INVESTIGATOR HANDBOOK

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MISSION

The mission of the Human Research Protections Program (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 the 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 submission deadlines).
- 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.
- Submit application online

FIRST TIME SUBMISSION

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

Investigators and sponsors are required to fill out the AllianceNet access form, to allow access into the electronic system, which are available in the "Forms" section of our website (www.irbco.com). IRBco also provides consultation to Investigators and Sponsors in developing consent forms and help designing research with appropriate measures in human research subject protection.

EDUCATIONAL REQUIREMENTS

IRBco requires Principal Investigators (PIs) have prior research experience. If the PI has no prior experience, s/he may complete educational modules on Collaborative Institutional Training Initiative (CITI) or show proof of alternate training. IRBco provides CITI training to investigators at no cost, and can be accessed through our website www.irbco.com under the "Training" section. IRBco also accepts alternate equivalent training in human research subject protection, links are also provided in the training section of our website. It will be necessary to submit proof of training with the application packet for review by the Board.

PRINCIPAL INVESTIGATOR NEW STUDY SUBMISSIONS

NEW SINGLE SITE TRIALS

The following information is required for new single site trials:

1. Investigator AllianceNet application
2. Study Protocol
3. All proposed subject consent forms (in editable electronic format)
4. Investigator's brochures, package inserts, or device background literature
5. Current curriculum vitae (CV) of PI. CVs must verify affiliation to at least one study site and must be current within 2 years.
6. Current professional license of PI. If PI is licensed in Massachusetts, a copy of the research license must also be included.
7. 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).
8. Any additional study-related documentation to be provided to the subject (diaries, logging equipment).

NEW MULTI-CENTER CLINICAL TRIALS

When IRBco is selected as the central IRB for a study, the sponsor must submit the following documents to IRBco on behalf of investigators:

1. Sponsor AllianceNet application
2. Study Protocol
3. All proposed subject consent forms (in editable electronic format)
4. Investigator's brochures, package inserts, or device background literature
5. Proposed template advertisement/recruitment material
6. Proposed study subject materials (diaries, questionnaires, instructions, etc.)

MULTICENTER SUBMISSION for Principal Investigator:

1. Investigator AllianceNet application
2. Site-specific information for the consent document, including: patient compensation, site-specific requirements for the subject information, any state and/or local requirements that are stricter than the Federal requirements.
3. Proposed site-specific advertisement/recruitment material.
4. Principal Investigator CV and current copy of medical license(s)

VULNERABLE POPULATIONS

When some or all of the participants in research studies conducted under the oversight of IRBco are likely to be vulnerable to coercion, 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, 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. At IRBco, we do not review research involving prisoners.

STATE REQUIREMENTS FOR RESEARCH

Several states have developed unique laws for clinical research. It is the responsibility of the PI to notify the IRB of state laws for clinical research where the research will be conducted. Some examples of state specific laws are below:

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)

Florida: the word "free" may not appear in any advertisement recruiting subjects in to clinical research.

IRBco has affiliation with commonwealth of Massachusetts to review research and IRBco can review research in all 50 states.

INVESTIGATIONAL NEW DRUG STUDY (IND)

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA regulations. 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. If so, the PI must indicate if there is an IND 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 could be a:

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

INVESTIGATIONAL DEVICE STUDY (IDE)

Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations. 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. 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 one that does not meet the definition for 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 is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.
4. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in “REPORTABLE EVENT REQUIRMENTS.”
5. For research involving investigational new drugs:
    a. The PI must inform the IRB when a study involving investigational drugs has been terminated by the sponsor.
    b. 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.
    c. 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 the IRB in the manner defined by the protocol.
        vii. IRB letters of approval.
        viii. Other documents as outlined in the Human Research Protection Program Standard Operating Procedures.
6. 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) The PI will maintain the following:
    i. Current curriculum vitae (CV)
    ii. Protocol
    iii. Records of receipt and disposition of devices
    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,
    vi. Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All Unanticipated adverse device effects are reportable.
    vii. IRB letters of approval and the EOC Committee approval letter if applicable.
    viii. Device training.
    ix. Other documents as outlined in the Human Research Protection Program Standard Operating Procedures.
c) 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. The Investigator will be required to comply with the regulatory responsibilities of a sponsor and IRBco will request the Investigator to submit a study monitoring plan and data safety monitoring plan (if applicable).

7. Researchers are required to update the IRB with new, significant financial interests within 30 days of acquisition or discovery.

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. The consent process is ongoing and comprehensive and should not be passive. Informed consent should be explained to research subjects in a simple manner and in language he/she can 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 lay 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 their legal rights or through which the investigator, the sponsor, 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.

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.

Parental Permission and Assent

Parental Permission

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.

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 the 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.

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 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.

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.

Assent forms should be 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.

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). 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
- Change of PI
- Change of site location or Addition of sites

IRBco 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

The responsibility to maintain study approval through the continuing review process is the responsibility of the Investigator. To assist investigators the AllianceNet system will send electronic reminders in advance of the expiration date; however, you should not rely solely on AllianceNet reminders to maintain approval. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review through AllianceNet:

- 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. 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 which can lead to suspension or termination of IRB approval.

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.

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.

An unanticipated problem involving risks to participants or others refers to any incident, experience, or outcome that meets **all** of the following criteria:

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;

(2) **related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(3) suggests that the research places subjects or others 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 all 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. The following events are possible examples of unanticipated problems:

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 deviation/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) Sponsor imposed suspension for risk.
11) Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

The Principal Investigator must provide a detailed report of the event according to the above timeline using the “Adverse Event / Unanticipated Problem Report” form.

NON-REPORTABLE EVENTS TO THE IRB

Investigator reporting of adverse events that *do not* represent possible unanticipated problems, as defined above, is not required. Adverse events that do not meet the definition of an unanticipated problem will be considered as ‘non-reportable’ and will not be reviewed by the IRB. Adverse events are non-reportable if:

1) they are consistent in terms of nature, severity, or frequency with the known or foreseeable risks of the research that are described in the approved protocol, consent document or investigator’s brochure; or

2) they are consistent with the expected natural progression of any underlying disease, disorder or condition of the subject experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

For further information regarding adverse event reporting requirements, review the January 2009 FDA guidance to investigators, sponsors and IRBs titled, “*Adverse Event Reporting to IRBs — Improving Human Subject Protection.*”

DEVIATIONS/EXCEPTIONS

A protocol deviation is defined as any departure or change from the protocol that is unanticipated and happens without any prior agreement (protocol visit scheduled outside protocol window, blood work drawn outside protocol window, etc.). 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. If a protocol deviation occurs, the Principal Investigator must provide a detailed report of the event promptly to the IRB using the “Protocol Deviation/Exception Report” form. The completed form will be forwarded to the IRB chair or designee for review. Repetitive deviations may be ruled by the IRB to constitute non-compliance and could result in suspension of IRB approval.

Deviations that increase risk and have potential to recur or undertaken to eliminate an immediate hazard would be considered an Unanticipated Problem and will be handled according to the IRB's policy on unanticipated problems.

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

1) The Principal Investigator provides protocol deviations by submitting a detailed report of the event promptly to the IRB. Each deviation report must include information as to what corrective and preventative actions the PI is implementing to minimize the chance of recurrence and to assure the safety of research participants and the oversight of data integrity
2) Upon receipt of the deviation report, IRB staff reviews and evaluates the deviation. If further information is needed, IRBco 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) After review and evaluation of the incident, the protocol deviation is acknowledged.

Protocol exceptions are defined as a one time, intentional action or process that departs from the IRB-approved protocol, intended for one occurrence or applies to a single individual. This action is approved by the Sponsor or funding agency, IRB and the FDA if applicable, **prior to its implementation.** Exceptions must be approved by the sponsor and IRB **before** being implemented. Exceptions may not increase risk or decrease benefit, affect the participant's rights, safety, welfare, or affects the integrity of the resultant data.

SITE VISITS

As part of our quality assurance and quality improvement program, IRBco conducts site visits. There are two types of site visits, a) directed, for-cause and b) random, not-for-cause. The purpose of these visits is to evaluate that sites are compliant with regulations and IRBco requirements and to provide education to Investigators and other research staff. When scheduling site visits, IRBco will make every effort to work with investigators to schedule visits at times least disruptive for investigators and staff. IRBco site visitors may review the study regulatory binder, consent form documentation and other study files as necessary. IRBco may also observe the informed consent process if appropriate. Sites will be given feedback after the board reviews the site visit report.

STUDY CLOSURE

The completion or termination of the study is a change in activity and must be reported to the IRB. Prior to study closure, the following activities must be completed: subject enrollment, research related activities, long term follow-up of participants, and data analysis at the site. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows files and records to be closed as well as providing information that may be used by the IRB in the evaluation and approval of related studies. The PI may submit a 'Final Report Form' in AllianceNet once all the requirements as outlined above have been met.

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

CONCLUSION

Please note that this handbook is not intended to preempt any applicable federal, state, or local laws or regulations that require additional protections for human subject research.

For further information about this handbook or any of the processes outlined in this handbook, contact IRBco at irb@irbco.com or at 714-562-0526.