. Sites will be notified before the visit and will be given feedback after the board reviews the site visit report. IRBCO site visitor may review the original 1572, investigator CV, informed consent process, site staff levels etc.

SPECIAL DISCUSSION

Children in research:

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

Allowable Categories

Research on children must be reviewed and categorized by the IRB into one of the following groups:

- 1) Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., **minimal risk**).
 - a) The IRB may find that the permission of one parent is sufficient.
- 2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject.
 - a) The risk is justified by the anticipated benefit to the subjects;
 - b) The IRB may find that the permission of one parent is sufficient;
 - c) Requires assent of the child.
- 3) Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.
 - a) The risk represents a minor increase over minimal risk;
 - b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - i) **Permission of either both parents, or legal guardian, is required- unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child;**
 - ii) Requires assent of the child.
- 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.
 - a) Federally-funded research in this category must be approved by the Secretary of Health and Human Services, and requires consent of either both parents, or legal guardian.
 - b) For non-federally-funded research, IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
 - i) That the research in fact satisfies the conditions of the previous categories, as applicable; or
 - ii) The following:
 - (1) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - (2) The research will be conducted in accord with sound ethical principles; and
 - (3) Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, **only if such research** is:

- 1) related to their status as wards; or
- 2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

HIPAA

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. The resulting Privacy Rule, finalized in August 2002, set a compliance date of April 14, 2003. While the main impact of the Privacy Rule will be on the routine provision of and billing for health care, the Rule will also affect the conduct and oversight of research. Researchers, IRB staff and members as well as research administration must be aware of these changes.

Waiver of Authorization

IRBCo reviews waiver of HIPAA authorization application under following circumstances:

- 1) Use or disclosure involves no more than minimal risk to privacy for the individual based on:
 - a) a plan to protect patient identifiers from improper use and disclosure;
 - b) a plan to destroy patient identifiers at the earliest opportunity, and
 - c) adequate written assurances that protected health information will not be reused or disclosed to others except as required by Law, for oversight of the research, or for other research that would be permitted by HIPAA.
- 2) The research could not practicably be conducted without the waiver;
- 3) The research could not practicably be conducted without access to protected health information; and
- 4) A brief description of the PHI necessary to do the research (i.e., minimum necessary); and
- 5) The privacy risks are reasonable in relation to the anticipated benefits to the individuals and the importance of knowledge gained through research.
- 6) Waiver of Authorization forms are available on our website and in eProtocol.