INVESTIGATOR HANDBOOK

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Liberty IRB Mission Statement

To protect the rights and welfare of research participants by ensuring that the risks never outweigh the value of human life.

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INTRODUCTION

Liberty IRB, Inc. is an independent institutional review board whose purpose is to protect the rights and welfare of human subjects. Liberty IRB provides this handbook of information about using Liberty as your IRB. The information is intended to provide guidance regarding submission questions, IRB review, informed consent, and other topics of interest to you and your research staff.

Liberty IRB operates in compliance with:

- ✓ FDA Regulations on Human Subjects Research, 21 CFR 50,56
- ✓ Protection of Human Subjects (DHHS), 45 CFR 46
  Standards for Privacy of Individually Identifiable Health Information, 45 CFR 160, 164
- ✓ State and Local laws
- ✓ AAHRPP (Association for the Accreditation of Human Research Protection Programs, Inc.)

If there are any questions or concerns about investigator responsibilities, please contact the CRO/Sponsor or call us at (386)279-4318. Please visit our website at www.libertyirb.com for forms, additional information, and useful links to sites that will assist you in your understanding of the clinical research process.

Public Outreach

Liberty IRB will provide clinical research participant information via the Liberty IRB website. Links to additional research related resources will also be placed on the website. In addition, Liberty IRB will make every opportunity to provide community speakers at public seminars to assist in the distribution of information to research participants.

Feedback

Liberty IRB encourages research staff, Sponsors, PI's, and subjects to contact us with any feedback or suggestions concerning the protection of human subjects. This can be done on our website at www.libertyirb.com by accessing any of the feedback tabs located under each corresponding section. You may also contact us directly at (386)279-4318.

We look forward to working with you and your staff!

THE BELMONT REPORT

(Ethical Principals and Guidelines for the Protection of Human Subjects of Research)

The Belmont Report represents the ethical principles upon which the Federal Regulations for protection of human subjects are founded. Liberty IRB recommends that all Principal Investigators and key research personnel read said report. Liberty IRB is guided by these principles regarding all research as set forth in the Belmont Report.

The following is taken from the Institutional Review Board Guidebook from OHRP.

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation were begun, sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence**,** and justice, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.

Respect for persons involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.

Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.

Justice requires that the benefits and burdens of research be distributed fairly.

The Report also describes how these principles apply to the conduct of research. Specifically, the principle of *respect for persons* underlies the need to obtain informed consent; the principle of *beneficence* underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of *justice* requires that subjects be fairly selected. As was mandated by the congressional charge to the Commission, the Report also provides a distinction between "practice" and "research." The text of the *Belmont Report* is thus divided into two sections: (1) boundaries between practice and research; and (2) basic ethical principles. The full text of the *Belmont Report*, which describes each of the three principles and its application, is provided on our website at http://www.libertyirb.com/subjects_documents_governing_human_research.

PRINCIPAL INVESTIGATOR RESPONSIBILITIES

Responsibilities

Investigators submitting research to the IRB are expected to comply with the guidelines of Good Clinical Practice (GCP) and the Code of Federal Regulations. Submitted research will be of sound scientific design.

Additionally, investigators, in maintaining their relationship with the IRB, will sign an Investigator Declaration where they attest that they are aware of their role and responsibilities in association with the conduct of a clinical trial on behalf of themselves and their sub-investigators, as follows:

I acknowledge that I have thoroughly reviewed the information provided on this report form and agree that the information provided is true and accurate.

I acknowledge that I have thoroughly reviewed and am familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigational brochure (if applicable), in the product information (if applicable) and in other information sources provided by the sponsor.

I agree to promptly report all changes in research activities and unanticipated problems involving risks to human subjects or others. This includes providing written reports to the sponsor, the IRB, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

I agree to promptly report to the IRB the premature completion if a study. If I terminate or suspend a clinical trial without prior agreement of the sponsor, I will inform Liberty IRB and the sponsor. If the IRB terminates or suspends approval of the clinical trial, I will promptly notify the sponsor.

I agree that I will not make any changes in the research without prior approval from Liberty IRB, unless the change is necessary to reduce the immediate risk to the subject.

I understand that under federal regulation, I am fully responsible for the conduct of all study personnel under my supervision.

I agree to personally supervise the conduct of this research trial.

I understand that it is my responsibility to see that each research subject has been given an oral explanation of the informed consent, and has been provided the opportunity to ask questions, PRIOR to obtaining their signature on the consent document.

I agree to report all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator's brochure) identifies as not needing immediate reporting. I will follow regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and to the IRB.

I agree to report to Liberty IRB within 5 business days of becoming aware:

- All unanticipated problems or other unanticipated information involving risks to participants or others;
- Internal adverse events which are unexpected and related to the research;
- External adverse events which are unanticipated problems involving risks to participants and others;
- Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm;
- Allegation or finding of non-compliance;
- Major protocol deviations or violations that might affect the rights, safety, and welfare of subjects; and
- Unanticipated adverse device effects;
- New information that may affect adversely the safety of participants or the conduct of the clinical trial
- Any changes significantly affecting the conduct of the clinical trial or increasing the risks to participants.

The Investigator Declaration further requires that the investigator attest that he/she is familiar with and understand the responsibilities as an investigator as they pertain to Liberty IRB and the Code of Federal Regulations 21 CFR 50 and 21 CFR 56.

Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's rights.

When a proposed research plan is to be conducted at another institution, the investigator must disclose to Liberty IRB any jurisdiction by another local IRB. If another IRB has jurisdiction, Liberty IRB will not review the proposed research until a waiver is received from the local IRB. This waiver must include the designation of Liberty IRB as the IRB of record with jurisdiction over the conduct of the trial.

In addition, the investigator is required to provide Liberty IRB with any rejections or failure of the local institution to approve the research plan.

Investigators or research staff with questions and concerns may contact a Liberty IRB Project Manager by phone at (386) 279-4318 or via the Liberty IRB website at: www.libertyirb.com

INVESTIGATOR TRAINING

Investigators submitting proposed research to Liberty IRB will be required to have had training in the conduct of clinical research. Such training will include Good Clinical Practice (GCP), Code of Federal Regulations (CFR) and Human Research Protection (HRP). Therefore, all investigators and their research staff will be qualified by training and experience to conduct research; including familiarity with the appropriate use of the investigational product(s), as described in the protocol, in the investigator's brochure (if applicable), in the product information(if applicable) and in other information sources provided by the sponsor. Education requirements must be met for all research activities before activities can begin unless the board decides that the specific activity does not require all education. An example of such a research activity is a HUD that is only used by a surgeon in a life-threatening event. Annually, in the Continuing Review Form, the education requirements must be updated for new sub-investigators and staff.

Investigators will be asked to declare their research training on the Principal Investigator Information Form with the initial submission and the renewal of any research project. IRB members will consider investigator and staff credentials and training in the approval of submitted research projects.

Investigators needing research related training should contact a Liberty IRB Project Manager for additional information.

DoD-approved education and training in human research protections are required for personnel involved in the conduct, review, or approval of research sponsored by a DoD Component. Each DoD Component has educational requirements in the ethical conduct of human subjects research. The type and extent of training depend, in part, upon the duties and responsibilities of the persons involved in the research. Further, research ethics training is incorporated into continuing education for activities of DoD Components that involve the conduct of human subjects research (DoD Directive 3216.02, March 02, 2002).

- The PI and research team complete all initial and continuing mandatory education requirements for human subjects protections in accordance with DoD policy.

- The PI is responsible for identifying specific educational or certification requirements of the sponsoring DoD Component and conveying those requirements to the IRB. The PI consults the DoD Component, as appropriate, to identify education requirements.

- ORC staff, with assistance from the PI, determine the need for orientation and/or education of the IRB chair, members, staff, and Institutional Official regarding DoD-specific education requirements.

- IRB staff assists the PI, study personnel, and all IRB personnel, as identified above, in accessing the necessary human subjects training and certifications required for IRB approval.

- The PI, study personnel, and IRB members and staff complete DoD-specific research ethics training, as applicable, and the PI submits documentation of training completion to the IRB and to the DoD Component, as appropriate.

- The IRB does not approve DoD-supported research until the PI and research team have completed required education and the appropriate certifications are in place.

Human Research Protection Plan

Investigators wishing to conduct research will be required to provide adequate resources to protect human participants, including:

- Sufficient time to conduct and complete the research;
- A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research related duties and functions;
- Access to a population that will allow recruitment of the necessary number of participants.

Liberty IRB will evaluate the investigator's resources utilizing the Principal Investigator Information Form at the time of initial protocol submission. This evaluation will include a review of the research staff and their availability to conduct the research.

Investigators conducting research at facilities other than their own practice will be required to secure the approval of those institutions prior to conducting the proposed research. Upon approval of a study involving one of these institutions, Liberty IRB will send a copy of the approval letter to the institution notifying them of the proposed research. It is the responsibility of the investigator to secure adequate resources including laboratory services, nursing staff and any other applicable services prior to the start of any study.

RESEARCH SUBMISSIONS

Liberty IRB is committed to making the study start-up process as efficient as possible. All submission forms are located on the Liberty IRB website at www.libertyirb.com and can be filled out electronically. If there are any questions, our staff will be happy to assist you at (386) 279-4318.

Enrollment of subjects into an investigational trial shall not commence until written IRB approval is received.

Institutional Review Prior to IRB Review

Certain studies presented to the IRB may require prior review by local hospital administration. The hospital administration has the authority to delay or disapprove a study based on the availability of hospital resources. The hospital administration does not however, have the authority to override any disapproval of the IRB or approve any study not approved by the IRB. Institutions contracted with Liberty IRB will be required to immediately notify the IRB of any studies failing to meet institutional approval.

Results of institutional reviews will be forwarded to the reviewer(s) for consideration at the time of initial study review.

Submission Timelines

For preparation and review Liberty IRB requires all submission materials be received by 5:00 PM EST on Friday in advance of the Thursday IRB meeting, which meets every week, excluding major holidays.

Liberty IRB also has a 2nd board that meets on some Mondays. The deadline for submission for the Monday meeting is 5:00 PM EST on Wednesday in advance of the IRB meeting. However, please contact Liberty regarding the currently scheduled Monday meetings.

All submission forms must be <u>fully</u> completed. Failure to complete or sign forms will result in a delay of IRB review.

Pre-Review of Documents

Liberty IRB is dedicated to helping our clients get their trials up and running to meet anticipated timelines. Therefore, Liberty offers a free pre-review of the documents and consents prior to the board meeting to determine any issues that may need to be addressed before the Board meets.

Freedom Portal

In addition, Liberty offers a secure portal called the Freedom Portal for submissions. Notify Liberty IRB of your upcoming submission and a username and password will be provided to you. You will then upload your documents to this portal which is located on the Liberty IRB website www.libertyirb.com. This portal will provide you with a central location for all submitted documents, as well as all approval documents from Liberty IRB.

Types of Study Review

Full Board Review

A Full Board Review requires a quorum of board members. If a research study is not classified as exempt or expedited, it requires review by the full IRB in a convened meeting.

Submitted studies will be reviewed at a convened IRB meeting by board members. The convened board will include members and representatives (i.e. children and prison representatives) required by the specific needs of the research to be reviewed. All findings and actions of the IRB will be recorded in the IRB minutes and reported to the investigator and the institution in writing. Minutes will include: (1) Attendance; (2) Summary of any opposing issues and resolutions; (3) Number of votes.

The Liberty IRB may decide any of the following:

- Unconditional Approval – approved as submitted
- Approval with modifications required to secure approval
- Deferral*- significant changes required, or remaining questions to be discussed
- Disapproved* - board decides that risks far outweigh benefits

* *The investigator will be contacted in writing, stating the reasons the board either deferred or disapproved a study. This is usually within two days of the convened IRB meeting. The investigator has the right to appeal the board's decision or make changes and resubmit the proposal. All appeals must be reviewed at a convened meeting of Liberty IRB.*

Expedited Review

An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced members designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 21 CFR 56.110 and 45 CFR 46.110. The Food and Drug Administration has established, and published in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the Federal Register.
http://www.fda.gov/ohrms/dockets/98fr/110998b.txt

Exempt Research Review

In order to be considered exempt, the proposed investigation must meet one of the following categories:

Category 1

1.1 The research is conducted in established or commonly accepted educational settings

1.2 The research involves normal educational practices, such as:

- Research on regular and special education instructional strategies
- Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

1.3 The research does not involve prisoners as participants

1.4 The research is not FDA regulated

Category 2

2.1 The research involved the use of one or more of the following:

Educational tests (cognitive, diagnostic, aptitude, achievement)

Survey procedures

Interview procedures

Observation of public behavior

2.2 If any disclosure of the participant's responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation.

- Information obtained is not recorded in such a manner that participants can be identified, directly or indirectly through identifiers linked to the participants

2.3 If the research involves children as participants:

The procedures do not involve any of the following:

- Survey procedures
- Interview procedures
- Observation of public behavior where the investigators participate in the activities being observed.

2.4 The research does not involve prisoners as participants

2.5 The research is not FDA regulated

Category 3

3.1 The research is not exempt under category 2

3.2 Research involving the use of one or more of the following:

- Educational tests
- Survey procedures
- Interview procedures
- Observation of public behavior

3.3 Either of the following is true:

The participants are elected or appointed officials or candidates for public office

Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

3.4 The research does not involve prisoners as participants

3.5 The research is not FDA regulated

Category 4

4.1 The research involving the collection or study of existing data, documents, records, pathological specimen, or diagnostic specimens.

4.2 Either of the following is true:

The sources are publicly available

The investigator records information in such a manner that participants cannot be identified, directly or indirectly through identifiers linked to the participants.

4.3 The research does not involve prisoners as participants

4.4 The research is not FDA regulated

Category 5

5.1 The project is a research or demonstration project

5.2 The research is conducted by or subject to the approval of federal Department of Agency heads

5.3 The research is designed to study, evaluate, or otherwise examine one or more of the following:

- Public benefit or service programs
- Procedures for obtaining benefits or services under those programs
- Possible changes in or alternatives to those programs or procedures
- Possible changes in methods or levels of payment for benefits or services under those programs

5.4 The program under study delivers a public benefit or service

5.5 The research is conducted pursuant to specific federal statutory authority

5.6 There is no statutory requirement that an IRB review the research

5.7 The research does not involve significant physical invasions or intrusions upon the privacy of participants

5.8 The research does not involve prisoners as participants

5.9 The research is not FDA regulated

Category 6

6.1 The research involves taste or food quality evaluation or is a consumer acceptance study

6.2 Either of the following is true:

- Wholesome food without additives are consumed
- If a food is consumed that contains a food ingredient or an agricultural chemical or environmental contaminant, the food ingredient or agricultural chemical or environmental contaminant is at or below the level and for a use found to be safe by the FDA, the Environmental Protection Agency, or The Food Safety and Inspection Service of the U.S. Department of Agriculture.

6.3 The research does not involve prisoners as participants.

Participant Protection in Exempt Research

The IRB Chairman and IRB Manager will use the following criteria to determine whether or not participants are protected in the proposed exempt research:

The research involves no more than minimal risk to participants;

Selection of participants is equitable;

If there is a recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data;

If there are interactions with participants, there will be a consent process that will disclose such information as:

The activity involves research;

A description of the procedures;

That participation is voluntary;

Name and contact information for the investigator.

There are adequate provisions to maintain the privacy interest of participants.

Submission of Exempt Research

Materials required for review will include:

- Request for Determination of Exemption Form;
- Copy of the protocol or detailed description of the research
- Copies of all data collection tools, including Case Report Forms and Surveys;
- Signed Submission letter requesting exemption;
- Signed and dated Curriculum Vitae;
- Copy of Medical License (if applicable) or online verification.

In addition, the investigator will be requested to provide a rationale for the request of exempt status.

Determinations of whether or not the proposed investigation is research involving human participants will be made by the IRB Manager and the IRB Chairman utilizing the steps listed above.

If a proposed investigation is determined to be exempt, the IRB Manager will convey this information to the investigator. The letter of IRB determination will also include one or more references to the exempt categories under which the exemption is granted.

DEPARTMENT OF DEFENSE REQUIREMENTS

If investigators are taking part, or are interested in taking part, in a study under the auspices of the Department of Defense (DoD) additional requirements must be met, including those for training and certification. These requirements are detailed under the DoD Directive 3216.02 entitled Protection of Human Subjects and Adherence to Ethical Standards and can be found at www.dtic.mil/whs/directives/corres/pdf/321602p.pdf.

Department of Defense Multi-Site Research

When following Department of Defense requirements for the conduct of multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

DETERMINATION OF IND OR IDE REQUIREMENT

Upon receipt of an IRB submission, Liberty IRB Project Managers will review the submission to determine if an Investigational Device Exemption (IDE) or an Investigational New Drug Application (IND) is present.

Investigational New Drug (IND)
An Investigational New Drug Application (IND) or waiver will be required for all investigational pharmaceutical products unless the drug meets the FDA exemptions for an IND. Upon receipt of a submission, the Project Manager will request this documentation if not provided. If the IND number is imprinted on the protocol, no further documentation is necessary. If it is not imprinted on the protocol, the FDA letter granting the IND number should be supplied to Liberty as documentation of the IND number.

Liberty IRB Project Managers will ascertain that a proposed investigation involving an investigational drug will have a valid IND. In accordance with 21 CFR 312.2, an IND or U.S. Food and Drug Administration waiver will be required for all clinical studies involving investigational pharmaceutical or biological products **unless** the IRB Project Manager determines the following criteria are met:

The drug product is lawfully marketed in the United States and:

The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor is it intended to support significant change in the labeling for the drug;

The drug is lawfully marketed as a prescription drug product and the investigation is not intended to support a significant change in advertising for the product;

The investigations do not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risk (or decreases the acceptability of risks) associated with the use of the drug product.

In the event that it is unclear to the IRB staff or board members as to whether or not an IND is required for an investigation, clarification will be requested through the U.S. Food and Drug Administration.

Investigational Device Exemption (IDE)

Medical Devices
There are three types of studies described in the regulations at 21 CFR Part 812: significant risk (SR) device studies, non-significant risk (NSR) device studies, and exempt studies.

On review of studies involving the use of medical devices on human subjects, the board members will determine if the device poses significant or non-significant risk to subjects. A significant risk device means an investigational device that:

• Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

• 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;

• 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

• Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Liberty IRB will consider all devices to be significant risk unless otherwise specified. Non-significant risk determinations will be conveyed to investigators in the Certificate of IRB Review.

All proposed investigation involving an investigational device will have a valid IDE. In accordance with 21 CFR 812.2, an IDE or U.S. Food and Drug Administration waiver will be required for all clinical studies involving investigational devices **unless** the following criteria is met:

- The device is legally marketed within the United States in accordance with current approved labeling;
- The device complies with the labeling requirements identified in 809.1c and is:

  Non-invasive;

  Does not require an invasive sampling procedure that presents significant risk;

  Is not intended as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.
- Consumer preference testing, testing of a modification, or testing of a combination of devices if the devices are legally marketed.

The IRB Project Manager will verify the IDE number of the protocol and sponsor communication. In the event that it is unclear to the IRB staff or board members as to whether or not an IDE is required for an investigation, clarification will be requested through the U.S. Food and Drug Administration.

510k and Exemption

For marketing of a Class I, II, and III device intended for human use, for which a Premarket Approval (PMA) is not required, a 510(k) application must be submitted to the FDA unless the device is exempt from 510(k) requirements.

If a study is cleared by a 510(k), documentation regarding the 510(k) number should be provided to Liberty IRB with the original submission.

If the device is exempt from the requirements of 21 CFR Part 812, the Liberty IRB Device Exempt Checklist must be submitted.

Additional information can be found in the FDA Frequently Asked Questions about Medical Devices document using the following link:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

INVESTIGATOR-INITIATED STUDY

If the IRB submission is investigator-initiated, Liberty IRB staff members will determine that the following criteria are met in accordance with 21 CFR 812 (IDE) or 21 CFR 312 (IND) regulation:

- The sponsor (or investigator) will label the device in accordance with appropriate regulatory criteria;
- The sponsor (or investigator) will comply with the requirements of appropriate regulation with respect to monitoring investigations.
- The sponsor (or investigator) will maintain the records and make the reports as required
- The sponsor (or investigator) will ensure that participating investigators maintain the records and produce the required reports
- The sponsor (or investigator) will comply with the regulatory prohibitions against promotion and other practices.

INFORMATION PROVIDED BY INVESTIGATORS

Initial Submission Requirements

All Investigators wishing to submit proposed research will submit the following items:

A cover letter (on company letterhead), personally signed by the Principal Investigator, requesting Liberty IRB services;

Completed Investigator Declaration, personally signed by the Principal Investigator;

Completed Principal Investigator Information Sheet;

Additional Research Location Form (if applicable);

Completed Protocol Information Sheet;

Proposed study protocol, including documentation of IND or IDE number. At a minimum, the protocol should include:

- Title of study;
- Purpose of the study (including expected benefits);
- Sponsor of study;
- Results of previous related research (if applicable);
- Subject inclusion and exclusion criteria;
- Justification for the use of any special/vulnerable subject populations;
- Study design;
- Description of procedures to be performed;
- Provisions for managing adverse reactions;
- Circumstances surrounding consent process and consent documentation process;
- Compensation provided for injured research subjects;
- Provisions for the protection of subject's privacy;
- Extra costs to subjects for participation in the study;
- Extra costs to third party payers because of subject's participation;
- Information regarding any Data Safety Monitoring Committees for the study.
- Proposed Informed Consent which contains all of the required elements of 21 CFR 50.25 (a), and when appropriate 21 CFR 50 (b). See additional information in the Informed Consent section.;
- Current (within 2 years) signed Principal Investigator CV, copy of current Medical License (if applicable), and copy of board certification (if applicable);
- Current (within 2 years) signed Sub-Investigators CV and copy of Medical Licenses (if applicable);
- Advertisement Submission Form and proposed advertisements (if applicable);

For Investigational Drug/Biologic studies, the following will also be included:

- Current version of Investigator's Brochure;
- Completed FDA form 1572

When conducting studies involving an investigative pharmaceutical product, a form 1572 must be completed and submitted prior to the start of the study by the Principal Investigator. This is a contract between the FDA and the PI. It outlines the responsibilities that the PI agrees to, in order to conduct the study. If there are changes to information contained on the 1572 (such as, an IRB address change, the addition of new sub-investigators, discontinuing the use of a clinical lab), the investigator should document the changes in the study records and inform the sponsor of these changes, so that the sponsor can appropriately update the IND. The 1572 itself does not need to be revised and a new 1572 need not be completed and signed by the investigator.

IND Number on protocol or Copy of FDA letter granting IND Number.

For Investigational Device studies, the following will also be included:

- IDE Number or Copy of FDA letter granting Investigational Device Exemption;
- Letter from sponsor requesting non-significant risk or exempt device classification.

Requests for Proposed Study Modifications

Requests for changes to the conduct of the study after initiation will be submitted to the IRB in writing by the investigator. Requests should be submitted utilizing the IRB Modifcation to Research Form. Required submission materials will include:

Request for proposed change to the research;

Description of proposed modification to the research plan;
Rationale for the proposed modification to the research paln;
Revised informed consent (if necessary).

All changes will require IRB approval prior to the implementation of the change, unless the requested change is necessary to reduce immediate risks to human subjects.

Following IRB Approval

After a protocol is approved, the sponsor will receive a Certificate of IRB Review and an electronic copy of the IRB approved consent forms for the study. Investigators will be notified whether or not his/her submission has been approved, and the sponsor with be copied on this information.

After study approval, sponsors and investigators still have the following obligations:

Report any changes in research activities;
Obtain IRB approval before initiating changes to approved research;

Obtain IRB approval for recruitment materials;
Report unanticipated problems including serious adverse events and major protocol deviations within 5 days of becoming aware of the event or deviation;
Submit a Site Status Report for continuing review and study closure.

If the conditions of Liberty IRB's approval are violated, the IRB may take action to see that these violations are resolved and not repeated. These actions could result in a site visit and suspension of study enrollment.

Continuing Review

During the course of the study, the investigator will be required to submit a Continuing Review Form at least annually to provide Liberty with information regarding the progress of the study.

Beginning two months before expiration, investigators will be notified by e-mail, phone and/or fax by the Project Manager of upcoming study expiration. These reminders will be sent out in advance of a study expiration date; however, it is the responsibility of the investigator to monitor the research study to ensure obtaining continuing review before expiration.

The submission of the Continuing Review Form must include a copy of page one of the informed consent(s) currently in use, including translations.

Failure of Investigator to Submit Continuing Review

In the event that an investigator fails to submit a continuing review report prior to the study expiration date, Liberty IRB may inform the investigator that IRB approval of the research study being conducted at this site has expired. This expiration will be communicated to the investigator by certified letter. If the study is FDA-regulated, expiration of IRB approval due to failure to submit continuing review will also be conveyed to the FDA via certified mail. The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not automatically constitute a suspension or termination of IRB approval, for reporting purposes under 21 CFR 56.113. However, the failure to meet continuing review obligations may be grounds for suspension or termination under 21 CFR 56.113, in particular where the lapse of approval is not the first to occur in a study. If the IRB notes a pattern of non-compliance with the requirements for continuing review, the IRB should determine the reasons for the non-compliance and take appropriate actions.

Interventions and interactions on current participants will continue only when the IRB chair or convened IRB finds an over-riding safety concern or ethical issue involved such that it is in the best interest of individual participants, or when the

research interventions hold out the prospect of direct benefit to the subjects (e.g. investigational chemotherapy regimen in an oncology trial). If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research protocol, data collection (especially safety information) should also continue for subjects.
Consideration for re-opening of a research site or continuing research during the lapse in review will be based on submission of continuing review materials and IRB approval The IRB should document why the lapse occurred and identify the steps taken to prevent any future lapses.

Final Report

Liberty IRB will require all investigators to complete a final report utilizing the IRB Closure Form when an approved study is completed or closed by the sponsor. In the event a closure form is not received, the study will be reported to the appropriate authorities (as applicable).

Obtaining Updated Information on Policies and Procedures

In order to obtain information about revisions to policies and procedures and revisions to the Investigator Handbook, investigators should:

- Go to Liberty IRB website periodically and look at the Investigator section as well as the News and Events section
- Review the Liberty IRB Newsletter that is sent via email quarterly
- Review emails sent by Liberty IRB. These are sent when new information regarding Liberty policies or FDA/DHHS regulations occur.

LEAD INVESTIGATOR RESPONSIBILITIES IN MULTI-CENTER TRIALS

When the investigator is the lead investigator of a multi-site trial, the investigator will be required to inform Liberty IRB of these responsibilities at the time of the initial protocol submission. The investigator will be required to provide information on the management of information that is relevant to the protection of participants, such as:

Unanticipated problems involving risks to participants and others;
Interim Results;
Data Safety Monitoring Committees;
Protocol Modifications.

At the time of initial protocol review, the IRB will review the submitted information to evaluate whether the proposed management of information relevant to the protection of participants is adequate.

INVESTIGATOR REPORTING RESPONSIBILITIES

The Investigator Declaration will serve as a contract between Liberty IRB and the Investigator, informing him or her of their reporting responsibilities.

Investigators will be required to promptly report, within 5 business days, to the IRB and organization any changes significantly affecting the conduct of the research or that increase the risk to participants, including all unanticipated problems involving risk to human subjects or others. Reporting of unanticipated events are to be submitted utilizing the IRB Reporting Form. The Reporting Requirements are listed below and are also provided with the original Certificate of IRB Review:

- Internal adverse events which are unexpected and related to the research;
- External adverse events which are unanticipated problems involving risks to participants and others, as determined by the study investigator;
- Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm;
- Other unanticipated information that indicates participants or others might be at increased risk of harm such as a new risk, identified in an interim safety analysis, revised package insert, revised investigator brochure, publication in the literature or a DSMB report.
- Unanticipated problems involving risks to participants or others will be defined as any report of information that is (1) unanticipated and (2) indicates that participants or others are at increased risk of harm.
- Allegation or finding of non-compliance;
- Major protocol deviations or violations that might affect the rights safety and welfare of subjects;
- Unanticipated adverse device effects (Any serious adverse effect on health safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights safety, or welfare of subjects.)

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- Unanticipated problems involving risks to participants or others will be defined as any adverse event found to be related or possibly related to the investigative drug, device or biologic which has not previously been recorded in the Investigator Brochure, product information, informed consent or pre-clinical studies.

All more than minimal risk unanticipated problems involving risks to participants will be reviewed by the fully convened board. The board will review the report and make a determination as to whether the incident constitutes an increase in risks to study participants. If it is decided that action is necessary, the board will take one of the following actions:

- Suspend the research;
- Terminate the research;
- Require notification of current participants when such information may relate to participants' willingness to take part in the research.

Additionally, the board may require:

- Modifications to the protocol;
- Modification of the information disclosed during the consent process;
- Providing additional information to past participants;
- Re--consenting of present participants;
- Modification of continuing review schedule;
- Monitoring of research;
- Monitoring of the consent process;
- Referral to other organizational entities.

In an effort to protect study participants, following the board's decision, a full report of the incident and board findings will be distributed to:

- The IRB;
- Specific institutional officials;
- OHRP, when the research is covered by DHHS regulation;
- Other federal agencies when the research is overseen by those agencies, and they require reporting separate from OHRP;
- FDA, when the research is FDA regulated.

The follow up reporting to all applicable agencies will be completed within 30 calendar days or the completion of the IRB's investigations and resulting opinion.

In addition, if the IRB terminates or suspends its approval of the clinical trial, the investigator will be required to inform the study sponsor.

EMERGENCY NOTIFICATION AND REPORTING PROCEDURES

In the event of a life-threatening emergency situation in which a test article must be used without prior IRB approval, this situation will be reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB approval and will not be used unless IRB approval is granted.

Emergency use is defined as the use of an investigational drug, device, or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. Life threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival.

The criterion for life threatening does not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Under FDA regulations, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

DHHS regulations do not permit data obtained from patients to be classified as human participant research, nor permit the outcome of such care to be included in any report of a research activity subject to DHHS regulations.

The emergency use criteria must be clearly documented by the investigator. The investigator must also notify the Liberty IRB within 5 working days after the use of the test article. Additionally, the Liberty IRB requires the investigator to supply a copy of this documentation to the IRB for review. The IRB Chair or the IRB Project Manager, as well as a physician board member, will review the use for a determination of whether the use follows FDA regulations. If the use did not follow FDA regulations, the matter will be handled as non-compliance.

In the event that Liberty IRB receives prior notification of an investigator's intent to use a test article on an emergency basis in a life-threatening situation where there is insufficient time to obtain prior IRB review and approval, these notifications will be forwarded to the IRB Chair or the IRB Project Manager, as well as a physician board member, who will determine whether or not the circumstances of the emergency follow FDA regulation.

Even in the event of an emergency, the investigator is required by the Liberty IRB to obtain informed consent in accordance with and to the extent required by FDA regulations and to document informed consent in accordance with and to the

extent required by FDA regulations, unless the circumstances meet the exception to this requirement.

The Liberty IRB also requires investigators to ensure that at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, their legally authorized representative, be informed of the use of the test article. The investigator must summarize the attempts to obtain informed consent and present this information to the Liberty IRB as soon as possible.

INVESTIGATOR CONFLICT OF INTEREST

Situations arise where financial or personal situations may compromise an investigators professional judgment. Liberty IRB is concerned about the potential for abuse. Liberty manages potential conflicts of interest by taking steps to ensure proper disclosure.

Due to the Public Health Service rule on individual financial conflict of interest changing to the DHHS rule on August 24, 2012 the disclosure thresholds have been changed.

Investigators submitting studies to Liberty IRB will be requested to declare any personal or immediate family members' (spouse or children) conflict of interest or financial relationship with the study sponsor on the Principal Investigator Information Form using the following criteria:

- Immediate Family will be defined as spouse and dependents.
- **Investigator will be defined as any individual involved in the design, conduct, or reporting of research.**
- Financial Interest Related to Research will be defined as financial interest in the sponsor, product or services being tested, or competitor of the sponsor, product or services being tested.

Specifically, investigators need to declare:

- Ownership interest, stock options, or other financial interest related to research unless it meets the following criteria:
    - The value of the interest does not exceed $5,000 when aggregated for the immediate family;
    - The interest is publicly traded on a stock exchange;
    - The value of the interest does not exceed 5% interest in any one single entity when aggregated for the immediate family;
    - No arrangement has been entered into where the value of the ownership interests will be affected by the outcome of the research.
- Compensation related to the research unless it meets the following criteria:
    - The value of the compensation does not exceed $5,000 in the past year when aggregated for the immediate family;
    - The value of the interest does not exceed 5% interest in any one single entity when aggregated for the immediate family;
    - No arrangement has been entered into where the amount of compensation will be affected by the research.
- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board or executive relationship related to research, regardless of compensation.

In addition to initial disclosure, the investigator must notify the IRB whenever his or her financial interests in the study change or at the time of continuing review. Financial conflict of interest should be disclosed to the IRB in writing via a letter from the investigator to the IRB Chairman. These interests will be sent to the full board for review and determinations of impact on the study. Investigators must report changes in financial conflict of interest within 30 calendar days of discovery.

A fully convened review board, upon notification of potential conflict of interest, will review the described relationship and management plan, if applicable, to make a determination regarding the impact on the proposed research or study participants. The board will, at a minimum consider:

Whether the financial interest will adversely affect the protection of participants in terms of the criteria for IRB approval; and

Whether the financial interest will adversely affect the integrity of the research.

The investigator will be notified of the determinations by the convened board.

INFORMED CONSENT REQUIREMENTS

Informed Consent allows potential research subjects to voluntarily decide whether or not to participate in a research study. It is an ongoing process that continues throughout the entire study. Information must be presented in such a way that provides the subject sufficient opportunity to decide. The fundamental purpose of the IRB review and approval of the consent document is to protect the rights and welfare of human subjects.

The PI is responsible for making sure that informed consent is properly obtained from participants in the research study. This includes ensuring that:

- All participants must sign and date the informed consent approved by Liberty IRB;
- The most recently approved informed consent should be used if more than one version has been approved for the study and subjects should be re-consented prior to any study procedures if additional information is included that would affect risks or provide new information that might change the subject's mind about participating in the study;
- Each study participant should be provided with a signed and dated copy of the informed consent for future reference;
- The PI is available to answer questions the study participant may have and to provide additional information regarding the study. (The PI does not have to be present during the entire consenting process);

All study participants should be provided with the following during the informed consent process:

- Time to consider their participation in the study
- A private location to read the informed consent and discuss it with research staff
- Research staff who can answer questions regarding the study
- The option to take the consent form home and discuss it with family or friends

  - Legally Authorized Representatives will not be allowed to provide consent for subjects unless the IRB approves it and the local and state law allows it;
  - Investigators are encouraged to submit informed consent documents in a reading level appropriate to their prospective research subjects, preferably at an 8th grade reading level;
  - The investigator will indicate who will be conducting the informed consent process on the Principal Investigator Information Form;
  - Signed consent forms are retained in compliance with federal regulation and any other applicable laws, and are able to be produced at Liberty IRB's request;

- Informed consent from all research participants is obtained unless the research is found to be exempt.
- The investigator and clinical research staff will not use exculpatory language when communicating with a prospective participant or the legally authorized representative.
- The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

Required Elements of Consent Form

The investigator will be required by the IRB to seek informed consent from all prospective research participants unless the research is found to be exempt from these requirements. All informed consent documents will contain items listed in the Code of Federal Regulations 21 CFR 50.25.

(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.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration or other regulatory agencies may inspect the records.
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(6) For research involving more than minimal risk, an explanation as to whether any compensation will be provided and an explanation as to whether any medical treatments are available if injury occurs. If medical treatments are available, what they will consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled,

and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(9) For alternative procedures or treatment that may be available to the participant, include important potential benefits and risks.

(10) A statement that the monitor, the auditor, the IRB, and the regulatory authority will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access.

When appropriate, one or more of the following additional elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
(3) Any additional costs to the subject that may result from participation in the research;
(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
(5) 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;
(6) The approximate number of subjects involved in the study.
(7) The amount and schedule of payments.

When the sponsor follows requirements pertaining to consent covered by ICH-GCP (E6):

- The alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks
- The monitor, the auditor, the IRB, and the regulatory authority will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access.
- The approval of the IRB

Liberty IRB board members will compare the informed consent document to the protocol to be sure all study related procedures are adequately represented.

Particular attention will be paid to areas of the consent dealing with risks, potential costs, compensation, and privacy measures. Investigators should ensure that all areas are included in the proposed research consent.
Liberty IRB requires that all investigators ensure that:

- A legally effective consent of the participant or the participant's legally authorized representative is obtained;
- The circumstances of the consent process provide prospective participants or the legally authorized representative sufficient opportunity to consider whether to participate;
- The circumstances of the consent process minimize the possibility of coercion or undue influence;
- The individuals communicating information to the participant or the legally authorized representative during the consent process will provide the information in a language understandable to the participant or the representative;
- The information being communicated to the participant or the legally authorized representative during the consent process will not include exculpatory language through which the participant or the representative is made to waive or appear to waive any of the participant's legal rights;
- The information being communicated to the participant or the legally authorized representative during the consent process will not include exculpatory language through which the participant or representative releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Translation of the informed consent document into a subject's native language may be requested utilizing the Translation Form found on the Liberty IRB website.

Amendments to the Consent Form

All changes to the consent form, changes in research personnel, and any other changes must be reported to Liberty IRB. An amendment may require full IRB review. Change in benefits or risks to subjects may require consent form modifications and re-consenting of subjects.

Assenting Requirements

For research studies involving minors, Liberty IRB generally may require, when applicable, written informed assent for children ages seven and older. Liberty IRB may require both parents to provide written permission in addition to the minor's giving his or her informed assent, based on the level of risk involved in the research. Children should always be asked if they want to participate in the

research and must affirmatively agree to participate. In certain studies Liberty IRB may waive assent requirements.

Liberty IRB recognizes that adults with decisional impairments may be vulnerable to undue influence. These adults, who lack the ability to consent, also may be asked to give their assent. Liberty IRB will evaluate whether or not assent of the participant will be necessary. Generally the IRB does not agree to involve these participants in research. The exception is if the research provides important potential benefit to the participant.

Assent should never be used to replace the consent of the parent or Legally Authorized Representative. It must be obtained in conjunction with the informed consent.

Informed Consent Waivers

The waiver of informed consent may only be conducted under two circumstances:

1. The research must not be subject to FDA regulations (this is due to the fact that FDA has no provision for waiver or alteration of the consent process); or
2. The planned research involves life-threatening emergencies where requirement to obtain prospective consent has been waived. (This research is governed by 21 CFR 50.24 and has been approved by the FDA or DHHS and the IRB, and publicly disclosed to the community in which the research will be conducted.

The DHHS regulations allow IRBs two options: the IRB may waive the requirement for consent entirely or may exclude or alter some or all of the requirements of the consent process. In both of these circumstances, the IRB must find that regulatory requirements allowing such waiver or alteration are met, and document those findings.

DHHS Regulation

DHHS regulations allow the IRB to waive the requirement to document the consent process in two situations:

1. The only record linking the participant and the research is the consent document and the principal risk is the potential harm resulting from a breach of confidentiality;
2. The research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context.

Review Process for DHHS Regulated Research

In the case of DHHS regulated research, Liberty IRB may waive or alter the consent process once it has determined that regulatory criteria for waivers and alterations are met. This may include the waiver of parental permission or the requirement for written consent documentation.

In the event that a waiver for written informed consent is requested, the IRB will review a written description of the information that will be presented to the participants.
When reviewing the request for waivers of the requirement to obtain written documentation of the consent process, the IRB will require the investigator to provide participants with a written statement regarding the research.

Waiver of Consent for Planned Emergency Research

In consideration of the rights and welfare of human subject research participants, Liberty IRB will not consider any requests for waiver of the informed consent for emergency planned research.

VULNERABLE POPULATIONS

There are special populations that may need additional protection. These subjects may be asked to sign an assent form, or may require a legally authorized representative (LAR) as defined by 21 CFR 50, 3 to provide consent on their behalf. Liberty IRB will evaluate the proposed research to determine whether or not the research involves participants vulnerable to coercion or undue influence. The IRB will evaluate whether or not the risks outweigh the benefits to these participants.

Materials for Review

In evaluating the proposed research the IRB will review the protocol, informed consent (if applicable) and the Protocol information Sheet provided by the investigator. The investigator will be asked to indicate his/her intent to enroll vulnerable populations. Vulnerable populations may include, but is not limited to:

- Children
- Pregnant women
- Fetuses
- Neonates
- Prisoners
- Adults who lack the ability to consent
- Families or employees of the sponsor, CRO or Investigator

In addition, Liberty IRB will review the submitted materials to determine equitable selection of participants. Review determinations will be based on:

- The purpose of the research
- The setting in which the research is to be conducted
- The selection (inclusion/exclusion) criteria
- Participant recruitment and enrollment procedures
- The amount and timing of payments to participants

Liberty IRB will determine if the use of a legally authorized representative (LAR) is appropriate for the protocol. The specifics for how to qualify an LAR are defined within the state laws and the PI is responsible to insure compliance with these laws. The PI should indicate any anticipation in using an LAR on the Site Information Questionnaire and has an obligation to discontinue a subject's participation in a study should the subject express fear, discomfort or disagreement, even if an LAR has authorized the participation.

Additional information about these special populations can be found at the Office of Human Research Protections, as follows:
http://www.hhs.gov/ohrp/policy/populations/index.html
or by contacting Liberty IRB (386) 279-4318

Research Involving Employees

In the event that an investigator may involve another investigator, research staff member, IRB member or staff, or employees in the proposed research, the investigator will be required to identify these individuals on the Principal Investigator Information Sheet. In response, the IRB members will consider the vulnerability of these subjects and make appropriate provisions, which may include requesting the subject's signature on a separate consent addendum. This consent form will inform these subjects of their rights as a research subject as it relates to their position within the research entity. Liberty IRB can provide a template for the consent to be used when research involves employees of the research site or their family members.

IRB OPERATIONS

Communications from the IRB

All investigators presenting studies to the IRB will receive notification of the board's decision in writing, in a timely manner, usually within one week of the convened IRB meeting. However, email notification of items requiring attention may be provided before the official letter to allow the investigator time to address any concerns in time for the next board meeting.

IRB letters of determination shall include the following:

Date of study review;
A list of items reviewed;
The process of IRB review (full board or expedited); and
IRB decision.

Written requests for more information and the basis for these decisions, in the event that modifications or explanations are needed to secure IRB approval, will also be provided to the investigator in writing. Review of responsive materials will be conducted initially by the Project Manager. Board requested modifications will need to be returned to the convened board for approval. Modifications requiring full board review prior to approval will be indicated on the IRB letter of determination.

Appeal of IRB Decisions to Disapprove a Study

Disapproval of a submitted research study will be conveyed to the investigator in writing. This notification will include a statement of the reasons for disapproval and a description of how the investigator may respond.

Upon the written notification of the IRB's decision to disapprove a study, the primary investigator has the right to initiate the appeal process. The primary investigator must submit a letter to the IRB Chairman within 30 days of disapproval notification. This letter will contain a request to appeal the IRB's decision and the reasons for the appeal. The primary investigator will be provided the opportunity to appear before the convened IRB or make a presentation via video/audio conferencing to present his/her case. Following the presentation by the primary investigator, he/she will be dismissed. The convened IRB will conduct a discussion and subsequent review of the material presented. A vote will be taken to determine the outcome of the appeal process. This decision will become final, and the investigator will be notified in writing. IRB decisions may only be appealed once. No outside agency may override the disapproval of the Liberty IRB.

QUALITY ASSURANCE

During the course of a study, it may become necessary for the IRB to audit a clinical research site. Audits may be of a routine nature or for cause.

Routine Audits
Routine investigator audits may be done periodically by the IRB in an effort to review an investigative site to verify the appropriate conduct of the clinical investigation. Sites will be randomly selected by the Liberty IRB clinical staff.

For Cause Audits
For cause audits will be conducted at the direction of the IRB and/or a senior member of the IRB Clinical Operations department. These audits will be conducted to verify the validity of data provided to the IRB and verify the safety and welfare of clinical research participants. For Cause audits will be conducted for any site that in the opinion of the IRB review panel may have:

- Endangered research participants;
- Failed to provide adequate oversight of the study resulting in protocol deviations or inaccurate reporting;
- Failed to follow IRB direction and/or blatant disregard for IRB oversight; and/or
- Participated in Investigator non-compliance or fraud.

Site audits will be conducted by a senior member of the IRB staff and/or a member or members of the review panel. The research site will be notified in writing of the anticipated date of the audit and a mutually agreeable time will be set. Sites failing to agree to accommodate reasonable efforts to schedule an IRB audit will be considered non-compliant and reported to the FDA per current regulation.

Site audits will involve the review of any or all studies currently under the jurisdiction of Liberty IRB. In addition, auditors will meet with the principal investigator and key personnel involved in the conduct of the study. Following the visit, the auditor will prepare a written report detailing the visit. This report will receive full board review and recommendations of the IRB will be conveyed to the principal investigator in writing.

PROTECTION OF PRIVACY INTERESTS IN RESEARCH PARTICIPANTS

The protection of privacy and confidentiality in human research subjects is required for the IRB approval of research initiatives.

Definitions

Privacy – Privacy refers to persons and their interests in controlling access of others to themselves.

Confidentiality – Confidentiality refers to the agreement between the investigator and participant as to how data will be managed and used.

Materials for Review

Investigators will be asked to complete the Principal Investigator Information Form and Protocol Information Form. The protocol and proposed consent document will also be utilized to determine whether or not privacy and confidentiality measures have been incorporated.

Investigators will be asked to provide (in the submission package):

A description of how research participant's privacy will be maintained;

A description of the type of personal identifiers that will collected during the course of the study;

A description of measures used to limit exposure of vulnerable subject;

A description of the handling of sensitive data and how subject's will be protected;

The type of methods employed to prevent direct linking of subjects with data that may put subjects at legal, social, employment and insurance related risk;

A description of provisions to maintain confidentiality of data;

Any other materials request by the board to help fully explain privacy and confidentiality measures associated with the proposed research.

Review Process

Upon review of all materials provided by the investigator, the Liberty IRB will review the provisions set forth for the protection of subject's privacy and confidentiality.

In order to approve the proposed research, the IRB will determine:

- That the informed consent document clearly states the measure provided for protection of privacy;
- That provisions for maintenance of privacy and confidentiality are appropriate for the type of research;

That the investigation as made adequate provision to maintain the confidentiality of the data.

PARTICIPANT RECRUITMENT GUIDELINES

The equitable selection of research participants and an appropriate consent process are affected by the recruitment methods, including advertisements and participant payment arrangements. The use of recruitment materials is the beginning of the informed consent process.

Materials for Review

In evaluating the recruitment methods of proposed research Liberty IRB will review the Protocol Information Sheet, Advertisement Submission sheet and the proposed advertisements provided by the investigator. The amount and payment schedule for all subject compensation will be carefully detailed by the investigator in the Investigator Information Sheet.

The IRB will review:

- The information contained in the advertisement;
- The mode of communication;
- The final copy of printed advertisements;
- Recruitment activities to ensure equitable and fair practice;
- The final audio/video taped advertisements.

Review Process

In review of presented materials, IRB members will ensure that advertisements do not:

- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document or protocol;
- Include exculpatory language;
- Emphasize the payment or the amount to be paid, by such means as larger or bold type;
- Promise “free treatment” when the intent is only to say participants will not be charged for taking part in the investigation.

FDA regulated research will also be reviewed to ensure that advertisements do not:

Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with FDA labeling;

Use terms such as “new treatment” or “new drug” without explaining that the test article is investigational;

Allow compensation for participation in the trial offered by a sponsor to include a coupon good for a discount in the purchase price of the product once it is approved for marketing.

When reviewing a compensation package to study participants, the board will review:

- The amount of the payment and the proposed method and timing of disbursement to be sure it is neither coercive nor presents undue influence;
- Study visit payments to be sure they are paid as the study progresses and is not contingent upon the participant completing the entire study;
- Study completion bonuses to be sure they are not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

All payment arrangements will be clearly explained in the informed consent document.

Liberty IRB will not approve any “finder’s fees” used to encourage referrals for study participation. Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (bonus payments) will be considered on a case by case basis by a fully convened board. The board will use all criteria to evaluate whether or not the enrollment bonuses lead to a coercive environment.

Advertisement Content

The content of advertisements, whenever possible, will be limited the information prospective participants need to determine their eligibility and interest, such as:

- The name and address of the investigator or research facility;
- The purpose of the research or the condition under study;
- In summary form, the criteria that will be used to determine eligibility for the study;
- A brief list of benefits, if any;
- The time or other commitment required of the participants;
- The location of the research and the person or office to contact for further information.