

Department: UAMS Institutional Review Board
Policy Number: 1.4
Section: Principles and Authority
Effective Date: July 31, 2002
Revision Date: February 25, 2005; March 5, 2004; November 18, 2002;
March 5, 2008

SUBJECT: Studies Requiring Review

Purpose: The purpose of this policy and procedure is to explain the types of studies for which the IRB has review oversight responsibilities.

Definitions:

Clinical Investigation: Any experiment that involves a test article and one or more human subjects and that is subject to the Food and Drug Administration (FDA) regulations. This includes all research using a test article in a human subject as well as experiments that support applications for research or marketing permits for products.

Human subject (subject and participant used interchangeably):

1) An individual who is or becomes a participant in research either as a recipient of a test article, as a control, or an individual on whose specimen an investigational device is used; OR

2) A living individual about whom an investigator (whether professional or student) conducting research obtains:

- a. Data, of any kind, through intervention or interaction with the individual; OR
- b. Identifiable private information even in the absence of intervention or interaction.

Provided an investigational device is not being used, research on cadavers or decedents, or data or specimens that are collected solely from decedents, is not Human Subject Research. It may, however, still be subject to HIPAA requirements and require submission to the IRB which also serves as the Privacy Board. If the Investigator only receives specimens/data that are stripped of all HIPAA identifiers as per Policy 13.3, and submits a signed assurance from the provider of the specimens/data reflecting this, then it is not Human Subject Research.

If the investigator is receiving coded private information, the proposal only qualifies as non-Human Subject Research, if the code is not derived from any one of the HIPAA identifiers; the specimens/data were not collected specifically for the proposed project; and there is no way for the investigator to readily ascertain the identity of the individuals from which the specimens/data was obtained (Examples: Code Key destroyed prior to research or there is a written agreement or SOP from code key holder that they will not share key with researcher).

Human Subject Research: Any activity that meets the definition of:

- 1) Research AND involves human subjects; OR
- 2) Clinical Investigation.

Interaction: Includes communication or interpersonal contact between Investigator and subject or participant.

Intervention: Includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject's environment that are performed for research purposes.

Non-Human Subject Research: An activity determined by the IRB to not meet the definitions of Human Subject Research as per this policy.

Private Information: Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place; and Information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, Medical records). Private Information must be individually identifiable (identity of subject is or may readily be ascertained or associated with the information) in order to constitute research involving human subjects.

Test Article: Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to FDA regulations.

Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Systematic: Activities must be systematic to be considered research. Activities that involve predetermined methods for answering a specific question, testing hypotheses or theories are systematic and might include interviews, program evaluations, and observational studies. Activities that are not normally systematic are training activities where an individual is trained to perform a certain technique or task or to teach proficiency in using a certain method.

Generalizable Knowledge: Activities must contribute to generalizable knowledge or have an intent to extend beyond an internal use or department. Many thesis, dissertation or preceptorship projects are intended to extend beyond the graduate's department and therefore are considered research. Activities that are typically not generalizable are course evaluations that cannot be generalized to others and quality assurance type activities that are only intended to improve the performance of a unit, division, or department.

Policy:

All activities, regardless of whether the activity requires full board review, or might qualify for one of the expedited or exempt categories, that are clearly Human Subject Research should submit a complete proposal, including protocol, to the IRB through either a New Biomedical Protocol Submission or a New Behavioral Submission in ARIA. No Human Subject Research study should be initiated prior to IRB approval.

The IRB has sole authority to determine whether an activity meets the definition of Human Subject Research. Any activity that might represent Human Subject Research should be submitted to the IRB for determination.

All research activities, including those deemed Non-Human Subject Research, must be carried out in an ethical and respectful fashion in compliance with the principles of the Belmont Report, all state and local laws and institutional policies.

Research conducted by, or under the direction of, any employee, faculty, staff or student of UAMS or any entity in which the UAMS IRB is designated as the IRB of record, is governed by these policies. This includes research conducted off site or research involving the use of non-public information to identify or contact human research participants or prospective participants.

Reference: Policy 1.3 Federalwide Assurances; Policy 2.3 To Other Institutions; Policy 2.7 Engagement

Procedure for Human Subject Research Determination:

1. Investigator will:

- 1.1 Email irb@uams.edu a proposal with the following information:
 - 1.1.1 Investigator's Name and contact information
 - 1.1.2 Any other personnel that will be involved
 - 1.1.3 All project locations
 - 1.1.4 Detailed synopsis of the project that includes the objectives, background and rationale of the project
 - 1.1.5 Identification of any test articles (whether approved or not) to be used
 - 1.1.6 Type of data or specimens to be studied and type of population from which they were, or will be, obtained

1.4 Studies Requiring Review

- 1.1.7 Whether the data/specimens were obtained systematically
- 1.1.8 Whether the data/specimens were collected for the purpose of contributing to generalizable knowledge (collected with a plan for dissemination outside of UAMS)
- 1.1.9 Whether the Investigator will receive or have access to identifiable private information (as defined above)
- 1.1.10 If Investigator is only receiving coded information, is there a link that would allow re-identification?
- 1.1.11 Whether there will be any interaction or intervention with a human subject (as defined above)?
- 1.2 If determined to be Non-Human Subject Research, notify the IRB if the project changes to assure changes do not affect original IRB determination.
- 1.3 If determined to be Human Subject Research, work with IRB Director or Designee to complete application in ARIA.

2. The IRB Director or Designee will:

- 2.1 For the purposes of determining whether a submitted activity is Human Subject Research, use the definitions and guidelines above to review the proposal and request additional information as needed.
 - 2.1.1 If the proposed activity is a Clinical Investigation, draft a letter of determination for Chair signature indicating that the full submission process must take place. Assist Investigator with ARIA submission to minimize duplication of effort.
 - 2.1.2 If the proposed activity is Research and involves Human Subjects, draft a letter of determination indicating that the full submission process must take place. Assist Investigator with ARIA submission to minimize duplication of effort.
 - 2.1.3 If the proposed activity is determined to be Non-Human Subject Research, draft a letter of determination for Chair signature indicating the reasons why the proposed activities do not meet the definition of Human Subject Research.
- 2.2 All correspondence, including Non-Human Subject Research, will be documented in ARIA.

Department: UAMS Institutional Review Board

Policy Number: 2.6

Section: Relationships

Effective Date: July 31, 2002

Revision Dates: February 8, 2005; March 5, 2004; November 18, 2002; April 5, 2007; March 5, 2008

Subject: Reporting to Appropriate Federal Oversight Bodies, Institutional Officials and Research Sponsors

The UAMS IRB and institutional officials are responsible for reporting under appropriate regulations, the terms of the Federal Wide Assurance, and IRB Policy. When required reporting includes an affiliate organization utilizing the UAMS IRB, the mechanisms will be outlined in an agreement with each affiliate. If an event meets the definitions of serious non-compliance as defined by 12.4, continuing non-compliance by 12.4, unanticipated problem involving risk to participants or others defined by 10.2, is placed on administrative hold as defined by 9.1, or is terminated or suspended according to policy 7.9; the following reporting procedure shall be followed:

Procedure for Classification (see policy 12.4)

At UAMS the institutional officials named in UAMS Policy 12.4 serve the role of classifying issues of potential noncompliance. **All compliance reports, reports of potential non-compliance, reports of potential continuing non-compliance, and unanticipated problems must be reported to Institutional Officials as outlined in IRB Policy 12.4 to determine appropriate classifications and remediation plans and subsequently to an IRB committee to determine if the rights and welfare of human subjects have been adequately protected.**

Activities that must be reported to the Office of Human Research Protections:

The IRB will assure the following issues are reported to appropriate agencies, institutional officials and the convened IRB promptly after the final determination of the convened committee by the end of a two week period following the receipt of the report :

1. Any unanticipated problems involving risk to participants or others (10.2).
2. Any event classified by the IRB as serious non-compliance (12.4)
3. Any even classified by the IRB as continuing non-compliance (12.4)
4. Any suspension or termination IRB approval by the convened committee (7.9).
5. Any administrative hold placed on a study (9.1)

Procedure for Reporting

1. Institutional officials defined in 12.4 will classify report to the IRB and Research Compliance any event classified under the five categories listed above.
2. The IRB will work with ORC to draft the report and assemble appropriate supporting documentation. The report will include:
 - a) A description of the event
 - b) Classification assigned by the IRB
 - c) Actions taken by the IRB and the reasons for these actions
 - d) Any administrative actions taken

- e) Any corrective action plans or plans for continued investigations
 - f) Outcomes and sanctions
3. If the report involves another institution, the IRB will work with the affiliate to draft the report.
4. Copies of the report will be sent to the OHRP If the IRB classified the event in any of the five activities above. It will also be sent to:
- a) The UAMS IRB
 - b) If the research is subject to any Common Rule agency, a copy is sent to that agency by the ORSP Director
 - c) FDA, if the research is regulated by FDA
 - d) IRB Chair,
 - e) Study file
 - f) Investigator
 - g) Investigator's Dept. Chair
 - h) VCAA/RA
 - i) ORC file
 - j) Institutional Officials at affiliate sites where UAMS IRB serves as the IRB of record, as applicable
 - k) UAMS Risk Management, if appropriate
 - l) Other indicated parties
5. The ORSP Director will forward a copy of the letter to the appropriate funding agencies or sponsors and to the Vice Chancellor for Institutional Compliance.
6. The IRB Chair will place the report on an IRB agenda as an information item.

Department: UAMS Institutional Review Board

Policy Number: 7.4

Section: Procedures for Study Review

Effective Date: July 31, 2002

Revision Dates: June 1, 2005; February 8, 2005; May 7, 2004; March 5, 2008

SUBJECT: Standard or Full Committee Review

Policy: The standard or full committee review category is used for research that does not qualify for expedited or exempt review. Substantive review of full committee protocols will take place at convened meetings where quorum is met and be individually presented and discussed. In order for the application to be approved, it must receive the approval of a majority of those members present at the meeting.

The chair and the IRB office will ensure that the committee is staffed with members who have expertise in the areas under review for a particular meeting, or invite outside individuals with the appropriate expertise in accordance with IRB policy 3.9.

Primary Reviewers. All reviewers will have access to all new materials submitted, as well as the history file. Two primary reviewers from among the Committee members will be assigned for each new standard review protocol. The primary and secondary reviewers should conduct an in-depth review of all pertinent documentation and present the protocol to the full Committee addressing each of the criteria for approval outlined in policy 7.1. Non-Scientist members are not restricted from being primary or secondary reviewers. The chair shall assign non-scientist members to be primary or secondary reviewers for any category of review for each meeting.

Other Committee Members: The other Committee members who are not assigned a specific protocol must review the Original Submission Form, the consent form and recruitment materials in light of policy 7.1 and must participate in the discussion and vote on each protocol. Other committee members have an obligation to raise issues encountered during their review of these documents. No IRB member should vote to approve a protocol unless they feel comfortable that the rights and welfare of the subjects are protected as much as possible.

Non-scientist members: Non-scientist members are no different from other committee members. Non-scientist members do not need to understand complex scientific or medical information or procedures in order to evaluate human subject protection issues which is the primary mission of an IRB member.

Investigators Responsibilities:

- 1) Submit new study in ARIA to the appropriate Committee, either Biomedical or Behavioral depending upon design of study. See IRB Policy 4.1.
- 2) Submit in ARIA the following new application materials:
 1. Complete Original Submission Form through ARIA
 2. Detailed Protocol or any standard operating procedures (SOPs) to be used in the research, addressing:
 - a. Study background with scientific rationale and aims;
 - b. Methods;

- c. List of all experimental procedures;
 - d. Anticipated risks and benefits to subjects and procedures to minimize risks;
 - e. Provisions to protect participant privacy;
 - f. Provisions to maintain the confidentiality of data;
 - g. Recruitment or enrollment procedures;
 - h. Participant selection criteria;
 - i. Data analysis method;
 - j. Additional safeguards to protect vulnerable participants; and references.
3. If a DHHS approved protocol exists, provide it as well and justification for any substantial deviations.
 4. Informed Consent Form or script, unless waiver requested.
 5. If a DHHS approved sample consent exists, provide it as well and justification for any substantial deviations.
 6. HIPAA Authorization, if applicable
 7. Any relevant merit reviews or grant applications
 8. Advertisements or subject information
 9. Surveys or questionnaires to be used
 10. Investigator's brochure (if applicable)
 11. Approvals from any other required institutional committees
 12. Letters of assurance from other research sites (if applicable)
 13. A simplified CV or accurate completion of profile in ARIA providing same information.

IRB Responsibilities:

- 1) The IRB may only approve an application when its decision is based on consideration and discussion of the criteria for approval outlined in IRB Policy 7.1.
- 2) Determine a category of risk as defined in IRB Policy 16.1.
- 3) The IRB must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk and as necessary to ensure the continued protection of the rights and welfare of research subjects. See Policy 16.1 for detailed risk-benefit analysis. Studies with a high risk and low probability for benefit may require approval periods of greater than just once a year.

The following are examples of studies that may need additional review:

- a. Involvement of vulnerable populations;
- b. Research conducted internationally;
- c. The involvement of recombinant DNA or other types of gene transfer protocols;
- d. The use of waiver of informed consent procedures, e.g. surrogate consent;
- e. Classified research;
- f. Research for which subjects would be exposed to additional risks, e.g. breach of confidentiality, continual non compliance with federal regulations, Phase 1 studies, disproportionate number or severity of SAEs;
- g. Previous suspension of the researcher due to compliance, record-keeping or other concerns
- f. Recommendations from other intra-institutional committees
- g.** The IRB will promptly convey the decisions and requirements for modifications by the IRB to investigators through ARIA. Decisions to decline a protocol will be

accompanied by reasons for the decision and an invitation for an opportunity for reply by the investigator, either in person or in writing.

Department: UAMS Institutional Review Board

Policy Number: 7.6

Section: Procedures for Study Review

Effective Date: July 31, 2002

Revision Date: June 1, 2005; February 05, 2005; March 5, 2008

SUBJECT: Continuing Review

Policy: The IRB must conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk. 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. The IRB must review each study at least once per year and can require more frequent reviews.

Periodic review of all human research activities is necessary to determine (1) whether the risk/benefit ratio has changed, (2) whether there are unanticipated findings involving risks to subjects, and (3) whether any new information regarding the risks and benefits should be provided to subjects. All non-exempt research protocols must be periodically reviewed, not less than one time per year, in accordance with this policy.

Studies deemed as Exempt will be asked to complete an Annual Update form. See Policy 7.3.

As a service, ARIA automatically emails continuing review expiration notices at approximately 8 and 12 weeks prior to the project's continuing review expiration date with a required return deadline. However, this service should not be seen as assuming any duty that an investigator retains for submitting and receiving continuing review approval on time. Sufficient time should be allowed for processing the report and IRB approval prior to the project's expiration.

Failure to submit a timely continuing review will result in expiration of the protocol. There is **no grace period** extending the conduct of the research beyond the expiration date of IRB approval. Extensions beyond the expiration date cannot be granted. If the IRB has not reviewed and approved a research study by the continuing review expiration date, ARIA sends out an automatic expiration letter stating that all research activities, including procedures with/on current participants and data analysis, must stop.

Only upon a finding by the IRB that it is in the best interests of individual subjects to continue participating in the research interventions or interactions, may any research activity continue after CR expiration. Investigators may not make this decision. Enrollment of new subjects cannot occur after the expiration of IRB approval.

Principal Investigator must immediately provide the IRB with a list of current participants whose safety might be at risk by stopping all research procedures. The IRB Chair will decide whether research procedures may continue for the currently enrolled subjects.

For CAVHS studies, the IRB Chair will consult with the VA Medical Center Chief of Staff

If continuing review expires on a drug/device study, the involved Pharmacy contact will be notified. If continuing review expires on a CAVHS study, a representative of the VA R&D Committee is automatically notified by ARIA, who in turn, notifies the VA R&D Chair.

This type of study expiration does not need to be reported to OHRP under DHHS regulations. (Note: If a study is actively suspended or terminated by a convened IRB meeting, OHRP must be notified.)

Process:

1. Regardless of continuing review by expedited or full IRB processes, the

Investigator must provide:

- a. A completed ARIA continuing review application;
- b. Informed Consent Document – ARIA automatically loads the currently approved consent document, if applicable, into the CR form. The Investigator **MUST** verify the accuracy of what is listed and correct if inaccurate.
- c. In addition to answering yes/no or proving a number in the ARIA form, a status report for all events since the last report should be submitted that includes a summary of the following:
 - i. All adverse events,
 - ii. Unanticipated problems involving risks to participants/others,
 - iii. Complaints about the research and resolution thereof
 - iv. Relevant recent literature
 - v. Interim findings
 - vi. Relevant multi-center trial reports
 - vii. Participant benefits
 - viii. Current risk-benefit assessment based on study results to date
 - ix. Gender, Minority status, and Vulnerable Population status and description (Example: Female, Caucasian, Prisoner)

This may be provided in Step 10 of the form, or in a separately uploaded document.

x. Reports from Data Safety Monitoring or IND Monitoring

Activities required in policy 7.8.

d. If an Investigator allows a study to expire before continuing review approval is received, the investigator must immediately provide the IRB with a list of current participants whose safety might be at risk by stopping research procedures. If the research involves CAVHS, the Investigator must also notify the R&D Committee Chair.

2. IRB Committee Operations

A. Primary Reviewer System. When a protocol is reviewed for continuing review at the IRB Committee, a primary reviewer system will be used. All reviewers will have access to the complete study file, including the Continuing Review Report (CRR). The Primary Reviewer will be responsible for reviewing the CRR, the study, making sure the requirements of this policy are met and presenting the study during the meeting for a vote. Other IRB members must examine (1) the initial protocol submission form, (2) the current consent document, and (3) the study report section

under continuing review. In order to discuss and vote on each study, all non-assigned reviewers should follow along during the meeting by reviewing the Continuing Review Report.

The following applies to Research reviewed by the Full IRB Committee or Research reviewed under Expedited Procedures.

B. Approval Criteria: The criteria for granting continuing review approval is the same as for initial review, as outlined in Policy 7.1. The Primary Reviewer must look to see that:

1. Risks continue to be minimized and reasonable in relation to the benefits,
2. Selection of subjects is still equitable
3. Informed consent is being obtained and documented appropriately
4. As applicable, provisions for monitoring of the data are still appropriate to ensure the safety of the subjects
5. As applicable, provisions to protect subject privacy and data confidentiality are adequate
6. Safeguards for vulnerable populations, as applicable, are still adequate

C. Documentation of Approval Period. The IRB must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk and as necessary to ensure the continued protection of the rights and welfare of research subjects. See Policy 16.1 for detailed risk-benefit analysis. Studies with a high risk and low probability for benefit may require approval periods of greater than just once a year. The following are examples of studies that may need additional review:

- a. Involvement of vulnerable populations;
- b. Research conducted internationally;
- c. The involvement of recombinant DNA or other types of gene transfer protocols;
- d. The use of waiver of informed consent procedures, e.g. surrogate consent;
- e. Classified research;
- f. Research for which subjects would be exposed to additional risks, e.g. breach of confidentiality, continual non compliance with federal regulations, Phase 1 studies, disproportionate number or severity of SAEs;
- g. Previous suspension of the researcher due to compliance, record-keeping or other concerns
- h. Recommendations from other intra-institutional committees

D. Verification from Outside Source. The IRB should also determine if verification from an outside source is needed regarding the study. Studies with very complex protocols with unusual risks or protocols being conducted by investigators who have failed to respond to other Chair or Committee requirement are examples of when the IRB might request verification from an outside source that no material changes have occurred since the previous review.

E. Continuing review for a research protocol will be subject to **full IRB review** each approval period, **unless:**

1. Originally reviewed under expedited procedures; or
2. Research is permanently closed to the enrollment of new subjects, all subjects have completed all research related interventions and the research is to remain open only for long-term follow-up of subjects; or
3. No subjects have been enrolled and no additional risks have been identified; or
4. The remaining research activities are limited to data analysis. When any of the above conditions are met, the IRB may determine that review should occur through expedited processes.

F. Expiration of CR. The IRB Chair or Committee must determine whether there is an over-riding safety concern or ethical issue such that the interests of individual participants would be best served by continuing with the research interventions or interactions. In CAVHS research, the Chair or Committee should consult with the R&D Committee Chair.

G. Review of the Consent Document. Review of the currently approved consent document must ensure that the information is still accurate and complete. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in an updated consent document. Review of currently approved or proposed consent documents must occur during the continuing review but may be done more frequently if new information becomes available.

H. Review of New Amendments to Protocol Submitted at Time of Continuing Review. Amendments and addenda to a research protocol may be submitted at the time of continuing review. A separate cover letter describing the change and all appropriate tracked or highlighted documentation (examples include consent form, protocol, brochures) must accompany the continuing review application.

Amendments may not be implemented by an investigator prior to review and approval by the IRB Committee.

I. Summary Status Report Must be reviewed in light of Approval Criteria. Continuing review responsibilities include reviewing reports of adverse reactions and unexpected events involving risks to subjects or others.

J. Continuing Review Date Determinations. Several scenarios for determining the date of continuing review apply for protocols reviewed by the IRB at a convened meeting. To determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs. (These examples presume the IRB has determined that it will conduct continuing review no sooner than within 1 year).

Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on October 1, 2002. Continuing review must occur within 1 year of the date of the meeting, that is, by October 1, 2003.

Scenario 2: The IRB reviews a protocol at a convened meeting on October 1, 2002, and approves the protocol contingent on specific minor conditions the IRB chair or his/her designee can verify. On October 31, 2002, the IRB chair or designee confirms that the required minor changes were made. Continuing review must occur within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the protocol, that is, by October 1, 2003.

Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2002, which requires major revisions or is tabled. The study is reviewed at subsequent convened meetings on October 15 and October 29, 2002. At their October 29, 2002 meeting, the IRB completes its review and approves the study. Continuing review must occur within 1 year of the date of the convened meeting at which the IRB reviewed and approved the protocol, that is, by October 29, 2003.

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 that meeting.

Example: A study's continuing review date expires on June 1, 2000. The IRB convened on May 15, 2000 and granted protocol approval. The next continuing review approval will expire on May 15, 2001.

Department: UAMS Institutional Review Board

Policy Number: 8.1

Section: Change in Protocol

Effective Date: July 31, 2002

Revision Date: June 1, 2005; February 1, 2005; March 5, 2008

SUBJECT: Changing Study Protocol/Modifications to previously approved research

POLICY: All major and minor amendments or revisions must be submitted to the IRB for approval. The IRB Chair or his or her designee shall be the only one to determine as to whether an amendment is major or minor, based on degree of risk involved in the change. **This determination must be made using all criteria in Policy 7.1.**

1. Investigator will:

1.1. Make all amendment or modification requests through ARIA. Each modification will include:

1.1.1. Description of the changes;

1.1.2. Reason for the change;

1.1.3. Investigator's opinion as to impact of change on study and on participants; and

1.1.4. Whether or not changes are needed to the consent form.

1.1.5. All documents, including but not limited to consents, protocols, recruitment materials, and Form 1572s, to be modified. If a sponsor or a granting agency has requested the amendment, a copy of the communication from the sponsor, as well as a copy of the amendment and/or the amended protocol should also be included. If the change affects the consent, provide both a tracked and a clean document.

Note: The IRB reserves the right to defer review if the changes are not highlighted or tracked on the document to be revised. If a document is received from a sponsor where tracking changes is not possible then an outline of the protocol changes must be provided.

1.2. Not implement any change until IRB approval, and as applicable Sponsor approval, is received. The only exception is a change necessary to eliminate apparent immediate hazards to the research participants. In such cases, the Investigator will promptly inform the IRB, and as applicable the Sponsor, of the implemented change.

2. IRB Chair or Committee Roles For Minor or Major:

The chair and the committee must always use the criteria in 7.1 to make a determination of whether approval can be granted. Upon notification of any new information or change which might affect the willingness of a participant to continue in the study or changes the risk-benefit balance for those already enrolled, the Investigator will be directed to notify participants. Depending upon the seriousness, the Investigator may be directed to contact the participants by letter, re consent at next opportunity, or phone participants to schedule a visit for immediate reconsent process.

In situations where changes are to address administrative type changes and do not

impact the participant or their ability to contact those associated with the study, the IRB typically will not required re-consenting of previously enrolled subjects.

A. Chair/Designee. Criteria in policy 7.1 must be followed when it affects any one of the criteria for review. Minor changes will be reviewed and approved by the Chair/Designee, reported to the Investigator, and reported to the Committee on a future agenda.

B. Committee. Proposed changes in research which increase risk or discomfort or decrease benefit will be considered major. The IRB must review and approve the proposed change at a convened meeting before the change can be implemented, unless the change is necessary to eliminate immediate hazards to the research participants. In the case of a change implemented to eliminate immediate hazards to participants, the Committee will review the change to determine that it is consistent with ensuring the participants' continued welfare.

The Office Notes section of the Agenda will list what items have been submitted to be reviewed. All members will have access to the materials in order to follow along, discuss the protocol and participate in the vote. Using the criteria in policy 7.1 as a guide, all committee members will be expected to review all modified documents along with the two primary reviewers assigned to the modification. The primary and secondary reviewers will present the changes to the committee in enough detail to enable discussion and a vote. All approvals or requested revisions will be reported back to the Investigator in writing.

Department: UAMS Institutional Review Board
Policy Number: 9.1
Section: IRB Decisions
Effective Date: July 31, 2002
Revision Date: June 1, 2005
August 26, 2004
April 5, 2007
March 5, 2008

SUBJECT: Range of IRB Decisions

Acknowledged: An action taken by the IRB or Chair/Designee to acknowledge documents submitted when approval is not required.

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. The exception is any VA investigator who must also obtain approval of the VA Research and Development Committee prior to starting. All contingencies and revisions must be approved by the IRB before an action of “approved” can be assigned to a project.

Approved with Major Contingencies: The project is not approved until the IRB convenes to discuss the requested revisions. The project requires major revisions, which the IRB can list as part of the motion. These must be addressed and re-reviewed by the convened IRB before the IRB can grant approval. The PI will be provided with comments explaining rationale for the decision and given an opportunity to respond. The response will be reviewed by the convened IRB. Major revisions are broad and unspecific such as “The IRB needs more information about why ARM 2 of the study is needed” or “The IRB is concerned that the PI has not done enough to reduce risks to human subjects. Please revise or explain” or “The consent form was written in a very scientific manner. Please revise so that it is understandable” or “the IRB is concerned that there are not enough resources to complete this project, please explain”

Approved with Minor Contingencies: The project is not approved until the chair or designee approves the specific requirements of approval that the IRB requires. A vote such as this incorporates all the noted contingencies. The project requires minor revisions which must be addressed before final approval can be granted. Minor revisions may be reviewed and approved through the expedited process. Minor revisions are very specific and direct so the Chair can verify them. Some examples are “Please revise consent form page 4 to add the study procedures described in your protocol on page 2” or “Please add the PIs name to the consent form page one in accordance with UAMS IRB policy” or “Remove ARM 2 of the study to reduce the risk of heart attack” or “Please remove the second sentence from your recruitment advertisement as it is coercive”

Declined: The project has serious deficiencies in submitted protocol affecting the safety and welfare of the projected subject population. These must be addressed in a new protocol and be reviewed by the convened IRB before the IRB can grant approval. The PI will be provided with comments explaining rationale for the decision so the project can be revised in a new submission.

Suspended for Cause: An action taken by the IRB to stop temporarily some or all research procedures until the outlined requirements are met. The IRB can, at its discretion, make a range of motions regarding the conduct of a given protocol in order to better secure the protection of participants. This action is a suspension of IRB approval and must be reported in accordance with UAMS policy 2.6.

Terminated for Cause: An action taken by the IRB to stop permanently some or all research procedures. The IRB can, at its discretion, make a range of motions regarding the conduct of a

given protocol in order to better secure the protection of participants. This action is a suspension of IRB approval must be reported in accordance with UAMS IRB Policy 2.6.

Administrative Hold: The Convened IRB or the IRB Chair or designee can place an administrative hold on a project if the IRB lacks enough information to make a decision. Administrative holds are suspensions of IRB approval and will be reported in accordance with IRB Policy 2.6. The hold will be lifted after the PI responds and a new classification will be selected from the above list.

Department: UAMS Institutional Review Board

Policy Number: 10.2

Section: Principal Investigator Responsibilities

Effective Date: July 31, 2002

Revision Date: June 1, 2005; February 08, 2005; July 7, 2004; October 10, 2002; March 5, 2008

**Subject: Unanticipated Problems Involving Risks to Participants or Others
– Investigator Reporting Requirements and IRB Actions**

Chairs and designees are assigned by the Vice Chancellor for Academic Affairs and Research to analyze unanticipated problems involving risk to participants or others.

Definitions:

- 1) Unanticipated Problem Involving Risks to Participants or Others: Any event that is a) Unanticipated, b) caused harm or placed a person at increased risk of harm and c) is Related to the research procedures.
- 2) Unanticipated: An event is “unanticipated” when it was unforeseeable at the time it occurred.
- 3) Serious: An event is “serious” if it involves considerable detriment or harm to one or more persons (who may or may not be participants), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. Serious adverse events include
 - a. Death
 - b. Life-threatening experience – Disease or condition where the likelihood of death is high unless the course of the disease/condition is interrupted or diseases/conditions with potentially fatal outcomes where the end point of the clinical trial analysis is survival
 - c. Inpatient hospitalization or prolongation of hospitalization
 - d. Persistent or significant disability/incapacity
 - e. Congenital anomaly/birth defect in participant’s offspring
 - f. Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

- 4) Related: An event is “related” if more likely than not it was caused by the research activity.
- 5) Unexpected: An event is “unexpected” when its specificity, nature, severity or incidence are not accurately reflected in the consent form previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected.
- 6) Substantive Action by the IRB: An action taken by the IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.
- 7) Sponsor: One who initiates a clinical investigation but who does not actually conduct the investigation.
- 8) Funding Source: The industry or government sponsor and/or grant holder for a study. Examples are National Institutes of Health, pharmaceutical companies, private foundations.
- 9) Risk– The probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a research study.

A. Investigator Reporting Responsibilities due either Immediately or no later than 10 days after Notification

- 1) The following must be reported to the IRB by the Investigator, and, except where noted, such reporting is due in ARIA no later than 10 days after the investigator’s first knowledge of the event:
 - a. Deaths that are related to the research must be reported immediately upon Investigator notification (NOTE: A death due to a terminal condition of the research participant would be considered anticipated and not related to the research and therefore not reportable under this policy, UNLESS the research hastened the death. However, it would need to be accounted for at the time of the next continuing review.)
 - b. Any event that in the Investigator’s opinion was Serious, Unexpected and Related to the research regardless of whether participant is on or off study (Note: This would include any Unanticipated adverse device effects and both on-site and off-site adverse events that are serious, unexpected and related.)
 - c. Any event that required prompt reporting, according to the protocol, to the Sponsor or to the FDA
 - d. An accidental or unintentional change (protocol violation) to the IRB-approved protocol that increases risk or decreases benefit, affects the participant’s rights, safety, welfare, affects the integrity

of the data, or has the potential to occur again. (NOTE: Any protocol violation that does not meet this definition should be reported with the next continuing review.)

- e. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- f. (NOTE: For all other deviations, the Investigator must submit a modification to the IRB and receive written approval prior to implementation of any change to the protocol.)
- g. Any publication in the literature, safety monitoring report including a Data and Safety Monitoring Report, interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research (Examples include MedWatch reports indicating a lower rate of response to a treatment than expected, or that a side effect is more frequent or severe than expected, or a publication showing that an arm of study is of no therapeutic value.)
- h. A breach in confidentiality that may involve risk to a participant or others (Examples include the loss of a laptop computer on which subject identifies are stored or inadvertent loss study records)
- i. Any Complaint of a participant that indicates an unanticipated risk
- j. Incarceration of a participant if study was not previously reviewed with the anticipation of enrolling prisoners (NOTE: No further interactions may occur with the participant until reviewed by IRB Prisoner Representative.)
- k. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- l. Restrictions, suspension or termination of study by the Sponsor, Principal Investigator, Funding Source, regulatory body, or institutional administration.
- m. Notifications of pending audits or inquiries by external bodies (e.g.
- n. Sponsor, FDA, NCI or NIH). This includes any communication that questions the conduct of the research or suggests an impending inquiry, audit or investigation. It does not include notice of any routine monitoring visits. NOTE: The PI must inform the IRB through ARIA and provide a copy of the notification to the Office of Research Compliance.
- o. Any other event that in the opinion of the investigators was unexpected, caused harm or placed a person at increased risk of harm (regardless of the seriousness of the harm) and is related to the research procedures

- 2) The Investigator is required to report any of the unanticipated problems listed above to the IRB even after the participant has completed the study or has withdrawn from the study until the study is closed in the IRB files.

Investigator's Reporting Process for Unanticipated Problems involving Risks to Participants or Others to the UAMS IRB

1. The investigator should describe the event in narrative format. Included in this narrative should be
 - Description of the event
 - Nature of the risk incurred
 - Relationship of the event to the research
 - Reasons for any deviations from the protocol or the use of any modifications not yet approved by the IRB
 - Any required modifications to the consent or protocol
2. The narrative should be attached to the completed Local or Non-Local AE or Death form in ARIA.

IRB Chair/Designee Responsibilities- Initial Review

1. In all cases, the IRB chair or designee must make a determination using the definitions in this policy and then document how she/he made the analysis and decision. This can be a note scanned to the file or in a comment field in ARIA.
2. The IRB Chair or designee will review the report, all attachments, and as necessary the ARIA study file.
3. The Chair/Designee will determine and record in ARIA whether the event represents an Unanticipated Problems Involving Risk to Participants or Others as defined above
4. If a full determination of the event cannot be made, the Chair/Designee will request additional information from the Investigator.
5. If the IRB Chair or designee determined that the event meets the definition of an unanticipated problem involving risks to participants or others, then the following actions will occur:
6. The event will be referred to the convened IRB for action
7. If participants are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair/Designee may immediately institute a suspension for cause or clinical hold according to IRB policy 7.9
8. The event will then be reported according to IRB policy 2.6
9. If the IRB Chair or designee determined that the event does not meet the definition of an Unanticipated Problem Involving Risk to Participants or Others, then the Chair/Designee will acknowledge the event and approve any

minor changes and the report will be placed in the notification to committee section of an upcoming agenda with no further action needed. If changes are determined to be major, the event will be acknowledged and the modifications will be placed in the updates to be reviewed by two reviewers section of an upcoming agenda.

IRB Committee Responsibilities relating to Unanticipated Problems Involving Risk to Participants or Others:

- 1) The Chair/Designee will attend the meeting and serve as a primary reviewer and present the Problem to the Committee in sufficient detail to allow Committee to take appropriate actions. The Chair may assign a secondary reviewer(s). All reviewers will have access to the reported event in order to follow along with report from the Chair/Designee, and as applicable secondary reviewer.
 - a. The IRB will take one of the following actions:
 - b. Accept the report
 - c. Accept the report, but require changes to the protocol and or the informed consent documents to address the changes in risk/benefit potential
 - d. Request re-consent of participants or require notification to participants (including past participants) of the changes. These changes must be reviewed by the IRB prior to notification
 - e. Request further information from the Investigator or Data and Safety Monitoring Board
 - f. Increase the frequency of continuing review
 - g. Request targeted reviews by the Office of Research Compliance or additional monitoring from an independent monitor.
 - h. Place a clinical hold on the study
 - i. Suspend the study for cause *per* IRB policy 7.9 with
 - k. Suspension of recruitment
 - l. Suspension of screening and enrollment
 - m. Suspension of intervention and interaction
 - n. Suspension of follow-up
 - o. Terminate the study for cause
 - p. Reporting to the Privacy Officer if the event involved any unauthorized use, loss, or disclosure of individually-identifiable patient information.

2) If the IRB determines that the event affects VA patients or VA policies, the UAMS IRB shall inform the VA IRB as appropriate..

3) The IRB and/or institutional officials designated in policy 12.4 will also determine and record whether the event represents serious or continuing

Statement
Re-Worded

noncompliance.

- 4) If deviations from the protocol occurred without prior IRB review to eliminate apparent immediate hazard to a research participant, the IRB will consider whether the changes were consistent with the rights and welfare of participants.
- 5) If the IRB determines that the event does not meet the definition of Unanticipated Problems Involving Risks to Participants or Others then the report will be acknowledged and filed to the study file with no further actions.

Two statements removed concerning review and reporting to VHA (Page 4 first paragraph & Page 5 section k)

Department: UAMS Institutional Review Board

Policy Number: 12.4

Section: Quality Assurances

Effective Date: February 04, 2005

Revision Date: June 1, 2005; April 5, 2007; October 5, 2007; March 5, 2008

Subject: Non-compliance with Human Research Protection Program Requirements - Formal Audit Reports as Findings of Noncompliance.

Statement
Re-Worded

Overview: The Vice Chancellor for Academic Affairs and Research Administration (VCAA/RA) or designees (hereafter VC) must review all formal audits from the Office of Research Compliance as findings of non-compliance. The VC bears the responsibility of examining the audit reports and classifying them as defined below under "Definitions". Reports of alleged noncompliance, protocol deviations, adverse events, unanticipated events or any other deviations from IRB approved protocols shall follow policy 12.5. All other findings of noncompliance shall follow policy 12.6.

The UAMS IRB, UAMS Office of Research Compliance (ORC) and the UAMS Vice Chancellor for Institutional Compliance (VCIC) are part of the University's Human Research Protection Program and therefore work cooperatively to assure compliance of all studies under the institution's purview. Institutions other than UAMS who use the UAMS IRB also have assurance requirements for compliance.

Definitions:

1. Minor Non-compliance: Failure to comply with applicable Federal Regulations, UAMS IRB policies and procedures, UAMS and/or other institutional policies and procedures, or the determinations of the UAMS IRB. Non-compliance may be unintentional or willful.

2. Serious Non-compliance: An action or omission taken by an Investigator (or study personnel) which places, or could place, a subject at risk of significant harm or affects the rights and welfare of human participants or violates the basic principles of the Belmont report to which the institution has promised to adhere. This category may also include actions that could compromise the validity and integrity of the research data.

3. Continuing Non-Compliance: A pattern of repeated actions or omissions taken by an Investigator (or study personnel) that indicates a deficiency in the ability or willingness to comply with Federal Regulations, UAMS and/or other institutional policies and procedures, or the determinations of the UAMS IRB or affects or could affect the rights and welfare of human subjects or violate the basic principles of the Belmont report to which the institution has promised to adhere.

If during review the VC suspects Scientific Misconduct, which is Fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results, the VC shall follow its institutional scientific misconduct policy

Audit Reports as findings of non-compliance

All audit reports are considered findings of non-compliance and must be investigated and acted upon as necessary. Such audit reports may be received from ORC, or from external auditing agencies as part of a routine audit or as a result of a directed audit.

Procedure for reviewing audit reports

1. Audit reports will be submitted to the VC for review and determination under this policy. Determinations shall be documented by completing the “Assessment of Noncompliance” form at the end of this policy. All other issues of alleged noncompliance or findings of noncompliance shall follow policies 12.5 and 12.6 respectively.
2. The VC may take immediate action prior to the convened IRB review if there is a finding of any imminent safety risks to subjects or possible significant deficiencies in the ability or willingness to comply with Federal Regulations, UAMS and/or other institutional policies and procedures, or the determinations of the UAMS IRB. The VC may temporarily suspend the study, terminate the study, and require other immediate remediation or additional protections as described below in part 4 and 5 respectively. If a drug study, VC will notify the appropriate Pharmacy of any suspension. The Investigator and the appropriate Research Pharmacist at the institution will be informed of such decisions by e-mail. All suspensions and terminations shall be reported to federal agencies as suspension of IRB approval.
3. After the VC assigns the level of noncompliance to the audit report, the decision is reported to the IRB. IRB members will have access to all the audit information at the convened meeting, but the Office of Research Compliance Director, or designee, will present a concise report of the findings, the classification, the remediation plan and/or the sanctions. At this meeting, the IRB will acknowledge the report and determine if the sanctions and remediation are adequate to protect the participants. The IRB shall notify the investigator and institutional officials of any additional requirements/decisions.
4. Sanctions the VC or IRB may consider and include in the notification to the Investigator but are not limited to the following:
 - a. Requiring additional information to make a determination.
 - b. Requiring additional investigator or study staff education.
 - b. Requirements for changes in study design or methodologies
 - d. Suspension of any or all of the following study activities:
 - i. Recruitment of subjects
 - ii. Screening and enrollment activities
 - iii. Research interventions and interactions or
 - iv. Follow up activities
 - e. Suspension of the investigator’s research privileges
 - f. Termination of the investigator’s research privileges
 - g. Termination of the study for cause
5. Additional protections may include, but are not limited to:
 - a. No further action may be needed if the Investigator has presented an adequate corrective action plan
 - b. Revision or modification of the protocol, consent or other study processes
 - c. Verification that subject selection is appropriate
 - d. Direct observation of the informed consent process by the ORC or individual IRB members
 - e. Require that current subjects be re-consented to participation
 - f. Enhanced monitoring of the research activity through such mechanisms as: the employment of data safety monitors or a data safety monitoring board, or continued evaluation by the ORC.
 - g. Request an off-cycle data and safety monitor or board review

- h. Request further directed reviews by ORC of targeted areas of concern
- i. Require the investigator to issue a status report after each subject receives an intervention
- j. Modify the continuing review cycle
- k. Require the Investigator and his or her staff receives focused education relevant to the area of non-compliance
- l. Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation
- m. Notification of other groups such as the CRC, PRMC, etc
- 6. Appropriate and timely communication to affiliate institutions involved will occur through the entire process.

12.4 Noncompliance Determination Form:

1. Did or could the event result in serious harm to subjects?
2. Did or could the event significantly impact the rights and welfare of human subjects?
3. Did or could the event significantly impact the research record or data integrity?
4. Was it an isolated event, first occurrence?
5. Was it part of a pattern of occurrences?
6. Was it reported by the investigator or by a third party?
7. Was it intentional?
8. Was it reckless?
9. Were laws, regulations or policies violated?
10. Was it serious as defined by this policy?
11. Was it continuing as defined by this policy?

Department: UAMS Institutional Review Board

Policy Number: 12.5

Section: Quality Assurances

Effective Date: March 5, 2008

Revision Date:

Subject: Reports of potential non-compliance

Formal audit reports will be handled in accordance with IRB Policy 12.4. However, other reports of potential non-compliance can come from investigators, members of the research team, study sponsors, OHRP, FDA, participants, committees on campus, interested third-parties and most of all during regular IRB review. These reports may be in the form of, but not limited to, deviations, violations, adverse event reports, publications, package insert changes, and complaints.

IRB Staff (including the Chair if available) shall review all reports of potential non-compliance by the following methods:

1. Compile information. If additional information is needed, contact the person who made the initial report and any other person involved to make sure all the facts are available.
2. Ask the following questions:
 - a) Does this information represent an action of non-compliance? If yes, refer to IRB Policy 12.6 regarding findings of noncompliance.
 - b) Is this information unanticipated AND does it indicate that participants or others are at increased risk of harm? If yes, place on IRB agenda and follow IRB Policy 10.2 and report as required by IRB Policy 2.6.If the answer to both questions is no, acknowledge the report.
3. If IRB Staff is unable to answer the questions in step 2, IRB staff will consult with IRB Director or IRB Chair for determination.

Department: UAMS Institutional Review Board

Policy Number: 12.6

Section: Quality Assurances

Effective Date: March 5, 2008

Revision Date:

Subject: Findings of non-compliance under IRB Policy 12.5

When IRB Staff, Chair or Director determine that information reported and reviewed under IRB Policy 12.5 rises to the level of noncompliance, these findings of noncompliance shall be classified using the federal regulation criteria for classification of noncompliance events. The IRB Staff (including the Chair) shall use the following format for each issue of noncompliance:

Classify – Report – Remediate - Follow Up Reports

Classify:

1. Minor Non-compliance: Failure to comply with applicable Federal Regulations, UAMS IRB policies and procedures, UAMS and/or other institutional policies and procedures, or the determinations of the UAMS IRB. Non-compliance may be unintentional or willful.

2. Serious Non-compliance: An action or omission taken by an Investigator (or study personnel) which places, or could place, a subject at risk of significant harm or affects the rights and welfare of human participants or violates the basic principles of the Belmont report to which the institution has promised to adhere. This category may also include actions that could compromise the validity and integrity of the research data.

3. Continuing Non-Compliance: A pattern of repeated actions or omissions taken by an Investigator (or study personnel) that indicates a deficiency in the ability or willingness to comply with Federal Regulations, UAMS and/or other institutional policies and procedures, or the determinations of the UAMS IRB or affects or could affect the rights and welfare of human subjects or violate the basic principles of the Belmont report to which the institution has promised to adhere.

If during review Scientific Misconduct is suspected, which is fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results, report the preliminary findings to the VC for Academic Affairs.

Report:

Report any incident of 2 and 3 to the IRB Chair immediately because subjects may be at risk. The IRB office must follow UAMS IRB Policy 2.6 for all incidents classified as 2;

and 3. Add to IRB agenda to allow the IRB to deliberate concerning remediation of the problem.

Remediate:

While not limited to the following, notification to the Investigator of the IRB determinations may include:

- a. Requiring additional information to make a determination.
- b. Requiring additional investigator or study staff education.
- b. Requiring changes in study design or methodologies
- d. Suspension of any or all of the following study activities:
 - i. Recruitment of subjects
 - ii. Screening and enrollment activities
 - iii. Research interventions and interactions or
 - iv. Follow up activities
- e. Suspension of the investigator's research privileges
- f. Termination of the investigator's research privileges
- g. Termination of the study for cause

5. Additional protections may include, but are not limited to:

- a. No further action may be needed if the Investigator has presented an adequate corrective action plan
- b. Revision or modification of the protocol, consent or other study processes
- c. Verification that subject selection is appropriate
- d. Direct observation of the informed consent process by the ORC or individual IRB members
- e. Require that current subjects be re-consented to participation
- f. Enhanced monitoring of the research activity through such mechanisms as: the employment of data safety monitors or a data safety monitoring board, or continued evaluation by the ORC.
- g. Request an off-cycle data and safety monitor or board review
- h. Request further directed reviews by ORC of targeted areas of concern
- i. Require the investigator to issue a status report after each subject receives an intervention
- j. Modify the continuing review cycle
- k. Require the Investigator and his or her staff receives focused education relevant to the area of non-compliance
- l. Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation
- m. Notification of other groups such as the CRC, PRMC, *etc*

6. Appropriate and timely communication to affiliate institutions involved will occur through the entire process.

Follow Up Reports

Because reporting under IRB Policy 2.6 requires very prompt turn-around, a preliminary report is often sent. After the IRB reviews non-compliance issues and decides on further remediation, a follow up report may be required in accordance with IRB Policy 2.6.

Department: UAMS Institutional Review Board

Policy Number: 15.5

Section: Consent Process

Effective Date: April 5, 2007 ; March 5, 2008

Revision Date:

Subject: The Informed Consent Process

Policy: In studies for which informed consent must be obtained, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such 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. This SOP describes, in general terms, the requirements for the informed consent process and the IRBs duty to monitor this process in certain situations. Additional requirements may also apply in certain instances, such as the inclusion of vulnerable populations, and are described in UAMS IRB SOP Nos. 17.1 through 17.13.

Procedure:

1. In the initial IRB submission, the PI will explain in detail the consent process, both initial and ongoing. Investigator should identify at a minimum:
 - Who will conduct the consent interview;
 - The timing of obtaining informed consent;
 - The waiting period between providing information about the research and obtaining consent;
 - Whether the medical or research record will be noted; and
 - How the Investigator will assure that there will be ongoing communication between the research team and participant regarding issues related to ongoing informed consent to participate.

The IRB may request further clarification of or amendments to the informed consent process as part of its study review.

2. The PI or study staff is also required to document the informed consent process in either the subject's research record or medical record. A note separate from the consent form itself that includes, at a minimum, the following items is appropriate documentation of the informed consent process:
 - 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

- A statement that the subject had an opportunity to ask questions about the research and have those questions answered and that they were given a copy of the signed form. The person who obtained consent should sign and date this note.

At the time of the informed consent process, each subject must be given a copy of the signed and dated informed consent document. For those subjects that have a medical record, a copy of the subject's informed consent should be placed in the medical record. The original should be retained by the PI.

Monitoring the Consent Process

The IRBs can have a third party observe the informed consent process in research projects as necessary. (AAHRPP Element II.7.G.) An IRB may require that a staff member or an outside third party observe the consent process as it takes place with the human subject accounting for the following:

- Is or was consent appropriately completed and documented?
- Did the participant have sufficient time to consider study participation and did the subject appear to be coerced by those consenting?
- Was the process understandable, both the form and the information presented on the day of consent?

The IRB can order monitoring of consent based on the following criteria:

- Risk greater than minimal
- Complicated procedures, interventions or research designs.
- Any vulnerable population.
- Staff with minimal experience.
- In any situation where the IRB sees the need for extra protections

Section removed from Page 3 third paragraph concerning special documentation practices at CAVHS

Department: UAMS Institutional Review Board
Policy Number: 18.3
Section: Drugs and Devices
Effective Date: July 31, 2002
Revision Dates: February 8, 2005; August 26, 2004; March 5, 2008

SUBJECT: Emergency Use of a Drug or Biologic (Source *FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators 1998 Update*)

Purpose: The purpose of this policy and procedure is to explain the limited circumstances where prior IRB approval is not required in the emergency use of an investigational drug or biologic.

Definitions:

Emergency Use means the 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 there is not sufficient time to obtain IRB approval.

Test Article. A test article is defined as any drug, biological product or medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act. As used hereafter, it shall only apply to investigational drugs or biological products. Emergency Use of a Medical Device is addressed in Policy 18.4.

Life Threatening. Life threatening includes the scope of both life threatening and severely debilitating, as defined below:

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

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Policy: The IRB acknowledges that there will be certain limited circumstances where IRB approval will not be obtainable prior to the first use of a test article. FDA requirements for emergency use must be met, and the IRB requires prior notification of test article use. The IRB will acknowledge this one time use and require a follow up report. Any subsequent use of the test article will require full IRB review and approval prior to use. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had time to convene a meeting.

Warning: Submission of a standing protocol is required within 30 days as a condition of emergency use

Warning: No new emergency uses will be granted without the protocol and failure to submit a protocol within 30 days will be treated as continuing non-compliance. For your patient's safety, please submit a protocol immediately.

Under FDA regulations emergency use of a test article is considered research. Under DHHS regulations emergency use of a test article is not research because it is not a systematic investigation designed to generate or contribute to generalizable knowledge. To maintain this distinction data from an emergency use cannot be used in any report of a prospectively conceived research activity.

Procedure:

1. Principal Investigator will:

1.1 Obtain an IND (Investigational New Drug) number from the manufacturer, if possible, or if the manufacturer elects not to name the PI on the IND, the PI should then contact the FDA directly for an IND or obtain evidence of an IND Exemption.

1.2 Notify the IRB, verbally, when a situation arises that calls for the emergency use of an investigational drug or biologic without an approved study protocol to obtain a determination from the IRB chair that the situation meets the regulatory requirements for an emergency use, and submit a letter to the IRB stating the following;

- a. The participant was in a life-threatening situation
- b. There is no standard acceptable treatment available
- c. There is not sufficient time to obtain IRB approval.
- d. The diagnosis, test article to be used and proposed use, and hospital.

1.3. Obtain the consent of the participant or the legally authorized representative of the participant unless the PI and a physician who is not otherwise participating in the clinical investigation both make all of the following assurances:

- a. Participant in a life threatening situation
- b. All other available treatments are either unproven or unsatisfactory
- c. Participant unable to give consent due to their medical condition
- d. There is no time to obtain consent from LAR

1.4. If in the PI's opinion, immediate use of the test article is necessary to

save the participant's life and time does not permit seeking the opinion of a physician not otherwise involved, the PI should make the above determinations and proceed with the use. Within 5 working days after the use of the article, the PI should have the use of the test article reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

1.5 Within 5 days of the use of test article, the PI should submit a follow up report to the IRB that includes

- a. Name of test article used, detailed conditions of use and date of IRB verbal acknowledgement
- b. Date, time and location of use
- c. Participant's diagnosis and outcome if known
- d. Any adverse events or unanticipated problems
- e. Copy of the signed informed consent OR letters from the PI and the independent physician stating:
 - i.. The participant was in a life threatening situation
 - ii. All other available treatments were either unproven or unsatisfactory
 - iii. The participant was unable to give consent due to their medical condition
 - iv. There was no time to obtain consent from a LAR

1.6 Evaluate the likelihood of needing to use the test article again. If additional use is anticipated, immediately submit protocol and consent for full IRB review under separate ARIA submission

2. IRB Chair or Vice Chair will:

2.1 Evaluate the Investigator's notice of intent to use a test article under these guidelines to determine whether FDA regulatory requirements are met.

2.2 Request the information listed in 1.2, assessment of consent process, or any other materials that will aid in the evaluation.

2.3 Provide initial verbal acknowledgement and shortly thereafter, written acknowledgement, through ARIA, of intent to use test article.

2.4 Review the follow-up report to determine whether FDA regulatory requirements are met. If FDA regulations were not met, the matter will be handled according to IRB policies and procedures for non-compliance.

2.5 Arrange for full committee notification on next available agenda.

Department: UAMS Institutional Review Board
Policy Number: 18.4
Section: Drugs and Devices
Effective Date: July 31, 2002
Revision Dates: February 8, 2005; August 26, 2004, March 5, 2008

SUBJECT: Emergency Use of an Unapproved Medical Device (Source *FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators 1998 Update*)

Purpose: The purpose of this policy and procedure is to explain the limited circumstances where prior IRB approval is not required in the emergency use of an unapproved investigational device.

Definitions:

Emergency Use means the 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 there is not sufficient time to obtain IRB approval.

Life Threatening. Life threatening includes the scope of both life threatening and severely debilitating, as defined below:

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

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Test Article: A test article is defined as any drug, biological product or medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act. As used hereafter, it shall only apply to unapproved investigational medical devices. Emergency Use of Drugs or Biological Products are addressed in Policy 18.3.

Policy: The IRB acknowledges that there will be certain limited circumstances where IRB approval will not be obtainable prior to the first use of an unapproved investigational device. FDA requirements for emergency use must be met, and the IRB requires prior notification of the use. The IRB will acknowledge this one time use and require a follow up report. Any subsequent use of the test article will require full IRB review and approval prior to use, and an approved IDE.

Warning: Submission of a standing protocol is required within 30 days as a condition of emergency use

Warning: No new emergency uses will be granted without the protocol and failure to submit a protocol within 30 days will be treated as continuing non-compliance. For your patient's safety, please submit a protocol immediately.

Under FDA regulations emergency use of a test article is considered research. Under DHHS regulations emergency use of a test article is not research because it is not a systematic investigation designed to generate or contribute to generalizable knowledge. To maintain this distinction data from an emergency use cannot be used in any report of a prospectively conceived research activity.

Procedure:

1. Principal Investigator will:

1.1 Determine whether device can be used under manufacturer's IDE or be able to justify to FDA that all emergency requirements are met.

1.2 Notify the IRB, verbally, when a situation arises that calls for the emergency use of an unapproved investigational device without an approved study protocol to obtain a determination from the IRB chair that the situation meets the regulatory requirements for an emergency use, and submit a letter to the IRB stating the following;

- a. The participant was in a life-threatening situation
- b. There is no standard acceptable treatment available
- c. There is not sufficient time to obtain IRB or FDA approval.
- d. The diagnosis, test article to be used and proposed use, and hospital.
- e. Assess the potential for benefits and have substantial reason to believe the benefits will exist

f. Assure the IRB that an emergency actually exists and decision is based on that and not that the IDE approval process takes more time than available.

1.3 Assure the IRB that the device manufacturer will notify the FDA of the emergency after shipping of the device. An unapproved device may not be shipped in anticipation of an emergency.

1.4. Obtain the consent of the participant or the legally authorized representative of the participant unless the PI and a physician who is not otherwise participating in the clinical investigation both make all of the following assurances:

- a. Participant in a life threatening situation
- b. All other available treatments are either unproven or unsatisfactory
- c. Participant unable to give consent due to their medical condition
- d. There is no time to obtain consent from LAR

1.5. If in the PI's opinion, immediate use of the test article is necessary to save the participant's life and time does not permit seeking the opinion of a physician not otherwise involved, the PI should make the above determinations and proceed with the use. **Within 5 working days after the use of the article, the PI should have the use of the test article reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.**

1.6 Within 5 days of the use of test article, the PI should submit a follow up report to the IRB that includes

- a. Name of test article used, detailed conditions of use and date of IRB verbal acknowledgement

- b. Date, time and location of use
- c. Participant's diagnosis and outcome if known
- d. Any adverse events or unanticipated problems
- e. Copy of the signed informed consent OR letters from the PI and the independent physician stating:
 - i.. The participant was in a life threatening situation
 - ii. All other available treatments were either unproven or unsatisfactory
 - iii. The participant was unable to give consent due to their medical condition
 - iv. There was no time to obtain consent from a LAR

1.7 Evaluate the likelihood of needing to use the test article again. If additional use is anticipated, immediately submit protocol, consent and approved IDE for full IRB review under separate ARIA submission. If IDE application is disapproved by the FDA, the device cannot be used even in an emergency.

2. IRB Chair or Vice Chair will:

2.1 Evaluate the Investigator's notice of intent to use a test article under these guidelines to determine whether FDA regulatory requirements are met.

2.2 Request the information listed in 1.2, assessment of consent process, or any other materials that will aid in the evaluation.

2.3 Provide initial verbal acknowledgement and shortly thereafter, written acknowledgement, through ARIA, of intent to use test article.

2.4 Review the follow-up report to determine whether FDA regulatory requirements are met. If FDA regulations were not met, the matter will be handled according to IRB policies and procedures for non-compliance.

2.5 Arrange for full committee notification on next available agenda.