



UAMS Institutional Review Board

INVESTIGATOR'S HANDBOOK

This Investigators Handbook has been provided by the University of Arkansas for Medical Sciences Institutional Review Board and the UAMS Office of Research Compliance to assist researchers in preparing their application for review of research involving human subjects in accordance with the guidelines set forth by the University.

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REVISIONS HISTORY

With this handbook, we are instituting a new system of indicating handbook editions. The new method will consist of the year, followed by a version number and a revision date. For example, the first handbook is the 2004 – Version 1 – Revised 08/31/2004 edition.

Archived Handbook versions can be found at the link
<http://www.uams.edu/orc/Links/Handbooks.htm>.

CHAPTER 1

The IRB At The University of Arkansas For Medical Sciences

Protecting human subjects involved in research is a collaborative effort that demands the vigilance of UAMS faculty, staff, and students in partnership with the local community, federal agencies and agencies sponsoring research. This guide is intended to help researchers meet their responsibilities.

[The Purpose of the University of Arkansas for Medical Sciences Institutional Review Board](#)

[Authority and Responsibility of the UAMS IRB](#)

[The membership and structure of the UAMS IRB](#)

[UAMS IRB Meeting Schedule and Submission Deadlines](#)

❖ **The Purpose Of The University Of Arkansas For Medical Sciences Institutional Review Board**

The purposes of the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board (IRB) are:

- To protect the rights and welfare of human research subjects.
- To approve the initiation of and conduct periodic reviews of biomedical and behavioral research involving human subjects.
- To terminate or suspend studies in human subjects.

The UAMS Institutional Review Board (IRB) is the deliberative body designated by the following institutions:

- University of Arkansas for Medical Sciences (UAMS)
- Arkansas Children’s Hospital Research Institute (ACHRI)
- Central Arkansas Veteran’s Healthcare System (CAVHS)
- Arkansas Department of Health (ADH)

This committee operates according to Federal, State, Institutional and Good Clinical Practices (GCP) guidelines. The UAMS IRB also recognizes the tripartite International Code of Harmonization (ICH).

The UAMS IRB has the authority to approve, disapprove or require modifications of research activities that fall within its jurisdiction. The UAMS IRB may work in conjunction with other university or institutional committees; however, it reviews research projects independently based upon the principle that human participants will be adequately protected.

❖ **Authority and Responsibility of the UAMS IRB**

The UAMS IRB operates under a Federalwide Assurance (FWA). This is an agreement between the UAMS IRB and the Department of Health and Human Services (DHHS), which outlines the responsibilities of the UAMS IRB for upholding the ethical principles regarding research involving human subjects. These principles are outlined in the report of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research titled, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (known as the “Belmont Report”).

The Office for Human Research Protections (OHRP) oversees research activities for DHHS. The Office of Research Oversight (ORO), formerly the Office for Research Compliance and Assurance (ORCA) also oversees studies involving veterans. Other agencies that the IRB report to include: The Food and Drug Administration (FDA), The Office of Research Integrity (ORI), institutional officials, sponsors, and funding agencies.

Normally, the IRB will agree to serve as the institutional review board for other institutions only if a staff member or faculty appointee of UAMS is involved as a principal or sub-investigator. However, the IRB will serve any state agency for a specific protocol by written request.. Many ACH, CAVHS, ADH, NCTR, and ASH scientists have academic appointments at UAMS and in general will utilize

or collaborate with clinical faculty of UAMS for their human studies. Appropriate agreements between the committee and the requesting institution will be required.

❖ **The Membership and structure of the UAMS IRB**

The Vice Chancellor for Academic Affairs and Sponsored Research at UAMS appoints members of the IRB, including the Chair. Appointments are for four-year periods. Federal requirements mandate that the IRB must have at least five members of varying backgrounds to promote complete and adequate review of research activities commonly conducted at this institution. IRB members must be knowledgeable about institutional commitments and regulations, applicable laws, standards of professional conduct, and practice. The IRB membership must be diverse in matters of race, gender, and cultural background; and include at least one person in each of the following categories:

- The member's primary concern is the scientific area
- The member's primary concern is the non-scientific areas
- The member is not affiliated with the institution and is not an immediate family member or a person who is affiliated with the institution.
- A representative from the CAVHS R & D Committee

Other representatives are present to consider protocol involving children and prisoners.

No member of the IRB may participate in the initial or continuing review of any project in which that member has a conflicting interest, except to provide information requested by the IRB. IRB members include healthcare providers from a variety of disciplines and lay representatives from the community at large.

❖ **UAMS IRB Meeting Schedule and Submission Deadlines**

The Biomedical Institutional Review Board (IRB) typically meets on four Tuesdays of each month. Meetings are held at 2:00 p.m. on the UAMS campus. The deadline for submission of protocols for IRB review is 10:00 a.m. two weeks prior to the scheduled meeting. Submissions not received in the IRB office by that day and time are held over for consideration at the next meeting. Adjustments can be made in the submission receipt date at the discretion of the IRB Chair.

The Behavioral and Social Sciences Institutional Review Board (IRB) meets the second Thursday of each month on the UAMS campus. The Behavioral and Social Sciences IRB studies reviewed by this committee are considered medically non-invasive and include studies involving questionnaires, surveys, interviews, focus groups, *etc.*

Select Meeting Dates and Deadlines may be found on the UAMS IRB website.

CHAPTER 2

WHAT IS SUBJECT TO IRB REVIEW?

The scope of the Institutional Review Board's (IRB) charge is broad. Generally, any University research that uses humans, human tissue, surveys of human subjects, human subjects' records, or in some cases human cell lines requires IRB review, irrespective of its funding source. The IRB's charge extends to research in the social and behavioral sciences as well as research in the health and biological sciences.

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❖ Scope Of IRB Review

IRB review and approval is required for any research involving human subjects if a staff member or faculty appointee of University of Arkansas for Medical Sciences (UAMS), Arkansas Children's Hospital (ACH), Central Arkansas Veteran's Healthcare System (CAVHS), or Arkansas Department of Health (ADH) is involved as a principal investigator or sub-investigator. However, the IRB will serve any state agency for a specific protocol by written request and once appropriate agreements are in place. IRB will review research that meets any of the following criteria:

- Research conducted or sponsored by faculty, staff, students, or employees of the respective institution.
- Research performed on the premises of UAMS and associated institutions.
- Research performed with equipment or in facilities belonging to UAMS.
- Research that involves UAMS patients, students, staff, or faculty.
- Research that involves UAMS patient data.
- Satisfies a requirement imposed by the University for a degree program or for completion of a course of study.
- Certified by a dean or department head to satisfy an obligation of a faculty appointment at the University, including clinical or adjunct appointments.

❖ Research Review Requirements

According to the United States Code of Federal Regulations, 45 CFR 46.102(d), *Research* means a systematic investigation, including research development, testing, and evaluation designed to develop or contribute to generalized knowledge. Examples of research activity include:

- Clinical trials
- Surveys
- Interviews
- Behavioral investigations
- Prospective or retrospective reviews of medical information
- Experiments with physiological fluids and tissue
- Demonstration or service programs.

The Food and Drug Administration (FDA) includes under the definition of reviewable research, the use of an FDA regulated product outside of its marketed use in the practice of medicine for the purposes of contributing to generalizable knowledge.

Example: Use of an FDA approved cardiac medicine for the treatment of neurogenic pain could be considered experimental and subject to IRB review.

To determine whether a proposed activity is research, apply the following criteria:

- Is the proposed activity intended for release to the Scientific Community as a contribution to knowledge? For example, publication in a medical or scientific journal and/or presentation at a medical or scientific meeting.
- Does the proposed activity involve an interaction or intervention with a living person that occurs solely for the purpose of the project?
- Will the proposed activity collect identifiable, private data/information in a form that is associable with the individual?
- Is the proposed activity portrayed (explicitly or implicitly) by university students, faculty, or staff as “research” or “experimental” investigation?
- Is the proposed activity intended to fulfill requirements for a master’s thesis, doctoral dissertation, or other research requirement?

If any one of the above criteria is answered “yes”, the protocol must be reviewed and approved by the IRB.

The IRB, not the investigator, determines if an activity is research.

❖ **Research Conducted By “Affiliated Faculty”**

Research conducted by "affiliated faculty" -- faculty members who hold clinical or adjunct appointments--is subject to the University's guidelines for research on human subjects and must be submitted for IRB review. Any research project that is conducted by or under the direction of any employee or agent of this institution, in connection with his or her institutional responsibilities, requires IRB approval.

❖ **Research Projects In Which The Researcher Is A Consultant**

UAMS IRB review is required unless the researcher has a strict consulting relationship in which:

- The researcher is hired on his or her own time.
- The researcher holds no rights in the work.
- Neither the researcher nor the institution retains any data.

All three of these criteria must be met, or the IRB will need to review the project.

❖ **Research Conducted By Students and Residents**

Independent class projects, senior theses, undergraduate research projects, master's projects, partial fulfillment of fellowship requirements, and similar exercises utilizing human research must be independently submitted to the IRB by the student/resident-researcher but **a physician/faculty member ultimately is responsible for the protection of the subjects and should be listed as the Responsible Staff Person in ARIA**. Advisers shoulder the responsibility for students or

residents engaged in independent research, and instructors are responsible for research that is conducted as part of a course. Because students and residents are transient, the faculty member sponsor must rigorously defend why they are not the Principal Investigator for such projects.

During the design of a project, advisors and faculty members should instruct students and residents on the ethical conduct of research and help them prepare applications for IRB approval. In particular, students and residents should do the following:

- Understand the elements of informed consent.
- Develop a readable consent form written in the second person and at a level equivalent to an eight grade education.
- Plan appropriate recruitment strategies for identifying subjects.
- Establish and maintain strict guidelines for protecting anonymity and confidentiality.
- Allow sufficient time for IRB review and completion of the project during the student or resident's matriculation.
- Obtain certificates for required Human Subject Training and HIPAA for Research.

As assurance that the University's guidelines will be followed, the adviser or instructor is required to be listed as the Responsible Staff Person in ARIA for the student's/resident's application for IRB approval and/or serve as the Principal Investigator.

After IRB approval, faculty members should take an active role in ensuring that projects are conducted in accordance with the IRB's requirements. One way to meet this responsibility is to meet periodically with students/residents to review their progress and to assist in submitting the continuing reviews required by the IRB.

❖ **Research Training**

The Office of Research Compliance functions as the auditing and compliance body as well as the training unit for the UAMS Institutional Review Board. This office is a component of the campus' Human Research Protections Program (HRPP) and reports directly to the senior research official at UAMS, the Vice Chancellor for Academic Affairs and Research Administration.

The ORC offers both the Online Human Subject Protection Training and the Online HIPAA For Research Training courses at <http://www.uams.edu/orc/Training/Training.htm>.

❖ **Research Conducted At Other Institutions**

For a UAMS researcher to participate in a research project at another site, the project needs to be reviewed by the UAMS IRB as well as by the other institution's IRB. For example, a UAMS researcher engaged in research at the CAVHS must secure approval from both the UAMS IRB and the CAVHS R&D Committee.

The UAMS IRB tries to accommodate researchers who work at multiple sites by streamlining the IRB approval process. In some cases, reciprocal review and approval arrangements with the UAMS IRB relieve the investigator of obtaining the independent approval of two IRBs. For more information, [contact the IRB](#).

Researchers who must submit a project to another IRB should work closely with the UAMS IRB to ensure that the appropriate agreements are in place prior to submitting to the UAMS IRB. The researcher may be asked to submit copies of the application and review of the non-UAMS IRB. Changes in protocol or consent forms required by the other IRB should be brought to the attention of the UAMS IRB.

❖ **Research That Is Part Of Multicenter Clinical Trials**

Approval of a proposal document at the national level is not sufficient to bypass approval at the local level. Researchers who conduct multicenter clinical trials sponsored by the National Institutes of Health (NIH) or the National Cancer Institute (NCI), for example, should include protocols and consent forms approved at the national level with their applications to the UAMS IRB. Although the documents should be identified as having been approved by a national IRB, the local IRB must review the material as it would any other submission. (OHRP Report Number 93-01).

Only the local IRB is vested with the authority to review and approve projects to be conducted at a given institution familiar with the particular circumstances of its research setting and is able to weigh critical considerations such as state and local laws, professional and community standards, institutional policies, and the needs of different patient and subject populations.

If changes are made to documents approved by the national IRB, the investigator must provide timely notification to the IRB. The UAMS IRB will rarely make substantive changes in the protocol or study plan and are more likely to request that the wording of a consent form be changed to reflect local standards or to include specific language required by the University.

❖ **Research In Foreign Countries**

Research conducted by UAMS investigators in foreign countries remains under University purview and guidelines. While the University cannot impose its standards for written documentation on other cultures, it does not relax its standards for ethical conduct or consent process.

The [Office for Human Research Protections \(OHRP\)](#) can determine whether procedures described by a foreign institution afford protections that are at least equivalent to U.S. regulations (45 CFR 46 101 [h]). Under this provision, OHRP investigates the foreign country's guidelines for human subject research, and if the foreign guidelines are found to be equivalent to U.S. regulations, the investigator is permitted to substitute those foreign procedures.

Researchers proposing international research should allow additional time for this review process.

❖ **IRB Review**

In performing reviewing tasks, the IRB shall request documentation of the following:

- 1) That the foreign study is done under the oversight of an IRB or Ethics Board in country of origin.
- 2) Subjects must have signed an IRB Ethics Board approved consent form.
- 3) If samples are involved,
 - ascertain if they are deidentified and when they will be destroyed.
 - that the PI will use them only for the methods in the signed consent form.

❖ **Research Involving Secondary Use of Data**

Projects that use data on human subjects gathered in earlier projects require IRB review.

If the data are gathered by someone who has legitimate access to the records and who gives the investigator only "blinded" or de-identified data (so that the investigator is unable to identify the subjects), the level of risk is lowered.

CHAPTER 3

IRB Review Requirements

This chapter defines the different types of IRB review for new protocols.

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❖ **When is IRB Review Required?**

All research or clinical investigations involving human subjects or data related to human subjects, and all other activities that even in part involve such research, regardless of sponsorship, must be reviewed and approved by the IRB. No intervention or interaction with human subjects or their data in research, including recruitment, may begin until the IRB has reviewed and approved the research protocol [45CFR46.101; 21CFR56.103(a); 45CFR].

❖ **Definition of Research**

Research is a systematic investigation, including research development, testing, and evaluation designed to develop or contribute to generalized knowledge [45CFR46.102(d)]. Examples of research activity include clinical trials, surveys, interviews, behavioral investigations, retrospective reviews of medical information, experiments with blood and tissue, and demonstration or service programs.

❖ **Definition of Human Subjects and Ethical Considerations**

A human subject is defined in Title 45 of the Code of Federal Regulations, Section 46.102 (f) as a living individual about whom a professional or student investigator conducting research obtains data through intervention or interaction with the individual or collects identifiable private information. Human subjects are also defined as an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A “subject” may be a healthy human or a patient [21 C.F.R. 56.102 (e)].

The Nuremberg Code is the first in a series of codes of ethical conduct for modern researchers. The use of human subjects for research demands that the investigator have a working knowledge of pertinent rules and regulations. One of the strongest threads binding the many rules and regulations together is the distinction between research subject (participant) and patient. If the activity that is planned for the subject is less effective or more dangerous than standard care, it is not “ethical” for that person to become a research subject except under notable exceptions. It is the ethical obligation of the investigator to make findings widely known and eliminate unnecessary risk to the former subject and patients.

In its review of human subject research, the IRB has jurisdiction over all aspects of research including:

- Methods of identifying potential subjects
- Methods proposed for contacting potential subjects
- Materials to recruit subjects and proposed compensation
- Pilot studies
- Proposals to use or provide stored blood, tissues, or confidential data
- Surveys and questionnaires
- The informed consent process and forms

- The protocol and summary of the research
- Any risks to subjects from the proposed research are reasonable in relationship to anticipated benefits
- Proposed changes to the research
- Unanticipated problems involving risk to the subject or others
- Continuing reviews
- Uses of investigational drugs and devices in emergencies
- Humanitarian uses of drugs and devices
- Determination of a protocol's eligibility for waiver of full review

The submission of any study for initial review should address those issues listed above that are pertinent to the protocol.

❖ **IRB Review Requirements**

The IRB is required by CFR 45 part 46.111 to consider all of the following during its review of proposed studies and continuing reviews:

- The IRB is required to assure that the selection of subjects is equitable and should be particularly cognizant of the special problems of research involving vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons.
- Risks to subjects are minimized through the use of procedures consistent with sound research.
- Risks to subjects are reasonable in relation to anticipated benefits and to the knowledge that may reasonably result.
- Informed consent is correctly obtained and appropriately documented.
- Subject privacy and confidentiality of the subject data is maintained.
- The research plan makes adequate provision for the monitoring of data to ensure subject safety.

❖ **Assigning Study Risk Category And Frequency Of Continuing Review Reporting**

The IRB committee meetings include a discussion and vote on new protocols, major modifications, and studies submitted for continuing review. New protocols are assigned categories of risk and frequency of continuing review. In order to approve research, the IRB must determine the degree of risk.

Below is the definition of risk categories derived from 45 CFR 46.

ADULT Minimal Risk	ADULT Greater Than Minimal Risk
<i>Activity where the probability and magnitude of harm or discomfort anticipated in the research is not greater in and of themselves than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests.</i>	<i>Research involving greater risk of harm than ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests, but presenting the prospect of direct benefit to the individual subjects; or the research presents no prospect of benefit to the subject, but is likely to yield knowledge about the disorder or condition</i>

Pediatric Category 1	Pediatric Category 2	Pediatric Category 3	Pediatric Category 4
<i>Minimal Risk</i>	<i>Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects</i>	<i>Greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield important generalizable knowledge about the subject's disorder or condition.</i>	<i>Otherwise not approvable, but presents an opportunity to understand serious health or welfare problems of children</i>

New Protocols not eligible for expedited review will be reviewed by at least two IRB members chosen on the basis of expertise with the particular subject matter of the study. These individuals will serve as the primary reviewers and will be responsible for presenting the protocol to the convened IRB for discussion.

The IRB must deliberate on all studies classified as greater than minimal risk for the purpose of assigning the frequency of continuing review reports. The IRB may decide to review greater than minimal risk studies more frequently than every twelve months.

❖ Type of IRB Review For New Protocols

There are three categories of review:

Exempt Review	Expedited Review	Full Review
<p>Some research is exempt from IRB review. Examples of this category are listed in 45 CFR 46.101.</p> <p>NOTE: Exempt research must be still be submitted to the IRB through ARIA for classification as Exempt by the IRB Chair.</p>	<p>The proposed research is defined as minimal risk and falls within one of the OHRP approved expedited categories.</p> <p>Review by the fully convened IRB is not necessary.</p> <p>Approval may be given by the IRB Chair and reported to the next convened IRB meeting.</p>	<p>Research involves issues that do not qualify for exempt or expedited review.</p> <p>The research is reviewed by 2 primary reviewers who present their findings to a fully convened IRB for discussion and vote.</p>

▪ Exempt Review

Under the Health and Human Services (HHS) regulations [45 CFR 46.101(b)], some research is exempt from meeting the requirements set forth in the regulations. Studies that are classified as “exempt” do not require full review by the IRB. These studies must still be submitted to the IRB through ARIA for classification as exempt. **These exemptions do not apply to any activity classified as greater than minimal risk or research involving prisoners, children, fetuses, pregnant women, or human in vitro fertilization** (See Research Involving Vulnerable Populations). Further, the exemption for certain research involving surveys or interview does not apply to research involving children. No research involving FDA regulated products is exempt under FDA regulations.

Consent forms are usually not required for exempt studies. The extent of the Consent Process will be determined by the IRB. Information sheets and/or verbal consent should generally be utilized for studies interacting with human subjects. These should be submitted in ARIA with the study.

If the IRB Chair agrees that the study is "exempt," the investigator will receive a letter confirming the exemption. If the study does not qualify as "exempt", if the issue is not clear,

or if any of the required approvals are missing, the investigator will be notified in writing as to what is required.

How To Apply For Exemption

Research that falls into any of the six categories listed below from 45 CFR 46.101 should be submitted in ARIA.

The IRB, NOT the Investigator, determines if a study may be considered in the exempt category.

Categories of Exemption From IRB Review (Per 45 CFR 46.101)

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
 - Research on regular and special education instructional strategies
 - Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subject
 - Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under the above, if:
 - The human subjects are elected or appointed public officials or candidates for public office.
 - Federal statute(s) require(s) without exception that the confidentiality of personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of Department of Health and Human Services, Federal Agency heads, and which are designed to study, evaluate, or otherwise examine:
 - Public benefit or service programs
 - Procedures for obtaining benefits or services under those programs

- Possible changes in or alternatives to those programs or procedures
 - Possible changes in methods or levels of payment for benefits or services under those programs
6. Taste and food quality evaluation and consumer acceptance studies, if:
- Wholesome foods without additives are consumed, or
 - A food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below a level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Any research plan that involves both exempt and non-exempt research activities must be reviewed by the IRB.

▪ **Expedited Review (Per 45 CFR 46.110)**

Some types of research do not necessitate review by the convened IRB. These types of studies may be approved by the IRB Chair and reported to the convened IRB at its next meeting. Decisions reached at the convened meetings may supercede any decisions made through the expedited review.

An investigator may apply for expedited review, or the IRB Chair may determine that the study is eligible for expedited review if it meets the regulatory criteria. If the IRB Chair determines that the project submitted for expedited review requires full committee review, the investigator will be notified in writing.

The IRB, NOT the Investigator, determines if a study may be considered in the Expedited Review category.

How To Apply For Expedited Review

- Investigator applies for expedited study status with the IRB through ARIA
 - Protocols submitted for expedited review **must** include all materials required for full review.
 - Research must be minimal or no risk.
- Committee Chair may determine a study is eligible for expedited review status
 - Committee Chair (or designee) conducts the review.
- Investigator notified if the project does not meet criteria and needs full review.

If the proposed research is minimal risk and is of a type that falls into one of the nine categories listed below (and published in the Federal Register by DHHS and FDA), the Chair may review and approve the research (expedited review).

There are nine categories of research that may be eligible for expedited review. The categories apply regardless of the age of subjects, except as noted. They are as follows:

Categories of Expedited Review

1. Clinical studies of drugs and medical devices only when one of the following conditions is met.
 - Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling
2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows:
 - From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 mL in an 8 week period and collection may not occur more frequently than 2 times *per week*.
 - From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 mL or 3 mL *per kg* in an 8 week period and collection may not occur more frequently than 2 times *per week*. (See Guidelines for Blood Draws in Pediatric and Adult Populations, Appendix R).
3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
 - Hair and nail clippings in a non-disfiguring manner.
 - Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
 - Permanent teeth if routine patient care indicates a need for extraction.
 - Excreta and external secretions (including sweat).
 - Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue.
 - Placenta removed at delivery.
 - Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

- Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
 - Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
 - Sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications. Examples:
 - Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy
 - Weighing or testing sensory acuity
 - Magnetic resonance imaging
 - Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity
 - Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where weight and health of the individual are appropriate
 5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
 6. Collection of data from voice, video, digital, or image recordings made for research purposes.
 7. Research on individual or group characteristics or behavior (including, but not limited to: research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
 8. Continuing review of research previously approved by the convened IRB as follows:
 - Where research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions and the research remains active only for the long-term follow-up of subjects.
 - Where no subjects have been enrolled and no additional risks have been identified.
 - Where the remaining research activities are limited to data analysis.
 9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight

(8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The nine categories listed above should not be considered to be of minimal risk simply because they are eligible for an expedited review. Inclusion on this list means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involves no more than minimal risk to human subjects.

Expedited Review May Not Be Appropriate In The Following Situations:

- Identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The information gained from the research is considered "classified" by the federal government.

The IRB must uphold the standard requirements for informed consent (or its waiver, alteration, or exception) regardless of the type of review (expedited or convened) used.

▪ **Expedited Review Process For Minor Changes In Research**

The IRB may approve minor revisions to already approved projects through expedited review (*e.g.*, changes of an administrative nature, minor revisions in the text of an informed consent document or advertisement, corrections in the text of documents, and other minor changes). These can only be expedited if the changes do not increase the risks involved.

When performing an expedited review, the reviewer(s) may exercise all of the authorities of the IRB except that they may not disapprove the research. Research may only be disapproved by the convened IRB. IRB Reviewers have access to all information submitted on any project which has received approval or been amended through an expedited review process

Similarly, Adverse Event Reports, that in the judgment of the Chair or an experienced reviewer do not appear to be serious or to be occurring with some frequency and do not appear to affect the degree of risk to subjects, may be reviewed by expedited review. However, all serious adverse event reports submitted by the Investigator will be presented on the agenda at the IRB meetings.

▪ **Full Review**

All applications except those qualifying for exempt or expedited status will be reviewed by the IRB at one of its convened meetings. The IRB utilizes primary review teams in conducting full reviews. A minimum of two reviewers will receive the full study protocol application. All committee members will have access to the IRB application forms,

protocol summary, and informed consent documents. The Primary Reviewers will present the protocol and issues to the convened IRB for discussion before a vote for approval can be cast.

A quorum (51% of the specific committee's voting membership including the chair, who votes only in the case of a tie) of members, including at least one non-scientific member, must be present for voting purposes on each review. After the vote, the investigator will be notified in writing regarding the status of the application.

❖ IRB Review Results

The IRB will review research protocols and approve, disapprove, or require modifications before approval is granted. Investigators are notified in writing concerning all IRB actions.

If the IRB disapproves a study, it will notify the investigator of the reasons for the disapproval, and allow the investigator an opportunity to respond. The investigator may appeal to the IRB to reverse the decision to disapprove a study, but no other authority may approve a study if the IRB disapproves it.

IRB Review results of new protocols fall into the following categories:

- ***Protocol Approved:***
The project and its study tools, including the informed consent documents, are approved as submitted. Once the investigator receives the IRB approval letter, the study may begin.
- ***Protocol Approval Deferred (Major or Minor):***
The project requires revisions. Minor revisions may be reviewed through the expedited process. Major revisions in the project as submitted must be addressed before the IRB can grant approval. Protocols with approval deferred for major deficiencies must be re-reviewed by the convened IRB before final approval is granted.
- ***Protocol Tabled:***
Serious deficiencies in a newly submitted protocol with issues to be addressed by the investigator before the IRB can grant approval. Protocols that are tabled must be resubmitted to the IRB as if submitting the protocol for an initial application.
- ***Protocol Disapproved:***
The project has serious deficiencies affecting the safety and welfare of the projected subject population. Protocols that are disapproved may not be resubmitted to the IRB. The protocol requires major revision of safety issues and a new protocol submission.

Any involvement of human subjects in research may not begin until the approval of the IRB has been received.

❖ Notification Of Investigators Following Review

The IRB office, through ARIA, notifies each investigator of the review of their initial protocol submission, correspondence received by the IRB office, protocol activities reported at the IRB meeting, and continuing review process. The notification should be issued within 14 business days and outline the IRB actions and any further issues which must be addressed by the principal

investigator. Upon receipt of that notification the PI, or designee, should make the required corrections, modifications, or resubmission of a new protocol through ARIA.

All correspondence with the IRB must be submitted in ARIA under the IRB Record number or reference the IRB Record number. Correspondence that does not identify the IRB number may be returned without further action.

❖ **Notification Of Institutional Officials**

The minutes of the IRB meetings reflect summarized discussion of protocol issues and documentation of the vote on each IRB action. Upon request, a copy of the IRB minutes will be sent to the Vice-Chancellor for Academic Affairs and Sponsored Research.

CHAPTER 4

Protocol Submissions

This chapter instructs investigators how to submit new protocols.

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[IRB Protocol Submissions Requirements Using ARIA](#)

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[How To Submit A New Biomedical Study Protocol Using ARIA](#)

❖ **Prior To Submission**

Prior to preparing a research application, investigators should consider the following:

- Does the project involve research, as defined below?
- Will the project involve living human subjects or their identifiable information?

❖ **Definition Of Research**

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalized knowledge, 45 CFR 46.102(d).

❖ **Responsibilities Of The Principal Investigator When Submitting A Study For IRB Approval**

The Principal Investigator (PI) has the responsibility of submitting his/her proposed research for approval prior to accessing any information or to any human subject enrollment. The PI must assure that all persons performing research activities under his/her direction are properly credentialed by the institution to perform the procedures or interventions outlined in the research protocol.

Approval by the IRB does not relieve the PI from the obligation to follow procedures and rules of the institution(s) at which the research is to be undertaken.

Each PI is responsible for providing assurance to the IRB that activity on the approved protocol is continuous. Investigators must also maintain continuous approval from each institution(s) where the research is being conducted. The study must be reviewed and re-approved by IRB not less than one year from the date of study approval. If this continuing review report (CRR) is not approved by the date specified, the study is considered out of compliance and a letter of study suspension will be issued. No subjects may be enrolled until approval of the CRR is obtained from the IRB. If the PI does not respond to subsequent IRB request for continuing review reports, the study will be terminated. Patterns of noncompliance by the investigator can trigger formal inquiries by the IRB.

The validity of the CRR information must be supported in the study records. The PI has the responsibility to monitor study records for completeness, accuracy, authenticity, and validity.

The PI (or his/her formally authorized designee) must sign ALL communication with the IRB. The IRB must approve the alternate or formally authorized signatory. Communication not signed by the appropriate person will be returned.

At the conclusion of any study, the PI must submit a Study Closure form to the IRB through ARIA, including applicable data analysis and long-term follow-up, so that the study can be closed. The final report of study results should be received by the IRB no later than 90 days after the completion of the study. When a protocol is complete **except for** data analysis or long-term follow-up, the PI should indicate the status of the protocol on the CRR so that approval can be expedited. Studies are not to be closed until the investigator has determined that the study is ready to be closed.

The PI is responsible for abiding by the Investigator's Agreement that includes the following items:

- No subjects will be recruited or entered into a protocol until the Investigator has received an approval letter from the IRB.
- No modification of the protocol or consent form will be initiated without prior written approval from the IRB, except when necessary to eliminate immediate hazards to the subjects. Exceptions for immediate hazards must be reported orally to the IRB Chair or Designee immediately.
- The PI will provide a prompt, written report to the IRB regarding any deviation from the protocol and/or consent form, adverse events that are serious, unanticipated and related to the study, or a death occurring during the study.
- Any unexpected serious problems, such as:
 - Psychological, physical, or legal harm/risk.
 - A breach of subject confidentiality such as, stolen or lost laptop computer, loss of research data, protocol deviations, complaints about study procedures, and complaints about research staff.
- Annual status reports for the protocol (CRR) will be completed and returned within the time limit stated on the forms.
- If the study involves any funding or resources from outside sources, the Grants Coordinator in the appropriate Institutional Research Administration Office must be contacted regarding a contract. Subjects cannot be enrolled prior to completion of the contract, unless specified by the institution.
- If the study involves industry sponsored trials at the VA, the PI must contact the Biomedical Research Foundation
- Informed consent will be obtained from all subjects using the method approved by the IRB for the research protocol.
- The IRB office will be notified within 30 days of a change in the PI.
- The PI will sign *via* ARIA a statement regarding the protection of human subjects and vulnerable populations.

Failure to abide by the approved research plan can lead to suspension or termination of studies or to suspension of the PI's research privileges by the IRB.

❖ Planning The IRB Submission

▪ Mandatory Education

As of January 31, 2004, all research staff involved with human subject studies must have completed the on-line Human Subject Training (HST) course and the on-line HIPAA for Research course.

Two different on-line HST courses are offered: the Biomedical Course on Human Subject Protection Training and the Behavioral and Social Science Course on Human Subject Protection Training. Only one HST course is required, and the research staff should select the one most appropriate to the type of research in which they will be involved.

The Biomedical Course is appropriate for persons whose research involves drugs, devices, and surgical/ invasive procedures. The Behavioral and Social Science course is relevant to those disciplines and is not appropriate for investigators whose research involves drugs, devices or surgical/invasive procedures. Both courses integrate UAMS IRB requirements.

All three of these on-line courses are found by selecting the Training button on the Office of Research Compliance website at www.uams.edu/orc. Then select "Online Course Registration". You will be asked to type in some demographic information. This will register you for the appropriate courses through WebCT.

The HIPAA for Research course is in addition to any general HIPAA course that may be required by an Institution for all of its employees.

▪ Study Design

Investigators should understand that the human research must be conducted using a research plan or "protocol" that has been submitted and approved by the IRB. All changes in the protocol must be approved by the IRB before implementing, unless the change is urgently required for the subject's safety. The PI must contact the IRB Chair immediately if such urgent safety conditions will alter the protocol or consent.

Investigators must submit a clinical research protocol detailing all aspects of the proposed human studies. This document is distinctly different than the grant application for funding the proposed project in that it provides the IRB with details of how all phases of the human studies will be conducted. Investigators must also submit the research portion of any grant proposal for which IRB approval is sought, however the IRB does not accept a grant proposal in lieu of a detailed description of how all human studies are to be accomplished.

Plans for human research should reflect appropriate consideration on the part of the Investigator of all aspects of the proposed research. Specifically, the questions that the PI

proposes to answer and the precise methodology needed to obtain those answers must be included in the research plan.

- **Designating The Principal Investigator**

A research project is headed by a principal investigator (PI). The PI leads the research team, directs the project, and bears ultimate responsibility for its conduct.

The IRB must ensure that the PI has the requisite training and experience that the project requires. Documented HST and HIPAA for Research training is required of the PI, investigators and the research team.

Whenever there is a change in the PI or in the PI's status that affects the project, the IRB must be notified.

- **Sub-investigators**

If the study requires collaboration from another area, a sub-investigator from that area can be designated. The sub-investigator should be consulted and familiarized with his/her responsibilities. A copy of the sub-investigator's curriculum vitae or resume and license (if appropriate) should be included in the study submission. If an FDA form 1572 is required for the study, it must be kept updated if there is a change in sub-investigators

Cooperative groups, such as COG (Children's Oncology Group) or SWOG (Southwest Oncology Group) does not allow non-members, including residents and students, to conduct research.

- **Student Conducted Research**

All activities that meet the definition of research with human subjects and that are conducted by students for a class project or for work toward a degree must be reviewed by the IRB. Resident physicians are considered students. For example, activities that must be reviewed and approved by the IRB include:

- a. All master's theses and doctoral dissertations that involve human subjects or their data; and
- b. All projects that involve human subjects or their data and for which findings may be published or otherwise disseminated.
- c. **Oversight by Faculty/Advisor.** All students/fellows residents in UAMS applying as PI on a study for IRB review must list their faculty advisor as a co-investigator. The faculty member should be listed as PI if there is contemplation of continuing the student's work following their matriculation.

- **Specifying The Number Of Research Subjects**

The IRB is required to protect subjects from the first contact for possible recruitment. All subjects who go through the recruitment process even if they fail or decline participation screening must be accounted for. Thus, total accrual is the number of subjects screened plus those enrolled in the study. Initial requests for subject accrual should be large enough to reflect accurate accrual.

Enrolled Subjects are subjects defined as those who met eligibility criteria and gave informed consent to participate in the larger study.

The application must specify the number of study subjects to be accrued (recruited and enrolled), grouped by age, gender, and population diversity. Exceeding the accrual limits approved by the IRB is a violation of the protocol. The IRB must give prior written approval for any increase in subject accrual.

Multi-center studies, in which data will be pooled and recruitment may vary, present a special problem for investigators. The application should provide information about the total picture, including both the number of subjects to be studied locally and the number studied at all sites.

- **Women And Minorities In Study Populations**

The study plan should be designed so that research benefits and burdens are fairly distributed. If an individual or group is denied access to a clinical trial that might be beneficial or if some people are singled out to bear the burden of risks associated with a study, the requirement for fairness is not met.

In accordance with the policies of the National Institutes of Health, the IRB requires researchers applying for federal funds to give breakdowns of their subject populations by gender and minority group. Studies with the potential to address issues relevant to both sexes must recruit both genders, and minority populations should be included in a study population wherever feasible. Researchers must justify the exclusion of any group of individuals. The IRB may make exceptions if there is adequate scientific justification for exclusion, such as when a disease predominates in one gender or the focus of the research question is on a specific group.

- **Students As Research Subjects**

When students are to be accrued for research, consent must state that students are allowed to refuse participation or withdraw early from a study without affecting their academic standing at UAMS. Prohibiting all student participation in research, however, may be an overprotective reaction. An alternative way to protect against coercion is to require that faculty-investigators advertise for subjects generally (*e.g.*, through notices posted in the school or department) rather than recruit individual students directly. As with any research involving a potentially vulnerable subject population, the IRB will pay special attention to the potential for coercion or undue influence and consider ways in which the possibility of exploitation can be reduced or eliminated.

Confidentiality is a concern raised by the involvement of students as subjects in research. The IRB will consider that research involving the collection of data on sensitive subjects such as mental health, sexual activity, or the use of illicit drugs or alcohol presents risks to subjects of which they

should be made aware and from which they should be protected, to the greatest extent possible. The close environment of the university amplifies this problem.

For more information, see Chapter 12, [Research Involving Vulnerable Populations](#) and IRB Policy 17.10 (Students, Employees and Healthy Volunteers).

▪ **Employees As Research Subjects**

The issues with respect to employees as research subjects are essentially identical to those involving students as research subjects: coercion or undue influence, and confidentiality. Employee research programs raise the possibility that the decision will affect performance evaluations or job advancement. Maintaining the confidentiality of personal medical information or research data when the subjects are also employees, particularly when the employer is also a medical institution [Meyers (1979)] is difficult. For issues regarding compensation each affiliated institution may have policies that apply. The investigator is responsible for following those policies.

For more information, see Chapter 12, [Research Involving Vulnerable Populations](#) and IRB Policy 17.10 (Students, Employees and Healthy Volunteers).

❖ **Research Informed Consent**

The research informed consent should be written according to federal regulations and IRB requirements and should be consistent with study protocols. All informed consent documents must be approved by the IRB. For more information on the Informed Consent process, see [Chapter 5, Informed Consent](#).

❖ **HIPAA**

According to the UAMS Administrative Guide, the scope of the HIPAA Research Policy (Research alone OR combined with treatment) applies to all UAMS physicians, faculty, employees and students performing research on human subjects (living or deceased), or conducting review of Protected Health Information (PHI) preparatory to research. For research conducted in a non-UAMS physical location, such as Arkansas Children's Hospital, the policies of that institution will apply.

UAMS policy is to protect the privacy and confidentiality of medical records and information contained in the medical records of persons who are subjects of UAMS Research projects, including any and all Protected Health Information as defined by the HIPAA Privacy Regulations. Protected Health Information of a Research subject, and the use or disclosure of such information, shall be governed by the UAMS Research policy and any other applicable UAMS policies.

This HIPAA Research Policy does not replace the legal requirements or UAMS policies concerning compliance with the Common Rule, FDA regulations, or other applicable laws.

❖ **Approval Bodies And Committees**

Approval or clearance from various bodies located in all of the institutions where the research will occur is required prior to beginning your study. Ideally, the investigator will present appropriate letters of approval with the protocol submission to the IRB for review. If gaining institutional

committee letters cause a significant delay, the investigator may submit copies of his letters requesting approval with the submission to the IRB.

If you plan to conduct your study at more than one institution that uses the UAMS IRB as its IRB of record, an approval letter or a copy of the application letter for each institution's appropriate committee (i.e., VA R&D, PRMC, radiation safety, biosafety, etc.) will be required prior to starting your research project. The PI remains responsible for ensuring that all of the appropriate committee approvals are in place prior to conducting the research. **Do not start any research until all approval letters have been received.**

A contact list for these committees and other resources at the various institutions covered by the IRB is listed in the *Resource List of Committees and Institutional Contacts*.

- **ACH/ACHRI**

Research at Arkansas Children's Hospital requires approval by the Arkansas Children's Hospital's Research Institute (ACHRI). For more information, contact the Legal and Human Protections Administrator, at 501-364-3571.

- **Ionizing Radiation**

If the study includes ionizing radiation, it is the investigator's responsibility to obtain approval from the Radiation Safety Committee in each institution where the research will be performed if approval is required. For more information on the UAMS Radiation Safety Committee, contact the Radiation Safety Officer at 501-686-5299 or visit the [UAMS Radiation Safety Committee website](#).

Example:

You plan to conduct a pulmonary study involving frequent chest x-rays and computerized tomography (CT) scans on subjects admitted to the VA and UAMS hospitals. An approval letter from or letter of application to each institution's radiation safety committee will be required with your submission to the IRB.

- **Oncology Research**

If the study involves oncology, the protocol may need to be submitted to the ACRC Protocol Review and Monitoring Committee (PRMC). This applies to both UAMS and CAVHS oncology protocols. The PRMC reviews all cancer protocols conducted under the auspices of the Arkansas Cancer Research Center for scientific merit, subject availability, and available resources. The PI is responsible for submitting oncology protocols to the PRMC for approval in addition to IRB approval. Clinical protocols that are NOT cancer-related, but have an ACRC member as a principal investigator do not require PRMC approval.

- **Recombinant DNA and/or biohazardous protocols**

Projects that require UAMS Biosafety Committee (IBC) approval before protocol submission to IRB include:

- Protocols involving NIH/CDC designated “select agents.”
- Experimentation using BL2 or BL3 infectious microorganisms
- Experimentation using carcinogenic (known or suspected) or highly toxic compounds.
- Recombinant DNA, if BL2 or BL3 organisms are involved or if genetic modification might increase pathogenicity, transmissibility, host range, or antibiotic resistance of a pathogen.
- The transfer of toxin genes lethal for vertebrates at an LD50 <100ng/kg.
- Modification of the germ-line genes of animals (transgenic)
- Human gene therapies even if recombinant DNA is produced elsewhere.

The UAMS Biosafety Committee completes its review of protocols as soon as possible after they are received. If the proposal involves the CAVHS, contact the VA research Office to submit to the VA Research Safety Committee. A list of contact numbers for the institutional subcommittees can be found in the [Resource List of Committees and Institutional Contacts](#).

- **General Clinical Research Center (GCRC)**

The GCRC is a National Institutes of Health (NIH) funded grant primarily intended to leverage federal funding for investigator-initiated, human-based research and serves the research communities of UAMS, CAVHS and ACH. The GCRC provides investigators with specialized research space, dedicated research nursing support, dietary consultation and metabolic kitchen, biostatistical support, informatics consultation, design and maintenance, and specialized core laboratories.

Protocols are reviewed by the GCRC Advisory Committee (GAC) and must be received by the second Friday of each month for review on the first Friday of each subsequent month. In addition to GAC approval, each protocol must gain both IRB approval and VA R&D Committee approval prior to initiation on the GCRC. For more information, please access the GCRC web site at www.uams.edu/gcrc or call 501-257-5890.

- **Grants and Funding Sources**

Studies done at UAMS must be submitted to the Office of Research and Sponsored Programs (ORSP). Studies conducted at CAVHS must also be submitted to the Biomedical Research Foundation. At ACH, the studies are to be submitted to the Arkansas Children’s Hospital Research Institute. Funds are usually not released until IRB approval and institutional approval is obtained.

If a research study is grant initiated, it has to be first sent to the respective Research and Sponsored Programs Office. Grants cannot be awarded until all approval letters are submitted. For example, if a research study is funded by a NIH grant, the PI has to submit

the study to the NIH first then submit it to the IRB. These submissions can occur simultaneously.

- **Pharmacy**

If the proposed research involves the use of a pharmaceutical, the pharmacy in each institution where the research will take place must be consulted. ACH, CAVHS, and UAMS all have policies requiring dispensing of all investigational drugs through their pharmacies. All pharmacies require Cost Impact Information forms to be completed.

The receipt, storage, and dispensing of drug will be overseen by each institution's pharmacy. Each pharmacy requires information about the protocol and a copy of each subject's informed consent documents. A list of Pharmacy Contacts is located in the [Resource List of Committees and Institutional Contacts](#).

- **VA R & D Committee**

Research at Central Arkansas Veterans Healthcare System (CAVHS) requires approval by the VA Research and Development Committee (VA R&D). If you answer 'yes' to any of the following four statements, your study must be approved by the VA R&D before the study can begin: (1) Principal Investigator receives any salary from the VA; (2) the study involves VA patients; (3) the study is funded by the VA; or (4) the study involves VA property (this includes a scenario in which the PI has office space on VA property). You will find submission instructions at www.lrvr-research.uams.edu. Additionally you may contact the Administrative Office for Research at 501-257-4816.

You may submit proposals simultaneously to the IRB and VA R&D. The VA R&D may approve a proposal 'pending IRB approval'. In these situations, once confirmation of IRB approval is received, the VA R&D will complete the 'final approval letter'.

Investigators conducting protocols with human subjects at CAVHS must complete training in the mandatory instruction on human subject protections. Instructions for this training are found on the website indicated above.

- ❖ **Using Investigational New Drugs**

For information on using investigational new drugs in research studies, see [Chapter 11, Investigational Drugs and Medical Devices](#).

- ❖ **Using Investigational New Devices**

For information on using investigational new devices in research studies, see [Chapter 11, Investigational Drugs and Medical Devices](#).

- ❖ **Advertising For Subject Recruitment**

Studies may require the use of print, television, Internet or radio advertisement in order to accrue the subject population. Advertisements used for recruitment of subjects to participate in research protocols must be submitted to and approved by the IRB prior to use. Any type of advertising for

research subjects that is intended to be seen or heard by possible subjects is considered to be part of subject selection process. The IRB must review both the information contained in the advertisement and the mode of its communications.

Information placed on a website for the purposes of study recruitment must receive prior approval from the IRB.

Advertisements should not be coercive and should not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to potential participants but would also be a violation of the FDA regulations concerning the promotion of investigational drugs and investigational devices.

Advertising should not use the terms “New Treatment,” “New Medication,” or “New Drug” but rather the term “Investigational.”

Advertisements should not promise “free medical treatment,” when the intent is only to say participants will not be charged for taking part in the investigation. The IRB will determine if the promise of treatment without charge is coercive to financially constrained participants.

Advertisement may state that participants will be paid, but should not emphasize the payment or the amount to be paid.

Advertisements must include

- The name and address of clinical investigator and/or research facility
- The condition under study and/or the purpose of the research
- In summary form, the criteria that will be used to determine eligibility for the study
- A brief list of participation benefits, if any (*e.g.*, a no cost health examination)
- The time or other commitment required of the participants
- The location of the research and the person or office to contact for further information.

❖ Collaborating With Other Institutions

Collaboration with other institutions may be conducted at various levels. The IRB should be notified of the level of collaboration in order to ensure appropriate procedures are instituted.

If Institutional Review Board (IRB) review is required at each collaborating institution, there are options to providing required review as *per* Federal regulations. If the collaborating institution has a federally approved IRB, that IRB will review the study unless they request that the UAMS IRB be the IRB of record. If a collaborating institution chooses for the UAMS IRB to be their IRB of record, additional agreements must be entered into between the two institutions.

If a research project at UAMS is to be carried out in conjunction with another institution or entity and the UAMS IRB will be responsible for the review of the project, the IRB incurs certain aspects of liability that require additional information from the investigator. An IRB

Authorization Agreement and a Federalwide Assurance (FWA) may also be necessary from the cooperating institution. A FWA is a document which formalizes an institution's commitment to protect human subjects and is required by any institution that participates in Federally supported human subject research. The UAMS Investigator should provide the UAMS IRB office contact information for the person at the collaborating institution with whom UAMS can work with to ensure that the appropriate agreements are in place for the collaborative research project.

The local IRB must approve all research studies conducted by CAVHS participants through the CAVHS Cooperative Studies program with other VA hospitals across the country.

Once all committee approvals (or submissions), grants and budgets information (this does not need to be finalized, just in process if applicable), and appropriate education certification has been documented, the PI can assemble the documents required for IRB review. While planning for the IRB review, it is a good time to prepare your submissions for the other institutional research bodies where the trial will be conducted

❖ Application Forms and Original Signatures

For information on submitting a new protocol, please see the following sections: [How To Submit A New Behavioral Study Protocol Using ARIA](#) and [How to Submit A New Biomedical Study Protocol Using ARIA](#).

The PI (or his/her formally authorized designee) must sign ALL communication with the IRB. The IRB must approve the alternate or formally authorized signatory. Communication not signed by the appropriate person will be returned.

❖ IRB Protocol Submissions Requirements Using ARIA

The PI must submit their entire protocol to the IRB for review using ARIA (Automated Research Information Administrator).

For assistance with obtaining an ARIA username and password or for assistance with submitting protocol using ARIA, please contact the IRB office at 501-686-5667.

The documents required for IRB Protocol Submissions have to be uploaded in ARIA or you **CANNOT** submit. All documents need to be in a PDF Format. If you will be submitting protocols, you will need to purchase a copy of the software Adobe Acrobat.

NOTE: The latest copies of Adobe Acrobat and Adobe Approval are now available through UAMS IT Procurement for UAMS tagged PCs. To obtain more information or a copy of the software, please contact the Help Desk at (501) 686-8555.

Information from the following documents is needed for Protocol Submissions *via* ARIA.

- HIPAA Authorization forms or Request a Waiver of HIPAA Authorization
- A copy of the consent form (see consent form directions in Appendix I).
- A complete protocol containing details of the proposed research project, including:
 - Study background including scientific rationale and aims
 - Methods
 - A list of all procedures which are experimental
 - Anticipated risks and benefits to subjects and procedures to minimize risks
 - A discussion of human subject protection issues and methods
 - Number of subjects
 - Additional safeguards for the protection of vulnerable subject populations
 - Applicable confidentiality issues
 - Data analysis method
 - References
- A copy of the investigational drug or device brochure (from the sponsor) if the protocol requires the use of an investigational drug or device.
- A copy of the study Standard Operating Procedures (SOPs) if used in conducting the study.
- If the study is being done at the CAVHS, a copy of the VA forms you plan to submit there.
- If the study is being done at ACH, the review of protocol letter from Arkansas Children's Hospital Research Institute (ACHRI).
- A copy of any survey or questionnaire to be used in the research.
- A copy of any advertisement to be used for subject recruitment.
- A simplified CV of the PI.
- Letters from appropriate committees, (*i.e.* Radiation Safety, PRMC, Biosafety Committees).
- If the study is funded by a grant, a copy of the **entire** grant application is required.

❖ How To Submit A New Behavioral Study Protocol Using ARIA

1. Access the ARIA web site <https://aria.uams.edu/default.lasso>

2. Select PI LOGIN.
3. Enter your Username and Password.
4. Click on the Login button.
5. The “Welcome To ARIA” page appears.
6. Select Profile and edit the information if needed.
7. Click the Continue button to return to the main menu.
8. Select New Submission.
9. Select a Protocol Type:
Is this a Behavioral, or Biomedical Study?
10. Select Behavioral.
11. Click the Continue button.
Complete the following steps by providing the requested information:
12. Contact Information.
13. Type of IRB Submission.
14. General Protocol Information.
15. Study Type (Check all that apply).
16. Special or Vulnerable Populations represented in Protocol (Check all that apply).
17. Informed Consent.
18. HIPAA Information.
19. Protocol Design and Subject Specifications.
20. Significant Financial Interest Disclosure.
21. Click the Continue Button.
22. General Personnel Information.
23. Funding Information.
24. Institutions and/or Facilities Used in this Research.
25. Click the Continue Button.
26. Add New Document.
27. Type in Title of Document.
28. Type in Version 1.
29. Date.
30. Click the Add Document button.
31. Click the Add File button.
32. Select File.
33. Click the Browse button to find file on your computer.

34. Click the Upload File button.
35. Is this document acceptable? Yes or no
36. Click Yes.
37. Add documents that are needed for this New Submission.
38. When you are finished adding documents, click the Cancel button at the bottom of the document page.
39. Click the Continue button.
40. Read the Investigator's Agreement.
41. Click on the "I AGREE" button. It becomes an electronic signature.

You will receive an email acknowledgement that the IRB has received the online submission form. For assistance with ARIA, you can access the [Tutorial Guide for ARIA Web Information System](#)

❖ **How To Submit A New Biomedical Study Protocol Using ARIA**

1. Access the ARIA web site at <https://aria.uams.edu/default.lasso>
2. Select PI LOGIN.
3. Enter your Username and Password.
4. Click on the Login button.
5. The Welcome Page appears.
6. Review your profile and edit if needed.
7. Select New Submission.
8. Select a Protocol Type
Is this a Behavioral, or Biomedical Study?
9. Select Biomedical.
10. Click on the Continue button.

Complete the following steps by providing the requested information:

General Protocol Information (Step 1 of 11)

- Title
- Type of IRB Submission
- General Information
- Study Type
- Special or Vulnerable Populations
- Consent
- Hit the Enter button
- Key in HIPAA information

General Personnel Information (Step 2 of 11)

- Personnel
- Primary Contact Information

Institutions/Facilities Used in this Research (Step 3 of 11)

- Locations

Funding Sources (Step 4 of 11)

- Funding

Drugs, Devices, and Procedures (Step 5 of 11)

- Drugs

Drugs, Devices, and Procedures (Step 6 of 11)

- Investigational Devices
- Approved Devices for Unapproved Use
- Approved Devices for Approved Use

Drugs, Devices, and Procedures (Step 7 of 11)

- Surgical or Invasive Procedures

Risks (Step 8 of 11)

- Laboratory Considerations
- Radiation Safety
- Oncology Research
- Genetic Testing Confidentiality Considerations
- Biosafety Considerations

Protocol Summary and Subject Specifications (Step 9 of 11)

This section documents information about the research design. Please refer to the guide which contains a checklist of information required in the written protocol.

- State the hypothesis, research question or purpose of the proposed research.
- Provide the relevant background pertinent to the research question or purpose including the rationale for the experimental procedure, drug, biologic and/or device (limit your answer to 150 words or less).
- Will you be Advertising for Research Subjects: Yes No
- If yes, indicate the type of advertising and attach a copy of your advertisement for review:
 - Posted Circulars

- Newspaper
- Magazine
- Television
- Radio
- Internet
- Will the subjects be recruited from an emergency room type setting:
Yes No
- Summarize the inclusion/exclusion criteria for the subject population.
- Describe the anticipated benefits to subjects in this research.
- Does the protocol exclude any vulnerable population (children, pregnant women, fetuses, prisoners or cognitively impaired persons that might benefit from the research) Yes No
- If yes, describe the scientific and/or ethical justification for this exclusion below:
- Summarize the protocol methodology (what is to be done to the subjects), including analysis of study data.
- Summarize the risks and side effects (physical, psychological, financial and social) to subjects in this research. List any precautions you are taking to minimize these risks.
- Investigator's assessment of risk category:
 - Adult Risk
 - Pediatric Risk 1 2 3 4
- List any cost/financial remuneration to the subject as a result of participating in this research. N/A
- If the protocol provides compensation to investigators or others for identifying and/or enrolling subjects, is it justified: Yes No N/A

Significant Financial Interest Disclosure

Please Check One

Significant financial interests are defined as interest valued at greater than \$10,000 or an equity ownership of more than 5% held by an investigator and the investigator's spouse or dependent children.

- N/A
- Salary or Other Payment for Services
- Equity Interests
- Intellectual Property Rights

- Other Significant Interest

Research Requires the Use of a Device, Drug, or System that is an Invention of the PI. If you selected a value other than NA, please refer to your institution's requirements for financial disclosure.

Click on the Continue button

Adding documents in ARIA (Step 10 of 11)

The documents must be in a PDF format to be uploaded.

Investigators Agreement (Step 11 of 11)

The PI clicks on the I Agree button and it becomes an electronic signature. The PI will receive an acknowledgement that the IRB has received the online submission form.

For assistance with ARIA, you can access the [Tutorial Guide for ARIA Web Information System](#).

CHAPTER 5

Informed Consent

Since the central requirement for human subjects research is that people participate voluntarily, the informed consent process is one of the most important parts of planning a research proposal. The process must assure that the potential subject understands the study and its risks and benefits and can certify his or her willingness to participate.

[A process - not a form](#)

[Informed Consent Requirements](#)

[Informed Consent And Assent Documents](#)

[Signature/Date Sample](#)

[Exceptions From The standard Informed Consent Procedures](#)

❖ **A Process - Not A Form**

The informed consent process begins with the presentation of the study to the subject and continues until the subject's study participation is completed. Obtaining the signature of the subject on an informed consent document is only one part of the process.

The informed consent process emphasizes that that the subject is volunteering to participate in a research study and has the ability to withdraw from the study at any time without affecting their medical care. The process starts with exchange of information, usually in an interview setting. The setting and the tone of the interview must be non-coercive. A thorough explanation of all the study along with risks and benefits, and alternatives to participation is essential. The individual must be given an opportunity to ask questions and have those questions satisfactorily answered. The subject must be fully informed in order for consent to be truly voluntary. The informed consent document and other materials are used as a guide to this interview which is documented by the signing of the informed consent document along with a note in the permanent record.

Consent forms should include a statement that there may be unknown risks to the fetus if a woman becomes pregnant while participating in a clinical trial.

❖ **Informed Consent Requirements**

No investigator may involve humans as subjects in research unless the investigator has obtained the informed consent of that subject or the subjects' legally authorized representative or a waiver has been granted by the IRB. An investigator will seek informed consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The informed consent document must include the following:

- A clear and concise explanation of the research to be conducted and the procedures to be employed
- Be written in language appropriate for the targeted subject population (e.g.; 8th grade reading level, English and foreign language versions for a multi-cultural study)
- Clear and precise language detailing all potential risks or discomfort and procedures to minimize such risks, duration of participation, and benefits of participation
- A statement defining the right of the subject to withdraw at any time without affecting medical care
- A statement describing alternatives to the proposed research activity, if any exist
- A statement that the data/information will be kept confidential
- A statement of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
- A statement that the subject is fully informed and agrees to participate on a purely voluntary basis

The IRB also requires specific elements to be included in each consent form in order to comply with federal, state and institutional regulations. Use the Investigator's Checklist for Informed Consent in preparing UAMS consent and assent forms prior to IRB submission. This can be found on the UAMS IRB web site (www.UAMS.edu/IRB).

For CAVHS patients, please use the VA Consent Form 10-1086. An interactive version of this form can be found at:

http://pws.prserve.net/vanjhcs_research/forms/VA_form_consent_10-1086.doc

For more information, visit the CAVHS website at [CENTRAL ARKANSAS VETERANS HEALTHCARE SYSTEM \(CAVHS\) web site](#).

❖ Informed Consent And Assent Documents

The informed consent form for an adult must provide signature lines along with dates and time for subject, Principal Investigator (PI), person obtaining consent, and witness. However, the person obtaining consent cannot serve as the witness, although a study team member may serve as the witness. The person serving as the witness is not required to be present during the explanation of the study, but must be present for the signing of the consent document by the subject. The IRB requires the PI's signature on all subject informed consent documents. The PI may designate someone to explain the consent and does not have to be present when the subject signs the consent but must subsequently sign this document signifying acceptance of the responsibility for all aspects of the study with regards to the enrolled subject..

If children from 7-17 years of age are subjects, signature lines with date and time should also be provided for the child's assent and for the parent(s) consent. If the IRB deems the risk of the study in children to be Pediatric Category 3 or 4, space for both parents' signature must be available

The PI must retain the original signed consent form document in the study file and provide a copy to the subject. The PI must retain copies of the completed consent forms for a period of at least three years following termination of the protocol. The IRB may request the PI to maintain a longer storage period for the executed consent form.

Each subject must be given a copy of the signed informed consent document. A copy of the subject's informed consent must be placed in the medical records. Pharmacies at each institution may also require a copy of the signed informed consent and protocol before dispensing study drugs.

Additionally, the **process** of informed consent must be documented by an entry in the subject's permanent or medical records. A progress note should be made that includes:

- The date the subject was entered into the study
- The title of the study
- The name of the principal investigator
- The name of the person obtaining the informed consent
- The subject had an opportunity to ask questions about the research and have those questions answered

- Note: CAVHS has special requirements for documentation and filing of informed consent. The Investigator should consult the VA R & D Standard Operating Procedures for complete information.

❖ **Signature/Date/Time Sample**

_____	_____
Subject	Date/Time
_____	_____
Principal Investigator	Date/Time
_____	_____
Witness	Date/Time
_____	_____
Person Obtaining Consent	Date/Time

The Investigator must retain the original signed consent form document in the study file and provide a copy to the subject.

If a pharmaceutical company commits to payment of any medical expenses resulting from research injury, the investigator must furnish a letter from the pharmaceutical company to the IRB confirming that commitment. The letter should be signed and dated by a duly authorized official of the company. The letter and consent form must state the extent to which the payment of medical expenses, injuries, and other losses will be made and include any conditions for payment (e.g. refusal to pay prior to submission for payment by subject's insurance carrier or other third party). If the company agrees to pay only after claims are submitted to the insurance carrier or other third party, the claim submission will indicate that the injury is the result of an adverse drug reaction as part of an investigational trial.

Each page of the consent form should be numbered and dated. (The date will change with each revision of the consent form.)

❖ **Exceptions From The Standard Informed Consent Procedures**

Emergency Research Protocols Where Prospective Informed Consent is Waived

It is possible to have a protocol involving enrollment of subjects in life-threatening situations when a signed informed consent is not feasible prior to use of an investigational test article. 45 CFR part 46.101(i) and 21CFR 50.24 provide specific requirements that must be met by both the IRB and Investigator who will conduct research in emergency research protocols. Both the Investigator and a second physician not otherwise participating in the clinical investigation must certify *in writing all of the following*:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed Consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject
- Time is not sufficient to obtain consent from the subject’s legal representative
- There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject
- Risks and benefits of the experimental treatment are reasonable in light of what is known about the condition and risks and benefits of other therapies

The IRB must approve a protocol that has requested waiver of consent for emergency research prior to administration of the test article.

Obtaining Informed Consent in Emergency or Compassionate Situations

Patient care situations may arise in which an investigator requires use of a non-approved drug or device in a life-threatening situation with insufficient time to submit a protocol for approval to the IRB or obtain informed consent. Please refer to the “Special Situations” section of the Handbook that elaborates on IRB requirements for these conditions.

Waiver of Written Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent for some or all subjects (45 CFR 46.117c) if it finds that:

- The only record linking the subject to the research would be the consent document, and the principal risk to the subject is the potential harm resulting from a breach of confidentiality. In that event, each subject should be asked if he/she wishes to have documentation linking the subject with the research. The subject’s wishes will govern OR
- The research presents no more than a minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases where the requirement of documentation is waived, the IRB may require that the investigator provide the subject with a written statement regarding the research.

The Investigator may request the IRB’s ruling on waived consent at the time the protocol is submitted.

Waiver of the Requirement to Obtain Prospective Informed Consent From Subjects in Non-Emergency Research

Federal regulations allow the IRB the ability to grant a waiver from the requirement to obtain any consent from research subjects in non-emergency research, but only under specific circumstances and only when the decision is made at a convened meeting.

If an investigator believes neither written nor oral consent can be obtained from *any* subjects without jeopardizing the conduct of the project, arguments to support this position should be articulated in the application. Consent waivers will be discussed during a meeting of the convened IRB.

In order to grant a waiver, the IRB must document that it believes the request meets the following criteria:

- a) The research involves no more than minimal risk to the subjects
- b) The waiver will not adversely affect the rights and welfare of the subjects
- c) The research could not be practicably carried out without the waiver
- d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

CHAPTER 6

Continuing Review

Institutional Review Board review is an ongoing process, not a one-time step. Regular reevaluation ensures that research is conducted responsibly. Even in responsibly conducted studies, a one-time review is inadequate, since risks can really be understood only after research has begun, and since the regulations for human subjects research are constantly being refined as the risks and benefits are better understood. Unexpected developments in a project can raise questions about the conduct of the research, and new findings can raise questions about the project.

[Continuing Review General Information](#)

[IRB Continuing Review Requirements Using ARIA](#)

[IRB Continuing Review Process](#)

[Notification of Investigators Following Continuing Review](#)

[How To View A Letter For Your Protocol](#)

[Continuing Review Summary Information](#)

❖ Continuing Review General Information

All human use protocols approved by the IRB are subject to substantive continuing review. The Office for Human Research Protections (OHRP) and the FDA require periodic

re-evaluation by the IRB of all approved research at intervals appropriate to the study's degree of risk.

Continuing Review must be reviewed AND approved at least every 365 days. There is absolutely **no grace period**. If Continuing Review approval expires, the study is out of compliance. Enrollment must cease and the investigator should immediately contact the IRB regarding the treatment of enrolled subjects.

The IRB may determine that the degree of risk warrants a more frequent review in order to protect human participants from harm. Some protocols can be reviewed on a quarterly or six-month review cycle, but the approval period will never exceed one year.

How Is The Continuing Review Date Determined? DHHS regulations at 45 CFR 46.108(b) and 109(e) require, respectively, that (1) except when an expedited review procedure is used, each IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas; and (2) an IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once *per* year. The IRB should decide the frequency of continuing review for each study protocol necessary to ensure the continued protection of the rights and welfare of research subjects.

For more information on Continuing Review, see [IRB policy 7.6](#).

❖ IRB Continuing Review Requirements Using ARIA

Effective July 2003, Principal Investigators (PI's) must submit their Continuing Reviews to the IRB using ARIA (Automated Research Information Administrator).

The mechanism for starting the continuing review process is through ARIA's on-line continuing review module located at <https://aria.uams.edu/default.lasso>.

For step-by-step instructions on submitting Continuing Reviews, access the [Continuing Review Submission Training Handout for ARIA Web Information System](#).

Each PI needs a username and password to access the ARIA system. For assistance with obtaining an ARIA username and password, please contact the IRB office at 501-686-5667.

The documents required for Continuing Review have to be uploaded in ARIA or you CANNOT submit. All documents need to be in a PDF Format. If you will be submitting protocols and continuing reviews, you will need to purchase a copy of the software Adobe Acrobat.

NOTE: The latest copy of Adobe Acrobat is available through UAMS IT Procurement for UAMS tagged PCs. To obtain more information or a copy of the software, please contact the Help Desk at (501) 686-8555 or the UAMS Bookstore at (501) 686-6160.

❖ IRB Continuing Review Process

At the time of initial review, the convened IRB determines how often research projects should be re-evaluated based on the level of risk. Assessment of level of risk includes physical, psychological, social and economic factors. Federal regulations require IRB Continuing Review approval every 365 days. Most research projects are re-evaluated according to this schedule.

Protocols more likely to be reviewed at least every six months include:

- Protocols found to present greater than minimal risk to vulnerable populations.
- Protocols involving a significant risk device.
- Protocols involving high-risk relative to the disease status.

The Principal Investigator is notified by electronic mail of the continuing review approvals expiration date for continuing review at the time the protocol is initially granted approval. Continuing review reports are required for all active research projects approved by the IRB even if all data analysis has been completed since the last approval unless the study has been closed by the IRB.

The continuing review expiration date may change from year to year. Each time the convened IRB conducts continuing review, the study calendar is reset to the date of the meeting.

Example: A study's continuing review date expires on August 1, 2003. The IRB convened on July 15, 2003 and granted protocol approval. The next continuing review approval will expire on July 15, 2004.

Continuing Review reminder notices are sent via electronic mail to the PI three months before the continuing review expiration date. In addition, another email will be sent two months before the end date alerting PI's to have the CRR submitted four weeks before the end date.

However, the PI remains ultimately responsible for obtaining continuing review, and should not depend solely on IRB notification as a prompt for submitting the Continuing Review Report (CRR) and request for renewal. Investigators are advised to submit Continuing Review Reports at least four weeks prior to expiration to allow sufficient time for processing the report prior to the project's expiration.

It is important to remember that there is no grace period. Continuing Reviews do not lapse – they expire. If Continuing Review Approval expires, study activity should cease and the IRB should be contacted.

The IRB utilizes the primary reviewer system in conducting continuing reviews. A minimum of one reviewer will facilitate the review among the committee members. The primary reviewer and the entire committee has access to a status report on the progress of the research, including:

- The number of subjects accrued.
- A description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research.
- A summary of any recent literature, findings obtaining thus far, amendments or modification to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research

- A copy of the current informed consent document.

The Primary Reviewers will present criteria required for review to the convened IRB with discussion of the protocol before a vote for continuing approval can be made. The IRB will vote separately on each continuing review. The vote will be recorded in the meeting minutes.

Continuing review may be conducted by expedited review only where the study falls into one of the expedited review categories and is minimal risk. Expedited review may also be used for continuing review if a study has been closed to accrual and intervention has been completed, but the investigator is still collecting follow-up data.

Continuing review rulings are as follows:

Protocol Re-approval: Follows review of satisfactory information submitted by investigator regarding an ongoing project.

Protocol Re-approval Deferred (Major or Minor): The information submitted by the investigator regarding an ongoing project is not sufficient for re-approval. Additional information from the investigator is required. Minor revisions may be reviewed through the expedited process. Major revisions in the project as submitted must be addressed by the convened IRB. **This information must be received as requested by the IRB or the study may be out of compliance and the investigator must stop enrollment.**

Protocol Suspended: Suspension follows review of information submitted by investigators regarding an ongoing project that addresses issues of concern or serious problems in risk/benefit analysis. Protocol enrollment and study procedures must stop until additional information can be reviewed by the convened IRB.

IMPORTANT REMINDERS:

Timely submission of continuing review reports (CRR) is the investigator's responsibility and is essential to the continuation of the study.

A copy of all continuing review reports (CRRs) and approval letters should be kept in the Investigator's study regulatory file.

All protocols not approved by the IRB by the project's continuing review expiration date are automatically suspended to subject accrual.

❖ Notification Of Investigators Following Continuing Review

All of the committee's action on the protocol's continuing review submission will be posted on ARIA in the LETTERS section.

Once the PI views the information in the LETTERS section posted on the ARIA website for the protocol, the PI should make the required corrections, clarifications or modifications, and resubmit them to the IRB office via ARIA.

It is the PI's responsibility to keep track of each Continuing Review submission and to check the ARIA website to know the current status of the protocol. Use the following steps to view a letter for your protocol:

❖ How To View A Letter For Your Protocol

- Access the ARIA web site at <https://aria.uams.edu/default.lasso>.
- Select PI LOGIN.
- Select the IRB # of the protocol you wish to view.
- The Protocol Detail screen appears with five options available:
 1. Documents
 2. Letters
 3. Adverse Events
 4. Continuing Reviews
 5. Modifications
- Select option 2, Letters.
- The Letters information appears with the following titles:
 - Status
 - IRB#
 - Message Type
- Click on any of the above titles.
- The letter opens via Internet Explorer and allows you to print from the browser.

❖ Continuing Review Summary Information

For studies where continuing review approval has expired, the IRB will determine on a case-by-case basis if it is appropriate to suspend interactions and/or interventions in currently enrolled studies. A notice is sent to the PI. The study will be terminated 30 days after study suspension notification if no response has been received from the investigator.

If the IRB's review of a project requiring continuing review results in termination, a new IRB application may be required to continue with the research. No new subjects may be enrolled, all ongoing research activities must stop, and subjects currently participating should be notified that the study has been terminated. **The regulations make no provision for any grace period extending the research beyond the date the CR expires.**

Termination notices due to non-compliance with the federal regulations for continuing review will be sent to the PI, the Department Chair, and the Office of the Vice Chancellor for Academic Affairs and Research Administration. The IRB must also notify study sponsors, the FDA and OHRP (if the studies are government funded). If the study is done at CAVHS, the VA Research and Development Committee (VA R&D) along with the Office of Research Compliance (ORC) will be notified of termination.

If a study's continuing review was performed before its approval deadline, but has approval deferred, subject enrollment may continue until the continuing review expiration date has passed. After the continuing review expiration date passes, the study enrollment must be suspended until the research has received final approval.

CHAPTER 7

Amending A Protocol

This section details the steps involving amending a research protocol.

[Protocol Amendments](#)

❖ Protocol Amendments

During the course of a research activity, the sponsor and investigator may decide that elements of the research require modification. If an investigator or sponsor finds it necessary to deviate in any way from an IRB approved protocol, consent forms, or eligibility requirements, an amendment or request in writing to the IRB must be submitted with the changes highlighted. If a change affects the approved consent form, it will be necessary to submit a revised consent with changes highlighted. New consent forms must have the version and date revised. The protocol amendments will be considered by the fully convened IRB.

Changes in the research may not occur until IRB approval of the amendment is received unless there is an immediate threat to the health of the patient. If such a situation were to occur, it would be the PI's responsibility to immediately report the event to the IRB as a protocol deviation and serve notice that an amendment to the protocol will be forthcoming.

Major changes to an existing protocol, such as a change in the aim of the study, or the degree of risk to the subject may require that a new protocol be submitted (usually with a new title) and the old protocol be closed.

After IRB approval of the protocol amendment, a copy of the approval letter should be sent to the sponsor by the investigator. The VA R & D Committee will also require copies of protocol amendment approval for research at CAVHS. A copy of the submission, approval letters, and amendments should be kept in the study's regulatory files.

Any changes or amendments to an already approved protocol must be submitted for review and approval by the IRB prior to initiation unless a serious patient safety issue exists.

CHAPTER 8

Research Record-Keeping And Reporting

This section details the information involving research record-keeping and reporting.

[ARIA Information](#)

[Record-Keeping Responsibilities Of The Principal Investigator](#)

[Investigator's Responsibilities For Test Article Accountability](#)

[Subject Information Regarding Investigational Drugs Or Devices](#)

[Investigator IRB Reporting Responsibilities](#)

[Communicating With Subjects](#)

[Reporting Responsibilities Of The Principal Investigator To The IRB](#)

[Adverse Event Reporting](#)

[How To Report A Death Or Serious Adverse Event](#)

[Reporting Protocol Deviations](#)

[Reporting Protocol Violations](#)

[Reporting Notification Of Pending Audits Or Inquiries](#)

❖ **ARIA Information**

All Serious Adverse Event (SAE) reporting (local, non-local, and death) must be submitted through the Automated Research Information Administrator’s (ARIA) on-line module located at <https://aria.uams.edu>

For more information on SAE reporting, access the [Serious Adverse Event Submission Training Handout For ARIA Web Information System](#).

For assistance with obtaining an ARIA username and password, please contact the [IRB](#) Office at 501-686-5667.

❖ **Record-Keeping Responsibilities Of The Principal Investigator (PI)**

Proper record keeping is integral to the validity and reliability of data collected during research trials. It is the PI’s responsibility to oversee the general organization and design of study records, both paper and electronic, and assure that all records are authentic. All data recorded on study recording forms and procedures performed should be supported by documents filed in the study file. Each study involving human subjects must have a log listing those enrolled and those who were approached to enter the study with identifying information. Identifying information can be encrypted.

The PI is also responsible for the proper organization of regulatory documents: such as protocols, protocol amendments, IRB submissions, CRR and approval letters, reports to all appropriate entities on adverse events, deaths, protocol violations and deviations.

Each study should have the following general records:

Regulatory	Individual Subject Files
Subject Log	Original signed informed consent form
Copies of all IRB correspondence	Copies of study recording forms (CRFs)
Approved Protocol	Subject medical record number and emergency contact information
Approved Consent Form	Supporting Documentation for: *
IRB Approval Letters	Inclusion/Exclusion criteria
Other Institutional approvals	Results of tests or procedures
Continuing review reports	Adverse events
Investigator’s Brochure	Deaths
Correspondence with sponsors	Communications with subject and follow up exams
Special Committee approvals	Protocol Violations
Study Standard Operating Procedures	Protocol Deviations
Sample questionnaires	

<p>Sample study forms with instructions</p> <p>Reports of deaths, protocol violations, protocol deviations and serious adverse events.</p> <p>Regulatory</p> <p>Drug Accountability Records</p> <p>Drug/Equipment Shipping Receipts</p> <p>Data Safety Monitoring Reports (if applicable)</p>	<p>Individual Subject Files</p> <p>* Completed study recording forms are not considered supporting documentation. Additional records are needed.</p> <p>Example A lab value recorded on a study form must be supported by a clinical laboratory report of that test.</p>
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These records and any other that assists in collection of data must be consistently maintained. The PI may delegate elements of record keeping activities, but remains responsible for accuracy, authenticity, validity and completeness of all study records. Investigators should consult each specific protocol for the length of time that study records should be maintained.

If the study is being carried out at Central Arkansas Veterans Healthcare System (CAVHS), the Investigator has additional record keeping responsibilities. A complete list can be obtained from the VA Research and Development (R & D) Committee. For more information regarding VA submissions, contact the CAVHS Administrative Office at 501-257-4816.

❖ Investigator's Responsibilities For Test Article Accountability

A pharmaceutical product, device or any other investigational product must be received, maintained, stored, inventoried and accounted for by the investigator according to Federal Guidelines. The investigator is responsible for the control and documentation of all test articles. **If investigational drugs are involved in a study, shipment from the sponsor must be coordinated through the institution's pharmacy.** Sponsors may ship investigational drugs directly to a subject only in very rare circumstances. It is also against federal law for anyone **other than the sponsor** to send investigational drugs or devices to an investigator. Arrangements with the pharmacy for the receipt of all investigational drugs should be completed prior to submitting the protocol for approval.

Example: You are new to the institution and plan to continue your study of implantable catheters. The protocol has received IRB approval. You must receive a new batch of catheters from the sponsor. You cannot obtain them from your previous workplace.

The investigator must assure the maintenance of a drug or device record that is current and includes the following:

- Date of delivery and shipping Invoice including name and address of consignee, type and quantity of drug or device and date of shipment
- Inventory log, with unique code numbers, reflecting use by each subject
- Location and environmental conditions of storage
- Security of storage (tamper-proof)

- Expiration dates, if applicable of drugs and devices
- Records validating that appropriate personnel used the drug or device according to protocol

For Investigational Drugs: Documentation should include the amount of drug that was dispensed, unused by the subject, wasted by the research staff and returned to the pharmaceutical company. Documentation records must also reflect subject identification, the reason for waste or return, and batch or lot numbers of returned materials.

For Investigational Devices: Documentation of the device used, including batch number, lot or identification number, subject identification, patient materials provided, devices returned to company and malfunctioning devices.

The Investigator must assure that test articles are administered or dispensed under his or her personal supervision or the supervision of the appropriate competent personnel. Arkansas State Law requires that only a physician or pharmacist may dispense drugs. An Investigator shall not supply a test article to any other person for administration or to use upon subjects for any other purpose, without the prior authorization of the sponsor [CFR 812.110 (c)].

If the test article is a controlled substance, the Investigator must assure that it is appropriately stored, dispensed and accounted for and take reasonable precautions against the drug's diversion. Controlled substances must be administered only those legally allowed to do so.

Unused test articles must be returned to the sponsor. Documentation of the shipment should be retained with the drug/device record. For studies conducted at the VA, the disposal of unused articles should be done through the pharmacy after a letter of direction sent by the PI.

❖ **Subject Information Regarding Investigational Drugs Or Devices**

The investigator or his designee must explain the correct use of the investigational product to each subject. Subjects should be followed up periodically to assure that they are using the products correctly. Additionally, sponsors often include device product identifiers, including lot numbers. These should be given to the subject. A copy of lot numbers or unique identifiers should be recorded in each subject's medical record. Drug information must be recorded in the subject's drug dispensing log.

❖ **Investigator IRB Reporting Responsibilities**

Communication between the Investigator and the IRB is critical to the Institution's ability to conduct research using human subjects. Timely communications from the PI and appropriate guidance by the IRB and the institution where the research is being performed is necessary for the protection of the subject, the maintenance of research compliance and the elevation of the quality of the research.

❖ **Communicating With Subjects**

Serious adverse events, deaths, changes in protocol and other new information regarding a study may need to be reported to subjects. Letters of this nature must be approved by IRB prior to mailing.

❖ Reporting Responsibilities Of The Principal Investigator To The IRB

The principal investigator is required to notify in writing both the IRB of **ALL** of the following:

INVESTIGATOR MUST REPORT THE FOLLOWING:	TIME FRAME FOR REPORTING THE FOLLOWING:
Serious adverse events	Within 7 days of event
Deaths	Within 3 days, if subject currently in protocol. Otherwise within 60 days of investigator's notification of the death.
Protocol deviations	Immediately, if it represents a significant alteration in the approved protocol and/or if it affects the safety or welfare of the subject. Otherwise, report during continuing review.
Protocol Violations	Immediately, if it represents a significant alteration in the approved protocol and/or if it affects the safety or welfare of the subject. Otherwise, report during continuing review.
Changes in approved research procedures or protocol (amendments)	Prompt notification within 30 days
Noncompliance with conducting of research protocols	Immediately upon discovery of noncompliance
Restrictions, suspension, or termination of study by the sponsor or principal investigator	Within 3 days
Any activity which involves a potential or actual unexpected risk to subjects or others	Within 7 days of activity

❖ Adverse Event Reporting

Your responsibility as a clinical investigator includes the prompt reporting to the IRB of serious adverse events associated with the use of either investigational drugs or devices. The PI should also inform the IRB if the SAE is expected or unexpected. Such adverse events must be reported promptly within seven (7) days while a subject is on a study protocol. A death occurring while a subject is on a study must be reported within three (3) days. A death of a subject that is not protocol related and part of long-term follow up (e.g. following until death on oncology protocols) should be reported within 60 days that the investigator is notified of the death. Reporting to the IRB does not substitute for a principal investigators' responsibility of reporting to a sponsor.

A serious adverse event is any adverse experience occurring at any dose that:

- Results in death.
- Is life-threatening (places the subject at immediate risk of death from the experience as it occurred).

- Results in a persistent or significant disability/incapacity.
- Results in or prolongs an existing in subject hospitalization (even if in the hospitalization is a precautionary measure for observation).
- Is a congenital anomaly/birth defect in offspring of subjects taking the product, regardless of time to diagnosis.
- Represents other significant hazards or potentially serious harm to research subjects or others.

You MUST report any death to the IRB office if:

- Protocol requires reporting of the death to the study sponsor or the FDA.
- The subject was being actively treated on an approved research protocol at the time of death.
- During the course of long-term follow up after completion of the experimental (i.e. active treatment) portion of an approved study protocol, the investigator becomes aware of the death of the research subject.

You do not need to report the death of a subject if:

- The study protocol has been officially closed and a final report has been received and accepted by the IRB.
- The study subject has completed participation in the protocol including long-term data collection (the study remains open).
- The study involves no physical risks to the subjects. This includes any protocol for which only invasion of privacy (data collection) concerns applies, but does not apply if any experimental treatment, procedures, medications, or devices were used. Examples: chart reviews, questionnaires, surveys, and videotaping.
- The experimental portion of the study involved collection of tissue or blood samples without long-term follow up or ongoing collection of additional subject information (i.e. ongoing invasion of privacy concerns), even if the samples are stored for future use and tests are performed at a future date.

❖ How To Report A Death Or Serious Adverse Event

The investigator reports deaths or serious adverse events by completing and submitting the Serious Adverse Event Reporting Form online on ARIA. The PI must also submit all SAE reports (local, non-local, death) online in the report format given and upload the documents at the prompt. In addition, the PI must also include any correspondence sent to the sponsor or FDA regarding the event along with any additional information related to the study. Remember to send a copy of the form and your report to your institution's research committees, e.g. VA Research & Development Committee, ACHRI, etc.

❖ Reporting Protocol Deviations

Protocol Deviations are study events that are not covered under the approved research protocol, which represent a failure to comply with the protocol. *Example: A subject does not have the kidney*

biopsy, which is required six months after beginning transplant medication because she is in the ICU. The PI should report a protocol deviation to the IRB immediately, if it represents a significant alteration in the approved written protocol and/or affects the safety and welfare of the subject. Use the guide in Appendix M for reporting protocol deviations. Note: Protocol deviations are often referred to as “protocol exceptions”. For the purpose of IRB reporting, the two are the same.

❖ **Reporting Protocol Violations**

Protocol Violations are those events clearly occurring outside of the approved research activity, which also represent a failure to comply with the protocol. The terms protocol deviation and protocol violation are similar, although a protocol violation refers to more serious non-compliance, which more often leads to exclusion of subjects from eligibility analysis or their discontinuation from the study.

Example: Enrolling a subject in a cancer study when the subject has no histological or clinically proven cancer is considered a protocol violation when a tissue diagnosis of cancer is a protocol inclusion criterion.

The PI must report protocol violations to the IRB, the sponsor, and all participating institutions. The report must be issued immediately if the health of welfare of the subject was jeopardized. Refer to Appendix M when reporting protocol violations.

❖ **Reporting Notification Of Pending Audits Or Inquiries**

Investigators conducting research involving human subjects are required to report ANY COMMUNICATION from a federal or state department or agency or sponsor that questions the conduct of research or suggests an impending inquiry audit or investigation. The Principal Investigator (PI) MUST inform the IRB and the Office of Research Compliance (ORC) by phone or electronic mail immediately upon notification of inquiry. A formal written notice to the IRB committee that includes a detailed description of the proposed inquiry is required within 3 working days from the notification of the investigator.

For more information, see [IRB Policy 10.2 \(Principal Investigator Reporting Requirements\)](#).

CHAPTER 9

Emergency Situations

This section gives information about emergency use of an investigational drug, biologic, or device.

[Emergency Use of an Investigational Drug or Biologic](#)

[Emergency Use of an Investigational Device](#)

❖ Emergency Use of an Investigational Drug or Biologic

Emergency use is defined in 21 CFR 50.23 as the use of a test article (e.g., investigational drug or biologic) on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

When a situation arises which, in the judgment of a physician, calls for the emergency use of an investigational drug or biologic in a single patient, an IND (Investigational New Drug) number is still necessary. The situation may arise when a patient does not meet the criteria of a study protocol, or where an approved study protocol does not exist. The usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for use (**in this one patient**) under the company's IND. Should the company elect not to name the physician as an investigator, the physician can contact the FDA directly for an IND. The physician will be placed in contact with a FDA physician familiar with the drug or biologic to review the proposed circumstances for use and the information to be submitted in the IND.

The investigator must seek verbal approval from the IRB Chairman and report to the IRB within five working days by letter explaining the circumstances.

The physician's letter to the IRB should include the following information:

- Diagnosis
- Proposed treatment
- Date of treatment
- Drug or device names, if applicable
- Patient's name and age
- Hospital number
- Hospital name
- Date of verbal approval of an IRB chairperson
- A copy of the signed consent form from subject or their legally authorized representative

Only one such Emergency Use should be given per research protocol. The PI is expected to submit a full protocol and informed consent documents for approval within 5 days before any further patients are included in the proposed research. The NIH will not accept patients admitted on emergency use as investigational subjects for a protocol.

For more information, see IRB Policies 15.2 (Consent Exceptions: Emergency Use of a Test Article) and 18.3 (Emergency Use of a Drug or Biologic)

Physicians sometimes decide they must administer a drug, biologic, or experimental agent that has not yet been approved for marketing by the FDA. When a physician must employ experimental medicines to care for a patient in a life-threatening situation, neither the IRB nor the clock nor the calendar should interfere.

The IRB trusts physicians to exercise their best clinical judgment, to use experimental medications when necessary, and subsequently to take the appropriate steps to request approval or inform the IRB.

When emergency medical care must be provided without prior IRB review and approval, the patient may not be considered a research subject. The emergency care may not be claimed as research, nor may the outcome be included in any report of research activity.

❖ **Emergency Use of an Investigational Device**

An unapproved medical device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520g of the Federal Food, Drug, and Cosmetic Act [21USC360(j,g) and 21CFR812;]. Medical devices that have not received marketing clearance under section 510k of the FD&C Act are also considered unapproved devices that require an IDE.

The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

Unapproved Medical Device. An unapproved medical device is a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act [21USC360(e)].

FDA Requirements for Emergency Use of Devices. Each of the following conditions must exist to justify emergency use:

1. The patient is in a life-threatening condition that needs immediate treatment;
2. No generally acceptable alternative for treating the patient is available; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer (Sponsor or Manufacturer) should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the Division of Emergency and Epidemiological Operations (202-857-8400).

FDA expects the physician to follow as many subject protection procedures as possible.

These include:

1. Obtaining an independent assessment by an uninvolved physician;

2. Obtaining informed consent from the patient or a legal representative
3. Notifying institutional officials as specified by institutional policies;
4. Notifying the Institutional Review Board (IRB); and
5. Obtaining authorization from the IDE holder, if an approved IDE for the device exists.

The physician's letter to the IRB should include the following information:

- Diagnosis
- Proposed treatment
- Date of treatment
- Drug or device names, if applicable
- Patient's name and age
- Hospital number
- Hospital name
- Date of verbal approval
- A copy of the signed consent form

After-use Procedures. After an unapproved device is used in an emergency, the physician should:

1. Report to the UAMS IRB within five days [21 CFR56.104(c); 45 CFR] and otherwise comply with provisions of the IRB regulations (21 CFR part 56; 45 CFR 46);
2. Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
3. If an IDE for the use does exist, the physician should notify the sponsor of the emergency use, or if an IDE does not exist, notify the FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results. The physician should also immediately inform the IRB Chair who may refer the matter to the Office of Research Compliance.

The physician should inform the IRB prior to emergency use when possible or as soon as practical thereafter. However, this notification should not be construed as an IRB approval. Notification will be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR56.104c; 45 CFR. 46. The documentation required shall be submitted to the IRB within 5 working days after the use of the test article. (21 CFR 50.23(c).

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that

could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

Exception for Informed Consent during Emergency Use of an unapproved device. Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the requirements of exception for consent in emergency research detailed in section 15.2 of this manual.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician's determination that the four conditions above apply, the physician should make the determination and in within 5 working days after the use of the article, have the determination reviewed and evaluated in writing who is not participating in the clinical investigations. Data from emergency use of a test article should not be used as research.

Procedures during business hours

If the need for emergency use arises during the business day, the procedure to secure a waiver is as follows:

- The physician notifies the IRB office by telephone of a pending request for emergency use.
- The IRB administrative staff refers the physician to the IRB chair, or to a physician designated by the chair, to secure oral approval.
- Within five working days of the request, the physician provides the IRB office with written documentation of the oral approval, a copy of the unsigned consent form used to document informed consent of the subject, and a report of the experience.
- The IRB provides the physician with written confirmation of its approval. This should be maintained with the physician's records.

Many drug companies require IRB certification of approval to release drugs or biologics. The investigator is responsible for the paperwork required by sponsors, drug companies, and the FDA.

Procedures outside of business hours

If the need for emergency use arises when the IRB office is not open, the physician should:

- Secure approval, or agreement, from another physician who is not involved in the treatment of this particular patient,
- Alert the IRB office of the intended use,
- Report the action to the IRB office in writing within five working days.

Please note: Neither the common rule or the FDA regulations provide for expedited IRB approval in emergency situations. Therefore “interim”, “compassionate”, “temporary” or other terms for an expedited approval process are not authorized. The IRB must either convene and give “full board” approval of the emergency use or, if it is not possible to convene a quorum with the time available, the use may proceed without IRB Approval. When this situation exists, the IRB may issue an acknowledgement letter that they have been made aware of the use.

CHAPTER 10

Genetic Research

This section deals with genetic research.

[Genetic Research](#)

❖ Genetic Research

The greatest risk to subjects participating in genetic research is the inappropriate release of personal and private information. Therefore, concerns for how investigators will maintain the confidentiality of the data and specimens collected during the conduct of the study is a primary concern to the IRB.

The protocol and informed consent should address the following points:

- Study information is coded and personal identifiers maintained securely
- Consent forms include information about who will receive the data derived (e.g. the subject, family members, non-participation family members, family physician, other investigators)
- Information as to whether clinically relevant information may be uncovered during the course of the study and whether subjects will be given the opportunity to decline receiving this information
- If children are to be research participants, how will consent be obtained and how will data be handled
- Participants may derive no benefit from participation.
- Study data should not be recorded in the subject's medical record; separate research records with controlled access are preferred.
- Whether there will be any possibility of individually identifying subjects
- Inform subjects of any special risks associated with their participation (e.g. changes in family relationships, risks to privacy, confidentiality, insurability, employability, immigration status, and paternity suits)
- Indicate if general study results will be made available to subjects
- Whether genetic counseling will be made available and who will pay for this counseling
- Length of time in maintaining specimens (limited, indefinitely) and/or discarding specimens
- Subjects' wishes to be re-contacted if clinically relevant information is developed
- If the investigator intends to share specimens acquired during the research with other investigators, this information must be included in the consent form and participants given the choice whether they are willing to permit this or not
- Should there be a potential commercial value derived from the research, the subject must be informed as to whether they will be asked to waive any rights or control over the tissue so used
- If the research involves the manufacture of a drug or biologic that is to be administered as a part of research, the Investigator should follow the 21CFR 210 "Good Manufacturing Practices" if required.

CHAPTER 11

Investigational Drugs and Medical Devices

This section concerns investigational drugs and medical devices.

[Using Investigational New Drugs](#)

[Using Investigational New Devices](#)

[Use Of Medical Devices In Research Studies](#)

[Studies Involving Devices Known To Be Of Significant Risk](#)

[IRB's Role In Distinguishing Between SR and NSR Device Studies](#)

[Investigator's Responsibilities Related To Investigational Devices](#)

[Studies Of Devices With The FDA 510K Designation](#)

[Emergency Use Of Investigational Devices](#)

[Humanitarian Use Devices \(HUD\) Or Custom Devices](#)

[Investigational Devices That May Be Eligible For Exemption](#)

❖ Using investigational new drugs

Researchers who employ a test article classified by the Food and Drug Administration as an investigational new drug must assure the IRB that they are complying with the FDA's IND regulations ([21 CFR 312](#)). The IND number assigned to the test article must be filed with the IRB when the application for review is submitted.

Experimental drugs require an IND number if they are used to develop information about their safety or efficacy.

Approved, marketed drugs may also require an IND, if proposed use is:

- Different from its previously FDA-approved use,
- Administered by an unapproved route or method of delivery, or
- An altered dosage form,
- Shipped by interstate commerce in order to conduct a clinical trial.

The FDA has published several exemptions to the IND requirements. Roughly, a clinical investigation may be exempted from the IND requirements if the drug is lawfully marketed in the U.S. and all the following apply:

- The results will not be reported to the FDA to support a new indication for use nor to support any other significant change in the labeling of the drug;
- The investigation will not be used to support a significant change in the advertising of a prescription drug that is already on the market;
- The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent set forth in Part 50; and
- The investigation is conducted in compliance with the requirements of section 312.7, which concerns the promotion and sale of investigational drugs.

The IRB requires detailed discussion of all these points when an exemption from IND requirements is requested.

❖ Using investigational new devices

Researchers who employ a significant risk device classified by the Food and Drug Administration as an investigational device must assure the IRB that they are complying with the FDA's Investigational Device Exemptions (IDE) regulations ([21 CFR 812](#) or [814](#)). The IDE number assigned to the test article must be filed with the IRB when the application for review is submitted.

❖ Use Of Medical Devices In Research Studies

The IRB considers an investigational device to be one that is not currently marketed in the United States. According to 21 CFR Part 812, two types of device studies exist. These types are “significant risk” (SR) and “nonsignificant risk” (NSR). An SR device is defined as “a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.” An NSR device study is defined as, “one that does not meet the definition for a significant risk study”.

NSR is not to be confused with the term “minimal risk” and studies of this type are not eligible for expedited review.

❖ Studies Involving Devices Known To Be Of Significant Risk (SR)

Devices that are known to be SR require an IDE from the FDA. A list of known SRs can be found in the FDA website www.fda.gov/cdrh/d861.html.

For studies involving SR devices, an IDE and appropriate information concerning the history of the device's use, proposed investigation plan, description of subject selection criteria and monitoring procedures must be included with the submission packet.

❖ IRB's Role In Distinguishing Between SR and NSR Device Studies

The IRB acts as the surrogate of the FDA with respect to the review and approval of NSR studies. If an investigator OR sponsor proposes the use of a device it claims to be NSR, the IRB *may* agree and approve the study. If the IRB grants approval of an NSR device, the study may begin immediately and no IDE will be required.

If the IRB does not agree and believes the device poses significant risk, the study may not begin until both the IRB and the FDA approve the investigation. The IRB will notify the sponsor and investigator of the SR decision. The investigator will be required to obtain an IDE from the FDA. The study, if approved by IRB, will be conducted as a SR device trial.

Information that the IRB must review in making the determination between SR and NSR include the following (which should be provided with the initial protocol submission):

- Reports of prior investigations conducted with the device
- The proposed investigational plan
- Subject selection criteria
- Monitoring procedures planned for the study
- Sponsor's risk assessment and rationale
- Sponsor's statement detailing any other IRBs that have reviewed the proposed study and what determinations were made.

- Sponsor’s statement regarding any assessments of the device’s risk that may have been made by the FDA.

The IRB’s risk determination is based upon the proposed use of a device in an investigation and not the device alone. Factors that must be considered by the IRB when evaluating the risk of a device include:

- The nature of the harm that may result from the device
- Is the potential harm to subject’s life threatening?
- Could the potential harm to subjects result in permanent damage to or impairment of body structure or function?
- Could the use of the device necessitate medical or surgical intervention to prevent damage to body structure or function?
- If the subject must undergo a procedure as a part of the investigation study, e.g., a surgical procedure, the IRB must consider the potential harm from the procedure *in addition to* the potential harm of the device.

The FDA makes the ultimate decision in determining if a device study is SR or NSR. If it does not agree with IRB’s decision that a device study presents an NSR, and IDE application must be submitted to the FDA. Likewise, if a sponsor or investigator requests an IDE from the FDA for a presumed SR device study, but the FDA classifies the study as NSR, the IDE application will be returned and the investigator should resubmit the study to the IRB as an NSR with the returned application.

❖ Investigator’s Responsibilities Related To Investigational Devices

21CFR 812.110 states that investigators may not obtain informed consent for the use of a device without first obtaining IRB and FDA approval. Investigators must assure that the device is placed under their direct supervision and supplied only to persons authorized to receive the device. If there is not a sponsor for an Investigational Device study, the Principal Investigator will be responsible for the internal monitoring and reporting functions of sponsors as listed in 21 CFR part 812. The Investigator is also responsible for the control, disposal and record keeping related to investigational devices. Investigators are also responsible for maintaining the case histories of the subjects involved in investigational device trials. Investigational devices may not be used outside the supervision of the investigator.

❖ Studies Of Devices With The FDA 510 K Designation

FDA regulations allow a manufacturer/sponsor to claim that a new device is substantially equivalent to models that FDA has already approved for marketing. Safety and efficacy testing of 510 K devices, or use of 510K devices in clinical protocols, requires review by the IRB and approval before the study may begin. Application to the IRB should include verification of the device’s 510K status.

❖ **Emergency Use Of Investigational Devices**

If, in the opinion of the investigator, a situation exists where an investigational device is required to protect the life or physical well being of a subject in an emergency, outside of the investigational trial, the investigator should contact the IRB Chairperson and request emergency acknowledgment. Emergency Use of Investigational Devices should be reported in writing to the sponsor and the IRB immediately by the investigator. Ideally, communication with the sponsor and the IRB should occur before any test article is used outside of the research context. If the investigator is the sponsor, he/she is required to notify the FDA of the emergency use within 5-working days of the event.

❖ **Humanitarian Use Devices (HUD) Or Custom Devices**

Investigators who wish to use devices classified by the FDA as Custom or Humanitarian Use should consult the IRB office for guidance before using such a device or submitting a protocol.

❖ **Investigational Devices That May Be Eligible For Exemption**

Some investigational devices are exempt from the FDA regulations. These included certain diagnostic devices, minor modifications of marketed devices or custom devices. *Investigators should request guidance from the IRB if unsure of the device status before use.*

All devices, including those exempt from FDA regulations, require review and approval by the IRB before use in patients or subjects.

CHAPTER 12

Research Involving Vulnerable Populations

Certain groups of human subjects are considered to be particularly vulnerable to coercion or undue influence in a research setting. These groups and their special attention during the research process are outlined in 45 CFR 46.111(b) and 21 CFR 56.111(b). The regulations identify additional requirements for review and approval of research involving fetuses, pregnant women, and human *in vitro* fertilization, 45 CFR 46 Subpart B, prisoners, 45 CFR 46 Subpart C, and children, 45 CFR.46 Subpart D.

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❖ Background Information

The following groups of human subjects are considered Vulnerable Populations:

- Children
- Wards of the State
- Prisoners
- Pregnant Women and Fetuses
- Persons Who Are Mentally Disabled or Otherwise Cognitively Impaired
- Other Potentially Vulnerable Populations:
 - Veterans
 - Minorities
 - Economically or Educationally Disadvantaged Subjects
 - Illiterate English Speaking Subjects
 - Employees as Subjects
 - Students as Subjects
 - Non-English Speaking Subjects
 - Terminally Ill Subjects

In reviewing research projects involving all categories of vulnerable subjects, the IRB must ascertain that their use is adequately justified and that additional safeguards are implemented to minimize risks unique to each group. A summary of the additional requirements for review and approval of research involving children, prisoners, and pregnant women and fetuses is presented below.

❖ Research Involving Children

Federal regulations (Title 45 CFR Part 46, Subpart D) require that investigators explicitly address the measures taken to protect the rights and welfare of children participating in protocols.

▪ Definition of Children

"Children" are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

In the state of Arkansas, "children" include any persons under the age of 18 (unless the child has been emancipated by court order, marriage, or is on active military duty).

Almost all research protocols involving children requires full review by the convened IRB.

Investigators submitting proposals to the NIH for human subject research must include children in the study unless there are scientific or ethical reasons not to include them. The proposals must specifically include a description of plans for including children. And, if children will be excluded, the application must present an acceptable justification for the exclusion. Investigators should review the NIH Policy and Guidelines before submitting their proposals.

National Institutes of Health (NIH) Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (March 6, 1998)

- **Categories of Research Involving Children**

45 CFR. 46, Subpart D, classifies research involving children into one of four categories depending upon the risks and benefits of the proposed research, which can be approved as follows:

CATEGORY OF RISK TO THE CHILD	CONSENT REQUIREMENTS
Category 1 Minimal Risk	One parent/guardian permission
Category 2 Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects	One parent/guardian permission
Category 3 Greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield important generalizable knowledge about the subject's disorder or condition.	Both parents' permission, unless one is not reasonably available, deceased, unknown, legally incompetent, or does not have legal responsibility for care of the child.
Category 4 Otherwise not approvable, but presents an opportunity to understand serious health or welfare problems of children	Generally not approved, requires a panel of experts

Category 1 Description:

"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. Minimal risk protocols on children are approvable in accordance with the general IRB review criteria provided that adequate provisions are made for soliciting the assent of the child and parental permission

Category 1 Research Example: Research on children's attitudes about food preferences, surveys about play activities.

Category 2 Description:

Research involving greater than minimal risk, but presenting the prospect of direct benefit to individual subjects is approvable in accordance with the general IRB review criteria if:

- The risk is justified by the anticipated benefit to the subjects
- The relationship of risk to benefit is at least as favorable as any alternative approach
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

Category 2 Research Example: Clinical drug trials for a new anticonvulsant in children with seizure disorders.

Investigation of coping strategies of children living in foster care, research on the effectiveness of drug-use intervention programs for children testing positive for drug use

Category 3 Description: Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield important generalizable knowledge about the subject's disorder or condition. Such research is approvable in accordance with the general IRB criteria if:

- The risks represent a minor increase over minimal risk
- The intervention or procedure presents risks to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition and
- Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

Category 3 Research Example: Research using a non-approved drug or device which will provide no direct benefit to the subject, but will likely provide important information concerning efficacy for future subjects.

Category 4 Description:

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. This research is generally not approvable by the IRB without the appointment of and review by a separate panel of experts.

Category 4 Research Example: Phase I drug study in seriously ill children.

- **Assent of Children**

“Assent “ means a child’s affirmative agreement to participate in research. A child who fails to object to participation is not necessarily assenting to participation. Assent is not passive.

The IRB must determine for all studies involving children

- The age of subjects where assent is required
- How and at what age assent is to be documented

Assent must be accompanied by the signed informed consent of the parent (parents) or legal guardian of the child. The investigator must also inform the child of the purpose and the voluntary nature of their participation. This must be modified to the child’s age and ability to comprehend. The following are guidelines for age ranges in obtaining assent from children. These guidelines are recommended and are not intended to replace any institutional policies and procedures regarding the assent of children.

- Children younger than 7 years of age:

If appropriate as determined by the child’s age and cognitive development, the investigator should administer a simple oral explanation of the study procedures to be conducted.

- Children 7 years of age and less than 18 years of age:

Written assent must be obtained from the child if it is an IRB requirement. Assent of a child should be obtained in the presence of a parent/legal guardian and witness.

The IRB encourages the Principal Investigator to submit classification information related to the study’s risk category, age required for assent and method of assent documentation in the initial study submission packet.

The IRB’s purpose is not to demand adherence to rigid criteria based solely on age, but to use the age ranges above as guidelines for approaching children after taking into account their emotional and cognitive development. For all children, but especially those with developmental disorders, the age ranges listed above refer to the cognitive rather than the chronological age.

The IRB reserves the right to require both parents’ permission on selected protocols if the committee waives child assent or if additional requirements from the PI are deemed necessary by the convened IRB. The IRB may consider a request from that PI that the permission of one parent is sufficient for research involving greater than minimal risk, if there is a clear prospect of direct benefit to the child-participant.

The requirements of parental permission may be waived in those cases where it is clear that the parents’ interests do not adequately reflect the child’s interests (e.g., research on child abuse or neglect). These research protocols require investigators to develop special procedures, which must be approved by the convened IRB that protects the rights and welfare of the children asked to participate.

There are NO exemptions for Research Involving Children’s Participation in Surveys or Interviews

Unlike research involving adults, the exemption at 45 CFR 46.101(b)(2) for research involving survey procedures, interviews, educational tests, or public observations (except where the investigator does not participate in the activities being observed) does not apply to research involving children. 45 CFR 46.401(b).

- **Child Abuse Reporting**

The State of Arkansas requires the reporting of suspected child abuse or neglect. Investigators must abide by this law. If the protocol involves interviewing children about topics that might lead to a suspicion or to knowledge on the part of the investigator of child abuse or neglect, the child (and parent or guardian) must be informed of the reporting requirement as part of the informed consent process.

The following sentence(s) should be integrated into the currently required Informed Consent Document among the statements about confidentiality and its limits:

“We will attempt to maintain the confidentiality of any information you/your child give us in the course of this study. However, you should be aware of limits to the confidentiality of your information.”

“The researcher may also be required to report any child abuse or any intention you have to hurt yourself or others. The researcher, if ordered to do so by a court of law, may be required to disclose information you have provided.”

- **Wards of the State**

Children who are wards of the state or any other agency, institution, or entity can be included in IRB research only if the IRB finds and documents that such research is: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research is approved, the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

A foster parent may NOT give permission for a ward of the state to participate in research. Such permissions must be obtained through the Arkansas Department of Human Services.

- **Emancipated Minors**

There are exceptions to the rule of obtaining assent and seeking parental consent for individuals considered emancipated minors by the state of Arkansas. "Emancipated minors" may include individuals under the age of 18, living on their own and financially independent from their parent or legal guardian, have borne a child, or are married. Consent is sought from an emancipated minor; not assent.

❖ Research Involving Prisoners

45 CFR 46, Subpart C, provides additional safeguards for prisoners since "Prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and un-coerced decision whether or not to participate as subjects of research."

A "prisoner" includes any person who is sentenced to a penal institution under a criminal or civil statute as well as individuals detained in other facilities by virtue of statutes or commitment procedures, which provide alternatives to criminal prosecution or incarceration in a penal institution 45 CFR 46.303(c).

Research involving prisoners does not qualify for exemption from IRB review. For more information, see IRB Policy 17.9, Prisoners in Research.

▪ Categories Of Research Involving Prisoners (45 CFR 46.306(a))

- Studies regarding the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
- Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects.
- Research on conditions affecting prisoners as a class after HHS publishes a notice in the federal register.
- Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects; however, if some of the prisoners will be assigned to control groups which will not benefit from the research, then the study must first be approved by HHS.

In addition to the general requirements for review, in reviewing prisoner research, IRBs are required by 45 CFR 46.305(a) to ensure that:

- The membership of the IRB reviewing the protocol includes a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity, and that the majority of the IRB is not associated with the penal institution involved. If no current member of the IRB meets the prisoner or prisoners' representative criteria, then the IRB Chair will identify and recruit a qualified individual to fulfill this requirement and advise the IRB. In addition, a majority of the IRB members at the meeting must not be associated with the prison.
- Any advantages that prisoners will realize as a result of participating in the research, when compared to the general living conditions within the prison, are not so great as to impair prisoner's ability to weigh the risks and benefits of participation and freely choose whether to participate.
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- Procedures for selecting subjects to determine are fair, and free from arbitrary manipulation by prison authorities or prisoners.

- Control subjects will be selected randomly from among the group of eligible volunteers, unless the PI justifies a different procedure.
- The information presented during the recruitment and consent procedures to ensure that it is in a language, and level of complexity, that is understandable to the subject population.
- The parole board will not take participation in the study into account, and that each prisoner will be informed that participation will have no effect on parole.
- Adequate provision will be made for follow-up care as necessary.

In addition, the FDA imposes specific restrictions on the use of prisoners in research involving FDA-regulated products. Use of prisoners in these studies is prohibited unless the specific requirements of this section are met (21 CFR Part 50, Subpart C.) When an IRB reviews research falling within this category, its assurance provides for OHRP to be notified that the above criteria have been met.

Prisoner Research Update

On June 20, 2003, the following information concerning research involving prisoners was published in the [Federal Register](#):

Certain parts of 45 CFR 46 subpart C were waived by DHS to allow DHHS to conduct or support certain important and necessary epidemiologic research on prisoners that presents no more than minimal risk and no more than inconvenience to the prisoners/subjects. The Secretary of DHHS specifically proposed waiving the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

- (1) In which the sole purposes are
 - (i) To describe the prevalence or incidence of a disease by identifying all cases, or
 - (ii) To study potential risk factor associations for a disease, and
- (2) Where the institution responsible for the conduct of the research certifies to the Office for Human Research Protections, DHHS, acting on behalf the Secretary, that the IRB approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that
 - (i) The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
 - (ii) Prisoners are not a particular focus of the research.

The specific type of epidemiological research conducted or supported by DHHS and subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The proposed waiver would allow DHHS to conduct or support a type of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).”

The range of studies to which the proposed waiver applies includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.

Minimal Risk Definition For Prisoner Research and Non-Prisoners

The federal regulations list a different definition of minimal risk for prisoners in research from non-prisoners in research. The following information is from the [OHRP Guidance on the Involvement of Prisoners in Research](#) dated May 23, 2003:

Definition of Minimal Risk in Prisoner Research 45 CFR 46.303(d)	Definition of Minimal Risk in 45 CFR part 46, subpart A, 45 CFR 46.102(i) (Non-Prisoners)
"Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. "	"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Do not enroll a prisoner in an ongoing, IRB approved study without the approval of the committee. If a study subject becomes a prisoner during the course of the research, notify the IRB immediately.

❖ **Research Involving Pregnant Women And Fetuses**

45 CFR 46 Subpart B, provides additional protections for research involving pregnant women. Pregnant women should not be excluded from research as participants if the risk to the fetus is minimal. If pregnant women are included in a research protocol, the informed consent must address the research activity and its possible impact on the fetus.

Researchers should obtain informed consent from both the pregnant woman and the father of the fetus. Consent by the father is not necessary if:

- The purpose of the study is to meet the health needs of the mother.
- The identity or whereabouts of the father can not be reasonably ascertained.
- The father is not reasonably available.
- The pregnancy is the result of rape.

Research targeting pregnant women as subjects can not qualify for an exemption.

❖ **Research Involving Cognitively Impaired Individuals**

The participation of cognitively impaired individuals in research typically falls in categories that cannot be reviewed using exempt procedures. In addition, projects involving cognitively impaired individuals must specifically address how an individual’s capacity to give informed consent will be determined. *Examples of cognitive impairment include: diagnosed mental retardation, dementia, and coma.*

The IRB is not in a position to determine if an individual identified with a cognitive impairment has the capacity to give informed consent. However, the IRB has developed a decision algorithm tool to assist investigators in making this determination.

CAVHS permits the use of a surrogate consent process for persons who are cognitively impaired.

The IRB advises the use of the decision algorithm when it is unclear if cognitive impairment may prevent a subject from giving informed consent.

❖ **Other Potentially Vulnerable Populations**

Veterans and minorities are also considered vulnerable populations in research along with the following:

▪ **Economically or Educationally Disadvantaged Subjects**

For research involving economically disadvantaged subjects, special care must be taken to assure that the financial inducements offered do not constitute the sole grounds for the subject participation in the research protocol. Financial inducements should also not be used to assume risks that subjects would not ordinarily incur.

The consent form for research involving educationally disadvantaged subjects should be written with special attention to assure that terminology has been sufficiently simplified. The investigator should discuss orally every aspect of the study with the subjects to insure their understanding.

▪ **Illiterate Subjects**

An investigator in an IRB approved study may enroll individuals who can speak and understand English, but cannot read or write. The potential subject must be able to place a written mark on the consent form.

The subject must also be able to

- Comprehend the concepts of the study and understand the risks and benefits of the study as it is explained verbally, and
- Be able to indicate approval or disapproval for study enrollment.

If an investigator uses the above method to obtain consent, there must be documentation on the subject's consent form specifying what method was used to communicate the information and the specific means that the subject communicated agreement to study participation.

▪ **Employees as Subjects**

Employees may be recruited as study subjects. However, investigators should avoid using their own employees as research participants because of potential coercion and undue influence. The preferred method of recruiting employees for research studies is notices on institutional bulletin boards or third party notification, e.g. word of mouth. No directed advertising among one's own employees should be used. Recruitment notices, including

bulletin board or newspaper ads, are to be submitted to the IRB before they are posted or submitted for publication.

- **Students as Subjects**

Recruiting students as subjects represents a potential problem for investigators. Possible coercion is an issue from a student participating in a study conducted by his or her advisor. Undue influence is an issue whenever a student's participation will be made known to someone who holds power over his or her academic status. How the investigator plans to handle potential problems of coercion and undue influence must be addressed in the initial submission of the study to the IRB. In particular, activities that involve students who report directly to the investigator or attend a class for which the investigator has responsibility must be described.

- **Non-English Speaking Subjects**

Non-English speaking subjects may not be excluded from therapeutic studies on the basis of language use if there is a possibility that they might benefit by participating in the study.

If a research subject does not understand English, the informed consent document should be in the language readily understood by the subject to meet the requirements of 21 CFR 50.20. If the principal investigator anticipates that consent interviews will be routinely conducted in a language other than English, the IRB requires a translated consent document be submitted with the original protocol for approval. It is the investigator's responsibility to ensure that the translation is accurate.

As required by 21 CFR 50.27, a copy of the consent document must be given to each subject. While a translator may be helpful in facilitating conversation with a non-English speaking subject, verbal translation of the consent document must not be substituted for a written translation.

If a Non-English speaking subject is unexpectedly encountered, see IRB Policy 17.7, Non-English Speaking Research Subjects.

- **Terminally Ill Subjects**

From the Office of Human Research Protections (OHRP) IRB Guidebook:

Terminally ill patients are those who are deteriorating from a life-threatening disease or condition for which no effective standard treatment exists. It is generally considered unacceptable to ask such persons to participate in research for which alternative, not similarly burdened, populations of subjects exist. Nevertheless, it may often be necessary to involve terminally ill patients in research concerning their disease and its treatment. Further, terminally ill persons should not be excluded from research in which they may want to participate simply because of their status. One can imagine that altruism and a desire to bring good from adversity may well motivate persons suffering from life-threatening illnesses to become involved in biomedical or behavioral research. Still, terminally ill individuals are a vulnerable population of research subjects, and, therefore, require additional protection against coercion and undue influence

45 CFR 46.111(b)].

The risk of coercion and undue influence may be caused by a variety of factors. In addition to the fact that severe illness often affects a person's competence, terminally ill patients may be vulnerable to coercion or undue influence because of a real or perceived belief that participation is necessary to receive continuing care from health professionals or because the receipt of any treatment is perceived as preferable to receiving no treatment. Although terminally ill patients should be protected from an understandable tendency to enroll in research under false hopes, IRBs should not take too protective an attitude toward competent patients simply because they are terminally ill. Some terminally ill patients may find participation in research a satisfying way of imparting some good to others out of their own misfortune.

It is important to distinguish between risks that may be justified by anticipated benefits for the research subjects and risks associated with procedures performed purely for research purposes. A particularly difficult issue relating to research involving terminally ill patients arises in connection with the conduct of Phase 1 drug trials in which the drugs involved are known to be particularly toxic (e.g., a new form of cancer chemotherapy). In some of these studies, any benefit to the subject is, at best, highly unlikely. Despite the "therapeutic intent" of the investigators to benefit the subject, subjects may in fact experience a decline in health status, no improvements in terms of quality of life, or lengthened life for only a short time. It is extremely important that prospective subjects be clearly informed of the nature and likelihood of the risks and benefits associated with this kind of research. The challenge to the investigator and the IRB is to provide patients with an accurate description of the potential benefits without engendering false hope.

CHAPTER 13

Payment/Reimbursement of Research Subjects

This section concerns the payment and reimbursement of research subjects.

[Payments To Subjects](#)

[Billing Of The Research Subject at UAMS](#)

[Billing For Research Activities](#)

❖ **Payments To Subjects**

Federal regulations and the various codes of ethics governing human subject research require that no “undue inducements” be offered potential research subjects in order to secure their participation in a study. Payment is not considered a benefit of study participation. To comply, the IRB has adopted the following guidelines regarding payments to subjects:

- Subjects should not be induced to participate in research primarily by the prospect of financial gain. Payment is not a benefit. It is compensation for services.
- There must be parity in compensation for completion of research activities whether subjects, controls, or active participants.
- Investigators who plan to provide any payment/reimbursement to subjects for any reason must indicate this clearly in the informed consent, which must be approved by the IRB.

❖ **Billing Of The Research Subject at UAMS**

Principal investigators are required to follow the policies and procedures of the institution when billing research and clinical costs. At UAMS, the PI is to follow the policy “Billing for Research Procedures”(Appendix Q). All efforts should be made to assure that research subjects are billed in a correct and ethical manner. Consent forms should clearly differentiate what costs the subject will be responsible for and what costs the study will pay.

❖ **Billing For Research Activities**

Prior to submission of the protocol, make plans to establish correct billing procedures for research.

PURPOSE

The purpose of this policy is to define the procedure of processing payment requests for research subjects that are not employees of the University of Arkansas for Medical Sciences. Payments to employees are processed through Human Resources and procedures are detailed on a separate Policy Statement.

PROCEDURE

1. For payments to non-employees that are individually less than \$200 each, a Petty Cash Voucher is submitted to the Treasurer’s Office. This form list names, addresses, amounts and fund/account/cost center numbers that will be charged in the General Ledger accounting system. The form must have the approval signature of an authorized departmental disbursing officer. Checks will be prepared and either released to departmental representatives or mailed directly to the research subjects. Payments to research subjects participating in projects requiring anonymity will also be processed through Petty Cash, with checks payable to an authorized departmental representative.
2. For IRS reporting purposes, payment requests for non-employees in amounts equal to or greater than \$200 must be processed on a Purchase Requisition and sent to the Procurement

Department. The social security number for each subject will be required information on the Purchase Requisition. For individuals receiving \$600 or more during a calendar year, an IRS 1099 form will be sent to the individual subjects and reported to the IRS as taxable income.

3. If anticipated total payments to an individual research subject exceed \$600, the department should process the payment request through Procurement on a Purchase Request, even if individual payments may be less than the \$200 limit. This will allow the capture of information for 1099 reporting to the IRS.

For more information on payments to research subjects, see [Policy 8.7.01 in the UAMS Administrative Guide](#).

CHAPTER 14

Educational Policies And Resources

This section concerns educational policies and resources.

[Investigators And Study Staff](#)

[Training Links For Researchers Using UAMS IRB](#)

[Additional Training Links For Researchers At CAVHS](#)

[Training Policy](#)

❖ **Investigators And Study Staff**

IRB policy is that all investigators desiring to engage in research using human subjects must familiarize themselves with IRB policies and procedures and related federal regulations. Investigators should maintain an on-going relationship with the IRB to gain assistance in following policies and procedures during the conduct of their studies. This will help assure that both investigators and the IRB remain in compliance with all state and federal regulations regarding research involving human subjects.

❖ **Training Links For Researchers Using UAMS IRB**

Human Subject Protection Training – www.uams.edu/ORC

HIPAA for Research Training – www.uams.edu/ORC

❖ **Additional Training Links For Researchers At CAVHS**

Office of Research Development Training –
<http://www1.va.gov/resdev/fr/PRIDE/training/>

VHA Privacy Policy - <http://www1.va.gov/resdev/fr/PRIDE/training/>

❖ **Training Policy**

For more information regarding UAMS education policy, see [Policy Number 12.1.06 in the UAMS Administrative Guide](#).

CHAPTER 15

IRB Authority In Non-Compliance Issues

When the IRB is notified of events for which review is necessary by the convened IRB, the IRB chair or designated Chair will bring the issue to the attention of the IRB for appropriate action.

If the IRB is notified of events that indicate potential regulatory noncompliance, the committee will attempt to provide assistance through written contingencies to assist the investigator with achieving compliance without the imposition of sanctions. However, in cases where investigator cooperation does not occur and/or when it is determined that the safety or welfare of subjects or the integrity of the institution are or have been placed at risk, sanctions may be imposed.

[Non-Compliance Issues](#)

[Study Closure](#)

[Reopening Of A Closed Study](#)

[Suspension](#)

[Termination](#)

[Appeals Procedures For IRB Actions](#)

❖ Non-Compliance Issues

The IRB has the regulatory authority to:

- Increase the frequency of continuing review
- Appoint a subcommittee of appropriately qualified IRB members to investigate alleged non-compliance issues and advise the convened IRB
- Suspend study approval until compliance is achieved
- Terminate individual research protocols
- Report specific non-compliance activities of the investigator to appropriate governmental entities
- To request the UAMS Office of Compliance to perform a directed audit of study records and data

The IRB also has the regulatory authority to recommend additional sanctions to the Vice Chancellor for Academic Affairs and Sponsored Research. These sanctions include:

- Research privilege probation
- Suspension of research privileges
- Termination of research privileges
- Embargo of publications.

The principal investigator will be notified in writing if the IRB is investigating non-compliance issues and may be requested to cease all accrual of subjects. Following the investigation and subsequent deliberations of the IRB, the investigator will be provided written findings with one of the following actions:

- The research may continue
- The research may continue after contingencies are satisfactorily addressed
- The research may not continue due to placement or recommendation of sanctions

The IRB is required to report to the Vice-Chancellor for Academic Affairs and Sponsored Research, institutional officials, sponsoring agencies, the US Office for Human Research Protections (OHRP) and grants management officers concerning any suspension or termination of research protocols. If the protocol involves drugs or devices, the IRB is also required to notify the Food and Drug Administration (FDA).

If the protocol involves the Veterans Administration, the IRB will also notify the VA R & D Committee and the Office for Research Oversight (ORO).

The IRB is also required to report to these agencies any unanticipated problems involving risks to subjects or others, and serious or continuing non-compliance as determined by the IRB {45 CFR Part 46.103(b) (5)}.

❖ Study Closure

Study closure is a voluntary process and carries no punitive implications. Closure is not reported to institutional officials or to the department or agency head. Closure typically applies in the following situations:

- At the completion of the study (*i.e.*, new enrollment is closed and all data collection and analysis are completed);
- If the investigator chooses to close the study (*e.g.*, the study has not met its enrollment goal, but the investigator does not plan to enroll new subjects, collect additional data from enrolled subjects, or perform any additional data analysis);
- The investigator leaves the institution and does not intend to transfer responsibility for the study to another investigator.

The investigator must request study closure. The IRB office must be notified when a study is completed. This notification should be sent when all participants have completed treatment and follow-up phases of the study and analysis is completed to the point that the participant's records will no longer be needed. The Investigator must complete the **Study Closure Form** through ARIA that addresses the following:

- Protocol title and record number
- Name of PI
- Number of subjects accrued
- Number of subjects completing study
- Any publications that have resulted from data collected during the study
- Any adverse events that have not been previously reported.

The IRB office must be notified within 90 days of closure of the study. If no subjects have been enrolled in the previous five years and all data collection is complete, the investigator should close the study. Studies that are not closed properly by the PI may be terminated.

For studies classified as “exempt”, the IRB office needs only notification that the study has been closed.

❖ Re-opening Of A Closed Study

An investigator may re-open a closed study within one year of that closure with a written request to the IRB and updated information. After one year of closure, a protocol must be resubmitted.

❖ Suspension

Suspension is a non-permanent interruption of research activities. Suspension may occur for the following reasons:

- Unexpected and serious adverse effects that significantly increase risks relative to benefits
- Evidence that an investigator failed to adequately protect participants in a research study

- Willful or repeated failure to comply with federal regulations, state laws, or institutional rules that govern human research activities
- Proven research fraud or scientific misconduct
- At the request of institutional officials who have been charged with responsibility for oversight of research involving human subjects (*e.g.*, the Chancellor or the Vice Chancellor for Academic Affairs and Sponsored Research)
- At the request of the study sponsor, the FDA, the Office for Human Research Protections, or other duly authorized regulatory or governmental department or agency head
- Any other reason deemed necessary by a simple majority vote of a convened IRB Committee (a quorum must be present)
- The IRB or the investigator decides that new enrollment and risk-bearing activities should be interrupted pending an investigation into any problem or alleged problem with a particular study
- The continuing review application has not received final approval within 12 months after the last review (or less than 12 months if the study was designated for review at more frequent intervals). This suspension occurs automatically if more than 12 months have passed since the last approval was granted. This is the only situation for which suspension is automatic (*i.e.*, without any action on the part of the committee). Automated Research Instruction Administrator (ARIA) will provide the investigator of record two different e-mail notifications beginning two months prior to expiration of approval. The investigator has the responsibility to respond to the ARIA notices in a timely manner.
- Any study may be suspended by majority vote of the IRB members at a convened meeting with a quorum present. A study that is suspended may be reopened without resubmission as a new protocol and consent form. If discontinuation of study-related therapy might result in increased risk of significant harm to an individual or a group of study subjects, the IRB reserves the right to permit continued therapy with an investigational drug, device, or biologic for subjects who are already enrolled in a treatment study. Enrollment of new subjects generally will not be permitted. However, at the request of the investigator, the IRB Chair or a designee may permit enrollment into a suspended study if and only if there is no alternative therapy for a life-threatening condition.

At the time the study is suspended, the IRB will establish a unique and specific plan that, if completed, by the PI, will lead to re-review of the study resulting in a decision as to whether to continue or end the suspension or to terminate the study. An audit of the investigator's studies may be undertaken. As a minimum, the unique and specific plan will include a set of questions or conditions that must be addressed completely by the investigator and a specified time period during which the investigator must provide a written response. The IRB may not end the suspension for continuing review delinquency until the requested information is provided by the investigator and is reviewed and approved by the committee.

If an emergency occurs, institutional officials, the IRB Chair, or an appropriately appointed designee may suspend a study until the next regularly scheduled meeting of the IRB. Alternatively, the Chair may convene an emergency meeting of the full committee to consider suspension of a study before the next regularly scheduled meeting. In the event that an emergency suspension is considered, the

Chair must notify the PI and appropriate institutional officials (*e.g.*, the Chancellor, the Vice Chancellor for Academic Affairs and Sponsored Research, the Director of the ORSP, direct supervisors of the PI, and the appropriate department or agency head). The full committee at the next scheduled meeting must review all emergency suspensions.

❖ Termination

Termination is a non-voluntary process that results in **permanent** discontinuation of all study-related activities. The IRB may require a study that has been terminated to be entirely resubmitted and re-approved with a new protocol. Termination may occur for the following reasons:

- Unexpected and serious adverse effects that significantly increase risks relative to benefits
- Evidence that an investigator failed to adequately protect participants in a research study
- Willful or repeated failure to comply with federal regulations, state laws, or institutional rules that govern human research activities
- Proven research fraud or scientific misconduct
- At the request of institutional officials who have been charged with responsibility for oversight of research involving human subjects (*e.g.*, the Chancellor or the Vice Chancellor for Academic Affairs and Sponsored Research)
- At the request of the study sponsor, the Federal Drug Administration, Office for Human Research Protections, or other duly authorized regulatory or governmental department or agency head
- The investigator leaves the institution and fails to request closure of the study or fails to reassign the investigator's responsibilities and duties to another qualified investigator
- Failure to respond to repeated requests from the IRB regarding required actions on the part of the investigator to maintain an active protocol
- Any other reason deemed necessary by a simple majority vote of the convened IRB (a quorum must be present)

A research study that is terminated by the IRB will be reported to the study sponsor, institutional officials, and to the appropriate department or agency head. Disciplinary action or sanctions may be appropriate. Decisions will be made on a case-by-case basis. At the IRB level, appropriate sanctions might include a request for further information, an audit of ongoing clinical research activities, or suspension of all ongoing research conducted by the same investigator or group of investigators until all research activities are shown to be free of similar problems. The investigator will be reminded that if a study is terminated, no further enrollment or data collection is permitted.

If discontinuation of study-related therapy might result in increased risk of significant harm to an individual or a group of study subjects, the IRB reserves the right to permit continued therapy with an investigational drug, device, or biologic for subjects who are already enrolled in a treatment study. Enrollment of new subjects will not be permitted.

Institutional officials have the right to terminate any research activity without review by or approval of the IRB. Institutional review is broader in scope and may result in termination for reasons, other than those listed above.

❖ **Appeals Procedures For IRB Actions**

Information pending.

CHAPTER 16

IRB Records

This section concerns IRB records.

[IRB Records](#)

❖ IRB Records

The HRAC office maintains the following records:

- A current list of HRAC membership and qualifications.
- Agenda and minutes of meetings, including information regarding member attendance, discussions held, decisions made, and voting results.
- All materials submitted to the committee for initial and continued review of each study including: IRB applications, protocols, submitted and final consent forms, serious adverse event and death reports, proposed amendments, progress reports, correspondence generated between the committee and the investigators, and, where applicable, correspondence from sponsoring agencies.

All records are retained electronically following the inactivation or closure of a project.

CHAPTER 17

Office of Research Compliance

This section offers information about the Office of Research Compliance.

[ORC Information](#)

❖ ORC Information

The Office of Research Compliance (ORC) was established to help researchers and the University as a whole, achieve and maintain compliance with federal regulations and institutional requirements governing research. The primary purpose of the Office of Research Compliance is to support those activities that protect human research subjects and elevates the general level of research through systematic evaluation of research activities. The ORC coordinates the implementation and oversight of a comprehensive research compliance program for the University. As part of its role, the ORC conducts audits, educates research staff on research and regulatory compliance, and reviews potential noncompliance.

The ORC is a Department of the Academic Affairs Division and reports directly to, the UAMS Vice Chancellor for Academic Affairs and Research Administration. It also functions as the auditing and compliance body for the UAMS Institutional Review Board.

Audits of research studies conducted by the ORC include random audits, directed or “for cause” audits, and specific document or process audits. The IRB may request the ORC to conduct an audit based on an investigator’s protocol activities (large numbers of active protocols, subject enrollment, reported protocol deviations and/or serious adverse events). Audit findings are reported to the UAMS IRB, investigator and the Vice-Chancellor for Academic Affairs and Sponsored Research.

The ORC, upon the request of research staff, will conduct a review of documents in preparation for an external agency audit such as the FDA or NIH.

Education is a very large focus for the ORC. Education of researchers and their staff is accomplished through quarterly coordinator training classes, monthly one-hour Question and Answer seminars, and through advisory consultation sessions. Interactive web-based training programs are available in the areas of Protection of Human Subjects, Biomedical and Behavioral, as well as a Research HIPAA certification course.

Regulatory consultations for the preparation of Sponsor-Investigator Investigational New Drug (IND) exemptions and Monitoring of IND studies as well as informational packets on the their preparation are available for investigators who want to conduct research under their own IND.

The ORC will review and advise on protocols and protocol preparation when requested. This office also serves in an advisory capacity, to those investigators preparing their own dosage forms, on the current Good Manufacturing Practices (cGMP).

To contact the Office of Research Compliance:

Telephone: 501-526-6876

Facsimile: 501-526-6272

Website: <http://www.uams.edu/orc/>

CHAPTER 18

References

This section offers references that can be used in research.

[Ethical Principals And Codes](#)

[Federal Regulatory & Advisory Guidelines](#)

[Federal Regulatory Agencies](#)

[Local References](#)

[Accreditation References](#)

❖ Ethical Principles And Codes

- [Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research](#)
- Guidelines for Good Clinical Practice
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- ICH Considerations for Clinical Trials
- National Bioethics Advisory Commission
- [Nuremberg Code](#)
- World Medical Association Declaration of Helsinki

❖ Federal Regulatory & Advisory Guidelines

- Code of Federal Regulations
- Department of Veterans Affairs M3-Part I
- FDA Information and Regulations
- Institutional Review Boards 21 CFR 56 – U.S. FDA
- Investigational Devices 21 CFR 812 – U.S. FDA
- Investigational Drugs 21 CFR 312 and 314 – U.S. FDA
- NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects
- Protecting Human Research Subjects: Institutional Review Board Guidebook (NIH/OPRR)
- Protection of Human Subjects 21 CFR 50 – U.S. FDA
- Protection of Human Humans 38 CFR 16 – U.S. FDA
- Protection of Human Subjects 45 CFR 46 – U.S. FDA
- HIPAA Privacy and Research 45 CFR 164

❖ Federal Regulatory Agencies

- National Institutes of Health
- Office of Biotechnology Activities
- Office for Research and Compliance
- Office of Human Research Protections

- U.S. Food and Drug Administration

❖ **Local References**

UAMS Faculty Handbook

UAMS Federalwide Assurance

UAMS IRB Investigators Handbook for Human Studies

UAMS IRB Policies and Procedures

❖ **Accreditation References**

Association for the Accreditation of Human Research Protection Programs Accreditation Standards, updated May, 2004.

VA Human Research Protection Accreditation Program Accreditation Standards, NCQA, Version 1.0 August 16, 2001.

CHAPTER 19

Glossary

This section contains glossary items.

[Glossary Items](#)

❖ Glossary Items

- Accrual

The process of getting subjects into a trial or the number of subjects in a trial or planned to be in a trial. The number of subjects includes the sum of those screened and enrolled (regardless of whether they completed the study).

- Assent

A child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent [45 CFR 46.405 (b)].

- Arm

Any of the treatment groups in a randomized trial.

- Audit

A comparison of Raw Data and associated records with the interim or Final Study Report in order to determine whether the Raw Data have been accurately reported, to determine whether testing was carried out in accordance with the protocol and Standard Operating procedures (SOP), to obtain additional information not provided in the Final Study Report, and to establish whether practices were employed in the development of data that would impair their validity.

- Benefit

A valued or desired outcome; an advantage.

- Blind

Used with respect to a randomized trial, a randomized trial is blind if the subject is not told which arm of the trial he or she is on.

- Certificate of Confidentiality

Where data are being collected from subjects about sensitive issues (such as illegal behavior, alcohol or drug use, or sexual practices), researchers can obtain an advance grant of confidentiality from the Public Health Service that will provide protection against involuntary disclosure of the research subject's identity and the subject's participation in the study, even against a subpoena for research data.

- Children

Persons who have not attained the legal age for consent to treatment procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.402 (a)].

- Clinical Trials

Any form of planned experiment, which involves subjects and is designed to elucidate the most appropriate treatment of future subjects with a given medical condition. The essential characteristic of a clinical trial is that the results based on a limited sample of subjects are used to make inferences about how treatment should be conducted in the general population of subjects who will require treatment in the future.

- Cognitively Impaired Individuals

Those persons having a psychiatric or developmental disorder that affects cognitive or emotional functions to the extent that the capacity for judgment and reason is significantly diminished.

- Compassionate Use

Use of an investigational drug for treatment of an individual subject for a single use or a single course of treatment that is not covered by an existing IRB approved protocol.

- Compliance

Action in accordance with a request or institution.

- Double Blind

Used with respect to a randomized trial, a randomized trial is Double Blind if neither the subject or the subject's investigator or physician are told which Arm of the study he or she is on. The purpose is to prevent any bias in treatment or reporting of results from being introduced.

- Economically Disadvantaged Individuals

Those persons who struggle to provide basic necessities for themselves and their families or communities. The use of financial incentives for research participation is a special issue with economically disadvantaged persons.

- Educationally Disadvantaged Individuals

Those persons who may have educational deficits, learning disabilities, or cultural backgrounds that limit communication with a researcher.

- Elderly Subjects

Persons over the age of 65 years of age.

- Emancipated Minor

A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by a virtue of assuming adult responsibilities.

- Emergency Use

Use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which is not sufficient time to obtain IRB approval (21 CFR 50.27).

- Experimental Group

The Arm of a randomized trial that gets the new or "experimental" treatment. In some randomized trials, both of the treatments are standard treatments.

- Federalwide Assurance (FWA)

Document, which formalizes an institution's commitment to protect human, subjects and is required by any institution that participates in Federally supported human subject research.

- Guardian

An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402 (3)]. May also apply to an individual who can provide consent for an incapacitated subject, cf., Surrogate.

- Human Subject

A living individual about whom a profession or student investigator conducting research obtains data through intervention or interaction with the individual or collects identifiable private information 45 CFR 46.102(f). An individual who is or becomes a participant in research, either as a recipient of a test article or as a control 21 CFR 56.102(e).

- Informed Consent

The process of ongoing explanations to help a subject make educated decisions about whether to begin or continue participating in a research protocol or procedure.

- Informed Consent Document

A written summary of the research protocol (including its purpose, treatment procedures and schedule, potential risks and benefits, alternative to participation, etc.) and explanation of the rights of a research subject. Designed to begin the informed consent process.

- Inspection

Officially conducted audit by relevant authorities at the site of investigation and/or at the sponsor site to verify adherence to regulations.

- Institutional Review Board

Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects [21 CFR 56.102(g)].

- Investigation Device Exemption (IDE)

The process by which the FDA permits a device that otherwise would be required to comply with a performance standard or to have pre-market approval to be shipped lawfully for the purpose of conducting investigations of that device.

- Investigational New Drug Application (IND)

The process by which new drugs or biologics, including the new use of an approved drug, are registered with the FDA for administration to human subjects. An IND number is assigned by the FDA to the drug or biologic for use in tracking.

- Investigator (Principal investigator)

An individual who conducts an investigation, i.e., under whose immediate direction research is conducted, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

- Investigator/Sponsor

A term defined in the FDA regulations as an individual with responsibility for initiating and conducting a research study.

- *In vitro* fertilization

Any fertilization of the human ova that occurs outside the body of a human female.

- Life-Threatening

Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

- Mature Minor

Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor.

- Minimal Risk

A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

- Multi-center

Refers to a study that is being done at several hospitals or institutions simultaneously.

- Non-Significant Risk (NSR) Device

A device that does not meet the definition of a significant risk device.

- Permission

The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402 (c)].

- Placebo

An inert substance, such as a sugar pill.

- Pregnancy

The period of time from the confirmation of implantation until the expulsion or extraction of the fetus.

- Prisoner

Any person who is sentenced to a penal institution under a criminal or civil statute as well as individuals detained in other facilities by virtue of statutes or commitment procedures, which provide alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)].

- Protocol

A document, which states the rationale, objectives and statistical design and methodology of the trial, with the conditions under which it, is to be performed and managed.

- Protocol Deviation

An unplanned or unforeseen change in an ongoing study that is not covered under an approved IRB protocol.

- Protocol Violation

An unplanned or unforeseen change in an ongoing study that is not covered under an approved IRB protocol. Usually represents a more serious non-compliance problem than a protocol deviation and is noted after the fact or based on a technical error resulting in the protocol or standard operating procedure not being followed.

- Randomized Trial

A clinical trial with at least two arms, in which the decision as to which arm a new subject is assigned, is made by chance, for instance, by the flip of a coin or by using a computer to select randomly.

- Research

A systematic investigation to develop or contribute to general knowledge.

- Risk

The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk."

- Significant Risk (SR) Device

A device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an impact; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject (21 CFR Part 812)

- Sponsor

Any person or entity that takes responsibility for and initiates a research study. The sponsor may be an individual, pharmaceutical company, device manufacturer, governmental agency, academic institution, private organization, or other organization.

- Standard

A broad description of performance expectation.

- Standard Operating Procedure

A written set of methods or steps to be followed for the uniform performance of a function or activity.

- Surrogate

A person that can provide legal consent for an incapacitated subject, cf. Guardian

- Vulnerable Subjects

Individuals whose willingness to volunteer in a research study may be unduly influenced or coerced; and individuals with limited autonomy. These individuals may include, but are not limited to, children, prisoners, pregnant women, mentally disabled, or economically or educationally disadvantaged persons.

CHAPTER 20

Abbreviations

This section contains abbreviations.

[Abbreviations](#)

Abbreviations

Arkansas Area Health Education Centers	AHEC
Arkansas Cancer Research Center	ACRC
Arkansas Children’s Hospital	ACH
Arkansas Children’s Hospital Research Institute	ACHRI
Arkansas Department of Health	ADH
Arkansas State Hospital	ASH
Automated Research Information Administration	ARIA
Case Reporting Forms	CRF
Central Arkansas Veterans Healthcare System	CAVHS
Code of Federal Regulations	CFR
Continuing Review Record	CRR
Food and Drug Administration	FDA
Federal-wide Assurance	FWA
General Clinical Research Center	GCRC
Good Clinical Practice	GCP
Health and Human Services	HHS
Health Insurance Portability and Accountability Act of 1996	HIPAA
Human Subject Training	HST
Institutional Review Board	IRB
International Conference on Harmonisation	ICH
Investigational New Drug	IND
Multiple Project Assurance	MPA
National Institutes of Health	NIH
Office for Human Research Protections	OHRP
Office of Research and Sponsored Programs	ORSP
Office of Research Oversight	ORO
Principal Investigator	PI
Protocol Review and Monitoring Committee	PRMC
University of Arkansas for Medical Sciences	UAMS
UAMS Biosafety Committee	UBC
VA Research and Development	VA R/D

CHAPTER 21

Resource List of Committees and Institutional Contacts

This section contains the contact information for Arkansas Children’s Hospital (ACH), Arkansas Children’s Hospital Research Institute (ACHRI), Central Arkansas Veterans Healthcare System (CAVHS), and university of Arkansas for Medical Sciences (UAMS).

[Arkansas Children’s Hospital](#)

[Arkansas Children’s Hospital Research Institute](#)

[Central Arkansas Veterans Healthcare System](#)

[University of Arkansas for Medical Sciences](#)

Resource List of Committees and Institutional Contacts**[ARKANSAS CHILDREN'S HOSPITAL \(ACH\) web site](#)**

Main Number	(501) 364-1100 (Phone)
Research Pharmacy	(501) 364-2596 (Phone) (501) 364-2595 (Fax)
Pediatric Clinical Research Unit	(501) 364-2338 (Phone)
Radiation Safety Committee	(501) 364-3800 (Phone)

[ARKANSAS CHILDREN'S HOSPITAL RESEARCH INSTITUTE \(ACHRI\) web site](#)

Assistance with IRB Submissions, ARIA, and HIPAA Clinical Trials (Pharmaceutical/Industry), Confidentiality and Study Agreements	(501) 364-3571 (phone) (501) 364-2705 (Fax)
CUMG Awards Federal and Private Grants	(501) 364-3581 (Phone)
Education Coordinator Pediatric Clinical Research Unit Coordinator Procedure Prices for Research Research Coordinator Pool Subject Tracking System	(501) 364-2760 (phone)
Manuscript Grant Writing/Editing	(501) 364-2469 (Phone)
Research Accounts	(501) 364-2513 (Phone)
Research Compliance Officer	(501) 364-2861 (Phone)
Research Computer Systems	(501) 364-3570 (Phone)

CENTRAL ARKANSAS VETERANS HEALTHCARE SYSTEM (CAVHS) web site

Main Number	(501) 257-1000 (Phone)
Biomedical Research Foundation	(501) 257-4517 (Phone) (501) 257-4623 (Fax)
Subcommittee for Research Safety	(501) 257-4816 (Phone) (501) 257-4821 (Fax)
Radiation Safety Committee	(501) 257-6108 (Phone)
Research Compliance Office	(501) 257-5558 (Phone) (501) 257-4821 (Fax)
Research & Development Committee	(501) 257-4816 (Phone) (501) 257-4821 (Fax)
Research Pharmacy	(501) 257-6338 (Phone) (501) 257-6339 (Fax)

VA Research Website

University of Arkansas for Medical Sciences (UAMS) web site

Main Number	(501) 686-7000 (Phone)
Animal Research Committee	(501) 686-5347 (Phone)
Biosafety Committee, Dr. Lee Soderberg Biohazards Committee DNA Committee	(501) 686-6368 (Phone)
Dr. Charles Winter, Associate Dean of Research College of Medicine	(501) 686-5347 (Phone) (501) 686-8501 (Fax)
General Clinical Research Center (GCRC) Steven C. Elbein, MD Professor of Medicine, Program Director Suzanne Ritter Lumpkin, MS, JD GCRC Administrator	(501) 257-5399 (Phone) (501) 257-5817 (Fax) GCRC web site
Institutional Review Board (IRB) Including ARIA Usernames/Passwords Jennifer Sharp Associate Director, ORSP	(501) 686-5667 (Phone) (501) 686-7265 (Fax) IRB web site 501-686-8062
Office for Clinical Trials Dr. Thomas G. Wells, Director Julia Washam, R.N. Liaison Specialist	(501) 686-8572 (Phone) (501) 686-8501 (Fax) Office for Clinical Trials web site
Office of Research and Sponsored Programs Tim Atkinson, Director Research Privacy Officer	(501) 686-5502 (Phone) (501) 686-8359 (Fax)
Office of Research Compliance Danna K. Carver, Director Kevin Simmons, UAMS Compliance Educator	(501) 526-6876 (Phone) (501) 526-6272 (Fax) Office of Research Compliance web site
Pharmacy Committee Mike Parr, Pharm.D.	(501) 686-6220 (Phone) (501) 296-1133 (Fax)
Protocol Review & Monitoring Committee (PRMC) Angie Smith, LCSW, CRA PRMC Administrator	(501) 686-8274 (Phone) (501) 296-1466 (Fax)
Radiation Safety Committee	(501) 686-5299 (Phone)