AURORA HEALTH CARE
RESEARCH SUBJECT PROTECTION PROGRAM (RSPP)

HUMAN SUBJECT RESEARCH INVESTIGATOR MANUAL

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Acronyms used in this document
RSPP – Research Subject Protection Program
IRB—Institutional Review Board
RCA – Research Compliance Analyst
FDA – Food and Drug Administration
OHRP – Office of Human Research Protections

Many of the terms that are found within this document are defined by the Aurora RSPP Glossary.

What is the Research Subject Protection Program (RSPP)?
The RSPP is responsible for the overall coordination and administration of the duly constituted IRB that oversees human subject research conducted at all Aurora Facilities: the “Aurora IRB”. The RSPP provides guidance and support to investigators and research coordinators in the preparation, pre-review, and ongoing oversight of human subject research conducted at Aurora.

The RSPP is guided by the ethical principles applied to all research involving humans as subjects, as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, titled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the “Belmont Report”).

The RSPP manages the Aurora IRB, which has been established by and empowered under the auspices of Aurora executive authorities, and, by Aurora’s Federal Wide Assurance (FWA) with the federal Office for Human Research Protections (OHRP). Each of the individual Aurora IRBs subscribes to the same underlying principles and authorities. Aurora requires that ALL research projects involving humans as subjects (including involvement of humans in one or more of the categories of research exempted or waived under the federal regulations), or the use of identifiable protected health information be reviewed and approved by an appropriately constituted the assigned IRB prior to initiation of any research related activities, including recruitment and screening activities. The Aurora IRB is the sole body designated to make human subject research determinations at Aurora HealthCare.

A complete description of the responsibility and authority of the RSPP can be found on the Aurora RSPP/IRB website under Guidance Documents [“RSPP Guidance Document”] or in the Statement of Authority found in the SOP section.

How to contact the Aurora RSPP/IRB office to get answers to my questions?
You can contact the Aurora RSPP/IRB office either by phone: 414-219-7744, or by email: IRB.office@aurora.org. Your call/email will be managed by our Senior Administrative Assistant. If further assistance is required, you will be forwarded to one of the Research Compliance Analysts (RCA).
If your issue requires more help than a phone call or email can provide, we are always willing to meet with you. Our offices are located on the Aurora Sinai Medical Center campus or we can make arrangements to meet with you at your location, or a location of your choosing. Just contact us and schedule a time to meet.

Standard Operating Procedures (SOPs) for the Aurora RSPP/IRB can be found on our website: www.aurora.org/irb. We also have a Glossary of terms on our website.

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding Aurora’s Research Subject Protection Program that cannot be addressed by contact the IRB office, contact the Research Compliance Officer.

**What is the purpose of this manual?**

The Investigator Manual is designed to guide you through policies and procedures related to the conduct of Human Subject Research that are specific to Aurora.

General information regarding Human Subject Research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see below: “What training does my staff and I need in order to conduct Human Research?”
What is Human Subject Research?

The Aurora RSPP “Statement of Authority” defines the activities that this organization considers to be “Human Research” as defined in DHHS regulations at 45 CFR §46.102(d) and 45 CFR §46.102(f) and as defined in FDA regulations at 21 CFR §56.102(c), 21 CFR §56.102(e), and 21 CFR §812.3(p). Use these definitions for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

It is your responsibility to ensure that IRB review is conducted and approval granted BEFORE human subject research begins. If you have questions about whether an activity is Human Subject Research, contact the IRB office who will provide you with a determination. If you wish to have a written determination, provide the IRB office with a completed Human Subject Research Determination form.

What is the Research Subject Protection Program?

The Aurora IRB’s Statement of Authority (found on the Aurora RSPP website) describes this organization’s overall plan to protect subjects in Human Research.

- The mission of the Research Subject Protection Program.
- The ethical principles that the organization follows governing the conduct of Human Research.
- The applicable laws that govern Human Research.
- When the organization becomes “engaged in Human Research” and when someone is acting as an agent of the organization conducting Human Research.
- The roles and responsibilities of individuals within the organization.

What are the different regulatory classifications that research activities may fall under?

Submitted activities may fall under one of the following four regulatory classifications:

- **Not “Human Subject Research”**: Activities must meet the DHHS or FDA definition of “research” involving “human subjects” for the activity to fall under IRB oversight (see Glossary). Activities that meet neither definition of “Research” or involving “Human Subjects” are not subject to IRB oversight or review. For more information on process for making this determination, see below. The Aurora RSPP/IRB has created a Human Subject Research Determination form that will allow for the Aurora IRB to make such a determination. NOTE that this form is not currently available in our electronic submission system (CyberIRB).

- **Exempt**: Certain categories of Human Research may be exempt from the regulations but require IRB review (see Aurora IRB SOP 302). It is the responsibility of the IRB, not the investigator, to determine whether Human Research is exempt from IRB review. The Exempt Submission application
includes the criteria for a study to be considered exempt from the regulations. You may also submit exempt research studies within the electronic submission system (CyberIRB).

- **Review Using the Expedited Procedure:** Certain categories of non-exempt Human Subject Research may qualify for review using the expedited procedure (see *Aurora IRB SOP 401*). These studies are those that are **not greater than minimal risk** in nature. Submission of research falling under one of these categories may be done via submission of the *Initial Submission Application* or within the electronic submission system (CyberIRB).

- **Medical Record/Database Review for Research:** For convenience, the Aurora RSPP/IRB has created an expedited category of research that allows for the prospective/retrospective collection of data for research purposes. In order to qualify for this abbreviated submission process/application, there are criteria that must be met: there can be no direct interaction with human subjects, the data cannot leave Aurora, the sponsor cannot be federally funded, etc. – see *Aurora IRB SOP 306*. Submission of research projects that meet the criteria established for this type of research may be submitted on the form entitled *Application for Review of Medical Records and/or Databases for Research Purposes (Medical Record Research)*. NOTE that this form is not currently available in the electronic submission system (CyberIRB).

- **Review by the Convened IRB:** Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB (see *Aurora IRB SOP 301*). Submission of research projects that meet the criteria established for this type of research must be submitted on the form entitled *Initial Submission Application* or within the electronic submission system (CyberIRB).

**TIP:** Most forms discussed in this manual can be found on the Aurora RSPP/IRB website or within the electronic submission system (CyberIRB). The forms attempt to provide guidance to the submitter with regard to whether the research qualifies for that category/submission classification.

**What human subject research training do we need?**

For all Human Subject Research and research determined to be Exempt from the IRB regulations, any **Key Personnel** delegated duties by the Principal Investigator (PI) must complete the *Aurora Research Certification* program. The certification program includes: 1) a requirement for completion of training modules found within the Collaborative Institutional Training Initiative (CITI) – an online training program for human subject research; 2) a registration form that documents attestations of the individual relative to the conduct of research at Aurora. The CITI site can be accessed at [www.citiprogram.org](http://www.citiprogram.org). Research Certification is valid for a three-year period, after which time a refresher CITI course must be completed.

**TIP:** In order to prevent your study from being held by the RSPP office or returned as “incomplete”, make sure that all Key Personnel have completed this training/certification program **PRIOR** to submission of the study to the Aurora IRB.
TIP: Remember, even if personnel are delegated duties in the research study, the Principal Investigator (PI) is ultimately responsible for the conduct of the research study.

**What should I do FIRST - before I submit a human subject research application to the Aurora RSPP/IRB?**

The following items must be complete PRIOR to submission to the Aurora RSPP/IRB office:

A. Submit a Research Administrative Preauthorization (RAP) request to the Aurora Research Institute (see Appendix A). Preauthorization must be received from Aurora Research department prior to submission to the Aurora RSPP/IRB office. You must include a copy of the preauthorization with your submission. Note that preauthorization requires a research proposal be submitted. Please review the information included in Appendix A for specifics on this process.

B. All Key Personnel listed on the submission application must complete the research questionnaire in COI Smart.

C. All Key Personnel must have completed Research Certification.

D. Write or obtain a study plan/protocol that outlines the research and how it will be conducted at Aurora. This document will assist you when you are preparing your Preauthorization proposal (see “A” above) and the appropriate research submission application.

**A few important notes:** the Research protocol required by the Aurora RSPP is NOT the same document that is required by the Aurora Research Institute for the pre-authorization process. You may use this document to prepare your RAP submission but the RAP submission MAY NOT be submitted as your research protocol to the RSPP Office.

All research conducted at Aurora requires a written protocol EXCEPT for studies that qualify as Exempt Research or Medical Record/Database Review for Research.

Protocol templates may be found on the Aurora RSPP website. Once the above items are complete, you can then submit the human subject research application and applicable attachments to the Aurora RSPP/IRB office. **Note that your submission will not be accepted by the office as “complete” until these items are complete.**

**How do I write a Study Plan/Protocol?**

The Aurora RSPP/IRB requires a written protocol for any research study that meets the Expedited or Convened review classifications (see above). Note that the all submissions EXCEPT those that qualify as Exempt or Medical Record Research must include either a sponsor or investigator-initiated protocol.

There are two [Human Subject Research Protocol templates](#) available on the Aurora RSPP/IRB website: one for minimal risk research, and one for convened board review (greater than minimal risk research). Use these template documents as starting points for drafting your research protocol. The templates provide instruction and references that will
assist you in providing the IRB with all of the information necessary for their review of your research project.

Here are some key points to remember when developing a protocol:

- Remember to provide a version date on the protocol. This version date will be referenced in your approval letter. This version date should be updated whenever you revise the protocol contents. A new version date will be required on the modification form that you submit to the IRB.
- The italicized bullet points in the templates serve as guidance to investigators when developing a Human Research Protocols for submission to the IRB. All italicized comments are meant to be deleted prior to submission.
- When writing a protocol, always keep an electronic copy. You will need to modify this copy when making changes to the protocol.
- Note that, depending on the nature of your research, certain sections of the protocol template may not be applicable. Indicate this as appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria as the inclusion of subjects in these populations has regulatory implications.
  - Adults unable to consent (decisionally incapacitated)
  - Individuals who are not yet adults (infants, children, teenagers)
  - Pregnant women
  - Prisoners

**TIP:** Remember to write/include a protocol for all research that cannot be classified as Exempt or Medical Record Research. This will prevent your submission from being labeled as “incomplete”.

**TIP:** In order to approve a research study, the IRB must find that the research meets the regulatory Criteria for Approval. You are encouraged to write your protocol to address these criteria.

**Human Subject Research (HSR) Determination**

You may review OHRP’s guidance and decision tree that discusses when an activity becomes human subject research.

If, after reviewing this algorithm, you still have questions as to whether your project is human subject research, please review the materials included on the Aurora RSPP/IRB website. The Aurora RSPP Office has created a guidance document entitled: “Is My Project research/human subject research?” that may help you.

We have also created a Human Subject Research (HSR) Determination form. After completing this form, you can submit it to the Aurora RSPP/IRB office where we will make the determination as to the type of activity (quality assurance, general research or human subject research) your project entails. You will receive a copy of this determination for your records. This determination will direct you in your next steps –
that is, whether you must submit your project to the Aurora IRB as human subject research OR if may you proceed with your project as a quality assurance/improvement or as a general research activity.

**NOTE** that, more often than not, journals and scientific organizations look for a human subject research determination to be made by the IRB. The IRB’s determination that you will receive can be used when you would like to publish or present your findings.

**How do I Submit a Human Subject Research Study to the Aurora RSPP/IRB?**

This section includes a summary of the important steps surrounding submission of a human subject research study to the Aurora RSPP/IRB. The following points appear on most/all Aurora human subject research submission applications, and the applications will be the same no matter if you submit in CyberIRB or via PDF. If you have questions on a specific question or any of the requested information on a form, please call the Aurora RSPP/IRB office at (414) 219-7744.

**Types of Human Subject Research submission applications:**

- Convened IRB Research Study Submission
- Expedited Research Study Submission
- Exempt Research Study Submission
- Medical Record/Database Research Submission – see next section for more information

All of these forms, except the Medical Record submission application are available within CyberIRB.

**Completing the application form:**

Below are some key points that are included in most/all Aurora IRB research application forms. If you have questions about any of these areas or any others in the submission application, please contact the Aurora RSPP/IRB office for clarification/assistance:

1. **Protocol Name**
   
   Enter the full protocol name. If applicable, include in parentheses the cooperative group or sponsor protocol code or number.

2. **Principal Investigator (PI)**
   
   This is the person with overall responsibility for the conduct of the Human Subject Research. There can only be one investigator with this overall responsibility.

3. **Funding Sources**
   
   Name of the sponsor of the funding source(s). If the study is PHS-funded, provide the appropriate response.

4. **Contact**
This is the person who will receive ALL communications related to the study. This entry cannot be left blank. Re-enter the name of the Principal Investigator if applicable.

5. **Key Personnel**

The staff working on the study that meet Aurora IRB’s definition (see also “investigator”) must be included. A [Delegation of Authority log](#) noting all key personnel and their delegated duties **MUST** be included with every submission.

6. Check that all applicable documents are included with the submission. This includes: study protocol (either the sponsor protocol or one written by the PI), any/all consent documents (including sponsor template consent), written subject/recruitment materials, investigational drug brochure, package insert or device manual for all investigational agents, grant application, copy of surveys questionnaires provided to subject, case report forms or data collection tool(s), PI CV/resume, [Preparatory to Research/Waiver of Authorization form](#) (502-A form).

7. **Approvals Required Prior to Initiating Research**

Include all additional approvals that are required by the research:

a. Radiation Safety Committee – when radioisotopes are being used for reasons other than clinical care.

b. Biohazard Committee – this will be an external committee when any biohazards are used for purposes of the research.

c. Departments, Facilities, Clinics within Aurora required for participation in the research.

d. Aurora Privacy Officer if a [Data Use Agreement](#) is necessary for the study.

8. Studies that propose to include members of a vulnerable population (children, pregnant women, fetuses or neonates, and prisoners) may require extra justification within the application form.

9. There may be other areas of the submission application that cause problems or question. If so, please contact the Aurora RSPP/IRB office at 414-219-7744.

**To Submit:**

Complete the appropriate research application – either in the [Aurora Cyber IRB](#) or by providing responses on the forms created in WORD and found on the RSPP/IRB website. Once finished, the WORD document should be signed, scanned into a PDF, and attached to an email addressed to the [IRB.Office@aurora.org](mailto:IRB.Office@aurora.org). In addition to the PDF, the WORD (.doc or docx) version of the form and all required documents (as indicated on the form) should be attached to the same email (you may send more than one email if there are many attachments – please indicate this in the Subject line of the email).

If you completed a [CyberIRB](#) submission, upload all required documents (as indicated in CyberIRB) and “send” the application to the PI for his/her electronic signature. The submission will NOT be sent to the Aurora RSPP/IRB office until the PI takes this action.
If you need any help/instruction on how to submit – including instructions on using CyberIRB, please contact the Aurora RSPP/IRB office at (414) 219-7744.

Tip: Remember to attach/upload any ancillary documents that are required/requested. The checklist on the application form will help you remember what is needed. The inclusion of this key information will prevent your submission from being returned as “incomplete”.

Tip: Be as complete and thorough as possible in providing the necessary information on the forms. This will make your submission easier for the office staff and the IRB members to review. Remember, if a question is truly not applicable to your research you may state that.

How do Medical Record (MR) studies differ?

A specialized process, application, continuing review application and expedited review category (#10) have been developed to streamline review of research activities that solely involve review/collection of protected health information, that pose no more than minimal risk to subjects, and to which no federal regulations apply. This process, which ensures the application of equivalent protections, can be used for both retrospective review (reviewing records that exist at the time the request is submitted to the IRB for review) and prospective review (review of any information placed in the medical record after the request is submitted to the IRB for review) of data.

The following is a list of the criteria that must be met for this specialized review process to be used:

1. You are an Aurora caregiver (you may not be a student or a volunteers).
2. Your research is not federally (PHS) funded.
3. Data will not be sent to or reviewed by an entity or individual outside Aurora Health Care.
4. Your research or data is not going to be submitted to or reviewed by FDA, or another agency or sponsor.
5. You will not be contacting patients or obtaining informed consent for this research study.
6. There are no conflict of interests with the research for any investigator/key personnel that cannot be managed within the confines of the study (ie. no disclosures to subjects is necessary).

If your study meets all of the criteria listed above, complete the Application for Review of Medical Records and/or Databases for Research Purposes. Make sure that all questions are addressed.

Informed Consent

Informed consent is more of a conversation/process than a means for obtaining a signature of the research participant. Federal regulations require written informed consent (meaning the use of an IRB-approved written consent form which is signed by the participant or the participant's legal representative). Occasionally there are reasons to waive written consent or to alter the requirements of consent. Researchers are required to inform participants in written or verbal form of the primary purpose of the research
project and of any procedures which they will undergo. Additionally, participants are to be informed of their rights regarding the study (voluntary participation, protecting anonymity and privacy) and any risks or benefits associated with the project.

Under certain circumstances, the use of written consent documents may be waived or alteration of the consent process may be approved. Investigators must justify a waiver or alteration of the consent process in the protocol submission application in order to be considered by the IRB. The IRB will take into consideration the risks and potential harms involved in these requests to approve.

**Waiver of Documentation of Informed Consent (Waiver of Signed Consent)**

The IRB may waive the requirement for written consent if it finds that:

- the only record linking the participant and the research would be the consent document and the principal risk would be the potential harm resulting from breach of confidentiality; or
- 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 [45 CFR 46.117 (c)(1)(2)].

This type of waiver applies especially to anonymous interviews (including face-to-face and telephone interviews) where the researcher's sole knowledge of the identity of the participant would come from the consent document. **Waiver of written consent procedures does not imply waiver of the researcher's responsibility to obtain consent from the participant.**

In all cases, the researcher must provide the participant with an information sheet or cover letter describing the research that includes all relevant elements of informed consent. This waiver, however, does not relinquish of the researcher's responsibility to obtain consent from the subject.

**Examples of studies where a waiver of written consent MAY be approved:**

- the only record of the name or other identifying information of the subject would be the signed consent form and knowledge of an individual's participation or information provided could lead to potential legal, social, or physical harm.
- online survey research on evaluation of the effectiveness of a smoking cessation program among its participants. Informed consent can be "documented" by requiring participants to click on a link or image that indicates acceptance of the consent form (i.e. a button that says "I accept" or "I agree", and advances participants to an online study web page that is otherwise inaccessible.

**Waiver of Informed Consent**

The IRB may waive part or all of the normal consent requirements if:

- the research involves no more than minimal risk to the participants;
- the waiver or alteration of normal consent procedures will not affect adversely the rights and welfare of the participants;
- the research could not be carried out effectively without the waiver or alteration; and
• whenever appropriate, the participants will be provided with additional pertinent information after participation [45 CFR 46.116 (d)(1-4)].

This category of waiver includes those cases in which the researcher desires to withhold from the participant some information about the project that, if known by the participant, would bias the results of the study. Ordinarily, the researcher would plan a debriefing session after completion of the individual's participation in order to provide the individual with the missing information, and provide the participant the option of including his/her data in the study or having it destroyed. **The researcher is required to give participants full consent information and to obtain their voluntary consent orally.** In no case should a researcher seek to withhold information about the research or the participant's role in the research solely to reduce the chance that the individual will refuse to participate.

**Examples of studies where a waiver of consent elements MAY be approved:**

• A psychological study that is actually about peer pressure but participants are told the study is about perception of visual phenomenon. Deception is required to adequately measure peer pressure. [Note that justification of the need for deception in the research is required within the submission application.]

• A study that requires covert observation of interpersonal behavior and, if participants know they are being observed, they may alter their behavior.

• Parent/guardian permission forms are sent home to parents and returned to the investigator without a verbal discussion, questions being addressed, and an evaluation of understanding.

**Note that research qualifying for exempt review does not need to obtain waivers of written consent from the IRB.**

**How do I create a consent document?**

The Aurora RSPP/IRB has created many consent templates – adult subject consent, children assent, parental permission, future research consent, research information sheet – that are available for use on the Aurora RSPP/IRB website. These templates were created to ensure that the required and additional, appropriate elements of informed consent disclosure required by the federal regulations are included in the consent/permission document submitted for Aurora IRB review. Please do not delete language included in the Aurora consent where applicable.

Note that the Aurora IRB uses a combined consent and HIPAA authorization document. Therefore, the templates found on the website are compliant for HIPAA authorization as well – no separate authorization document is necessary.

**TIP: The Aurora IRB templates include all of the required and applicable additional elements of informed consent required by the regulations. Therefore, please do NOT remove any of the template language – including the HIPAA authorization language – without discussing with the Aurora IRB office. If you do so, you take the risk that your consent document will not conform to the regulations.**
TIP: All consent/assent templates include a place in the header for a version date. We recommend that you date the revisions of your consent documents to ensure that you use the most recent version approved by the IRB. When you make revisions to the consent document, remember to update the version date of the document, and include the new version date on the modification form.

**What are the decisions the IRB can make when reviewing a protocol?**

To approve human subject research, the IRB must determine that all the regulatory Criteria of Approval are met. The IRB may make the following decisions on a human subject research study:

- **Approval:** Made when all criteria for approval are met.
- **Modifications Required to Secure Approval:** Made when IRB members require specific modifications to a protocol before approval can be finalized.
- **Deferred:** Made when the IRB determines that the board is unable to approve a protocol and the IRB suggests modifications the might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- **Disapproval:** Made when the IRB determines that it is unable to approve a protocol and the IRB cannot describe modifications the might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

**How does the IRB decide whether to approve Human Research?**

To approve human subject research, the IRB must determine that all the regulatory Criteria of Approval are met. You are encouraged to write your protocol in a way that addresses the criteria for approval.

**What will happen after IRB review?**

After the IRB’s review (either convened IRB or expedited review mechanism), the Research Compliance Analyst (RCA) will provide the Principal Investigator and the study contact person with an email noting that the IRB has approved the Human Research, requires modifications (‘conditions of approval’) to secure approval, has deferred the study, or has disapproved the study.

- **If the IRB has approved the Human Subject Research:** The Human Subject Research may commence once all other institutional requirements have been met. IRB approval is good for a limited period of time which is noted in the approval letter. **Research cannot commence until this final approval is received.**
- **If the IRB requires modifications to secure approval (conditions of approval):** Make the requested modifications as indicated in the email from the RCA, and return them to him/her when completed. Do not make ANY other changes to the
study. The changes made will be compared with the conditions of approval. If all requested modifications are made, the IRB will issue a final approval once all other institutional requirements have been met. **Research cannot commence until this final approval is received.** If you do not agree with the requested modifications, you may respond in writing to the IRB or address the IRB in person at future meeting. NOTE that no other changes besides those requested as conditions of approval may be made before the final approval letter is issued.

- **If the IRB defers the Human Subject Research:** The IRB will provide a letter noting the reasons for deferral, and if possible, suggestions to make the study approvable. You will have an opportunity to make the suggested revisions and resubmit the study for future IRB consideration. If you do not agree with the suggested changes, you do have the right to respond in writing to the IRB or address the IRB in person at future meeting.

- **If the IRB disapproves the Human Subject Research:** The IRB will provide a letter noting the reasons for disapproval and give you an opportunity to respond in writing or address the IRB in person at future meeting. If you do not respond within 30 days, the study will be closed with the IRB.

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**What are my obligations after IRB approval?**

1) **Do not start Human Subject Research activities until you have the final IRB approval letter.**

2) **Personally conduct or supervise the Human Subject Research.**
   
   a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB.
   
   b) When required by the IRB ensure that consent or permission is obtained in accordance with the relevant submission as approved by the IRB.
   
   c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
   
   d) Protect the rights, safety, and welfare of subjects involved in the research.

3) **Submit necessary documents/updates to the IRB within the required timelines:**
   
   a) Proposed modifications as described in this manual. (See “How do I submit a modification?”)
   
   b) New information that affects or may affect the conduct of the study or the safety/protection of the human research subjects
   
   c) A continuing review application as requested. (See “How do I submit continuing review?”)
   
   d) A final report when the Human Subject Research is closed. (See “How Do I Close Out a Study?”)

4) **Review Aurora IRB SOP 403** for important information on your obligations after approval has been issued. In summary:
a) Report any instances of noncompliance or unanticipated problems involving risk to subjects or others on the appropriate form (noted below);
   ii) Report any adverse events/effects that meet immediate reporting criteria on a Local or External Unanticipated Problem/Event Reporting form.
   iii) Submit changes in the approved research in a timely fashion.
   iv) Report any significant deviations/violations that meet immediate reporting criteria on a Significant Deviation/Violation Reporting form.

b) Report any complaints (from subjects, Aurora personnel, research staff, etc.) immediately.

5) Do not accept or provide payments to professionals in exchange for referrals of potential subjects (“finder’s fees.”)

6) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (“bonus payments.”)

7) Maintain signed and dated consent documents for three years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for five years after completion of the research.

8) **When subjects withdraw from FDA-regulated clinical trial follow the [Aurora IRB Guidance](#) on subject withdrawal, and the [FDA guidance on data retention with subject withdrawal](#).**

9) For FDA-regulated research involving investigational drugs comply with the following FDA regulations: [21 CFR §312.7, §312.57, §312.59, §312.60, §312.61, §312.64, §312.66, §312.68, and §312.69](#).

10) For FDA-regulated research involving investigational devices comply with the following FDA regulations: [21 CFR §812.7, §812.100 and §812.110, §812.145, and §812.150](#).

11) For research involving clinical trials, comply with the [International Council on Harmonization – Good Clinical Practice Guidelines (E6)](#). Also noted in [Appendix C](#) of this document.

12) See additional requirements of various federal agencies in [Appendix B](#).

**How do I document consent?**

Remember, consent is a process. It should include an in-depth conversation with the potential subject. The documenting/signing of consent should follow the conversation with the potential subject.

The Aurora IRB template combines the Human Subject Research consent with the HIPAA authorization. This combined document allows the subject to sign only once.

1. Some study sponsors require that the subject initial each page of the consent document. **IF your study sponsor requires subject initials on each page, make sure that this is included in your approved consent document and this task is completed by the subject.**
2. If your IRB approved consent document includes areas within the document for the subject to note their wishes (e.g. check boxes), make sure that these are completed.

3. The regulations (federal and ICH GCP) require that the potential subject sign and date the consent. Fulfillment of these requirements is accomplished by obtaining the subject’s (or their legally authorized representative – LAR) signature on the appropriate line of the signature page. Note that the Aurora IRB’s consent template also includes the time that the subject signs the consent document. This is to ensure that the enrollment of the subject preceded any research interventions.

4. Sometimes an Impartial Third Party Witness to the consent process is required. The witness – an individual independent of the study team and not related to the subject – must then sign on the signature page.

5. The individual that obtains consent (i.e. conducts the consent process) must sign, date and enter the time that consent document was signed.

6. Other items that are necessary:
   a. Provide the subject with a copy of the signed consent document/authorization.
   b. The research staff member designated within the Delegation of Authority log (see TIP below; and also, the preamble of section V of the submission application) to conduct the risks, benefits and alternatives discussion with the potential subject (typically a physician in a treatment study) must sign and date the consent as well.
   c. Complete the Documentation of Informed Consent section.

_TIP: The research application submitted to and approved by the IRB denotes who has been delegated the responsibility to obtain consent/authorization as well as conduct the risk/benefit/alternative discussion with the prospective subject. Make sure that you are following what you told the IRB as to who will obtain consent. If revisions are necessary, please submit a modification._

**What happens if I unexpectedly encounter a potential research subject who cannot speak or read the consent document?**

If the subject cannot read or sign the document for him/herself, call the Aurora RSPP office for guidance. Aurora IRB SOP 701 is available to provide assistance as well as a guidance document created by the Aurora RSPP Office on this topic.

**What happens if I unexpectedly encounter a potential research subject who is decisionally incapacitated?**

If you unexpectedly encounter a prospective subject who is decisionally incapacitated such that he/she cannot consent for him/herself, contact the Aurora RSPP office for guidance. If your study includes a patient population who is decisionally incapacitated, you may request the IRB to approve a research plan to use a legally authorized representative to enroll subjects (see Aurora IRB SOP 702).
Whenever required by the IRB, the subject’s or representative’s signature is to be witnessed by an individual who signs and dates the consent document.

A copy of the signed and dated consent document is to be provided to the subject.

**How do I enroll a subject who does not speak/read English?**

If you unexpectedly encounter a prospective subject who cannot speak or read English, please go to the folder on the Aurora RSPP website that specifically addresses this issue. The folder includes a complete guidance document that outlines the steps that must be followed to enroll such a subject into your research study. It also includes short form that has been translated into several foreign languages. **REMEMBER:** you must obtain permission from the Aurora IRB before using these short form consent documents as outlined in the guidance document.

If your research study includes an eligible patient population who cannot speak or read English, you may request the IRB to approve a research plan to enroll such subjects (see Aurora IRB SOP 701). The submission form includes a section that must be completed in order for the IRB to consider such a request. **NOTE** that you should get the consent/authorization document approved in English before getting it translated into the alternative language.

**How do I submit a modification?**

Per federal regulations, once a human subject research study has received approval by an IRB any subsequent changes to the study must be reviewed and approved by the IRB prior to implementation except when necessary to avoid an immediate apparent hazard to a subject. You may submit modifications to the approved research study by completing the Aurora IRB Modification Form or the appropriate form (Significant Modification or Minor Modification) in Cyber IRB. Make sure that all necessary questions are addressed – especially those related to a revision of the protocol or consent document (see below).

Examples of modifications to submit to the Aurora IRB:

- **Consent revisions:** If you are revising the currently approved consent document remember to “track” your changes. The IRB Chair needs to know what has been added/removed from the approved consent document. If you do not track the changes in the consent, the modification will be returned to you. If possible, include the sponsor’s template consent with the revision as well.

Make sure to address the questions on the modification form that ask whether or not you are going to obtain consent from already enrolled subjects. You must also indicate whether you are going to have subject sign the revised consent document or if you are going to provide the new information in a consent addendum. You must also provide consideration/justification on the method that you will use to obtain the re-consent (in-person, telephone, mail, etc).

- **Protocol revisions:** If the modification is revising the currently approved protocol, please include a “tracked” version of the protocol if possible. If a tracked version of the protocol has not been provided by the study sponsor, you will need to include/provide a document that specifically outlines the changes that have been
made in the revised protocol. If not provided by the sponsor you may list the changes in the “other” box on the modification form.

**Changes to key personnel:** You must notify the Aurora RSPP/IRB of all changes in study personnel. If new study personnel are being added, the modification must be submitted – and approved by the Aurora IRB – before the individual conducts any research procedures or interacts/intervenes with research subjects.

**Addition of key personnel:**

1. All newly added key personnel **MUST** have completed their research training and COI disclosures for research before the modification is submitted [see this section].
2. In addition to the modification form, a revised Delegation of Authority log must be submitted outlining the research roles of the individual(s).
3. If the research study involves a device or an “implant” procedure, the Aurora RSPP/IRB will obtain documentation the Aurora Medical Staff department that this individual is appropriately credentialed by before the modification is approved. Please plan accordingly.

**Removal of key personnel:**

1. A revised Delegation of Authority log must be submitted with the removal of the individual from the study.

**NOTE** that the approval date of the modification requesting the addition/removal of key personnel will be used as the start/end date of his/her participation.

**Other types of modifications:** There are many other types of study modifications (including a temporary closure of enrollment) that can – and should – be submitted to the Aurora IRB. If you have questions please feel free to contact the Aurora RSPP/IRB office.

If completing the modification as a WORD document, sign the form and copy it into a PDF file. Attach the PDF and any required documents to an email addressed to IRB.Office@aurora.org.

If completing the modification in Cyber IRB, upload the required attachments and send the form to the study PI (if a Significant Modification) or to the IRB office (if a Minor Modification).

**Please note that unless the change is to alleviate an immediate, apparent hazard to a subject, research must continue to be conducted without inclusion of the modification until IRB approval is received.**

**Tip:** Remember to change the version date of any revised consent documents so that you will know which is the most current version of the consent. The most current approved version of the consent must ALWAYS be used to enroll subjects. The modification form (whether WORD or Cyber IRB) asks for the version date of the revised consent. This is the date that will be noted on your approved modification form – you will receive a copy of the approved modification form.
Tip: A copy of the modified/approved consent document will be uploaded into Cyber IRB if this program is used to submit the modification. You will be able to print a copy of this document for use in enrolling subjects. If you submit a WORD modification form, you will be expected to “accept” the tracked changes prior to printing the consent to enroll subjects. **DO NOT CHANGE THE MODIFIED CONSENT VERSION DATE WHEN ACCEPTING THE TRACKED CHANGES.**

**How do I temporarily close a study to new enrollment?**

There are times when you may need to temporarily close a research study. The reasons that a temporary closure may be necessary are numerous – for example: to allow time for interim analysis’ allow the sponsor to review collected data for safety or efficacy purposes; to allow the manufacturer to make necessary changes to the drug/device and/or for FDA review of the changes; etc. The [Aurora IRB Modification form](#) must be submitted when a temporary closure is requested. Documentation from the sponsor on the need for the temporary closure is necessary in most cases.

When the sponsor is ready to reopen the study to accrual of subjects, the submission of another modification form requesting this action is necessary. Documentation from the sponsor to reopen the study is required in most cases.

**Continuing review – what is it?**

Research approved by the Aurora IRB may continue only for the time period established by the IRB during their review. Such time periods are controlled, in part, by the DHHS and FDA regulations for human subject research. Per regulations set forth at 45 CFR 46.109(e), an IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Therefore, in order to conduct research for more than one year, ongoing approval is necessary – at Aurora this is achieved by conducting a continuing review at least once per year.

The Aurora IRB, during the course of their initial or continuing review, may approve a research study for a defined time period of not more than one year minus one day. The Aurora IRB has the authority to approve a research study for a period of less than one year, limit the number of study participants, or require monthly or six-month reports – depending on the degree of risk in the research and any other factors which affect the health and welfare of the study participants. IRB approval automatically expires at the time or event set by the IRB. The IRB review process for a continuing review application may be conducted at either a convened meeting or via expedited review (an expedited review process may only be conducted if the application meets all regulatory requirements that make it eligible for an expedited review).

When conducting continuing review, the IRB starts with the working presumption that the research, as previously approved, does satisfy all of the regulatory criteria for approval. The IRB focuses on whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB’s prior determinations, particularly with respect to the IRB’s prior evaluation of the potential benefits or risks to the subjects.
Investigators are responsible for fulfilling requirements associated with continuing review in time for the IRB to carry out continuing review prior to the expiration date of the current IRB approval. In particular, investigators are responsible for submitting sufficient materials and information for the IRB to meet its regulatory obligations, and should follow the institutional policies and procedures for continuing IRB review of research that are required by 45 CFR 46.103(b)(4) and referenced in the institution’s OHRP-approved Federalwide Assurance (FWA).

See [OHRP guidance on Continuing Review](#) for more information.

**How am I made aware that continuing review is necessary?**

Per the regulations, the investigator is responsible for fulfilling the requirement for continuing review in time for the IRB to carry out its review prior to study expiration date. The Aurora IRB sends a COURTESY REMINDER to the PI and designated study contact person approximately **2.5 months** prior to the IRB meeting scheduled immediately before study expiration. [If possible, studies due for continuing review are brought before the convened board two meetings before study expiration. It should be therefore noted that this continuing review schedule may cause an abbreviated approval period.]

The request for continuing review includes a DEADLINE for returning the application to the Aurora RSPP office. This deadline allows sufficient time for the Aurora RSPP office to review the application, and obtain IRB determination on approval prior to study expiration. PLEASE be respectful of the deadline for return of your continuing review application to the Aurora RSPP office to ensure that your study gets appropriate IRB approval prior to study expiration.

If the Aurora RSPP office has not received the completed continuing review application from the study PI five weeks prior to the provided DEADLINE, the PI and study contact will receive ONE FURTHER REMINDER from the Aurora RSPP office that continuing review is due – the deadline will not change from the initial notification.

If the continuing review application is not received by the Aurora RSPP office four weeks prior to the IRB meeting scheduled immediately before study expiration, the PI and/or study contact will receive a written or verbal notification from the RSPP Director. This notification will serve to remind the PI of the following:

- It is his/her obligation, per the federal regulations and Aurora IRB policy, to obtain ongoing approval for their research;
- The federal regulations do not provide for a grace period which would extend the conduct of the research beyond the expiration date of IRB approval without continuing review and re-approval by the IRB;
- There will be no further reminders from the Aurora RSPP office;
- Should continuing review not occur prior to the end of the approval period, approval automatically expires at midnight of the expiration date; and

It will be reinforced that the Aurora RSPP office will make every effort to work with the research team to get a submitted continuing review application to the convened board
prior to the expiration date, however the lateness of the application may not allow for convened board review prior to expiration.

**What happens if my study approval lapses due to non or late submission of a continuing review application?**

The federal regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB; OR the IRB cannot conduct continuing review by the expiration date of IRB approval.

**If the approval of the research study expires**, all human subject research procedures related to the protocol must **cease**, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information. **The continuation of human subject research procedures without IRB approval is a violation of federal regulations.** [See SOP 404 for more information]

The IRB has the authority to allow continued participation of subjects in research for which IRB approval has lapsed while the continuing review process occurs if there is an overriding safety concern or ethical issues that indicates it is in the best interest of the participants to continue. In such cases where participants may continue in the research, data analysis must stop until the IRB completes the review process. If approval lapses, the IRBs do not have the authority to allow new enrollment while the continuing review process is conducted.

If current subjects will be harmed by stopping research procedures that are available outside the research context, provide this care on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping research procedures that are not available outside the research context, immediately contact the IRB chair and provide a written list of the currently enrolled subjects and why they will be harmed by stopping research procedures.

**How do I submit my continuing review application?**

When requested to submit a continuing review application, complete the [Continuing Review/Final Report form](mailto:IRB.Office@aurora.org) (WORD document) that was sent with the reminder notification OR complete the Continuing Review application in Cyber IRB. Make sure that all necessary questions are addressed.

Note that the forms are divided into three sections – you only have to complete the sections required by the current status of your research study (e.g., active research participation, closed to enrollment, open for data analysis only, etc.). The forms are designed to assist you in determining whether you need to complete one, two or all three of the sections. Please call the RSPP office if you have questions.

If completing the Continuing Review form as a WORD document, sign the form and copy it into a PDF file. Attach the PDF and any required documents to an email addressed to [IRB.Office@aurora.org](mailto:IRB.Office@aurora.org).

If completing the Continuing Review in Cyber IRB, upload the required attachments and send the form to the study PI.
REMEMBER: the continuing review is a snapshot of the study at the moment in time that you are completing the form. The application should only include elements of the study that have already been approved by the Aurora IRB. It should not include any proposed modifications.

TIP: Respect the DEADLINE date provided to you by the Aurora RSPP office for return of the continuing review application. The date that is provided will allow time for the Primary Reviewer to review the continuing review application and address any missing or questionable items before the continuing review application is sent to the convened board. If you are not able to return the completed application by the due date, please contact the Aurora RSPP office.

How do I close a study with the IRB?

If ALL research-related activities with human subjects have been completed, and all data collection and analysis of identifiable private information described in the IRB-approved research plan have been completed, then the human subject research study has been completed, and the study may be closed with the IRB.

NOTE that full closure is a different action from temporarily closing a study to accrual. With a temporary closure to accrual, there is the possibility that study enrollment may resume with IRB re-review of the study/issue. Once a study is fully closed with the IRB, the research is considered complete, and no further research activities may occur.

Once a study has been completed, investigators may keep the data they collected, including de-identifiable private data, if consistent with the IRB-approved protocol. There are times that the IRB may approve the retaining of identifiable private data even after the study closure. This MUST be requested within the submission application for IRB consideration. After a study is closed, investigators should continue to honor any confidentiality protections of the data, as well as any other commitments that were agreed to as part of the approved research (e.g., providing information about the study results to research subjects, or honoring commitments for compensation for research participation).

When a human subject research study has been completed, the investigators no longer are required to obtain continuing review and approval of that study. No further research activities can be done including access of medical records to finalize data queries by the sponsor. Therefore, make sure that all data collection required by the study has been completed prior to study closure.

To close a study with the IRB, you will need to submit a Final Report (WORD document) OR complete the same process within Cyber IRB. You are only required to complete section I of this form. Should the sponsor wish for you to submit external adverse events/effects that did not require immediate reporting, or a list of minor violations that occurred since the last Continuing Review application, you may attach with the Final Report.

TIP: When a human subject research study has been completed, the investigators no longer are required to obtain continuing review and approval of that study. Closing a study with the IRB means that IRB approval and oversight of the study is done. Therefore, no further research activities can be done including access of patient medical
records to finalize data queries by the sponsor. Therefore, make sure that all data/information from the human subjects or their identifiable medical records is obtained before submitting the Final Report to the IRB.

**How long do I keep records?**

See [Aurora IRB SOP 305](#) for specific information. Maintain your human subject research records, including signed and dated consent documents, for at least three years after closing out the study. Maintain HIPAA authorizations and other records related to HIPAA compliance for seven years.

If your study is sponsored by industry or some other outside agency, contact the sponsor before disposing of any research records.

**What if I need to use an unapproved drug or device in a life-threatening situation and there is no time for prior IRB review?**

The FDA allows the use of investigational drugs and biologics or devices for the treatment of serious or life-threatening conditions for a single patient when no effective alternative treatment exists outside of a clinical trial (“Emergency Use”, 21 CFR 56.104(c)). Although not research, human subjects protection regulations (21 CFR 50 & 56) apply due to the use of an investigational product. See [Aurora IRB SOP 1301](#) for specific information or contact the RSPP office.

If the test article is used in an emergency situation, follow-up reports are required to be sent to the RSPP Office per SOP 1301. Failure to submit the follow-up report may result in the review of the event per the noncompliance SOP (Aurora IRB SOP 601).
Appendix A – Research Administrative Preauthorization (RAP) Process

RAP review is required for ALL research conducted at Aurora PRIOR to submission of the study to the Aurora IRB. This requirement includes research that may be deferred to an outside IRB for human subject protection oversight.

In order to submit a project for RAP review, send an email to research.preauthorization@aurora.org and request a copy of the Proposal Template Form. Note that the RAP Proposal is NOT the same as the Protocol you will submit to the IRB. You may use information in the Protocol to assist you in completing the RAP Proposal, but these are different documents.

You will receive an email describing the outcome of this review; a favorable pre-authorization is required before you can continue with the project approval, for example: submission to the IRB/IACUC, medical record release, etc.

Introduction & Purpose
The purpose of RAP is to ensure that research being proposed at Aurora is meritorious and in alignment with the priorities and mission of Aurora Health Care and the Aurora Research Institute (ARI).

Pre-authorization focuses on a proposal’s clinical significance, scientific merit, and feasibility. The intent is to provide early feedback to the investigator early-on before time and resources are spent writing an in-depth protocol and submission to other reviewing bodies, such as the IRB or IACUC.

RAP is also designed to identify and offer potential support for those projects which may need facilitation, additional expertise, resources, and if external, an Aurora collaborator. The Senior Vice President for Research & Academic Relations (who serves as President of ARI) is responsible for conferring administrative pre-authorization. However, this authority may be delegated as outlined below.

II. Delegation Of Pre-Authorization
RAP review can be transferred or delegated only by the Senior Vice President for Research & Academic Relations. Delegation can be revoked at any time for any reason. The following areas are eligible for delegation to the appropriate identified leaders such as the examples listed:
1. Industry/Govt.-sponsored clinical trials - Director of Clinical Trials
2. AUWMG and CUPH Research - Director AUWMG Research
3. Nursing profession/education/operations related studies - Director Nursing Operations
4. Cardiovascular research (fellows and specific areas as recommended by ACS Research Committee) - Fellowship Director
5. Investigator-initiated Research - Director Investigator Initiated Research

* One exception to the RAP review delegation process is Caregiver Surveys & Participation. The Chief Human Resources Officer has asked that only the Sr. VP for Research review and approve studies involving Aurora employees/staff.
Appendix B  Research Conducted or Funded by Federal Departments

Per SOP 402, the Aurora IRB is authorized to oversee research conducted or funded by Federal Departments (e.g. Department of Justice, Department of Defense – which includes Navy, Army and Airforce, Environmental Protection Agency, Department of Energy and Department of Education). All of these Departments have additional requirements that must be taken into consideration when submitting this research to the Aurora IRB, OR that must be followed by the IRB during its review. Some of these are outlined below. When anticipating the submission of Research Conducted or Funded by Federal Departments, contact the Aurora IRB as early as possible for considerations of all applicable regulations.

Department of Defense (DOD) Research

When Human Research is conducted or funded by the Department of Defense (DOD), the organization commits to apply DOD Directive 3216.02, which includes the requirement to apply 45 CFR §46 Subparts B, C, and D. When Human Research is conducted or funded by the Department of the Navy, the organization commits to apply SECNAVINST 39000.39D.

The following additional requirements should be taken into consideration when submitting DOD research studies to the Aurora IRB.

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.

2. The IRB must consider the scientific merit of the DOD supported research activity during the IRB review process. The IRB may rely on outside experts to provide an evaluation of scientific merit, such as a departmental or grant (if applicable) reviewer or by calling upon an outside consultant.

3. Research involving human subjects who are not U.S. citizens or DOD personnel, conducted outside the United States, and its territories and possessions, requires permission of the host country. The laws, customs, and practices of the host country and those required by this instruction will be followed. An ethics review by the host country, or local Naval IRB with host country representation, is required.

4. Research supported by the Department of Defense must apply 45 CFR Subparts B, C, and D with the some additional stipulations.

5. For research involving more than minimal risk to subjects, an independent research monitor must be appointed by name. Research monitors may be physicians, dentists, psychologists, nurses, or other healthcare providers capable
of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety.

6. When research involves human beings as experimental subjects (an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction), the IRB may not waive the requirement for informed consent. The Secretary of Defense may waive the prohibition in this section with respect to a specific project to advance the development of a medical project necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws.

7. There are special considerations that must be placed into the research when involving DOD personnel (military or civilian) as research subjects.

8. A legally authorized representative may provide informed consent on a subject’s behalf only when the research is intended to benefit the individual subject.

9. There are also limits on the compensation able to be received by military personnel who are research subjects. Department of Defense employees (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments.

10. Department of Defense components might have stricter requirements for research-related injury than the DHHS regulations. Follow the requirements of the DOD component.

11. There may be specific Department of Defense educational requirements or certification required.

12. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

13. Principal investigators may not be sponsors for INDs and IDEs.

14. Surveys of DOD military members and their families and DOD civilian personnel must be approved through the appropriate DOD authority prior to implementation to ensure surveys provide maximum benefits. Surveys must be administered according to the requirements outlined in OPNAVINST 5300.8C

Note there are definitions (minimal risk, classified) that are specific for DOD research, and special considerations for these types of research. See Glossary for these definitions.

**Department of Navy (DON) Research**

The following additional requirements should be taken into consideration when submitting DON research studies to the Aurora IRB.
1. Surveys usually require Department of Navy review and approval. See SECNAVINST 5300.8B for more information.

2. When conducting research with the Navy, a formal agreement is required to specify the roles and responsibilities of each party including a Statement of Work (SOW) and specific assignment of responsibilities. The agreement should briefly describe the research, specific roles and responsibilities of each institution, responsibility for scientific and IRB review, recruitment of subjects, and procedures for obtaining informed consent. The agreement also should describe provisions for oversight and ongoing monitoring, reporting requirements, documentation retention, and compliance for the entire research project. See SECNAVINST 3900.39D section 6f for more information.

Department of Energy (DOE) Research

When Human Research is conducted or funded by the Department of Energy (DOE), the organization commits to applying DOE O 443.1A.

1. You must report the following within ten business days to the Department of Energy human subject research program manager
   a. Any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken or to be taken.
   b. Any suspension or termination of IRB approval of research.
   c. Any significant non-compliance with HRPP procedures or other requirements.

2. You must report the following within three business days to the Department of Energy human subject research program manager
   a. Any compromise of personally identifiable information must be reported immediately.

Department of Education (ED) Research

When Human Research is conducted or funded by the Department of Education (ED), the organization commits to applying 34 CFR §97 Subpart D (equivalent to 45 CFR §46 Subpart D), 34 CFR §98.3, 34 CFR §98.4, 34 CFR §356.3, and 34 CFR §99.

The following additional requirements should be taken into consideration when submitting ED research studies to the Aurora IRB.

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children\(^1\) involved in the research\(^2\) must be able to inspect these materials.

3. The school in which the research is being conducted must have policies regarding the administration of physical examinations or screenings that the school may administer to students.

**Environmental Protection Agency (EPA) Research**

When Human Research is conducted or funded by, or when the results of research are intended to be submitted to or held for inspection by the Environmental Protection Agency (EPA), the organization commits to applying 40 CFR §26, which includes the requirement to apply 45 CFR §46 Subparts B and D.

**Department of Justice**

When Human Research is conducted or funded by the Department of Justice (DOJ), the organization commits to apply 28 CFR §22. When Human Research is conducted with the federal Bureau of Prisons (DOJ), the organization relies on the Bureau Research Review Board to ensure compliance with 28 CFR §512.

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\(^1\) Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

\(^2\) Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.
Appendix C - ICH Good Clinical Practice (GCP) E6 Complianance

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with GCP assures that the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible. This International Conference on Harmonization (ICH) guidance provides a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions.

This list provides a summary of investigator responsibilities required for compliance with ICH Good Clinical Practice (GCP) Guidance. If the research study requires ICH GCP E6 compliance or the investigator has agreed to conduct the research in compliance with ICH GCP E6, he/she may use this list to determine if mechanisms are in place to ensure compliance these regulations.

<table>
<thead>
<tr>
<th>GCP E6 4.1 and 4.2</th>
<th>Investigator Qualifications, Agreements and Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The investigator must:</strong></td>
<td></td>
</tr>
<tr>
<td>4.1.1</td>
<td>Be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. The investigator should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).</td>
</tr>
<tr>
<td>4.1.2</td>
<td>Be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.</td>
</tr>
<tr>
<td>4.1.3</td>
<td>Be aware of and follow Good Clinical Practice guidance and the applicable regulatory requirements.</td>
</tr>
<tr>
<td>4.1.4</td>
<td>Permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).</td>
</tr>
<tr>
<td>4.1.5</td>
<td>Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Have sufficient time to properly conduct and complete the trial within the agreed trial period.</td>
</tr>
<tr>
<td>4.2.3</td>
<td>Have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.</td>
</tr>
<tr>
<td>4.2.4</td>
<td>Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.</td>
</tr>
<tr>
<td><strong>GCP E6 4.3</strong></td>
<td>Medical Care of Trial Subjects</td>
</tr>
<tr>
<td><strong>The investigator must:</strong></td>
<td></td>
</tr>
<tr>
<td>4.3.1</td>
<td>Ensure a qualified physician (or dentist, when appropriate), either yourself or a sub-investigator for the trial, will be responsible for all trial-related medical (or dental) decisions.</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Ensure that adequate medical care is provided to a subject for any adverse events (including clinically significant laboratory values) related to the trial, both during and following a subject's participation in a trial? The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.</td>
</tr>
</tbody>
</table>
4.3.4 Make a reasonable effort to ascertain subjects’ reason(s), for withdrawing prematurely from a trial while fully respecting the subject’s rights.

### ICH Good Clinical Practice (GCP) Compliance Summary (cont’d)

<table>
<thead>
<tr>
<th>GCP E6 4.4</th>
<th>Communication with the IRB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The investigator must:</strong></td>
<td></td>
</tr>
<tr>
<td>4.4.1</td>
<td>Retain written and dated approval from the IRB for the research application, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.</td>
</tr>
<tr>
<td>4.4.2</td>
<td>Provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, you must provide a copy of the updated Investigator's Brochure to the IRB, unless the sponsor is submitting the document to the IRB on behalf of investigators.</td>
</tr>
<tr>
<td>4.4.3</td>
<td>Provide the IRB with all documents subject to review according to the IRB’s requirements.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GCP E6 4.5</th>
<th>Compliance with the IRB-Approved Research Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The investigator must:</strong></td>
<td></td>
</tr>
<tr>
<td>4.5.1</td>
<td>Conduct the research in compliance with the research application that was given approval by the IRB and sign the research application to confirm agreement.</td>
</tr>
<tr>
<td>4.5.2</td>
<td>Ensure that the investigator will not implement any deviation from the IRB-approved research application without prior review and documented approval from the IRB of a modification. If necessary to eliminate an immediate hazard to research subjects, an investigator may deviate from the IRB-approved research application without prospective IRB approval.</td>
</tr>
<tr>
<td>4.5.3 and 4.5.4</td>
<td>Document and explain any deviation from the approved protocol that occurs without prospective IRB approval. If the investigator deviates from the IRB-approved research application to eliminate an immediate hazard(s) to research subjects without prospective IRB approval, the investigator must submit a modification and explain the deviation to the IRB.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GCP E6 4.6 and 4.7</th>
<th>Investigational Product(s) and Randomization Procedures and Unblinding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The investigator must:</strong></td>
<td></td>
</tr>
<tr>
<td>4.6.1</td>
<td>Take responsibility for investigational product(s) accountability at the research site(s).</td>
</tr>
<tr>
<td>4.6.2</td>
<td>Assign some or all of the investigator’s duties for investigational product(s) accountability at the research site(s) to an appropriate pharmacist or another appropriate individual who is under your supervision.</td>
</tr>
<tr>
<td>4.6.3</td>
<td>Maintain records of the product's delivery to the research site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and research subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. This responsibility may be delegated to an appropriate member of the research staff.</td>
</tr>
<tr>
<td>4.6.4</td>
<td>Ensure that the investigational product(s) will be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).</td>
</tr>
<tr>
<td>4.6.5</td>
<td>Ensure that the investigational product(s) are used only in accordance with the IRB-approved research application.</td>
</tr>
<tr>
<td>4.6.6</td>
<td>Explain the correct use of the investigational product(s) to each subject and periodically check that each subject is following the instructions properly. This responsibility may be delegated to an appropriate member of the research staff.</td>
</tr>
<tr>
<td>4.7</td>
<td>Follow the trial's randomization procedures, if applicable, and ensure that the code is broken only in accordance with the IRB-approved research application? If the research is blinded, the investigator must promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).</td>
</tr>
</tbody>
</table>
### ICH Good Clinical Practice (GCP) Compliance Summary (cont’d)

<table>
<thead>
<tr>
<th>GCP E6 4.8</th>
<th>Informed Consent of Trial Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The investigator must:</strong></td>
<td></td>
</tr>
<tr>
<td>4.8.1</td>
<td>Comply with the applicable regulatory requirement(s) and adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki in obtaining and documenting informed consent. Prior to the beginning of the research study, the investigator must have the IRB’s written approval of the written informed consent form and any other written information to be provided to subjects.</td>
</tr>
<tr>
<td>4.8.2</td>
<td>Ensure that the written informed consent form and any other written information to be provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised consent form and other written information provided to subjects must receive the IRB’s approval in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the research, and the communication of this information should be documented.</td>
</tr>
<tr>
<td>4.8.3</td>
<td>Ensure that neither you nor the research staff will coerce or unduly influence a subject to participate or to continue to participate in the research.</td>
</tr>
<tr>
<td>4.8.4</td>
<td>Ensure that none of the oral and written information concerning the trial, including the written informed consent form, contains any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.</td>
</tr>
<tr>
<td>4.8.5</td>
<td>Fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the research including the written information and the approval by the IRB. This responsibility may be delegated to an appropriate member of the research staff.</td>
</tr>
<tr>
<td>4.8.6</td>
<td>Ensure that the language used in the oral and written information about the research, including the consent form, will be as non-technical as practical and will be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.</td>
</tr>
<tr>
<td>4.8.7</td>
<td>Ensure that you, or a designee you have appointed, will provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the research. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.</td>
</tr>
<tr>
<td>4.8.8</td>
<td>Ensure that the written consent form is signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion prior to a subject's participation in any research procedures.</td>
</tr>
<tr>
<td>4.8.9</td>
<td>Ensure that, if a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness will be present during the entire informed consent discussion. After the written informed consent form, and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.</td>
</tr>
</tbody>
</table>
### ICH Good Clinical Practice (GCP) Compliance Summary (cont’d)

<table>
<thead>
<tr>
<th>Section</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8.10</td>
<td>Ensure that, the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:</td>
</tr>
<tr>
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<td>• That the trial involves research.</td>
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<td>• The purpose of the trial.</td>
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<td></td>
<td>• The trial treatment(s) and probability for random assignment to each treatment.</td>
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<td></td>
<td>• The trial procedures to be followed, including all invasive procedures.</td>
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<td></td>
<td>• The subject’s responsibilities.</td>
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<td>• Those aspects of the trial that are experimental.</td>
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<td>• The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.</td>
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<td>• The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.</td>
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<td></td>
<td>• The compensation and/or treatment available to the subject in the event of trial-related injury.</td>
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<td>• The anticipated prorated payment, if any, to the subject for participating in the trial.</td>
</tr>
<tr>
<td></td>
<td>• The anticipated expenses, if any, to the subject for participating in the trial.</td>
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<tr>
<td></td>
<td>• That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.</td>
</tr>
<tr>
<td></td>
<td>• That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.</td>
</tr>
<tr>
<td></td>
<td>• That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.</td>
</tr>
<tr>
<td></td>
<td>• That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.</td>
</tr>
<tr>
<td></td>
<td>• The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.</td>
</tr>
<tr>
<td></td>
<td>• The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.</td>
</tr>
<tr>
<td></td>
<td>• The expected duration of the subject's participation in the trial.</td>
</tr>
<tr>
<td></td>
<td>• The approximate number of subjects involved in the trial.</td>
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</tbody>
</table>

*Note: items in italics are required only by ICH GCP and not by FDA.*

<table>
<thead>
<tr>
<th>Section</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8.11</td>
<td>Ensure that, prior to participation in the research, the subject or the subject's legally acceptable representative will receive a copy of the signed and dated consent form and any other written information provided to the subject. During a subject's participation in the research, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated revised consent form and a copy of any updates to the written information provided to subjects.</td>
</tr>
</tbody>
</table>
ICH Good Clinical Practice (GCP) Compliance Summary (cont’d)

4.8.12 Ensure that when research (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the research with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject will be informed about the research to the extent compatible with the subject's understanding and, if capable, the subject will be given the opportunity to sign and personally date the written informed consent.

4.8.13 Ensure that, except as described in 4.8.14 (below), non-therapeutic research (i.e., research in which there is no anticipated direct clinical benefit to the subject), will be conducted in subjects who personally give consent and who sign and date the written informed consent form. 4.8.14 Non-therapeutic research may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- The objectives of the research cannot be met by means of research in subjects who can give informed consent personally.
- The foreseeable risks to the subjects are low.
- The negative impact on the subject's well-being is minimized and low.
- The research is not prohibited by law.
- The approval of the IRB is expressly sought on the inclusion of such subjects, and the IRB’s written approval covers this aspect.

Such research, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 Ensure that in emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, will be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject requires measures described in the research application and/or elsewhere, with documented IRB approval to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative must be informed about the research as soon as possible and consent to continue and other consent as appropriate (see 4.8.10 above) should be requested.

GCP E6 4.9 Records and Reports
The investigator must:

4.9.1 Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Ensure that data reported on the CRF derived from source documents are consistent with the source documents? If there are any discrepancies, they should be explained.

4.9.3 Ensure that any change or correction to a CRF will be dated, initialed, and explained (if necessary) and will not obscure the original entry (i.e., an audit trail should be maintained). This applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. As the investigator, you should retain records of the changes and corrections.

4.9.4 Maintain the research documents as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.
ICH Good Clinical Practice (GCP) Compliance Summary (cont’d)

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9.5</td>
<td>Ensure that essential documents will be retained until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. If required by the applicable regulatory requirements or by an agreement with the sponsor, these documents may need to be retained for a longer period. It is the sponsor’s responsibility to inform the investigator as to when these documents no longer need to be retained.</td>
</tr>
<tr>
<td>4.9.6</td>
<td>Ensure that the financial aspects of the study are documented in an agreement between yourself and the sponsor.</td>
</tr>
<tr>
<td>4.9.7</td>
<td>Make available for direct access all requested research-related records upon request of the monitor, auditor, IRB, or regulatory authority.</td>
</tr>
</tbody>
</table>
| GCP E6 4.10 | **Progress Reports**  
*The investigator must:*  
4.10.1 Submit written summaries of the research status to the IRB annually, or more frequently if requested by the IRB.  
4.10.2 Promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the research, and/or increasing risks to subjects. |
| GCP E6 4.11 | **Safety Reporting**  
*The investigator must:*  
4.11.1 Immediately 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. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the research subjects rather than by the subjects' names, personal identification numbers, and/or addresses. As the investigator, you should also comply with the applicable regulatory requirement(ies) related to the reporting of unexpected serious adverse drug reactions to the IRB and regulatory authority(ies).  
4.11.2 Report adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.  
4.11.3 Supply the sponsor and the IRB with any additional requested information for reported deaths (e.g., autopsy reports and terminal medical reports). |
| GCP E6 4.12 | **Premature Termination or Suspension of a Trial**  
*The investigator must:*  
4.12.1 Inform the sponsor and the IRB if the investigator terminates or suspends research without prior agreement of the sponsor. The investigator should provide the sponsor and the IRB with a detailed written explanation of the termination or suspension.  
4.12.2 Promptly inform the IRB if the sponsor terminates or suspends a trial and provide a detailed written explanation of the termination or suspension.  
4.12.3 Notify the sponsor if the IRB terminates or suspends its approval of the research, and provide the sponsor with a detailed written explanation of the termination or suspension. |
**ICH Good Clinical Practice (GCP) Compliance Summary (cont’d)**

<table>
<thead>
<tr>
<th>GCP E6 4.13</th>
<th>Final Report(s) by Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The investigator must:</strong></td>
<td>Inform the IRB and provide a summary of the research results, and provide any reports required by the regulatory authority(ies).</td>
</tr>
</tbody>
</table>
Comparison of FDA and ICH Regulations

The ICH guideline published May 9, 1997 in the Federal Register and has been adopted as guidance in the US. US regulatory requirements (FDA regulations) must be met for studies conducted in the US. For studies conducted outside for the US in ICH regions compliance with ICH E6 ensures that the studies will be accepted for review by the FDA as non-US, non-IND studies (per FDA regulation for accepting non-US non-IND studies).

<table>
<thead>
<tr>
<th>Topic Area</th>
<th>ICH</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IRB Responsibilities</strong></td>
<td>ICH requires IRB submission of Subject recruitment procedures&lt;br&gt;Written information provided to subjects&lt;br&gt;Information about subject compensation&lt;br&gt;Investigators current CV and or other documents evidencing qualifications</td>
<td>FDA and ICH require the IRB to review ICF, Protocol, advertisements and the Investigators Brochure (ICH requires that the clinical investigator provide the IRB with a copy of the IB) FDA only requires that the pharmaceutical co. sponsor provide the IB to the Investigator however many sponsors require documentation of receipt from the Investigators IRB</td>
</tr>
<tr>
<td></td>
<td>ICH requires a statement from the IRB that it is organized and operates according to GCP.</td>
<td>FDA does not require sponsors to obtain such a statement.</td>
</tr>
<tr>
<td><strong>IRB Composition</strong></td>
<td>ICH and FDA require IRBs to be composed of the following members:&lt;br&gt;• At least 5 members&lt;br&gt;• One non-scientific member&lt;br&gt;• One member not affiliated with the institution&lt;br&gt;• Members involved in the protocol not have a voting role.</td>
<td>FDA also requires:&lt;br&gt;• One scientific member&lt;br&gt;• Diversity in race, gender, cultural backgrounds&lt;br&gt;• Varying backgrounds-not composed of only one profession&lt;br&gt;• Members qualified to assess the acceptability of the protocol with institutional SOPs &amp; professional particle standards</td>
</tr>
<tr>
<td><strong>Investigator Agreements</strong></td>
<td>ICH requires Investigators to maintain a list of appropriately qualified persons to whom significant trial-related duties have been delegated.</td>
<td></td>
</tr>
<tr>
<td><strong>Investigator Resources</strong></td>
<td>ICH requires Investigators to demonstrate potential for recruiting the required number of patients within the agreed recruitment period&lt;br&gt;• Retrospective data&lt;br&gt;• Patient database analysis</td>
<td></td>
</tr>
</tbody>
</table>
### Comparison of FDA and ICH Regulations (cont’d)

<table>
<thead>
<tr>
<th>Subject Medical Care</th>
<th>ICH requires investigators to inform subjects when medical care is needed for an Intercurrent illness</th>
<th>FDA Guidance Investigator Responsibilities, October 2009: Investigator should ensure reasonable medical care is provided for any AE related to trial participation. They should also inform participant when medical care is needed for conditions/unrelated to the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Compliance</td>
<td>ICH recommends that Investigators inform the subjects primary physician of trial participation (with subject permission)</td>
<td></td>
</tr>
<tr>
<td>Protocol Compliance</td>
<td>ICH requires Investigators to make every reasonable effort to ascertain the reason(s) for subject early withdrawal (the subject is not obligated to give a reason)</td>
<td></td>
</tr>
<tr>
<td>Protocol Compliance</td>
<td>ICH requires Investigators(or their designees) to document and explain any deviation from protocol</td>
<td></td>
</tr>
<tr>
<td>Protocol Compliance</td>
<td>ICH requires that the sponsor and investigator sign the study protocol</td>
<td>FDA doesn’t have this requirement but most sponsors</td>
</tr>
<tr>
<td>Investigational Product</td>
<td>ICH allows the delegation of study drug dispensing, patient counseling and drug accountability to a designee</td>
<td>FDA has no regulations or guidance concerning delegation of these duties</td>
</tr>
<tr>
<td>Investigational Product</td>
<td>ICH requires that the Investigator maintain records that document adequately that the subjects were provided the doses specified by the protocol and RECONCILE all investigational products received from the sponsor</td>
<td>FDA requires only the return of unused supplies and does not specify who is responsible for reconciliation.(312.62)</td>
</tr>
<tr>
<td>Investigational Product</td>
<td>ICH prohibits the sponsor (or CRO) from providing investigational product until all required documentation from the IRB has been obtained.</td>
<td>FDA does not address this (most sponsors have internal SOPs covering this)</td>
</tr>
</tbody>
</table>
Comparison of FDA and ICH Regulations (cont’d)

| Informed Consent | Element differ between ICH 4.8.1 ICH requires certain elements that the FDA does not:  
1. Discussion of trial related treatment and probability of random assignment,  
2. subject responsibilities, 3. anticipated payment if any, 4. important potential risks and benefits of alternative treatment, 5. authorization to access medical records by regulatory authorities | And FDA 50.25 a and 50.25b |
| ICH requires the subject receive a SIGNED and DATED copy of the written ICF | FDA requires that a copy be given to the subject but does not state that it must be a signed copy. |
| Records and Reports | ICH requires Investigators or Designees to  
• Document explanations for discrepancies between data in the CRFs and the source documents  
• Initial data and explain all CRF changes/corrections. CRF designees must be documented otherwise the Investigator is required to initial changes.  
• Endorse and retain records of all CRF changes made by the Sponsor. | FDA does not require documentation of authorization to initial CRF changes |
| ICH requires the retention of “essential document for at least 2 yrs after the approval of a marketing application in an ICH region or until there is no pending or contemplated applications in an ICH region or development is formally discontinued. | ICH compliance generally requires longer retention time than FDA regulations. |
### Comparison of FDA and ICH Regulations (cont’d)

<table>
<thead>
<tr>
<th><strong>ICH requires Sponsor to inform Investigators in writing of:</strong></th>
</tr>
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<tbody>
<tr>
<td>- Study record retention requirements</td>
</tr>
<tr>
<td>- Notification of when records are no longer needed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sponsor QA/QC</strong></th>
<th>ICH requires Sponsors to secure agreement from all involved parties to ensure direct access of study records to foreign regulatory authorities.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compensation</strong></td>
<td>ICH requires sponsors to provide insurance or indemnify the investigator against claims arising from the trial.</td>
</tr>
<tr>
<td></td>
<td>FDA does not have this policy but most investigators request and obtain it from the sponsor</td>
</tr>
<tr>
<td><strong>Financial Records</strong></td>
<td>ICH requires that the clinical investigator make all trial related records available for direct access by the CRA, auditor, IRB or regulatory agency.</td>
</tr>
<tr>
<td></td>
<td>FDA currently requires disclosure of the Investigator’s financial relationship with the sponsor.</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>ICH requires sponsors document management review and follow up of the monitoring report as prepared by the CRA</td>
</tr>
<tr>
<td></td>
<td>FDA does not require sponsors to document review of the CRA monitoring reports.</td>
</tr>
<tr>
<td></td>
<td>ICH requires a copy of the CRA Study Initiation Visit Report be stored in the Investigators files and relevant communications (letters, meeting notes, telephone call records)</td>
</tr>
<tr>
<td></td>
<td>Not required by FDA at this time</td>
</tr>
<tr>
<td></td>
<td>ICH requires that monitors qualifications be documented</td>
</tr>
<tr>
<td></td>
<td>FDA specifies that Sponsors shall monitor the progress of all clinical investigations and that monitor be qualified by training and experience</td>
</tr>
<tr>
<td></td>
<td>ICH requires that monitors verify that trial functions have not been delegated to unauthorized individuals</td>
</tr>
<tr>
<td></td>
<td>FDA has a Monitoring guidance document (1998)</td>
</tr>
</tbody>
</table>
Comparison of FDA and ICH Regulations

<table>
<thead>
<tr>
<th>ICH</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH puts the responsibility for ensuring that all study documents are on file at the Investigational site on the CRA and requires that the CRA confirm that all necessary documents are at the site prior to closing the site.</td>
<td>FDA holds the investigator responsible for the accuracy and completeness of the records related to the clinical trial.</td>
</tr>
<tr>
<td>ICH requires CA of both the PI and any Sub-Investigator</td>
<td>FDA does not require Sub I CV although this is typically a sponsor requirement</td>
</tr>
<tr>
<td>Protocol and IB</td>
<td>ICH has more detailed outline of contents of the protocol and IB than FDA regulations</td>
</tr>
<tr>
<td></td>
<td>ICH requires that the protocol identify any data to be recorded directly on the CRFs and to be considered source data.</td>
</tr>
</tbody>
</table>
| Essential Documentation | ICH requires the following documents not specified by the FDA:  
  - Subject Screening log  
  - Subject Identification log  
  - Signature Sheet |
| | Currently FDA does not require these documents but they are typically required by the sponsor |
Comparison of FDA, DHHS and ICH regulations for Informed Consent

<table>
<thead>
<tr>
<th>Required Element</th>
<th>FDA Studies</th>
<th>DHHS Studies</th>
<th>ICH Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A statement that the study involves research</td>
<td>21 CFR 50.25(a)(1)</td>
<td>45 CFR 46.116 (a)(1)</td>
<td>ICH E6 4.8.10 (a)</td>
</tr>
<tr>
<td>An explanation of the purposes of the research</td>
<td>21 CFR 50.25(a)(1)</td>
<td>45 CFR 46.116 (a)(1)</td>
<td>ICH E6 4.8.10 (b) (c)</td>
</tr>
<tr>
<td>(ICH adds -the trial treatment(s) and the probability for random assignment to each treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The expected duration of the subject’s participation</td>
<td>21 CFR 50.25(a)(1)</td>
<td>45 CFR 46.116 (a)(1)</td>
<td>ICH E6 4.8.10 (s)</td>
</tr>
<tr>
<td>A description of the procedures to be followed</td>
<td>21 CFR 50.25(a)(1)</td>
<td>45 CFR 46.116 (a)(1)</td>
<td>ICH E6 4.8.10 (d)</td>
</tr>
<tr>
<td>(ICH adds, including all invasive procedures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The subject’s responsibilities</td>
<td>----------------------------</td>
<td>---------------------------</td>
<td>ICH E6 4.8.10 (e)</td>
</tr>
<tr>
<td>Identification of any procedures that are experimental</td>
<td>21 CFR 50.25(a)(1)</td>
<td>45 CFR 46.116 (a)(1)</td>
<td>ICH E6 4.8.10 (f)</td>
</tr>
<tr>
<td>A description of any reasonably foreseeable risks or discomforts to the subject.</td>
<td>21 CFR 50.25(a)(2)</td>
<td>45 CFR 46.116 (a)(2)</td>
<td>ICH E6 4.8.10 (g)</td>
</tr>
<tr>
<td>A description of any benefits to the subject or to others which might be expected from the research</td>
<td>21 CFR 50.25(a)(3)</td>
<td>45 CFR 46.116 (a)(3)</td>
<td>ICH E6 4.8.10 (h)</td>
</tr>
</tbody>
</table>
Comparison of FDA, DHHS and ICH regulations for Informed Consent (cont’d)

<table>
<thead>
<tr>
<th>A disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subject.</th>
<th>21 CFR 50.25(a)(4)</th>
<th>45 CFR 46.116 (a)(4)</th>
<th>ICH E6 4.8.10 (i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH adds (alternative procedures and their risks and benefits)</td>
<td></td>
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</tr>
<tr>
<td>A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and</td>
<td>21 CFR 50.25(a)(5)</td>
<td>45 CFR 46.116 (a)(5)</td>
<td>ICH E6 4.8.10 (o)</td>
</tr>
<tr>
<td>A statement that notes that the FDA may inspect the records.</td>
<td>21 CFR 50.25(a)(5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject’s original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that by signing the informed consent form, the subject or the subject’s legally authorized representative is authorizing such access.</td>
<td></td>
<td></td>
<td>ICH E6 4.8.10 (n)</td>
</tr>
<tr>
<td>For research involving more than minimal risk,</td>
<td>21 CFR 50.25(a)(6)</td>
<td>45 CFR 46.116 (a)(6)</td>
<td>ICH E6 4.8.10 (j)</td>
</tr>
<tr>
<td>(1) an explanation as to whether any compensation and</td>
<td></td>
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<tr>
<td>(2) an explanation as to whether any medical treatments will be available if injury occurs and, if so, what they consist of, and</td>
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<tr>
<td>(3) where further information may be obtained</td>
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</tr>
</tbody>
</table>
### Comparison of FDA, DHHS and ICH regulations for Informed Consent (cont’d)

<table>
<thead>
<tr>
<th>Description</th>
<th>FDA Reference</th>
<th>DHHS Reference</th>
<th>ICH Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>An explanation of whom to contact for answers to pertinent questions:</td>
<td>21 CFR 50.25(a)(7)</td>
<td>45 CFR 46.116 (a)(7)</td>
<td>ICH E6 4.8.10 (q)</td>
</tr>
<tr>
<td>(1) about the research (PI name and number), and,</td>
<td></td>
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<tr>
<td>(2) research subject’s rights (IRB contact info), and,</td>
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<tr>
<td>(3) who to contact in the event of a research-related injury to the</td>
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<tr>
<td>subject.</td>
<td></td>
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<tr>
<td>A statement that participation is voluntary</td>
<td>21 CFR 50.25(a)(7)</td>
<td>45 CFR 46.116 (a)(8)</td>
<td>ICH E6 4.8.10 (m)</td>
</tr>
<tr>
<td>A statement that refusal to participate will involve no penalty or loss of</td>
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<tr>
<td>benefits to which the subject is otherwise entitled.</td>
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</tr>
<tr>
<td>A statement that the particular treatment or procedure may involve risks</td>
<td>21 CFR 50.25(b)(1)</td>
<td>45 CFR 46.116 (b)(1)</td>
<td>ICH E6 4.8.10 (g)</td>
</tr>
<tr>
<td>to the subject (or to the embryo or fetus, if the subject is or</td>
<td></td>
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<tr>
<td>becomes pregnant) which are currently unforeseeable.</td>
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</tr>
<tr>
<td>Anticipated circumstances under which the subject’s participation may be</td>
<td>21 CFR 50.25(b)(2)</td>
<td>45 CFR 46.116 (b)(2)</td>
<td>ICH E6 4.8.10 (r)</td>
</tr>
<tr>
<td>terminated by the investigator without regard to the subject’s consent.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional costs to the subject that may result from participation in the</td>
<td>21 CFR 50.25(b)(3)</td>
<td>45 CFR 46.116 (b)(3)</td>
<td>ICH E6 4.8.10 (l)</td>
</tr>
<tr>
<td>study.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensation or payment to subjects for participating in the trial.</td>
<td>---------------</td>
<td>---------------</td>
<td>ICH E6 4.8.10 (k)</td>
</tr>
<tr>
<td>The consequences of a subject’s decision to withdraw from the course of</td>
<td>21 CFR 50.25(b)(4)</td>
<td>45 CFR 46.116 (b)(4)</td>
<td></td>
</tr>
<tr>
<td>the research, and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedures for the orderly termination of participation by the subject.</td>
<td></td>
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</tr>
</tbody>
</table>
Comparison of FDA, DHHS and ICH regulations for Informed Consent (cont’d)

<table>
<thead>
<tr>
<th>Item</th>
<th>FDA 21 CFR 50.25(b)(5)</th>
<th>DHHS 45 CFR 46.116 (b)(5)</th>
<th>ICH E6 4.8.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td>ICH E6 4.8.10 (p)</td>
</tr>
<tr>
<td>The approximate number of subjects in the study.</td>
<td>21 CFR 50.25(b)(6)</td>
<td>45 CFR 46.116 (b)(6)</td>
<td>ICH E6 4.8.10 (t)</td>
</tr>
<tr>
<td>Date of the subject’s (or legally authorized representative’s) signature.</td>
<td>21 CFR 50.27(a)</td>
<td>45 CFR 46.117(a)</td>
<td>ICH E6 4.8.8</td>
</tr>
<tr>
<td>A copy of the signed written ICF will be provided to the subject.</td>
<td>21 CFR 50.27(b)</td>
<td>45 CFR 46.117(a)</td>
<td>ICH E6 4.8.11</td>
</tr>
<tr>
<td>Signature of the subject or legally authorized representative</td>
<td>21 CFR 50.27(a)</td>
<td>45 CFR 46.117(a)</td>
<td>ICH E6 4.8.8</td>
</tr>
<tr>
<td>Signature of the person obtaining consent</td>
<td>----------------------</td>
<td>-------------------------</td>
<td>ICH E6 4.8.8</td>
</tr>
<tr>
<td>Signature of witness</td>
<td>21 CFR 50.27(b)(2) – short form</td>
<td>45 CFR 46.117(b)(2) – short form</td>
<td>ICH E6 4.8.9</td>
</tr>
<tr>
<td>ICH “impartial” witness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>