EVMS
Eastern Virginia Medical School

INSTITUTIONAL REVIEW BOARD

STANDARD OPERATING PROCEDURES

RESEARCH SUBJECTS PROTECTIONS
ANDREWS HALL, SUITE 128

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1. OVERVIEW OF EVMS INSTITUTIONAL REVIEW BOARDS

1.1 THE MISSION OF THE INSTITUTIONAL REVIEW BOARDS

The Institutional Review Boards (IRBs) at Eastern Virginia Medical School (EVMS) have the fundamental charge of protecting the rights and welfare of human subjects in behavioral, medical or health-related research studies. To achieve this, two EVMS IRBs have been established to review and monitor human subject research activities at EVMS and within the EVMS community. There are also opportunities to cede review to other IRBs depending on the type of study.

The federal regulations define research as a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge". The EVMS Research Subjects' Protections (RSP) office and/or the EVMS IRBs make determinations on whether certain projects meet the definition of research, as well as what level of review is needed for a research study.

The EVMS IRBs are registered with the Department of Health and Human Services (HHS) and a Federalwide Assurance (FWA) is on file with the Office of Human Research Protections (OHRP).

The EVMS FWA assures the HHS that activities related to human subject research are guided by the ethical principles of The Belmont Report and the Code of Federal Regulations, 45CFR46.

In addition to the Public Health Service Regulations 45 CFR 46, the EVMS IRB is also guided by regulations (21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 600, 21 CFR 812) of the Food and Drug Administration (FDA), which monitor the use of experimental drugs, biologics and medical devices. Also, with a few exceptions, the International Conference of Harmonization (ICH), Good Clinical Practice (GCP) and any applicable state and local laws and regulations guide the EVMS IRB.

1.2 ETHICAL CODES

The Nuremberg Code, the Declaration of Helsinki and the Belmont Report are three ethical codes that provide the foundation for reviewing human subjects research.

FUNDAMENTAL ETHICAL PRINCIPLES OF THE BELMONT REPORT

The Belmont Report was completed on April 18, 1979 and the drafters of the document included consideration of rules like the Nuremberg code in the identification of the broad ethical principles under which human subject research is conducted.

The three principles of The Belmont Report, which help guide human subject research are:
• Respect for Persons
• Beneficence
• Justice

The principle of "Respect for Persons" means that each individual is to be treated as autonomous, capable of making decisions about themselves and their personal goals. Potential research subjects must be given sufficient time and information upon which to base their decisions about participation. The process of informed consent is how the regulations apply this principle to research.

"Beneficence" means that researchers should maximize the benefits of participating in research studies and minimize the possible risks. The IRB applies this principal when conducting a risk/benefit analysis.

The principle of "Justice" evolves around the question of who ought to receive benefits of research and who ought to bear the burden of possible risks. Ensuring that there is a fair subject selection and that one group is not asked to bear the burden of risk when the benefit(s) may only apply to another group helps ensure the principle of justice is met.

These three principles of The Belmont Report are implemented through the processes of informed consent, risk/benefit assessment, and fair subject selection. The chart below summarizes how the three principles are applied to research studies.

Informed Consent	Risk/Benefit Assessment	Subject Selection
Sharing of information.	Weighing the balance of risks with the opportunity of benefits.	Selecting subjects on the basis of fairness.
Ensuring subject comprehension.	Do no harm.	Not selecting favorite subjects for beneficial studies or "undesirables" for risky research.
Selecting volunteers for study without coercion or undue influence.		

More information about The Belmont Report may be found on the Research Subjects' Protections website: (https://www.evms.edu/research/human_subjects_protection/). Also found there are the Code of Federal Regulations regarding human subject research, including 45CFR46, 21CFR50, 21CFR56, and the EVMS human subjects training program.

1.3 ROLE OF THE IRB IN ETHICAL REVIEW

Guided by the principles set forth in the Nuremberg Code, The Declaration of Helsinki, The Belmont Report, FDA laws and regulations, and Office for Human Research Protections (OHRP) laws and regulations, the IRB assures that:

Risks to subjects are minimized and are reasonable in relation to the anticipated benefits:
• Selection of subjects is equitable;
• Documented, informed consent is obtained from each prospective subject or the subject's legal guardian or healthcare decision-maker;
• Informed consent is appropriately obtained and documented;
• Provisions are made for the protection of the privacy of subjects and that confidentiality of data is maintained;
• Provisions are made for monitoring the data collected to ensure the safety of subjects; and
• Safeguards are included to protect members of vulnerable population groups.

The IRBs consist of physicians, research scientists, behaviorists, non-scientists, members from outside EVMS, and other members with varying backgrounds to promote complete and adequate review of research activities commonly conducted at EVMS as well as at the institutions that have signed an IRB Authorization Agreement or Reliance Agreement.

1.4 INSTITUTIONS REPRESENTED BY THE EVMS IRBS

Institutions which have designated the EVMS IRBs to serve as a reviewing body for human research conducted at their sites include: Children's Health System, including The Children's Hospital of The King's Daughters (CHKD), CMG and CSSG; Children's Specialty Group; Urology of Virginia, Sentara Healthcare (inclusive of hospitals and medical group), and Virginia Oncology Associates.

As designated by the FWA, the EVMS IRBs have the authority to approve, approve with modifications, or disapprove new research proposals or continuing studies involving research with human subjects for these institutions when such studies are submitted to or are under the oversight of an EVMS IRB. In addition, the IRB has the authority to terminate or suspend research for good cause.

All research protocols that are performed in the hospital or clinical care sites must also be submitted to the established mechanisms for review at those hospitals, for example, the CHKD Hospital Research Committee (HRC); the Sentara Health Research Center for all Sentara sites; etc.). No officials or committees of these organizations may approve human subjects research that has not been approved by an IRB. No new research can be started until both an IRB and any appropriate hospital committee grant approval. It is the sole responsibility of the investigators and research team to ensure that the appropriate approvals are in place *prior to* initiating research at any site. Not obtaining these approvals will be considered non-compliance with this policy.

1.5 RESPONSIBILITIES OF INVESTIGATORS

Responsibilities of Investigators
OBTAIN WRITTEN IRB APPROVAL BEFORE INITIATING ANY RESEARCH PROCEDURES OR ACTIVITY. For EVMS faculty, trainees and staff, approval must be through an EVMS IRB or an IRB approved by the Research Subjects' Protections office via a signed IRB Authorization Agreement (IAA) or Reliance Agreement. The agreement must be routed through the RSP office to be signed by the EVMS Institutional Official. Obtaining another IRB approval without a signed IAA or Reliance Agreement is not acceptable.
TRAINING: • Complete required human subjects training (CITI) and provide verification of completion *before* submitting protocols for IRB review. • Complete HIPAA research training (included in CITI online training modules). • Assure that human subjects training verification is submitted for all personnel directly associated with a human subjects research study *before* including those individuals on any research study. Investigators are not allowed to remove already approved team members for lack of training and then seek to add them later. Team members must be current and if not, can be removed but no longer assist with the study. • Review training materials and all relevant Federal and State regulations, and all EVMS policies regarding the protection of human research subjects. • Attend training sessions when provided by the institution. • Have a current Investigator Assurance (IA) on file with the EVMS IRB. The IA must be renewed every three years.
STANDARD OPERATING PROCEDURES AND FEDERAL REGULATIONS: • Submit and receive an EVMS IRB approval before initiating any human subjects research. If using an IRB other than EVMS, investigator must ensure an IAA is in place between EVMS and the other IRB before initiating ANY study activity. The IAA must be processed through the Research Subjects' Protections office. • Distribute current IRB policies and procedures to staff members. • Use the most current version of IRB forms. • Review relevant State and Federal regulations, legislation, and institutional assurance documents relevant to the proper conduct of research in human subjects, particularly those that are pertinent to subject populations involved in investigator's research studies (e.g., children, cognitively impaired individuals, pregnant women, fetuses and others). • Comply with all EVMS SOPs and federal, state and local regulations for human subject research. • Comply with the EVMS Federalwide Assurance.
PROTOCOL DOCUMENTATION: • Maintain active research protocols in an approved status for ongoing human subjects research. • Assure the accuracy and completeness of all documents submitted to the IRBs. • Each principal investigator and Department Chair must verify the scientific merit of a

Responsibilities of Investigators
new study before submitting the study for IRB review. Based on information submitted by the principal investigator, the appropriate department chair (or designee) certifies the scientific merit of the study for his/her department. If the PI has any EVMS faculty appointment, the EVMS Department Chair must sign. • Submit timely IRB documentation required for Federal grants or other funding sources.
PROTOCOL MANAGEMENT: • Ensure that changes in approved research are not initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to subjects. Any changes implemented for subject safety must be submitted to the IRB immediately as an amendment. • Provide written notification of a change in association with a research study or with the institution. These changes are recorded in the Board Minutes.
CONTINUING REVIEW: • Provide timely submission of Continuing Review reports, at least two months prior to the anniversary of the previous approval date. • Submission of the Continuing Review is the responsibility of the PI and should not be dependent of receiving any reminder notices. If a study expires, the PI must stop all study activities immediately until a review and renewal is conducted by the IRB. • Any data collected during a period where IRB approval was halted cannot be saved.
COMMUNICATION: • Promptly notify the IRB of protocol deviations that affect the risk/benefit ratio to subjects or the integrity of the research study. • Promptly inform the IRB of unanticipated problems and Adverse Events involving risks to human subjects or others. • Promptly communicate the results of ALL outside audits to the IRB. • Communicate IRB approvals and other communications to sponsors • Serve as the link between the IRBs and sponsors. The IRB or its representatives will not discuss studies directly with sponsors because it is important the PI is aware of and involved in all discussions.
REPRESENTATION: • All full-time EVMS faculty, trainee or staff engaging in human subject research must utilize an EVMS IRB or an IRB approved with via an IRB Authorization Agreement (IAA) or Reliance Agreement processed through the Research Subjects Protections office. • All EVMS faculty who are NOT full-time but using their EVMS credentials or referencing EVMS in the publication of human subjects research must use an EVMS IRB or an IRB approved with via an IRB Authorization Agreement (IAA) or Reliance Agreement processed through the Research Subjects Protections office. .

1.6 REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH SUBJECTS

All investigators and their research team members who engage in human subjects research must complete human subjects protections training. Training is mandatory and required to be

in place before IRB approval of all new protocols and re-approval of all active protocols. A research team member is anyone working on any part of a research project that required IRB review. All persons, including residents, students, coordinators, and data management, are considered team members if their effort contributes to a research study.

Contact the Research Subject's Protections office at (757) 446-8423 for additional information on all research training requirements. To complete the EVMS approved training, log into the CITI training site (https://about.citiprogram.org/en/homepage/), choose Eastern Virginia Medical School as your institution and complete the training. Training can be verified as long as you use the same name and email address that is used in the IRBManager protocol tracking system.

1.7 INVESTIGATOR ASSURANCE

All investigators conducting human subject research under an EVMS IRB or an IRB approved by EVMS are required to complete an "EVMS IRB Investigator Assurance." This document must be re-submitted every three years. The form is available on the IRB website under "Forms".

1.8 CONFLICT OF INTEREST (COI) - FINANCIAL, NON-FINANCIAL DISCLOSURE

Questions regarding the EVMS Conflict of Interest (COI) policy must be directed to the Office of Research, (757) 446-8480.

It is the responsibility of the Principal Investigator to notify the IRB when a potential for conflict of interest (COI) exists, whether significant financial interests (entitlements to payments in connection with the research not directly related to the reasonable costs of the research) or otherwise. It is the responsibility of the IRB to ensure that any potential COI does not pose a possible risk to subjects or potential subjects involved in the study. The IRB's concern about an investigator's possible COI is in the impact on human subjects' protection, specifically clinical decision-making by the investigator, the integrity of the consent process, including the rights of research subjects to have such information for consideration, and the integrity of the research (and thus its merit and the merit of putting subjects at risk).

Investigators submitting protocols through the EVMS IRB must indicate on IRB forms whether any research team member, their family members or any other person responsible for the design, conduct or reporting of the research have done the appropriate filing(s) with the Office of Research:

- If your project is sponsored you must meet the EVMS COI Policy requirements before a final approval can be issued. You also must notify the IRB of the COI determination.
- Refer to the Office of Research *Policy on Conflicts of Interest in Research and Sponsored Projects* (COI).
- For questions regarding the COI Policy and COI submissions contact the Office of Research at 446-8480.

If an individual has a sponsored project, they must be able to attest that all three of the above criteria have been met ***prior to* consideration by the IRB. EVMS policy requires these attestations before investigators can proceed with a submission. IRB/RSP staff cannot make exceptions, even in cases where funding may be in jeopardy. Therefore, it is imperative that investigators plan their submissions accordingly.**

2. WHAT IS SUBJECT TO REVIEW?

2.1 SCOPE OF REVIEW

All research that uses human subjects, tissues/specimens from humans, data/records from human subjects, or involves interaction or intervention with humans requires review and approval from the IRB. Quality assurance, quality improvement, and program evaluations as well some other projects have the potential to involve human subjects and therefore are subject to a determination by the Research Subjects' Protections office, which may defer a decision to an EVMS IRB.

Activities that may not fall under the purview of the IRB include operational activities such as: medical care, certain aspects of public health practice such as routine outbreak investigations and disease monitoring, fiscal or program audits, journalism, history, biography, philosophy, "fact-finding" inquiries such as criminal, civil and congressional investigations, and intelligence gathering. This list does not include all possible activities, so the Research Subjects' Protections office must be consulted *prior to* initiation to verify that an activity does not fall under the purview of the IRB.

Investigator requests for any type of review after a project has been initiated will not be granted and may be determined to be non-compliant with this policy and/or human subject research regulations.

2.2 WHOSE RESEARCH IS REVIEWED?

The EVMS requirement for an EVMS IRB review extends to human subject research conducted by:
• Any **EVMS full-time faculty**. This applies to all research that a full-time faculty member is involved in regardless of their role or the location of the research.
• Any **EVMS trainee** (student, resident or fellow).
• **Community faculty members** who do not have a full-time faculty appointment, but who will be using their EVMS credentials in conducting the research or in any publication or presentation of research results.
• Any **EVMS staff member** conducting research as part of their EVMS employment or use of their EVMS job title.

Each research study submitted for review can list only one principal investigator. A principal investigator may be EVMS faculty or staff, or staff at any institution that has an IRB Authorization Agreement with EVMS. Trainees may only be principal investigators if their department policy allows them to serve in that role and, when the IRB approves. Trainees who are conducting a project for degree requirements should have a written plan included in their study protocol to turn the project over to another investigator if not complete at the time of graduation. Co-investigators may be faculty members, community faculty, residents, students, nurses,

collaborators at other institutions, or others who are adequately trained to play a significant role in the research project. However, only individuals to be covered by the EVMS IRB review are to be included on the Application Form.

On occasion the EVMS IRBs may also review research conducted by independent researchers if an Independent Investigator Agreement is secured. The staff in the Research Subjects' Protections office can assist an investigator with this process.

In summary, all EVMS faculty members and trainees must submit their human subjects research to an EVMS approved IRB. If a community faculty member or EVMS staff member plans to use his/her EVMS credentials with a human subjects research study, an EVMS approved IRB must approve that study as well.

2.3 COLLABORATIVE PROJECTS

Projects with colleagues at other institutions need to be discussed with the Research Subjects' Protections office. Many funders now require or request that a Single IRB Review (sIRB) occur. This may be done by one of the institutions involved in the study or by a commercial IRB such as Advarra. Any arrangement for using other IRBs or asking EVMS to serve as the single IRB must be done with an appropriate agreement that is processed by the RSP office and then signed by the Institutional Official (or their designee) for each party.

In addition, EVMS participates in the SMART IRB initiative as a Relying Institution. SMART IRB is a platform designed to ease common challenges associated with initiating multisite research and to provide a roadmap for institutions to implement the NIH Single IRB Review policy (effective date: January 25, 2018).

3. IRB FEES

Basic Fees for funded studies reviewed by a Convened Board of one of the two EVMS institutional IRBs .*	Amount
New protocol requiring convened Board review [One time fee due as billed after the study has received Board review]	$1,750.00
Continuing Review of a study requiring convened Board review [Fee due as billed after the study has received Board review for continuation, due after each continuation decision]	$ 500.00
***Please Note:** This schedule **does not** apply to studies submitted to Advarra. Review by Advarra or any other IRB is allowed on a case-by-case basis. Investigators wishing to use Advarra should contact the Research Subjects' Protections office (446-8423) for information on Advarra services and fees. Sponsors or investigators must agree to all fees prior to submission and pay the IRB directly. Therefore, individuals must adequately plan the study budget.	

Full-time faculty, community faculty and non-EVMS investigators who use the IRB review and management process and receive extramural support for protocols are expected to remit the IRB fees upon billing by EVMS. Waiver of the fee may be considered in the event that protocols are not supported (see Wavier of IRB Fees under Forms on the IRB website). Fee waivers for convened Board review must be requested at the time of initial review.

No review fee is charged for protocols that are designated either "expedited" or "exempt" by the IRB.

4. NEW SUBMISSIONS – EVMS INTERNAL IRB APPLICATION PROCESS

4.1 SUBMISSION TIMELINE – NEW PROTOCOLS

New protocols can be submitted at any time electronically using the current IRBManager database. There are no set deadlines for submitting studies. Protocols are assigned to agenda based on the quality of submission, the type of study, and available agendas. New protocols are considered by the appropriate Board in the order they are verified as a complete submission by the Research Subjects' Protections staff. Electronic agenda packets are distributed 7-10 days prior to a meeting to the appropriate Chair, Vice Chair, and Board members for their review.

4.2 THE PROCESS OF INFORMED CONSENT

The process of informed consent is one of the most important parts of planning a research study. It is important that human subjects are allowed to exercise their right of free will in making the decision to participate. It is equally important that potential subjects be given the correct information, comprehend what is being explained and be able to read the document and have the time to make their own decision about participation. Discussion with family and others should be encouraged when asking an individual to participate in a research study. Allowing a potential subject to have a day or more to consider and discuss their options is a best practice that is especially encouraged in higher risk studies.

Any research team member may obtain Informed Consent by serving as a Designee for the PI. This Designee option must be noted in the signature block of the informed consent approved by the IRB. Anyone obtaining consent must take CITI training, be adequately trained by the PI, and be specifically approved by the IRB on the Application Form.

The following must take place during the consent process:
1. Review of recruitment materials
2. Verbal instructions
3. Written material – review the consent and protocol requirements in detail. As above, potential subjects must be given adequate time to consider participation. Consent must be done such that potential subjects have the opportunity make their decision in private and free from any coercion or undue influence.
4. Questions/answer sessions – Q & A may take some time to complete. There should be multiple opportunities for a potential subject to ask questions and the process should recur over time.
5. Agreement by documented signature – all parties MUST sign at the same time with the date (and, if applicable, time) noted on the consent document in the signature block.

Prospective participants may elect to not sign the consent form at the initial time of the consent discussion. Subjects should never be pressured to sign immediately. It is their right to take the consent form home and discuss it with family and friends. **However, prospective subjects may not participate in the study until they have signed the last IRB approved version of the consent form.**

Subjects must be informed that it is their right to withdraw from a study at any time. The consent form must be read to any subjects who cannot read and this process documented by using a witness (who is not a member of the research team). The witness must sign the Witness the consent in the appropriate signature block.

For subjects who do not read English, the consent form must be translated into a language the subject comprehends. All translations must be approved by the IRB prior to use. The translated submission must have a letter of attestation from a qualified translator.

In cases where the potential subject cannot read the consent form, it must be read to the individual and a witness signature is required on the form. This signature indicates that a witness was present during the reading/interpreting of the consent form and that it was presented in a manner that was comprehendible to the subject. The witness cannot be anyone associated with the study, such as an investigator or research team member.
Children and other vulnerable subjects may need information presented as simply and straightforwardly as possible. An "Assent of the Child" form must be provided for IRB consideration when submitting a study involving children 8 y.o. or older.

One or more (as appropriate) of the Subject Consent Form templates must be customized with details of the study and approved by the IRB and used during the consenting process. In cases where a model or template is available from a sponsor or other party, sites must start with the EVMS template and add in the other party's information where appropriate. The IRB may consider combining EVMS templates where it finds the combination makes for a more understandable process to the potential subject.

The IRB will consider telephone consent if it provides for the following:

- A very detailed script which must be followed by the telephone surveyor; and
- Written documentation sent to the subject summarizing the survey event (such documentation shall include the study title, date and time the survey took place and indicate that consent was given);
- A written log to be maintained by the investigative site containing the subject's name who was contacted by phone; did they consent (Y or N); who witnessed the verbal consent discussion; who obtained verbal consent; and the date and time the verbal consent was done.

The detailed script to be followed by the telephone surveyor must, at a minimum, include the following information:

- A description in "lay persons language" of the research activity, its purpose, duration of participation, the experience that will be encountered, and any procedures to be followed;
- A description of the benefits, if any, that the study subjects may reasonably expect to encounter;
- A description of any alternative to participating in the research project;
- The extent to which personally identifiable private information will be held in confidence;
- When applicable, if research-related injury (i.e. physical, psychological, social, financial, or otherwise) is possible in research that is more than minimal risk, an explanation must be given of whatever voluntary compensation and treatment will be provided;
- The identification of contact persons who would be knowledgeable to answer questions from the subject about the research, rights as a research subject, and research related injuries; and
- A clear statement, in compliance with 45 C.F.R. 46.11(a)(8) regarding the voluntary participation and the right of the participant to withdraw anytime.

4.3 DETERMINING THE TYPE OF EVALUATION

There are four levels of evaluation that a project or research study may undergo, depending on the level of risk to potential human subjects.

The four levels of review are:	
1.	Evaluation of whether the project is research vs non-research AND/OR for the involvement of human subjects;
2.	Exempt from regulations addressing IRB review;
3.	Expedited IRB review; and
4.	Convened IRB review.

NOTE: THE LEVEL OF EVALUATION *CAN ONLY* BE DETERMINED BY THE RESEARCH SUBJECTS' PROTECTION (RSP) OFFICE OR ONE OF THE EVMS IRBS USING A SINGLE REVIEWER OR COMMITTEE REVIEW PROCESS. Even if an investigator believes a study is exempt, no research may begin until RSP or the IRB reviews the protocol and issues a written final determination.

4.3.1 Evaluation of research vs non-research and for involvement of human subjects

The RSP office and/or the EVMS IRB has oversight authority to determine if a study can be classified as "Not Human Subjects Research (NHSR)" or "Not Research (NR)". These projects may be: 1) "research" by definition, however they do not involve human subjects; or, 2) other projects such as quality assurance or program evaluation that do not meet the definition of "research".

DOCUMENTATION REQUIRED

The process to have a study evaluated for the involvement of human subjects requires the submission of a one-page summary or other available document that outlines the details of the project. Case report forms, data sheets or materials that will be given to individuals to gather information must be attached. The request must be made through the current electronic submission process.

4.3.2 EVALUATION OF HUMAN SUBJECT INVOLVEMENT

Evaluation of the project will be done by the IRB Director, Assistant Director or other IRB office personnel. If there is a need for further evaluation, then either an IRB officer (Chair or Vice Chair) or a sub-committee of the IRB will be asked to make the decision as to whether the study is research that involves human subjects. If the determination is made that the study is human subjects research, it is referred back to the principal investigator for preparation for exempt, expedited or convened Board review. If the study does not involve human subjects, a letter is provided to the investigator documenting the review and decision. These studies are entered into the IRB database, but do not require annual reporting. IRB numbers are assigned for tracking purposes.

5. EXEMPT FROM BOARD REVIEW

5.1 TYPE OF RESEARCH QUALIFYING FOR EXEMPTION

Exempt status may be granted by the IRB for research that meets one or more of the criteria listed in the federal regulations. EVMS policy requires that investigators submit to the IRB for an exempt approval; investigators are not allowed to make any such determination:

Research that may be considered as exempt from the requirements in the federal regulations includes the following categories:
Category 1: Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
Category 2: Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met: The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
Category 3: Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met: The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

Research that may be considered as exempt from the requirements in the federal regulations includes the following categories:

Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Category 4:

Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

The identifiable private information or identifiable biospecimens are publicly available;

Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b); or

The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private

Research that may be considered as exempt from the requirements in the federal regulations includes the following categories:
information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*
Category 5: Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects.
Category 6: Taste and food quality evaluation and consumer acceptance studies: If wholesome foods without additives are consumed, or If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
Category 7: Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).
Category 8: Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met: Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d); Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117; An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the

Research that may be considered as exempt from the requirements in the federal regulations includes the following categories:
study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

5.2 DOCUMENTATION REQUIRED FOR EXEMPTION

The application process to have a study evaluated for exempt status is the same as that for Convened Board review (see Section 7). A complete submission includes an Application, protocol and other supporting documents. (For information regarding the content of a protocol, see Section 7.) Case report forms, data sheets or materials that would be given to subjects, or other items that could possibly contain subject identifiers or descriptors must be attached.

EVALUATION OF EXEMPTIONS

It is the responsibility of the IRB, not the investigator, to determine if a study qualifies for exempt status. A sub-committee of the IRB makes the decision as to whether the study qualifies for exempt status. If the study qualifies for exempt review and is approved, a notice confirming approval for the study will be sent to the principal investigator. Exempt studies are tracked by the IRB Office until completion.

If the study does not qualify as exempt, it is referred back to the principal investigator for preparation for either a convened Board review or an expedited review.

6. EXPEDITED REVIEW

6.1 TYPE OF RESEARCH QUALIFYING FOR EXPEDITED REVIEW

In research studies qualifying for Expedited Review, human subjects can incur no more than minimal risk. Special abbreviated consent form formats are available for tissue collection, registries and data/art drawings/questionnaires that meet criteria for Expedited Review.

Research activities that may qualify for Expedited Review are:*
• Certain kinds of research on drugs and devices, when an investigational new drug (IND) or an investigational device exemption (IDE) is not needed;
• Collecting blood by stick or venipuncture with limits for age, health and pregnancy status;
• The prospective collection of specimens for research purposes by noninvasive means;
• Data collected through noninvasive means (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding x-rays and microwaves;
• Materials that have been collected, or will be collected solely for non-research purposes;
• Voice, video, digital or image recording made for research purposes;
• Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program or human services evaluation, and quality assurance methodologies.

*For a more detailed list of the specific criteria, see the OHRP Website.

6.2 DOCUMENTATION REQUIRED FOR EXPEDITED REVIEW

The application process for consideration of Expedited Review is the same as that for Convened Board review. A complete submission includes an Application, protocol, consent form(s), and other supporting documents. (For information regarding the content of a protocol, please see Section 7).

6.3 IRB EVALUATION OF EXPEDITED REVIEW STUDIES

Applications for Expedited Review will be reviewed by an IRB sub-committee for exempt and expedited studies. The sub-committee may exercise all of the authorities of the IRB, except that the sub-committee may not disapprove the research. Only the convened Board may disapprove a study. Therefore, if the sub-committee does not agree with the request for expedited review the study will be send to the convened Board for consideration. The PI may need to provide additional documents in order to facilitate the review process.

If the study qualifies for Expedited Review and is approved, a notice confirming approval of the study will be sent to the principal investigator. It is the responsibility of the principal investigator to notify the sponsor of IRB decisions. The IRB file will cite the specific criteria used in making the Expedited Review decision. EVMS studies approved by Expedited Review are subject to Continuing Review.

7. CONVENED BOARD REVIEW

7.1 TYPES OF RESEARCH REQUIRING CONVENED BOARD REVIEW

Research studies that do not meet the exempt or expedited review levels and/or that involve greater than minimal risk for human subjects require convened Board review.

Research that requires convened Board review includes:
• Some research involving children or other vulnerable populations.
• Research that involves experimental (non-approved) drugs or devices.
• Research that involves invasive procedures.
• Research that involves deception.
• Some survey research or interviews that involve sensitive questions, information about HIV, or result in stress for human subjects.
• Some research studies requesting a Waiver of Consent, especially if the research involves children.

7.2 DOCUMENTATION REQUIRED FOR CONVENED BOARD REVIEW

The IRB staff screens all applications before they are assigned to an IRB and specific reviewers. Protocols are placed on the Board Agenda for the appropriate IRB in the order that completed submissions are received. The sooner a study is submitted in the cycle, the more likely it will be reviewed at the next Board meeting. The Boards meet on the 1st Thursday and 3rd Tuesday of each month.

The Boards require that incomplete applications or poorly written consent forms be returned to the principal investigator for revision before being considered at a Board meeting. This is done administratively through the RSP/IRB office in what is known as a Pre-Review. Applications not on the appropriate forms, packets missing protocols or other required documents, informed consent forms missing required language will be returned to the investigator for completion prior to assignment to an agenda.

Documentation required for convened Board review includes:

7.2.1 APPLICATION FOR APPROVAL OF RESEARCH INVOLVING HUMAN SUBJECTS.

All sections must be completed and the form signed by the PI and Department Chair. Identify each specific performance site. Indicate the street address (no P.O. Box numbers) and the address of the investigator, if it differs. For protocols involving the use of a non-FDA-approved drug, biologic or device, include the IND or IDE number and date.

- **The principal investigator remains responsible for ensuring that proper informed consent is provided for each subject in the study.** The principal investigator is responsible for training any named individual(s) in the process of consent and making

sure that they are knowledgeable about the study, the process, and can answer questions about the scientific basis of the protocol. For details, see section titled "Responsibilities of Investigators."

- **The principal investigator is responsible for ensuring all research team members have required training.** All investigators and their research team members who engage in human subjects research must complete human subjects protections training prior to engaging in any protocol activities. Training is mandatory and required for IRB approval of all new protocols and renewal of all active protocols. A research team member is anyone working on any part of a research project that requires IRB review. All persons, including residents, students, coordinators, and data management, are considered team members if their effort contributes to a study.
- **The principal investigator is responsible for obtaining review from all appropriate specialty areas or for including a co-investigator(s) from all treatment areas included in the study.** When a study is proposed that involves an aspect of medicine generally considered to be outside the traditional training and practice of the principal investigator, the principal investigator must include colleagues with appropriate expertise as co-investigators. The principal investigator may be asked to provide the IRB with written confirmation that the investigatory team possesses the level of training and expertise to adequately conduct the study and to ensure patient safety.
- **The principal investigator on a research proposal must have an approval by the appropriate Departmental Chairperson.** This includes investigators with an EVMS faculty appointment, trainees and staff. An appropriate Departmental Chairperson (or designee) or Program Director is defined as having a faculty appointment and doctoral level training (MD and/or PhD). ***The designee must also have these same qualifications.*** A Chairperson may delegate this responsibility to a peer review committee if the membership includes the same qualifications. Research proposals submitted to the IRB with no EVMS faculty investigators (e.g., hospital staff as investigators) will need to be approved by the appropriate hospital department or division head.

7.2.2 THE RESEARCH PROJECT BUDGET

Include an explanation of any financial transactions (physician's fees, reimbursement for tests or medications, reimbursement of subject's expenses, etc.). Compensation, including personal salaries, should be omitted or blacked-outt. The budget submission to the Research Subjects' Protection office is not an approval process, but a communication of the level of funding. If subsequent funding levels differ by more than 15% from the budget initially reviewed, notification should be sent to the IRB.

7.2.3 IRB FEES

- Funded studies requiring a convened Board review are assessed a one-time IRB administrative fee of $1,750 when reviewed by an internal EVMS IRB. Fees are to be paid at the time of billing by check or interdepartmental charge. Using the "Waiver of the IRB Fee" form, a waiver of the IRB fee may be granted by the Assistant Dean or IRB Director of the Research Subjects' Protections office for studies that require a convened Board review but do not have funds for IRB fees.
- Sub-contracts through federal agencies may be charged a fee if the original grant budget approved by the agency included the fee. Studies receiving partial funding must include the IRB fee as well. Any request for a fee waiver for a funded study must include a justification as to why the PI did not request the fee in the budget. If the fee is not waived, the fee will be charged to the grant account. PI's may request a reduced fee in lieu of the full fee in special circumstances.

7.2.4 PROTOCOL

- Include sufficient information to permit the IRB to assess the rationale, scientific merit, potential risks to subjects, benefits to subjects, what the subject is being asked to do, how the data will be analyzed, and alternatives available to the subject.

The following must be provided:
Objectives of the study
Background and rationale, including literature review
Description of procedures to be performed
Description of subject population with justification for use of vulnerable subjects
Identification of inclusion and exclusion criteria
Detailed research methodology
An outline of how the informed consent process will occur, keeping the potential subject's confidentiality in mind.
Data collection and statistical analysis
Curriculum vitae (if not an EVMS investigator)
The following must also be included, depending on the type of protocol: Safety information Adverse event reporting Record management Investigator Brochure

7.2.5 GENDER AND ETHNICITY IN RESEARCH

- It is the policy of NIH that women and members of minority groups and their subpopulations are included in all NIH-supported biomedical and behavioral

research involving human subjects. Any exclusion of minorities and women must include a justification stating why it is inappropriate with respect to the health of e subjects or the purpose of the research. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources.

- The IRB requires, in accordance with NIH policies, that studies being funded by NIH include a breakdown of subject populations by gender and minority group. The Research Plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic groups and provide a rationale for the selection of these subjects. The plan should also contain a description of the proposed mechanism for recruiting women and minorities as participants.

7.2.6 MONITORING

NIH now requires investigators conducting smaller-scale early clinical trials (Phase I and Phase II) to submit Clinical Trial Monitoring Plans to the NIH at the time of application, and expect the investigators to submit these plans to the IRB. NIH already requires larger Phase III studies to have Data Monitoring Boards (DMBs). The FDA will also issue guidelines for DMBs and define their relationship with the IRB.

The EVMS IRBs evaluate monitoring plans for human subjects research at the time of initial review and at each Continuing Review period.

7.2.7 INFORMED CONSENT: THE SUBJECT CONSENT FORM

The process of informed consent and the form signed by participants indicating their willingness to be in the study are crucial elements of the protection of the rights of human subjects. The consent form must be in an EVMS template format. The consent forms provided on the RSP website are the only consent forms that have been approved for use by the Boards. For further information, call the IRB office at (757) 446-8423.

- **Suggested Birth Control Wording for Consent Forms Includes:**
  "If you are a woman of child bearing age, you must not be pregnant at the time you enter the study and must not become pregnant at any time during the study. This study could seriously harm your fetus if you are pregnant or become pregnant. You and your partner should use effective birth control during this study. Methods that protect more than 95 in 100 couples per year from pregnancy include: male condoms plus added vaginal spermicide (to kill sperm), the birth control patch, ring or pill. Methods that prevent pregnancy in more than 99 of 100 couples per year include total abstinence, male sterilization (vasectomy), female sterilization (tubal ligation), implants, injection contraceptives (Depo-Provera or Lunelle), or intrauterine contraceptives (IUD) (Paragard or Mirena). Be aware that emergency contraception is available to you or your partner within 72 hours of any situation where you think your method

may have failed or you failed to use your method properly. Please call the study investigator or your regular physician to obtain this."

Addendum Consent Forms

Addendum consent forms accompany the main Subject Consent Form (or one of the other "stand-alone" consent forms). See Appendix A for all consent form formats. Addendum consent form formats include:

- **Addendum Consent Form –** used for additional consent, usually after a study has started, and a factor such as risks, compensation, etc. changes.
- **Assent of the Child Addendum –** for children ages 8 through 17, depending on the subject's level of maturity and capacity for judgment. For children less than 18, parental or guardian consent is required, and the Board also requires assent by a competent child. This form must contain a brief lay language description of the study and what the child is being asked to do as a participant.
- **Employee/Student Addendum –** investigators planning to recruit employees or students as research subjects must indicate so on the Application of Approval of Research Involving Human Subjects and attach a copy of this addendum to the Subject Consent Form. **Employees or students should only be recruited through advertisements such as a flyer or a notice on a bulletin board**. Investigators should be particularly careful to ensure that no coercion is used in the recruitment of this population.
- **Identified Tissue/Specimen For Future Research Addendum –** investigators planning to use/collect tissue for future research that is part of the "main study" must indicate so on the Application of Approval of Research Involving Human Subjects and attach an appropriately edited copy of this addendum to the Subject Consent Form. All samples collected for future use must be governed by an IRB approved protocol specific to the collection and storage of samples.
- **Unidentified Tissue/Specimen for Future Research Addendum –** investigators planning to use/collect tissue for future research that is part of the "main study" must indicate so on the Application of Approval of Research Involving Human Subjects and attach an appropriately edited copy of this addendum to the Subject Consent Form. All samples collected for future use must be governed by an IRB approved protocol specific to the collection and storage of samples.
- **Data/Drawing/Questionnaire Consent Form –** investigators planning to gather data, have subjects complete a drawing, or administer a questionnaire may use this stand-alone consent form.
- **Registry Consent Form –** investigators planning to enroll subjects in a registry *only* may use this stand-alone consent form.

- **Consent for the Use and Storage of Identified Human Biological Materials –** investigators planning to use tissue or specimens may use this stand-alone consent form. All samples collected for future use must be governed by an IRB approved protocol that specifically allows the collection and storage of samples.
- **Consent for the Use and Storage of Unidentified Human Biological Materials –** investigators planning to use tissue or specimens may use this stand-alone consent form. All samples collected for future use must be governed by an IRB approved protocol specific to the collection and storage of samples.

7.2.8 DATA COLLECTION SHEET OR CASE REPORT FORM

Include a copy of materials used to record data, indicating whether variables identify participants or not. **For data that is coded, provide the linking key along with either a sample of the data or explanation of the field headings.**

7.2.9 SPONSORED STUDIES

EVMS requires a congruency review of the grant application or proposal provided to Sponsored Programs (SP) and the IRB approved protocol before funding may be released to an EVMS site. Please ensure the two submissions adequately address the planned activities to avoid any delays in either process.

7.2.10 STUDIES FUNDED BY NIH

Federally funded studies must seek to use a Single IRB Review (sIRB) for all sites. This may be done through Reliance Agreements or other means. Contact the RSP office for assistance in determining the best process for the study based on the collaborating institutions.

7.2.11 INCENTIVES

All incentives (whether labeled “gifts,” “compensation,” or otherwise) must be outlined in detail in the consent document. If an incentive is added after enrollment has closed, an addendum consent form may be used. Incentives must be available to all subjects who participate in the research, even if they were previously enrolled and have completed the study. If an incentive is increased during the study, all previously enrolled subjects must receive the adjusted amount.

Incentives for studies involving children or minors as subjects should be geared towards the minor and not a parent or LAR. Providing a payment per visit or a travel reimbursement to parents/LARs should NOT be considered an incentive to a child research subject. Incentives for a minor may include in-kind items that a child of their age would use (such as toys, games, backpacks, etc.); a gift card to a store or event that is geared towards youth may be appropriate; and, for older minors cash or gift cards that they can control may be acceptable. If multiple choices are available to participants, all items must be of the same value.

7.2.12 ADVERTISEMENTS AND INFORMATIONAL MATERIAL

The IRB reviews the methods that investigators use to recruit subjects, because direct advertising for study subjects starts the informed consent process and subject selection process. Direct advertising for subjects is considered to be a reasonable recruitment practice as long as the advertisement has been reviewed and approved by the IRB. Examples of direct advertising include methods such as ads in the newspaper and on the radio; brochures, posters, flyers, bulletin board "tear sheets," and videos; and internet communications designed to reach potential subjects. This includes any material referencing a full-time or community faculty member's affiliation with EVMS. Numeric values of compensation or gratuity should not be listed on advertisements unless approved by the IRB.

When appropriately worded, the following items *may* be included in advertisements:
• The name and address of the clinical investigator 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 commitments required of the subjects, and
• The research location and the person or office to contact for further information.

Copies of advertisements, videos, or any other materials used for the recruitment of subjects must be submitted with the IRB protocol for approval and remain as part of the IRB records.

The IRB reviews advertising when:
• It is submitted with a new study for either convened Board or Expedited Review:
• Advertising is added to a study after approval, and
• When previously approved advertising is changed.

Use of marketing companies for recruitment: Telephone scripts used by marketing companies on behalf of study sponsors to pre-screen potential subjects who, if they meet the study criteria, would be referred to the principal investigator as candidates for ongoing studies often elicits personal information that is subject-identifiable. n addition, the IRB must approve of the final script/recruitment material. If approval is not given the PI may not use this source for locating potential subjects.

The FDA has issued guidelines for these situations which an investigator must address in a request for IRB review of subject-identifiable materials:
The IRB will need to have assurances that the marketing company handles the personal and confidential information appropriately. A simple statement such as "confidentiality will be maintained" does not adequately inform the IRB of the procedures that the company will adhere to.
What happens to personal information if the potential subject ends the interview or simply hangs up? Are the data sold to others? Are the data shredded or put out in the trash? Are the names of non-eligible subjects and their data maintained for future or other studies?

All advertisements that reference a full-time or community faculty member, trainee or staff affiliation with EVMS **MUST** receive EVMS IRB approval prior to publication; and upon IRB approval, must include a caption that indicates "Advertising approved by the EVMS IRB, IRB #(insert assigned IRB number)".

An advertisement must not claim, implicitly or explicitly, that the research is treatment and it may not pressure readers into participating.

The following types of advertising *do not require IRB approval* but must still be approved by EVMS Marketing & Communications:
Communications intended to be seen or heard by health care professionals.
News stories as long as there is no attempt at recruitment of potential subjects included as part of the story.

Publicity intended for other audiences, such as financial page advertisements aimed at prospective investors.
Internet listings in which the system format limits the information provided to basic trial information such as the: study title, protocol summary, basic eligibility criteria, study site location(s), and how to contact the site for further information. If the listing references the investigators affiliation with EVMS, the PI MUST seek an EVMS IRB approval.

8. REVIEW OF STUDIES SUBMITTED TO THE CONVENED BOARD

8.1 CRITERIA USED FOR REVIEW OF BOARD STUDIES

The following criteria are used in the Board review:
Subject selection: Is it fair? The IRB considers the purposes of the research, the setting, and is particularly cognizant of vulnerable populations.
Risk/benefit relationship: Risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk; are reasonable in relation to anticipated benefits; include safeguards to protect the rights and welfare of vulnerable subjects.
Voluntariness: What are the recruitment practices; advertisements; and is there any coercion or undue influence?
Confidentiality: Have adequate provisions been made to protect the privacy of subjects and maintain the confidentiality of the data? Also, are potential subjects given the opportunity to ask questions and consent in private?
Review of the consent form(s): To ensure adherence to guidelines and to ensure that information is presented in a manner that will enable comprehension. Informed consent will be sought and documented from each appropriate prospective subject or each subject's legally authorized representative.
Monitoring of data: Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

8.2 RISK/BENEFIT RATING FOR PEDIATRIC STUDIES

In addition to the above criteria, pediatric studies are also rated according to the relationship of risks to benefits and the solicitation of assent of the child and permission of their parents or guardians. The risk category for each pediatric study is noted in the Board minutes.

OHRP Regulation Citations	Risk Description	Signatures Typically Needed for Consent and Assent
45CFR46.404	Research not involving greater than minimal risk.	1 Signature and Assent if child is 8-17 years old
45CFR46.405	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.	1 Signature and Assent if child is 8-17 years old

OHRP Regulation Citations	Risk Description	Signatures Typically Needed for Consent and Assent
45CFR46.406	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.	2 Signatures (unless 1 parent or guardian has sole custody) and Assent if child is 8-17 years old (Table continued next page)
45CFR46.407	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research studies at this risk level require prior review by the Secretary of the U.S. Department of Health and Human Services.	2 Signatures (unless 1 parent or guardian has sole custody) and Assent if child is 8-17 years old

FDA Regulation Citations	Risk Description	Signatures Typically Needed for Consent and Assent
21CFR50.51	Clinical investigations not involving greater than minimal risk.	1 Signature and Assent if child is 8-17 years old
21CFR50.52	Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.	1 Signature and Assent if child is 8-17 years old
21CFR50.53	Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition	2 Signatures (unless 1 parent or guardian has sole custody) and Assent if child is 8-17 years old

FDA Regulation Citations	Risk Description	Signatures Typically Needed for Consent and Assent
21CFR50.54	Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research studies at this risk level require prior review by the Commissioner of Food and Drugs.	2 Signatures (unless 1 parent or guardian has sole custody) and Assent if child is 8-17 years old

8.3 STUDIES CONDUCTED AT AREA HOSPITALS

Research protocols that are performed in local hospitals or clinical care sites must also be submitted to the established mechanisms for review at those hospitals as well as to the EVMS IRB.

For more information about a particular hospital, please contact the offices listed below:

Site	Phone Number
Children's Hospital of The King's Daughters	(757) 668-9991
Bon Secours Hospitals	(757) 889-5309
Sentara Health Research Center (All Sentara sites)	Website
Shore Health Services	(757) 442-8676

IMPORTANT: There may be special permissions and/or approval requirements needed for studies being conducted at a hospital, facility or other location (including obtaining data from these sites). Allowing research at these sites or accessing data through a system at these sites is not included in the IRB approval and must be sought separately through the appropriate institution.

Investigators are responsible for obtaining permission and/or approval ***prior to*** initiating the research and ensuring compliance with the institutions policies and procedures.

8.4 STUDIES INVOLVING CERTAIN POPULATIONS

Research protocols involving medical students, health professions students, student records, and/or standardized patients must receive approval from the offices with oversight of the programs prior to review by the IRB. Signatures from the heads of these offices are required on

the IRB application at the time the protocol is submitted for review in order for the protocol to be added to an IRB agenda.

Contact the offices listed below for additional guidance:

Site	Phone Number
Medical Students and Health Professions Students: Assistant Dean for Student Affairs	757.446.5244
Standardized Patients: Director, Clinical Skills	757.446.8458

9. OUTCOMES OF BOARD REVIEWS:

The review of studies by the Board will result in one of the following actions:
• Approval as is - without changes;
• Approval with specific modifications;
• Tabled until further information is received from the investigator; or
• Disapproval (limited to convened Board reviews)

If the Board granted a tentative "approval with specific modifications" a letter identifying the required changes to be made to the appropriate study documents is sent to the principal investigator. In reply, the investigator must submit two (2) electronic copies of the document(s) requiring modification, with the changes highlighted on one of the copies. (This same procedure applies if the matter is tabled for further information; or, if the study is disapproved and the PI wishes to appeal the decision.)

NOTE: THE STUDY IS NOT CONSIDERED APPROVED AND MAY NOT BEGIN UNTIL THE INVESTIGATOR RECEIVES A LETTER DOCUMENTING THAT THE IRB CHAIR (OR DESIGNEE) APPROVED THE MODIFICATION.

IMPORTANT: There may be special permissions and/or approval requirements needed for studies being conducted at a hospital, facility or other location (including obtaining data from these sites). Allowing research at these sites or accessing data through a system at these sites is **not included** in the IRB approval and must be sought separately through the appropriate institution. Investigators are responsible for obtaining permission and/or approval ***prior to*** initiating the research and ensuring compliance with the institutions policies and procedures.

For hospital contact information, see the section titled "Studies Conducted at Area Hospitals". **It is the responsibility of the PI to know when additional approvals are necessary and obtain those approvals prior to initiating the study at another site.**

9.1 MEETING SCHEDULE

Convened IRB Meetings start at 8:30 a.m. on their respective meeting dates. Each meeting usually lasts approximately two hours. The IRB meeting is a closed meeting and is not open to attendance by visitors without an invitation from the Board or an IRB approved request to attend for learning purposes.

An individual wishing to attend a meeting for learning purposes must be sponsored by an active IRB member and should complete a "Request to Attend an IRB Meeting" form that includes a rationale for attending a meeting. The Board decides whether to allow a visitor to attend on a case-by-case basis. Visitors are required to sign a confidentiality agreement and may be excused from the room for any sensitive discussions. Individuals wishing to attend an IRB meeting should contact the IRB office well in advance of the intended meeting date to ensure approval can be arranged.

IRB Sub-Committees to review exempt and expedited applications meet on the same day as the convened meeting. While there are no regulatory requirements for these meetings, at least two voting members (may include alternates) must be present for a sub-committee meeting to occur.

As approved by OHRP and the FDA, the Board reserves the option of holding a convened IRB meeting via telephone conference call or video conference, or a hybrid of in-person and telephone/video conferencing. For such a meeting, each member must: 1) receive all pertinent material prior to the meeting, and 2) be able to actively and equally participate in the discussion of all studies. Minutes of such meetings must clearly document that these two conditions have been satisfied in addition to the usual regulatory requirements (e.g., attendance; initial and continued presence of a majority of members including at least one non-scientist member; actions taken by the IRB; the vote on such actions; discussion and resolution of controverted issues).

9.2 NOTIFICATION OF OUTCOME

After the meeting, a letter with details of the outcome will be sent to the principal investigator. It is the responsibility of the principal investigator to notify a sponsor of IRB decisions. Once an IRB final approval letter is received by the site and after appropriate hospital or other necessary approvals have been obtained, the project may begin.

Each notice includes:
• The investigator's name and address,
• The EVMS IRB number,
• The study title,
• The method of review/evaluation,
• All study documents approved by the IRB (e.g., protocol, consent form, investigator brochure, advertising, etc.),
• When the study may begin, and
• If appropriate, the date the first progress report is due.

Research that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Disapproval of any study must be reported to any other IRB reviewing the same study. There is no defined process to appeal a decision made by the Board, but the Board is willing to meet with the investigator and discuss alternatives that might allow eventual approval of a rejected study. Investigators attending a meeting for this purpose are expected to be well prepared to discuss the merits of the study and issues of concern noted by the IRB, as well as have current knowledge of the regulations and policies applicable to human subjects' research.

10. PRIVACY RULE

The Health Insurance Portability and Accountability Act (HIPAA) implementation date was April 14, 2003.

10.1 WHAT IS HIPAA?

10.1.1 THE THREE MAIN COMPONENTS OF HIPAA ARE:

- Uniform standards for electronic transactions;
- Security for information transmitted;
- Privacy rights of individuals

10.1.2 TWO GOALS OF HIPAA ARE TO:

- Create uniform, comparable national data on utilization, payments, epidemiological patterns, and clinical practices;
- Enable patients to control uses and disclosures of their health information.

The movement toward uniform computerized health information will present benefits and risks for patients/research subjects. On the one hand, physicians will have quick access to a patient/subject's medical information in emergency situations but on the other, inappropriate access to patient/subject information may result in denial of medical insurance, employment opportunities, or result in personal embarrassment. That is why HIPAA is necessary: to ensure that the medical information is available when necessary but is protected from inappropriate access.

The IRB plays a role in this concern for the protection of privacy of research subjects. The Privacy Rule portion of HIPAA requires that patients/research subjects give authorization for the use of their protected health information. For example, a patient who comes to EVMS for clinical care would not expect to have his/her protected health information viewed or used by or disclosed to others for the purpose of research, without specific permission. Permission to have their information used by or disclosed to others for research purposes is specified in the Subject Consent Form.

There are however, situations where PHI may be used without the permission of the individual. This may occur when:

- Documentation is obtained by the IRB for a waiver of authorization;
- Representation is made by the researcher that the PHI use or disclosure is "preparatory to research;" or
- PHI being sought is on decedents.

10.2 WAIVER OF AUTHORIZATION

The IRB Chair or designated member must approve a written statement that the IRB has determined that the research meets the criteria for waiver of authorization. For specific criteria, please the IRB form titled *"Waiver for Use of Protected Health Information (PHI)."*

10.3 PREPARATORY TO RESEARCH

The IRB Chair or designated member must approve a written statement that the IRB has determined that the project meets the criteria that allows for the use or disclosure of PHI without prior authorization in preparation for research or for the identification of potential research subjects. For specific criteria, the IRB form titled "*Application for Use of Protected Health Information (PHI) for Protocol Preparation or to Identify Whether a Research Study Can Be Developed.*"

10.4 RESEARCH ON DECEDENTS

The Privacy Rule allows for the use or disclosure of PHI without prior authorization in preparation if the researcher justifies that:

- PHI is being sought solely for decedents;
- PHI being sought is necessary for research; and
- Documentation of the death of decedents is provided (if requested).

10.5 SUBJECT CONSENT FORM

The Subject Consent Form template includes the additional required elements required by the Privacy Rule, such as the section titled "What About Confidentiality?"

10.6 MINIMUM PHI NECESSARY

Researchers must not only be specific about the information that they will use or disclose but must also limit their use or disclosure of PHI to the minimum necessary. Under the Privacy Rule, viewing or using a patient's record for research purposes is not permitted, unless a specific justification has been made to and approved by the IRB that the entire record is necessary.

10.7 USE OR DISCLOSURE OF DE-IDENTIFIED INFORMATION

PHI may be used if it is stripped of the identifiers currently defined by the Privacy Rule. Once the identifiers have been removed, it is no longer considered PHI. The list of identifiers includes:

- Name
- Address (all geographic subdivisions smaller than state, including street address, city county, and zip code)
- All elements (except years) of dates related to an individual (including birthdate, admission date, discharge date, date of death, and exact age if over 89)
- Telephone numbers
- Fax number
- Email address
- Social Security Number
- Medical record number

- Health plan beneficiary number
- Account number
- Certificate or license number
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web URL
- Internet Protocol (IP) Address
- Finger or voice print
- Photographic image - Photographic images are not limited to images of the face.
- Any other characteristic that could uniquely identify the individual

PHI may also be used or disclosed if a knowledgeable statistician determines that the risk of identifying an individual subject from the information is "very small" and documents the methods and results used to come to that conclusion. Generally, this method of "de-identifying information" is discouraged because of the vagueness of the term "very small."

Psychotherapy notes (used only by a psychotherapist) are held to a higher standard of protection because they are not part of the medical record and were never intended to be shared with anyone else.

There will be specific Federal penalties if a patient's right to privacy is violated (for further information, see the final regulation web site at *http://www.hhs.gov/ocr*.).

10.8 HIPAA AND FDA REGULATION OF DEVICES AND DRUGS

Personal, identified health information may be disclosed without authorization for purposes related with the quality, safety or effectiveness. Such purposes include, but are not limited to the following.

Disclosures to the FDA without Authorization:
• To collect or report Adverse Events (or similar activities regarding food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations.
• To track FDA-regulated products.
• To enable product recalls, repairs, or replacement, or for a look back (including locating and notifying persons who have received products that have been withdrawn, recalled, or are the subject of a look back).
• To conduct post-marketing surveillance.

See Section 26 for further details and information on Research - Use and Disclosure of Protected Health Information

11. REVIEW OF STUDIES ANALYZING DATA, TISSUE, OR SPECIMENS

Two main concepts govern this area of human subject research:

- Whether specimens or data are linked to the identity of a person; and,
- Whether specimens or data already exist.

Definitions:

- **Anonymous:** absolutely no links, no codes, no identifiers. It is not possible to identify or match individuals to the specimen and/or data.
- **De-identified:** there is a link, code or other identifier retained and individuals can be matched to the specimens and/or data.
- **Identified:** there are direct identifiers on the item, such as a name, DOB, etc.

11.1 LINK TO THE IDENTITY OF THE SUBJECT

A link is any kind of information that makes it possible to determine the subject's identity. Depending on the subject population, such information as birth date coupled with diagnosis might make it possible to identify the subject. Coding makes specimens and data identifiable if the researcher has a key that can be used to link identifying information with the subject. In addition, consideration is given as to whether any combination of other information may allow an investigator to ascertain the identity of an individual subject.

11.2 EXISTING SPECIMENS OR DATA VERSUS PROSPECTIVELY COLLECTED SPECIMENS OR DATA

- **EXISTING SPECIMENS OR DATA** are those that have already been completely collected **BEFORE** the research is proposed to an institutional official or the IRB - regardless of the source of the specimens or data.
- **PROSPECTIVE SPECIMENS OR DATA** are those that will be collected after the research has been proposed to an institutional official or the IRB to determine whether the research is exempt - even if the specimens or data are collected as part of normal patient care. Typically, prospective collection of any data or specimen requires informed consent.

11.2.1 Anonymous and Retrospective

In cases where data or specimens are collected anonymously (no identifiers, codes, or links) and are completely retrospective, the research may be exempt from IRB approval. However, only the IRB can make that determination. This is also the case for material obtained from public or commercial sources

An application using the "Application for Approval of Research Involving Human Subjects" form in Appendix B must be sent to the IRB (via the Research Subjects' Protections office). Should the project meet the criteria for "exemption," a letter from the IRB will be sent indicating that this is the case, and the research may begin after any other appropriate local approvals.

11.2.2 Prospective Studies With or Without Identifiers

Guidelines by the NIH describe the review and consenting procedures for studies using specimens prospectively. These instructions cover human tissue and bodily fluids including blood, saliva, and urine that may be collected for research purposes.

Investigators collecting and storing specimens and/or data for future use in addition to a specific protocol use, must submit the *"Addendum Identified Specimen and/or Data Consent Form*" or "*Addendum Unidentified Specimen and/or Data Consent Form"*. All specimens/data collected for future use must be governed by an IRB approved protocol (repository) specific to the collection and storage of specimens/data.

For specimens/data that are collected for current or future use, investigators must use the "Identified Specimen and/or Data Consent Form" or "Unidentified Specimen and/or Data Consent Form" when specimens are collected as a standalone study. All specimens/data collected for future use must be governed by an IRB approved protocol (repository) specific to the collection and storage of specimens/data. See the "Repository Guidance" on the IRB website under "Resources" for guidance on what to include in a repository protocol.

11.3 SPECIMEN/DATA MAINTENANCE

Specimen/Data Maintenance should be discussed including the administrative process used to maintain specimens. During evaluation the following issues should be addressed:

- Will the specimen be made available to other investigators?
- What is the plan for control, use and disposal of the specimens in the future?
- What safeguards are in place to prevent unapproved access to the database?
- Will the subject have the right to request that *identified specimens* be destroyed if he/she decides to withdraw from the study?
- Is it possible that commercial products will be developed from the specimens?

11.4 MAKING COLLECTION OPTIONAL

- In treatment studies with a potential benefit for subjects, the collection of specimens or data for banking should be optional.
- Subjects must not be denied a promising experimental treatment because they are unwilling to allow their specimen or data to be banked for *unspecified future purposes*.
- Some national cooperative study groups are requiring banking for *unspecified future purposes* as a condition of study participation. Such banking very often raises serious ethical concerns and will be considered very carefully by the IRBs.

11.5 SPECIAL ISSUES

GUIDELINES FOR GENE THERAPY RESEARCH

- All studies involving genetic research must be reviewed and approved by the Institutional Biosafety Committee (IBC) ***prior to*** submission to the IRB.
- When appropriate, principal investigators (and sponsors) must provide verification of the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) review along with RAC comments. For information about RAC, the following web site http://www4.od.nih.gov/oba/ can be consulted.

11.6 SPECIMEN OR DATA BANKING / REPOSITORIES ONLY

A specimen and/or data bank is a repository of material and/or information for use in future research projects to be conducted by the collecting investigator or by a different investigator.

IF AN INVESTIGATOR WANTS TO ESTABLISH A DATA OR SPECIMEN BANK, A PROTOCOL ESTABLISHING THE RULES GOVERNING THE DATA/SPECIMEN BANK MUST BE REVIEWED AND APPROVED BY AN EVMS IRB. PLEASE SEE THE REPOSITORY/BANK AND DATA USAGE GUIDANCE DOCUMENT.

A specimen and/or data banking protocol must address the following:

INFORMED CONSENT

- The *"Consent for the Use and Storage of Data/Biological Materials"* (choose Identified or De-Identified), "*Specimens/Data for Future Research Addendum Consent Form"* (choose Identified or De-Identified) or the *"Registry Consent Form"* formats must be used as a template that includes all of the relevant elements required in a written consent form.
- The consent form must acknowledge that collector-investigators are prohibited from providing recipient-investigators with access to the identities of donor-subjects or to information through which the identities of donor-subjects may readily be ascertained.
- If specimens and/or data are being obtained from a bank or registry not under the EVMS IRB jurisdiction, a copy of the local IRB approval for the collection of samples or data must be provided by the principal investigator in the request for IRB review and approval.
- If human genetic research is anticipated, informed consent information must include information about the consequences of DNA typing.

SECURITY AND CONFIDENTIALITY

- Provisions to protect the privacy of subjects and maintain the confidentiality of the specimen/data must be detailed. It is recommended, and sometimes required, that the collectors of tissue samples obtain a Certificate of Confidentiality. For NIH funded studies, a Certificate is automatically issued when NIH funds a study. Certificates

protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a research participant. Certificates do not protect against accidental or intentional loss of confidentiality. For information about Certificates of Confidentiality, the following web site http://grants1.nih.gov/grants/policy/coc/faqs.htm can be consulted

- Recipient-investigators must not be provided access to the identities of donor-subjects or to information through which the identities of donor-subjects may readily be ascertained.
- It must be specified who will keep the specimen/data secure. A secure database must be used to keep track of specimens/data and any criteria for their use. A description of security measures must be included when submitting a repository request to the IRB.

GIVING OR SELLING SPECIMENS TO OTHER RESEARCHERS OR TISSUE BANKS

- Specimens/data may be provided to other researchers only after it has been determined that those researchers have received appropriate approval or exemption from the appropriate IRB or Ethics Committee. A letter confirming such approval must be kept on file by the EVMS principal investigator of the repository. The PI must inform the EVMS IRB after specimens are provided to another investigator or entity (internal or external) by submitting a listing of transfers with the continuing review.
- Specimens and/or data may only be sold for a reasonable cost to transfer the items to the purchaser and the plans to do such must included in the repository protocol that is IRB approved. Each transfer must be documented and included in the continuing review submission for the repository.
- Only anonymous or de-identified data and/or specimens be forwarded to the recipient-investigator. In cases of de-identified items, a key may be kept by the repository center. However, the key may not be subsequently shared to a recipient-investigator.

USAGE AGREEMENT FOR RECIPIENT-INVESTIGATORS SHOULD INCLUDE THE FOLLOWING:

- "Recipient acknowledges that the conditions for use of this research material are governed by the EVMS IRB in accordance with DHHS regulations at 45CFR46. As the recipient, I agree to comply fully with the research project and any unanticipated problems involving risks to subjects or others. Recipient remains subject to applicable State laws or regulations and institutional policies which provide additional protections for human subjects."
- "This research material may only be utilized in accordance with the conditions stipulated by the specimen/data repository IRB and, where appropriate, by an IRB at the recipient site, which must be established under an applicable OHRP-approved Assurance."

11.7 DISCARDED SPECIMENS

Research with normally discarded (leftover) specimens after a standard clinical procedure does not typically meet the definition of research involving human subjects. This determination must be made by the IRB office as noted under Section 4.3 of this SOP. Specimens must meet the conditions for anonymous or de-identified specimens noted above.

Important Notes:

- An investigator may not de-identify data and/or specimens under his or her control (e.g., specimens generated by the investigator from a clinical procedure) for future research uses without IRB review.
- For material to be considered discarded or leftover no person associated with the research can be involved in the clinical procurement of the material.

12. WAIVER OF CONSENT AND WAIVER OF DOCUMENTATION OF CONSENT

Convened Board review may be required for some studies that request a Waiver of Consent or Waiver of Documentation of Consent. For information regarding whether Convened Board or Expedited Review is needed, please consult with the IRB Administrator at (757) 446-8423 or via email at IRB-Info@evms.edu. Typically, convened Board review is done when there is the opportunity for an investigator or research team member to obtain consent but a waiver is requested instead.

Note: When there is the possibility of interacting with subjects, the IRBs expectation is that the investigator will obtain consent.

12.1 WAIVER OF CONSENT FOR NON-FDA STUDIES

There are some instances where the process of informed consent may be appropriately waived for studies. For specific criteria, please see the IRB forms titled "*Application for Waiver of Consent" and/or "Waiver for Use of Protected Health Information (PHI)."* Adequate justification must be provided by the investigator in order for the request to be granted.

12.2 PRIVACY RULE

There are some instances where the process of authorization may be appropriately waived for studies using protected health information. For specific criteria, the IRB forms titled "*Application for Waiver of Authorization for PHI" and/or "Waiver for Use of Protected Health Information (PHI)."*

12.3 WAIVER OF DOCUMENTATION OF CONSENT FOR NON-FDA STUDIES

An IRB may waive the requirement for an investigator to obtain a signed consent form for some (or all) subjects (or a subject's legally authorized representative) if it finds that any of the below are true. Keep in mind that EVMS generally requires consent be obtained when there is contact with potential subjects.
The only record linking the subject and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality. The subject must be allowed to decide whether he/she wants documentation that might provide a link with the research.
The research presents no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context.
If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

12.4 FDA STUDIES: EXCEPTION FROM GENERAL REQUIREMENTS OF INFORMED CONSENT OR EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH

An IRB may grant an exception from the requirement for an investigator to obtain a signed consent form for some or all subjects or a subject's legally authorized representative if it finds either:
1. The research meets the criteria for *Exception from general requirements (21CFR50.23)*. This is for use if a test article in an emergency situation that does not involve planned, prospective research and the subject is in a life-threatening situation.
2. The research meets the criteria for *Exception from informed consent requirements for emergency research (21CFR50.24)*. This is for prospective, planned emergency research in subjects who may not be able to give informed consent or have a Legally Authorized Representative (LAR) who could provide consent. This requires prior consultation with representatives of the community; public disclosure to the community; as well as additional subject protections and other requirements for IRB consideration.

13. SHORT FORM CONSENT FOR FOREIGN LANGUAGES

When enrolling a non-English speaking person into a study, the informed consent information needs to be presented in a language understandable to the subject and documented (DHHS: 45 CFR 46.116 and 45 CFR 46.117, FDA: 21 CFR 50.25 and 21 CFR 50.27).

The two (2) main options for written consent are:

1. The entire written IRB-approved English informed consent form (ICF) may be translated into the language understandable to the subject; **OR**
2. A foreign language "short form" may be used.*+

   * If a study will enroll only a specific non-English speaking population, a foreign language short forms may not be used. Translation of the entire IRB-approved English ICF is required.

   + If it is expected that more than five (5) persons of a specific non-English speaking population will be enrolled within a twelve month period, the approved English ICF should be translated into the specific foreign language.

13.1 USE OF A FOREIGN LANGUAGE SHORT FORM

To ensure that non-English speaking persons are not excluded from participating in research a foreign language "short form" may be used. Every study is eligible to use a short form ICF unless the IRB specifically determines to not permit the use of a short form as it relates to a particular study. Under certain circumstances, the IRB may determine to not allow the use of a short form ICF, for example based on the level of risk associated with the study (e.g., a gene transfer research study). Use of a short form is allowed unless specifically stated otherwise in the *IRB Approval* letter and provided the study sponsor allows use of a short form.

A signed short form basically documents the oral presentation of the entire written IRB-approved English ICF in a language understandable to the subject. For industry sponsored research, Principal Investigators are advised to confer with the sponsor prior to the enrollment of a non-English speaking subject and obtain the sponsor's support for such an enrollment. Up to five (5) short forms in the same language may be used in a study in a twelve (12) month period.

As with consent of English-speaking persons, the IRB will count every subject who has signed a short form as enrolled, whether or not that subject completes the study. That is to say, that each signed short form "counts" toward the five (5) that may be used in a study in a twelve (12) month period.

If the initial approval of the study did not allow for the short form consent process the investigator should submit an amendment to the IRB study to use a short form. This can be done ahead of time if foreign language subjects are expected to present for enrollment or it can be on a case-by-case basis.

13.2 REQUIREMENTS

When using a short form with a non-English speaking person, the following must be completed:

1. Insert study specific information, including department name, title of study, Principal Investigator, and contact information (this text can be inserted in English) into the short form document and then print the document for use. **This information must be typed and the fields on all the pages of the short form document need to be completed.**

2. The subject must be given a copy of the short form in the language understandable to him/her to read.

3. A translator/interpreter who is fluent in the subject's language and English should briefly explain the consent process to the prospective subject and **must orally present the entire IRB-approved English ICF to the subject in the language understandable to the subject.**

   Note: A family member of the subject can act as a translator/interpreter. If a member of the research team is fluent in the language understandable to the subject and English s/he can act as the translator/interpreter and the person obtaining consent; however, s/he may not act as the witness in any situation.

4. The prospective subject's questions or concerns should be relayed by the translator/interpreter to the person obtaining consent, and the answers translated back to the prospective subject. *Adequate time* should be afforded the participant to make an informed decision regarding participation in the study.

5. The entire consent process must be witnessed by an individual who is fluent in both English and the language understandable to the subject.

   Note: The witness may be the translator/interpreter, a family member, or another person. A member of the research team acting as both translator/interpreter and the person obtaining consent may **NOT** also serve as the witness. The witness must be physically present for the entire consent discussion. A research team member may not be a witness in any situation.

6. If the potential subject decides to participate, the IRB-approved English ICF must be signed by the investigator authorized to obtain consent and the witness to the consent process.

7. The short form in the language understandable to the subject must be signed by the subject and the witness to the consent process.

8. The subject must be given signed copies of both the IRB-approved English ICF and the short form in the language understandable to the subject; **AND**

9. The original signed English ICF and the original signed short form should be placed in the subject's research record and a copy of both placed in his/her medical record, if appropriate.

13.3 SHORT FORM CONSENT PROCESS

During the consent process the translator/interpreter should briefly explain the consent process to the prospective subject. The prospective subject's questions or concerns should be relayed by the translator/interpreter to the person obtaining consent, and the answers translated back to the prospective subject. *Adequate time* should be afforded the participant to make an informed decision regarding participation in the study.

13.4 SOURCE FOR ACCEPTABLE TRANSLATED SHORT FORMS

The Office of Intramural Research, Office of Human Subject Research Protections has many translated versions available on their website. An investigator should download the appropriate language document under the heading "TRANSLATED SHORT FORM CONSENTS / Revised Common Rule Short Form Consents". Once downloaded, insert the required information as noted in item 1 under Section 13.2 (above) within the header and footer of the document.

For more information about short form consent requirements and obtaining consent, please refer to the following guidance

FDA: A Guide to Informed Consent

OHRP: Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English

14. SPECIAL CONSIDERATIONS FOR VULNERABLE POPULATIONS

14.1 DEFINITIONS OF VULNERABLE POPULATIONS

Vulnerable populations may be the following individuals, some of which are define by regulations and others which are defined by an ethical standard:
Children, including newborns and minors, because of their diminished autonomy and incomplete comprehension; especially, wards of states as their situation may not allow for them to make an autonomous decision;
Fertilized ova, pregnant women, and viable fetuses, both in utero and ex utero;
Cognitively impaired persons with conditions that affect their decision-making abilities;
Subjects with limited civil freedom, such as residents or clients of institutions for the mentally ill; prisoners; or, other incarcerated persons;
Subjects that are recruited in emergent health care situations;
Subjects whose economic conditions predispose them to certain incentives;
Subjects who may be influenced by a faculty member, a supervisor, or a healthcare provider relationship;
Subjects in a compromised situation, e.g. having a severe or terminal medical condition/disease or a feeling of obligation to a healthcare provider or other investigator.

14.1.1 STUDIES INVOLVING CHILDREN

Special considerations must be given when performing research with children/minors (less than 18 years of age in Virginia).

14.1.2 SUBJECT CONSENT FORM

For research studies that have greater than minimum risk to children as subjects and which offers no prospect of direct benefit, the consent should provide two signature lines for parents/guardians. A reasonable effort must be made to obtain the signatures of both custodial parents or legal guardian(s). However, one parent's signature is acceptable in cases where one parent is deceased, unknown, incompetent, or not reasonably available, or where one parent has legal responsibility for the care and custody of the child.

14.1.3 WARDS OF THE STATE

The following regulations (45CFR46.409, 21 CFR 50.56) apply to studies that may involve children who are wards of the state or any other agency, institution, or entity.

- Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 46.406/50.53 or 46.407/50.54 **only** if 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 under paragraph (a) of this section, the IRB will 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 or in loco parentis. Furthermore, the advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis. 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.
- SUBJECT CONSENT FORM – For studies involving greater than minimal risk and no prospect of direct benefit to individual subjects, in the signature box, add the following mandatory boilerplate language – "A child who is a ward of the state cannot be enrolled until the IRB has assigned an individual advocate, relative to this potential enrollment, to act on behalf of the child in addition to the guardian or in loco parentis." This language is meant to serve as a notice to all parties that enrollment cannot proceed without an assigned advocate's concurrence and signature.
- APPROVAL LETTERS – The investigator's meeting letter will note if the risk level assigned invokes the regulations related to wards of the state and a reminder will be provided that an advocate must be appointed by the IRB before enrolling a ward into a study.

14.1.4 WAIVER OF PARENTAL PERMISSION

- If a research protocol is designed for a subject population for which parental or guardian permission is not a reasonable requirement in order to protect the child subjects, the IRB may waive parental consent provided the following conditions are met:
  - An appropriate mechanism for protecting the children who will participate is substituted; **and,**
  - The waiver is not inconsistent with Federal, State or local law. **NOTE: The waiver of parental permission is not permitted for FDA-regulated devices, drugs or biologics.**

14.1.5 ASSENT OF THE CHILD

- Include the Assent of the Child Form for research studies involving children ages 8 through 17. It is assumed that children ages 0 through 7 are not capable of giving assent. The giving of assent depends upon the potential subject's level of maturity and judgment and should be made on a case-by-case basis. However, anytime a child/minor indicates an unwillingness to participate in a study, the investigator must honor that communication and not enroll the child.

14.1.6 WAIVER OF ASSENT OF THE CHILD

The investigator may waive the assent of the child if he/she determines the child does not have the capacity to give assent due to the level of maturity or psychological state of the child.

OVERRIDE OF ASSENT OF THE CHILD

When a child indicates by any means that they do not want to participate (or continue participating) in a study it is expected that the investigator will honor the child's wish. Only in extraordinary circumstances should an override occur, and only in circumstances approved by the IRB. Protocols involving children must address such circumstances in order for the IRB to make a determination as to whether the override may be allowed.

14.1.7 RESULTS OF PREGNANCY TESTING IN MINORS

In an effort to ensure the comprehension of parents and children regarding the risks involved in participating in a research study, the IRB requires the following statement in Subject Consent Forms for studies where pregnancy testing will be conducted among pediatric populations: "If the pregnancy test is positive, the subject (child) will be informed of the results and counseled by the physician." It is important that young women of child bearing age be allowed to discuss potential pregnancy issues privately with the study investigators. Investigators are encouraged (and occasionally required by the IRB) to offer a private discussion with an adolescent without the parent present. However, regulations do not allow investigators to discuss termination of a pregnancy with a subject. That must be done by an uninvolved medical professional who is trained in providing such guidance. If this is anticipated, such plans must be described within the research protocol.

14.1.8 INCLUSION OF CHILDREN IN RESEARCH

Because medical treatments applied to children are often based upon testing done only in adults and treatments have been less available to children due to barriers to include them in research, the NIH developed the following policy to address this problem.

It is the policy of NIH that individuals of all ages, including children (i.e. individuals under the age of 18) and older adults, must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific or ethical reasons not to include them. The inclusion of individuals across the lifespan as subjects in research must be in compliance with all applicable subparts of 45CFR46 as well as with other pertinent federal laws and regulations. This policy also applies to research that would otherwise be considered "exempt."

Applications or proposals for research involving human subjects must address the age-appropriate inclusion or exclusion of individuals in the proposed research project. Applications/proposals must include a description of plans for including individuals across the lifespan, including a rationale for selecting the specific age range justified in the context of the scientific question proposed. If individuals will be excluded from the research based on age, the recipient/offeror must provide an acceptable justification for the exclusion.

IRBs have the responsibility to examine ethical issues, including the equitable selection of research participants in accordance with Federal regulations. The participation of children in research, including children of both genders and children from minority groups, is important to assure that they receive a share of the benefits of research. IRBs have special review requirements (45 CFR 46, Subpart D, Sec. 401-409) to protect the well-being of children who participate in research. IRBs may approve research involving children only if the special provisions are met.

14.2 STUDIES INVOLVING WOMEN

PREGNANT WOMEN, FETUSES AND HUMAN *IN VITRO* FERTILIZATION

Federal regulations require that IRBs treat pregnant women as a vulnerable population because of the need to avoid unnecessary risk to the mother and fetus. IRBs have additional duties in connection with activities involving fetuses, pregnant women, or human in vitro fertilization. Additional protections for these populations may include the use of witnesses for the consenting process, requiring consultants or patient advocates to monitor the consent process, obtaining consent of the father, and limiting the scope of research activities. In addition, principal investigators must give scientific justification for the exclusion of pregnant or potentially pregnant females in research studies for "serious conditions."

14.3 STUDIES INVOLVING COGNITIVELY-IMPAIRED INDIVIDUALS

Great care must be taken when involving cognitively-impaired individuals in research studies.

CONSENT PROCESS

Assessing Capacity to Consent/Assent - Individual's capacities, impairments, and needs must be considered, in order to develop ethical approaches in allowing participation. Even for minimal risk studies, prospective subjects must demonstrate that they can make a choice for themselves and understand information relevant to the study. The potential subjects should also be able to demonstrate that they understand how this relevant information applies to their own situation, and be able to manipulate this information rationally. If the subject is unable to do any of the above, a legally authorized medical decision maker must give surrogate consent before the study activities may begin. There may be some circumstances in which the IRB will not agree to allow surrogate consent and will require that all subjects consent in order to be included in a research study. When surrogate consent is used, the IRB expects all subjects will be asked to Assent to the study and their wishes shall prevail. Exceptions to Assent must be discussed within the research protocol and the IRB will provide guidance.

The IRBs may ask a principal investigator to specify the conditions under which a legally authorized representative should make the decision regarding participation in the trial. It is possible that a subject can make the decision to participate. The following criteria should be used in making such a determination.

- Evidencing a choice: If a person makes a decision, any decision, he or she is considered competent.

- Reasonable outcome of choice: An individual who fails to make a reasonable decision is considered incompetent.
- Factual comprehension: The individual is expected to understand, or at least be able to understand, the information disclosed during the consent negotiations.
- Choice based on rational reasons: It is essential to test the person's capacity for rational manipulation of information.
- Appreciation of the nature of the situation: The person must display not only comprehension of the consent information but also the ability to use that information in a rational manner.

DEFINITION OF "LEGALLY AUTHORIZED REPRESENTATIVE"

- The parent or parents having custody of a prospective subject who is a minor;
- The agent appointed under an advance directive executed by the prospective subject, provided the advance directive authorizes the agent to make decisions regarding the prospective subject's participation in human research;
- The legal guardian of a prospective subject as defined by state laws;
- The spouse of a prospective subject, except where a suit for divorce has been filed and the divorce decree is not yet final;
- An adult child of the prospective subject;
- A parent of the prospective subject, even when the subject is an adult;
- An adult brother or sister of the prospective subject; or
- Any person authorized by law or regulation to consent on behalf of a prospective subject to such subject's participation in the particular human research.

14.4 STUDIES INVOLVING SUBJECTS IN EMERGENCY SITUATIONS

Subjects in emergency situations may not be able to consent for themselves or devote adequate consideration to their participation in a research study. See Section 11 for discussion of Emergency Use consent procedures.

14.5 VULNERABILITY DUE TO ECONOMIC STATUS

Subjects must not be coerced into participating in a research study because of financial inducements. The IRB reviews study procedures to ensure that any financial payment is appropriate.

INFLUENTIAL RELATIONSHIPS

When subjects are being sought from certain populations, the consent to participate may be unwittingly influenced by an investigator who is in a position of authority (such as a faculty member asking participation from a trainee or a supervisor approaching an employee). When this potential exists, the investigators must have measures in place to avoid coercion or undue influence. For example, a non-faculty person could be the only individual allowed to recruit and consent for a study involving trainees (students, residents and fellows). For EVMS studies an **Employee and Student Addendum Consent Form** is required when planning to recruit employees or students as research subjects.

14.6 COMPROMISED SITUATIONS

Health care providers must be particularly cognizant of the provider/patient relationship. Patients may agree to be in a study hoping to show appreciation for their care; or, may be more apt to agree because they do not differentiate between medical care from a provider and investigational options from the same provider who is conducting a research study.

15. SPECIAL CONSIDERATIONS FOR FDA STUDIES

15.1 INVESTIGATIONAL NEW DRUG/IND

Research involving a drug or biologic that has not yet been approved by the FDA for distribution to the marketplace, requires an Investigational New Drug (IND) application. The FDA critically reviews the IND applications to ensure that the risks for human subjects are reasonable.

Research sponsors submit FDA Form 1572 to the FDA for the IND. Each investigator participating in a drug or biologic study is required to sign Form FDA 1572 stating that the investigator agrees to comply with the stipulations on the back of the form. This is a legal document and investigators are held accountable by the FDA if the information they provide is falsified or if the commitments agreed upon are ignored. Please be sure to understand your responsibilities.

15.2 OFF LABEL DRUG USE

In order to conduct a research study which involves the use of an FDA approved drug but for an unapproved use WITHOUT obtaining an IND all six of the following criteria must be satisfied and verified by the principal investigator in writing to the IRB, preferably within the research protocol.

The research study meets all of the following conditions:
1. It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant changes in the labeling for the drug;
2. It is not intended to support a significant change in the advertising for the product;
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
5. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; **and**
6. it does not intend to invoke 21 CFR 50.24.

15.3 INVESTIGATIONAL MEDICAL DEVICES/IDE

Research involving a device that has not yet been approved by the FDA for distribution to the marketplace requires an approved Investigational Device Exemption (IDE). The IRB plays an integral role in this process. A separate vote is taken by the IRB in the review of a study to determine if the investigational device poses a significant risk or a non-significant risk to study participants. In addition, the sponsor of the study (industry or investigator) must document their risk determination in the protocol. If the two determinations disagree, the FDA is the final authority on the risk level.

NON-SIGNIFICANT RISK

When the sponsor and the IRB agree that the device is a non-significant risk, the device is considered to have an approved IDE with the FDA provided all the following are true:
1. The device is properly labeled;
2. The device has been approved by the IRB as a non-significant risk;
3. Investigators obtain and document informed consent;
4. Proper study monitoring is conducted; and
5. Compliance is assured for all IDE regulations.

SIGNIFICANT RISK

A significant risk device study is one where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

A significant risk device is define by the FDA as:
1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of the subject.

For studies with devices determined to be a significant risk, a FDA-approved IDE application is required. There are no exceptions. The sponsor must notify the FDA, submit an IDE application and the project may not begin until both are approved by the FDA and IRB. Documentation is similar to the FDA 1572 for INDs.

All investigators are listed on the application and must commit to comply with the regulations. In addition, significant risk devices must comply with the IRB, informed consent, monitoring, and compliance regulations.

Studies that contain significant risk devices may require a more frequent interval of IRB review.

15.4 STUDIES INVOLVING BOTH DRUGS AND DEVICES

Studies that involve both an experimental drug and device must first have a determination by the FDA as to whether it will be assigned an IND or an IDE. The IRB cannot review the protocol until this

determination is made as it allows the Board to ensure that the appropriate regulations are considered in the review process.

15.5 HUMANITARIAN DEVICE EXEMPTION (HDE)

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions where more than 4,000 people have the disease but fewer than 4,000 manifest the condition per year in the United States. The FDA makes the decision regarding whether a device qualifies as a HUD. The amount charged for a HUD cannot exceed the costs of research and development, fabrication and distribution and must have the approval of the FDA.

The statute and implementing regulation [21CFR814.100] require IRB review and approval before a HUD is used. While the study is not considered research, the same consideration is given to the risks, benefits and ethical issues as the IRB would normally do when reviewing a research application.

REQUIREMENT FOR INITIAL REVIEW:

- Full (Convened) IRB review.

REQUIREMENT FOR CONTINUING REVIEW: EXPEDITED REVIEW APPROPRIATE

- Unless the IRB determines that Full (Convened) Board review should be performed.
- Expedited Review procedures are appropriate for Continuing Review since the Full (Convened) Board would have performed the initial review and use of a HUD within its approved labeling does not constitute research.

IS THERE A REQUIREMENT THAT EACH INDIVIDUAL USE OF THE HUD RECEIVE IRB REVIEW AND APPROVAL?

- The IRB does not need to review and approve individual uses of a HUD as long as the use of the HUD is within the FDA approved indication.

IS INFORMED CONSENT REQUIRED WHEN TREATING/DIAGNOSING A PATIENT WITH A HUD?

- The Federal Food, Drug and Cosmetic Act and the HDE regulation do not require informed consent because an HDE provides for marketing approval, and so the use of the HUD does not constitute research or an investigation that would normally require informed consent.
- Most HDE holders have developed patient information to assist a patient in making an informed decision about the use of the device including a discussion of the potential risks and benefits of the device, the procedures associated with the use of the HUD and that the device is a humanitarian use device for which effectiveness for the labeled indication has not been demonstrated.

CAN A HUD BE USED IN AN EMERGENCY SITUATION OR FOR "COMPASSIONATE USE"?

Yes, as long as all appropriate measures are followed. If such a use is needed, please contact the IRB office for guidance or refer to the FDA guidance found at the following web page: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/humanitarian-use-device-hud-designation-program.

15.6 SPONSOR RESPONSIBILITIES IN FDA-REGULATED RESEARCH

The responsibilities of sponsors include:
Submitting IDE or IND to FDA;
Selecting qualified investigators to participate in the studies and securing their commitment to adhere to the regulations;
Monitoring the study, supplying new safety information regarding the study to the investigator, IRB and FDA;
Completing regulatory filings with the FDA and informing of any significant changes or findings, including unexpected Adverse Events, withdrawal of IRB approval, and filing of progress reports;
Controlling the distribution and disposition of all investigational test articles.

15.7 "EMERGENCY USE" WAIVER OF APPROVAL

The use of a non-FDA-approved drug or device may be needed in emergency situations when IRB approval is not feasible. In such cases, the IRB can grant a waiver for "emergency use." "Emergency use" is defined as the use of experimental drug, biological product or device on a human subject in a situation that is life threatening, in which no standard of treatment is available and in which there is not enough time to obtain full IRB approval. This provision in the FDA regulations is an exemption from *prior* IRB review and approval. The exemption may not be used unless it is a life-threatening situation. Any subsequent use of the drug or biological product will require *prospective* IRB review and approval.

Life-threatening, for the purposes of section 56.102(d), 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.

The regulations do not intend to limit the authority of a physician to provide emergency care in a life-threatening situation. If it appears probable that similar emergencies will require subsequent use at the institution, every effort must be made to sign on to the sponsor's protocol or to develop a protocol for future emergency use of the article. Either of these protocols would need to be prospectively reviewed and approved by the IRB.

THE PROCESS DURING BUSINESS HOURS, MONDAY-FRIDAY, 8 A.M.-5 P.M.:

- The IRB should be notified prior to use. This is not for approval; it is notification that is used as tracking to ensure the physician files a report within the 5-day time frame.
- Some companies require a written statement indicating that the IRB is aware of the proposed use and considers it to meet the requirements of 21 CFR 56.104(c). This letter, although not considered IRB approval, will allow the shipment of product to proceed.
- Informed Consent is still required by either the patient or the patient's legally authorized representative, unless both the physician and a physician who is not otherwise participating in the care certify in writing all of the following:
  - ✓ The patient is confronted by a life-threatening situation, available treatments are unproven or unsatisfactory;
  - ✓ Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the patient;
  - ✓ Time is not sufficient to obtain consent from the patient's legal representative. The physician will summarize efforts made to contact the legally authorized representative in the report to the IRB;
  - ✓ No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.
  - ✓ If there is no time to obtain an independent physician's opinion and the test article is required to preserve the patient's life, the physician must make the determination that the above four conditions are met, and use the test article.
  - ✓ After the use of the article, and within 5 working days, the physician should have the determination reviewed and evaluated by another physician who is not participating in the study.
  - ✓ The physician using the article must notify the IRB of the use of the test article within 5 working days of the use.
  - ✓ Protocols involving Waiver of Consent must be performed under a separate IND or IDE that clearly identifies them as protocols containing individuals that are unable to consent. The submission of these protocols in a separate IND or IDE is required, even if an IND for the same drug or an IDE for the same device already exists.

When the provision of "Emergency Use" of a test article or biological product takes place without prior IRB review and approval, it is deemed to be the provision of emergency healthcare and cannot be claimed as "research."

AFTER BUSINESS HOURS:

If the need for the emergency use provision arises after business hours, the investigator should secure agreement in writing from another physician who is not involved in the study and report the use to the IRB within 5 working days.

15.8 EXPANDED ACCESS

Sometimes called "compassionate use", expanded access is a potential pathway for a patient with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Expanded access may be appropriate when **all** the following apply:

- Patient has a serious or immediate life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Investigational drugs, biologics or medical devices have not yet been approved or cleared by FDA and FDA has not found these products to be safe and effective for their specific use. Furthermore, the investigational medical product may, or may not, be effective in the treatment of the condition, and use of the product may cause unexpected serious side effects.

Contact the IRB office for assistance with an Expanded Access request.

15.9 CONDUCTING PLANNED RESEARCH IN EMERGENCY SETTINGS

The consent of subjects involved in planned research in emergency settings may also be waived [21CFR50.24] if it meets certain regulatory requirements. The research must be planned in advance and approved by the IRB, the FDA, and publicly disclosed to the community in which the research will be conducted. The Waiver of Consent would apply to a limited class of research activities involving human subjects who cannot give informed consent because they have a life-threatening medical condition and do not have a legally authorized representative available to represent them. The concurrence of a licensed physician, who is either on the IRB or is a consultant for the IRB and is not otherwise participating in the study, is required for the study to be approved and must be documented in the IRB minutes. For a Waiver of Consent to be granted, the following requirements have to be met and clearly demonstrated in the research protocol provided to the IRB:

The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence (which may include evidence obtained through randomized, placebo-controlled investigations) is necessary to determine the safety and effectiveness of particular interventions.

Obtaining informed consent is not feasible because of the subject's medical condition; the intervention must be administered before consent from the subject's legally authorized representative is feasible; there is no way to prospectively identify the individuals likely to become eligible for participation in the clinical investigation.

Participation in the research holds out the prospect of benefit to the subjects because:

- Subjects are facing a life-threatening situation that necessitates intervention;
- Data from appropriate animal studies or other preclinical studies have been conducted and the data support the use of the intervention for direct benefit to the individual subjects; and
- Risk/benefit of both the standard of care and the proposed treatment is reasonable.

The clinical investigation could not practicably be carried out without the waiver.
The proposed investigational plan defines the length of the potential therapeutic window during which the investigator will seek consent from a legally authorized representative, rather than proceeding without consent. A summary of efforts to contact the legally authorized representative will be given to the IRB at the time of Continuing Review, or at the time of each subject's enrollment if requested by the IRB.

The IRB has reviewed and approved informed consent procedures and an informed consent document. These procedures and document will be used with subjects or their legally authorized representatives in situations where use is feasible.

Additional protections of the rights and welfare of subjects will be provided, including:

- Consultation with representatives from the community.
- Public disclosure to the community prior to the initiation of the clinical investigation, of plans for the investigation, and its risks and benefits.
- Public disclosure of sufficient information following the completion of the clinical investigation to apprise of the results.
- Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation. The data monitoring committee is established by the sponsor of the research, as an advisory body to the sponsor. Data monitoring committees receive study data on an on-going basis. Based on its review of the data, it may be recommended to the sponsor that the clinical investigation be modified or stopped.
- If obtaining informed consent is not feasible from the subject or legally authorized representative, the investigator must attempt to contact, within a therapeutic window, a member of the subject's family (who is not a legally authorized

representative) and ask whether the member objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this available to the IRB at the time of Continuing Review, or at the time of each subject's enrollment if requested by the IRB.

- If a legally authorized representative or family member provided consent, and the subject's condition improves, informed consent will also be obtained from the subject at the earliest opportunity. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation must be provided to the legally authorized representative or family member.

Protocols involving Waiver of Consent must be performed under a separate investigational new drug (IND) or investigational device exemption (IDE), even if an IND or IDE already exists for the same drug or device.

If an IRB determines that it cannot approve a study because it does not meet the criteria for Waiver of Consent, the IRB must document its findings and promptly notify the investigator in writing.

It is the responsibility of the principal investigator to notify the sponsor of all IRB decisions.

16. CONTINUING REVIEW AND CLOSING OUT A STUDY

16.1 REASONS FOR CONTINUING REVIEW

The process of IRB review is a continuing process. Projects are re-evaluated on a regularly scheduled interval, at least once per year, as required by the Federal government. The level of risk of a study determines the schedule of review; studies presenting higher levels of risk for subjects can be reviewed on a more frequent basis.

Reasons for Continuing Review include:
To ensure that the risk/benefit relationship is still acceptable;
To ensure that subjects remain protected from inappropriate risks;
To determine whether new information that may be important to the subject has surfaced;
To determine if unanticipated risks were discovered;
To ensure the protocol that was previously approved is being followed;
To ensure that the project adheres to regulations and guidelines, which may have been altered, since the project was previously approved.
To determine if the project is progressing as expected and enrollment can be fulfilled. This helps justify the continued enrollment of subjects into a viable study.

The interval for Continuing Review (requiring the submission of a progress report from the PI) is made at the time of initial IRB approval, but may be changed upon subsequent IRB review. The IRB has the authority to suspend, terminate, or place restrictions on a study that has previously been approved for reasons of non-compliance or if deemed necessary to ensure protection of human research subjects.

Continuing review is required if any of the following are true:

- Subjects are still being enrolled;
- Data is being collected or validated; or,
- Data analysis is ongoing.

16.2 DOCUMENTATION REQUIRED FOR CONTINUING REVIEW

The Continuing Review Report Form is the only Continuing Review form that has been approved for use by the Board (see Appendix B).

The following information is required for the submittal of Continuing Review reports:
A complete Continuing Review Report Form with a re-evaluation of risk-benefit by the investigator;
The most recently approved Subject Consent Form(s) updated to the EVMS templates published on the IRB office website if the study is still open to subject entry. All copies must

The following information is required for the submittal of Continuing Review reports:
show changes, additions and deletions to the form. The "Track Changes" option in Microsoft Word is recommended for tracking; however, the investigator may use other methods as long as all changes are shown.
The current protocol, which must be updated to include any changes made during the period of review. (Note: changes to the protocol or other documents must be submitted to the IRB prior to the initiation of the change, unless the change is needed for the safety of participating subjects.)

16.3 IRB FEE

Fee for Convened Board Review	Amount
Continuing Review of a study requiring convened Board review *[Fee is billed after the study has received Board initial review for continuation]*	$ 500.00

Full-time faculty, community faculty and non-EVMS investigators who use the IRB review and management process and receive ANY extramural support for protocols are expected to remit the IRB Continuing Review fee upon billing by EVMS. Waiver of the fee may be considered in the event that protocols are not supported but that decision is typically made at the initial review. No review fee is charged for protocols that receive an "expedited" Continuing Review by the IRB.

16.4 SUBMISSION TIMELINE – CONTINUING REVIEW

Continuing Review reports are due two months before the anniversary of the previous approval date. (For example: if you received approval of a study for twelve months and the study was approved in January, your next Continuing Review report will be due the following November.) The due date of the next Continuing Review report is always stated in the previous approval letter and other letters related to the study.

Email reminders that a Continuing Review report will be due are sent to the principal investigator starting four months before the study expires. However, **IT IS THE RESPONSIBILITY OF THE PRINCIPAL INVESTIGATOR TO SUBMIT THE CONTINUING REVIEW PACKET BEFORE THE DEADLINE REGARDLESS OF THE REMINDER.** It is recommended that investigators, especially those submitting large numbers of protocols, develop their own tracking mechanism for the submission of Continuing Review reports.

NOTE: Studies that are closed to subject entry but continue to follow subjects are still considered to be active studies and must continue to be reviewed and re-approved by the IRB. A consent form to be stamped will not be needed UNLESS a change in the protocol requires the re-consenting of subjects, or the sponsor requires re-consent at an annual visit.

16.5 CONSEQUENCES OF LATE CONTINUING REVIEW REPORTS

The IRB has the authority to suspend or terminate approval of research for non-compliance with Federal regulations and guidelines and institutional directives regarding continued approval.

Responsibilities Associated with Continuing Review and Consequences of Noncompliance
THE SUBMISSION OF TIMELY CONTINUING REVIEW REPORTS IS ALWAYS THE RESPONSIBILITY OF THE INVESTIGATOR.
The IRB will, in its initial correspondence regarding approval of the study, and in any subsequent correspondence, state the expiration date of the approval and the deadline for the submission of a continuing review report.
Although the IRB Office will try to provide reminders to investigators, **THE BURDEN OF RESPONSIBILITY REMAINS WITH THE INVESTIGATOR.**
If Continuing Review does not take place before the expiration date of previous approval, the study will fall into unapproved status. Submission of a report does not constitute a continuing review. There must be adequate time for the report to be received and accepted by the IRB office, and reviewed and approved by the IRB **BEFORE** the expiration date of the study.
Protocols risk falling in an unapproved status if appropriate monitoring of these deadlines does not take place by the investigative site.
During the period of unapproved status, no subjects shall be treated or recruited and all study-related activities including data analysis shall cease. One exception to this may be if the cessation of treatment poses a threat to the life or welfare of a subject. The PI should consult with the IRB if this is expected.
Recruitment of subjects under a non-approved status constitutes non-compliance and will jeopardize the investigator's ability to submit further protocols to the IRB and, in the worst case, may result in termination of protocols in the midst of data collection.
If a protocol falls into unapproved status, the IRB will suspend or administratively terminate the protocol and require a complete submission to the convened Board to re-establish approval.
Investigators, who have had a study terminated due to failure to report Continuing Review, will not be allowed to submit any new protocols until the terminated protocol is either re-established or closed out.
The administrative termination of approval will be provided in writing and shall include a statement of the reason(s) for the IRB's action.
This action will be reported promptly to the investigator, the Department Chairman, the Assistant Dean for Research Subject's Protections, any affiliate hospitals, and any appropriate sponsoring agency. Repeated noncompliance may be reported to the Food and Drug Administration (FDA) and/or Office for Human Research Protections (OHRP).

NOTE: If the study is completed, a closeout report is required.

16.6 EVALUATION OF CONTINUING REVIEW PACKETS

DETERMINING THE TYPE OF REVIEW

The IRBs reserve the option of making the decision regarding whether a Continuing Review packet will receive Convened Board or Expedited Review.

- **Expedited Studies**
  The review of studies that were originally approved on an expedited basis are screened by the IRB staff to ensure that risks to subjects remain minimal and can be approved on an expedited basis by the IRB Chair, Vice Chair, or designated IRB member.
- **Convened Board Studies**
  The review of studies that were originally approved by the convened Board are screened by the IRB staff to ensure that the project poses more than minimal risks to subjects, therefore requiring convened Board review. Some studies originally approved by a convened Board may qualify for Expedited Review if there is minimal risk associated with remaining study activities. Such studies can be approved on an expedited basis by the IRB Chair, Vice Chair, or designated IRB member.

16.7 CRITERIA USED FOR CONTINUING REVIEW

The criteria for the Continuing Review of projects are the same as those for initial review.

The criteria are:
Subject selection – is it fair? The IRB takes into account the purposes of the research, the setting, and is particularly cognizant of vulnerable populations.
Risk/benefit relationship - risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk; are reasonable in relation to anticipated benefits; include safeguards to protect the rights and welfare of vulnerable subjects.
Voluntariness – recruitment practices, advertisements, possibilities for coercion or undue influence
Confidentiality – have adequate provisions been maintained to protect the privacy of subjects and maintain the confidentiality of the data?
Review of the consent form(s) – to ensure adherence to guidelines and to ensure that information is presented in a manner that will enable comprehension. Informed consent will be sought and documented from each appropriate prospective subject or each subject's legally authorized representative.
Monitoring of data – where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
Ability to meet enrollment expectations to fulfil the objectives of the protocol. Continuing to enroll subjects into a protocol that cannot meet the study objectives is not appropriate. The IRB may terminate the study after discussion with the PI if the Board feels that continuation of the study and participation by subjects will not result in a viable study.

Any changes in subject population, recruitment plans, research procedures, study sites, study instruments or research personnel must be approved by the IRB prior to implementation. Changes to any risk level to subjects most likely will need convened Board approval.

Of particular concern is the surfacing of unanticipated risks or new information that would affect a subject's decision to remain in the study.

16.8 CRITERIA USED TO DETERMINE WHETHER VERIFICATION FROM SOURCES OTHER THAN THE INVESTIGATOR THAT NO MATERIAL CHANGES HAVE OCCURRED SINCE THE LAST IRB REVIEW:

During the period of review:
A study participant or other concerned individual discussed a problem or concern associated with the study with the EVMS Institutional Official; with an IRB Chair; or with the IRB Director.
Significant consenting errors were identified in a routine audit.
The investigator reported a large number of unexplained participant withdrawals.

16.9 CLOSING OUT A STUDY

Filing a close out report is an important element of the research study process. Besides informing the IRB that a study has concluded, it provides data on local subject ethnicity and gender, Adverse Events and other information accumulated during the study, as well as study results. Failure to submit either a Continuing Review report or a close out report by the expiration of the study approval date will result in administrative termination of the study. Federal guidelines may require that terminated studies be reported to the FDA and OHRP, as well as to the sponsor and other institutional officials.

The procedure for close out reporting is very similar to that of Continuing Review. Data on subject recruitment, adverse events and other information must be provided when this final report is filed. Close out reports are reported to the Board.

A close out must be reported at the conclusion of all study related activities. **NOTE: JUST BECAUSE A STUDY IS CLOSED TO SUBJECT ENTRY, DOES NOT MEAN THAT THE STUDY HAS CONCLUDED.** After meeting enrollment and closing to new subject entry, data may still be collected on previously enrolled subjects. Once all subjects complete participation in a study, there is still the need to analyze the study data and this requires continued IRB approval.

Once a study is closed, the file is withdrawn from the active IRB files and placed in archive for a minimum of 3 years.

16.10 NOTIFICATION OF APPROVAL/DISAPPROVAL

Please see Section 9 (Outcomes of Convened Board Review) for policies and practices associated with notification of Board decisions.

17. ADDITIONAL ACTIONS REQUIRING IRB REVIEW / APPROVAL

17.1 REVIEW OF AMENDMENTS / REVISIONS

Any proposed changes to the protocol, consent form(s), advertisements, or other study-related material must be promptly submitted to the IRB office for review. Changes in approved research cannot be initiated without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects already participating in the study.

17.2 TYPE OF REVIEW

The decision regarding whether an amendment will be reviewed as expedited or by the Convened Board is made by the IRB staff when an administrative or pre-review of submitted materials occurs. If necessary, the staff will consult with the IRB assistant director, director or chair and/or vice chair.

Expedited – if the changes are minor:

Examples of Minor Changes Include, but are not Limited to:
Changes in the investigatory team;
Administrative changes (e.g., names of contact, individual's phone numbers, and addresses);
Changes in study-related activities (e.g., extra visits, additional questionnaires or subject diaries, or additional low risk activities such as blood draws).

Convened Board – if the changes are found to be significant. Significant changes include:

Example of Significant Changes Include, but are not Limited to:
Fundamental changes in experimental design;
Some new dosing regimens;
Addition of substantial numbers of new subjects; or
New treatment groups.

17.3 DOCUMENTATION REQUIRED FOR EXPEDITED REVIEW

- **Amendment Assessment by the Investigator – one (1) copy.** The principal investigator must sign the Amendment form unless they are unavailable AND the amendment is for immediate patient safety concerns, in which case a co-investigator may sign. A unique identifier must be supplied for each revision – protocol, consent or otherwise (e.g., Amendment # ___ on [date]).
- **Changes in Protocol or other non-consent documents – one (1) clean copy and (1) highlighted copy.** A protocol with the changes identified using ~~cross-outs~~ for deleted items and highlighting for added items. A **Detailed Protocol Summary** showing all changes (before and after) may be provided instead of marking changes on the protocol but **a new updated**

protocol must always be submitted. **Note:** An IRB approval will not include any changes that are not clearly identified by the investigator.

- **Changes in Consent Form(s)** – **two (2) copies**. *One (1) highlighted* copy must have all changes identified using ~~cross-outs~~ for deleted items and highlighting for added items; and *one (1) copy* must be clean so that it may be stamped and returned to the investigator. An **Addendum Consent Form** may be used to provide new information about the study to subjects or to extend the participation of a subject beyond the original protocol. An addendum may not be used for extensive revisions, which may require approval from the Convened Board (e.g., changing subjects from a placebo-controlled trial to an open-label trial). **Note:** An IRB approval will not include any changes that are not clearly identified by the investigator.
- **Last approved Consent Form(s) – one (1) copy**. Include one copy of the last approved, stamped consent form(s).

17.4 DOCUMENTATION REQUIRED FOR CONVENED BOARD REVIEW

The IRB office notifies the investigator in writing if an amendment requires convened Board review. The investigator is then required to provide packets that include the following:

- **An Amendment Assessment by the Investigator –one (1) copy.** The principal investigator must sign the Amendment form unless they are unavailable AND the amendment is for immediate patient safety concerns, in which case a co-investigator may sign. A unique identifier must be supplied for each revision –protocol, consent or otherwise (e.g., Amendment # ___ on [date]).
- **Changes in Protocol** – **one (1) clean copy and (1) highlighted copy.** A **protocol** with the changes identified using ~~cross-outs~~ for deleted items and highlighting for added items. **Note:** An IRB approval will not include any changes that are not clearly identified by the investigator.
- **Detailed Protocol Summary – one (1) copy if available.** With the changes identified using ~~cross-outs~~ for deleted items and highlighting for added items.
- **Changes in Consent Form(s)** – **one (1) clean copy and (1) highlighted copy**. Copies must have all changes identified using ~~cross-outs~~ for deleted items and highlighting for added items. An **Addendum Consent Form** may be used to provide new information about the study to subjects or to extend the participation of a subject beyond the original protocol. An addendum may not be used for extensive revisions, which may require approval from the Convened Board (e.g., changing subjects from a placebo-controlled trial to an open-label trial). **Note:** An IRB approval will not include any changes that are not clearly identified by the investigator.
- **Last approved Consent Form(s) – one (1) copy**. Include one copy of the last approved, stamped consent form(s).

The review of the amendment/revision by the convened Board will result in one of the following actions:

The review of an Amendment by the convened Board will result in one of the following actions:
Approval without changes;
Approval with modifications;
Tabled for additional information; or
Not approved/Disapproved.

17.5 NOTIFICATION OF APPROVAL/DISAPPROVAL

Please see Section 8.2 (Outcomes of Convened Board Review) for policies and practices associated with notification of Board decisions.

17.6 CIRCUMSTANCES REQUIRING RE-CONSENT OF SUBJECTS

The IRB may decide that subjects need to be re-consented because of:
Significant changes in the research design,
A change in the risk/benefit relationship,
The addition or subtraction of procedures for subjects,
Other changes that significantly change the conduct of the study.

If the amendment is approved, the IRB indicates whether or not subjects need to be re-consented in documents returned to the investigator.

17.7 NOTIFICATION OF APPROVAL/DISAPPROVAL

Please see Section 8.2 (Outcomes of Convened Board Review) for policies and practices associated with notification of Board decisions.

17.8 ADVERTISEMENTS

For information related to the review and approval of advertisements, please see section 7.1.2.8. Note that advertisements submitted after a study has received initial approval are considered amendments and must receive IRB review and approval before they may be initiated.

17.9 RESEARCH SUBJECT INTERVIEWS BY THE PRESS

The principal investigator or clinical coordinator (e.g., only these individuals involved with the study) may ask a subject if he/she would like to be interviewed. In the initial inquiry with the subject, there must be no coercion, participation must be voluntary, and the option of retaining anonymity of the subject must be extended to the subject. If the subject agrees to be interviewed, then the coordination of the interview must be handled through EVMS Marketing and Communications.

18. REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Both the OHRP and the FDA require prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others. The monitoring of unanticipated problems by the IRB is important to identify any pattern of unexpected events that may be developing and uncover new information about a therapy or intervention that may or may not be reported as an adverse event.

OHRP REQUIREMENTS FOR REPORTING UNANTICIPATED PROBLEMS

OHRP requires reporting of two categories:

- Adverse Events that are Unanticipated Problems; and,
- Unanticipated Problems that are not Adverse Events.

OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets ALL of the following criteria:

(1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
(2) related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
(3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The OHRP regulations at 45 CFR part 46 do not define or use the term ***adverse event***, nor is there a common definition of this term across government and non-government entities. The term *adverse event* in general is used very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

OHRP defines ***unexpected adverse event*** as follows:

Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.
  (Modified from the definition of unexpected adverse drug experience in FDA regulations for IND Safety Reporting at 21CFR312.32(a).)

Adverse events may be caused by one or more of the following:

- the procedures involved in the research;
- an underlying disease, disorder, or condition of the subject; or
- other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by (2) or (3) would be considered unrelated to participation in the research.

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*.

OHRP defines ***serious adverse event*** as any adverse event that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21CFR312.32(a).)

OHRP considers adverse events that are unexpected, related or possibly related to participation in research, and *serious* to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed

consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

However, other adverse events that are unexpected and related or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

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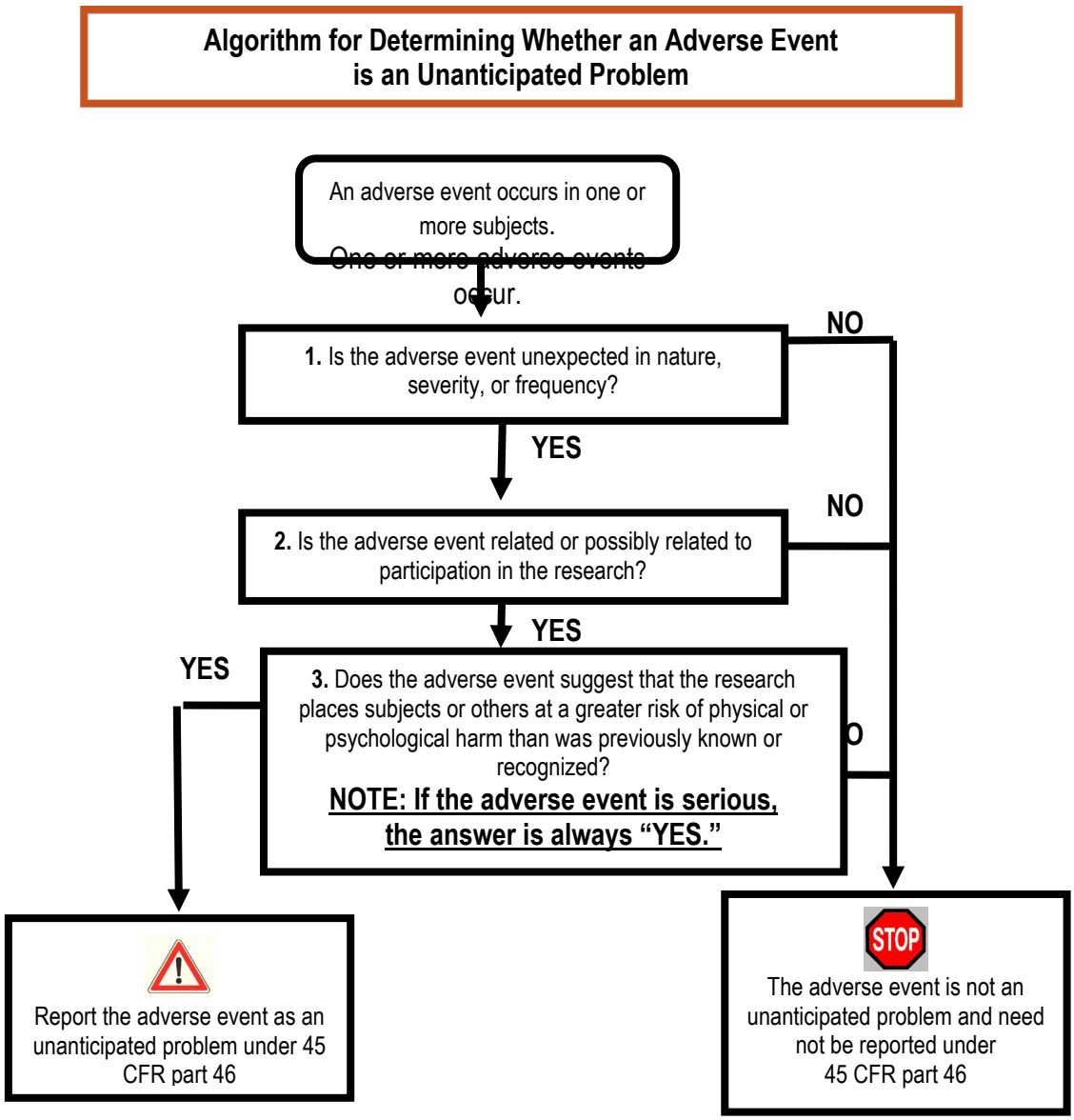
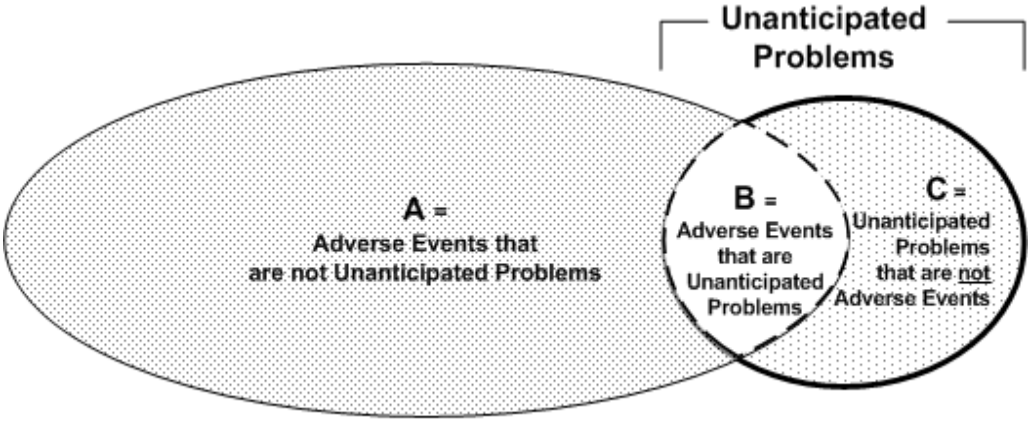
The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR part 46.



Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB. Such reports are to be submitted to the IRB by investigators. Reports must include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.



Under 45 CFR part 46: Do not report A; Report B and C.

18.1 FDA REQUIREMENTS FOR REPORTING UNANTICIPATED PROBLEMS

In addition to reporting unanticipated problems, the FDA has specific requirements for the reporting of Adverse Events, as outlined below.

The FDA Definitions Include:
SERIOUS ADVERSE DRUG EXPERIENCE as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. [21CFR312.32(a)]
UNEXPECTED DRUG EXPERIENCE as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. [21CFR32(a)]
UNANTICIPATED ADVERSE DEVICE EFFECT as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect,

The FDA Definitions Include:
problem, or death was previously identified in nature, severity, or degree of incidence in the investigational plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects.

FDA IND/IDE Regulations Require:
That CLINICAL INVESTIGATORS notify: • The sponsor of any adverse effect that may be reasonably regarded as caused by, or probably caused by, the drug. EVMS IRB policy also requires the investigator to simultaneously submit this information to the IRB. • The sponsor and the IRB of any unanticipated adverse device effect within 10 working days.
That SPONSORS notify: • The FDA and all participating investigators of any adverse experience associated with the use of the drug (or biologic) that is both serious and unexpected as soon as possible, but not later than 15 calendar days after the sponsor determines it to be "reportable". • Clinical investigators of all "new observations" particularly with respect to adverse effects and safe use. • The FDA, all participating investigators, and all reviewing IRBs the evaluation of any unanticipated adverse device effect within 10 working days of the sponsor's receipt of the information.

18.2 BEHAVIORAL AND SOCIAL SCIENCE

In behavioral and social science research:

- A SOCIAL RISK EVENT is defined as an adverse social consequence or outcome to a study participant as a result of study participation.

18.3 EVENTS REPORTED BEFORE EVMS APPROVAL OR AFTER EVMS CLOSURE

IMPORTANT: Unanticipated problem reports and adverse effect reports are not accepted by the EVMS IRB for **closed** studies, nor are such reports accepted for the period **before** the study was initiated at EVMS. Such reports will be returned to the site without any IRB review or comment. Investigators should provide this section of the SOPs to sponsors for notification of this policy.

18.4 REPORTING MECHANISM FOR LOCAL EVENTS

The mechanism for reporting unanticipated problems and Adverse Events is dependent on whether they are **local events or events at other sites** (non-local) **AND** whether they are **Adverse Events or Serious Adverse Events. The death of a local subject is to be reported in all cases.**

***LOCAL EVENTS*:** Those events experienced by subjects enrolled by the investigator(s) under the EVMS IRB approval.

Investigators must report ALL local unanticipated problems and/or serious adverse events immediately to the IRB via the Office of Research Subjects Protections.

Documentation Required:

✓ **Local Unanticipated Problem or Adverse Event Reporting Form – one (1) copy.** The EVMS Unanticipated Local Problem Reporting Form is located on the IRB website. All reports must include as an attachment, a copy of the last approved, stamped consent form.

Local Event reports must:
• Be reported in writing to the IRB within five (5) business days.
• If reported by telephone, follow-up must be made in writing by the principal investigator within five (5) business days by completion of the appropriate SAE form.
• Provide the facts of the event, including a description and date.
• Provide the risk determination at the time of report.
• Provide a statement by the investigator as to whether the event provides new information about the study risks and whether a change needs to be made to the consent form, protocol or study
• Include as an attachment, a copy of the last approved, stamped consent form.

18.5 REPORTING MECHANISM FOR NON-LOCAL EVENTS

***ON-LOCAL EVENTS*:** Those events experienced by subjects enrolled by investigators at other institutions engaged in the multi-center clinical trial where sites other than those approved by the EVMS IRB are participating.

For Adverse Events that occur at other (non-local) sites, the sponsor provides reports of unanticipated problems and/or Adverse Events to the investigator who, in turn, must promptly review the report to determine if it is serious and either directly related to the study being conducted (e.g., same study, different site) or to other studies using the same drug, device or agent.

Reporting requirements for Non-Local Events:

Report immediately upon the investigator becoming aware of the event:

- All Serious Adverse Events directly related to the study.
- Events determined not to be serious but which are occurring more often than anticipated in the approved protocol and other study documents.

Report in summary at next continuing review

All Serious Adverse Events not directly related to the study. These reports are to be summarized and forwarded to the IRB at the next continuing review.

Do Not Report:
Events determined not to be serious and not occurring more often than anticipated in the approved protocol and other study documents. Any such submissions will be returned without review.

Documentation Required

✓ **Non-Local Unanticipated Problem or Adverse Event Reporting Form.** The EVMS Non-Local Unanticipated Problem or Adverse Event Reporting Form is located on the IRB website. All reports must include as an attachment, a copy of the last approved, stamped consent form.

18.6 IRB REVIEW OF UNANTICIPATED PROBLEMS AND ADVERSE EVENT REPORTS

Review of Unanticipated Problems and Adverse Events:
• Unanticipated problems and adverse events are reviewed using an expedited process.
• The IRB reserves the right to review any report at a convened meeting if deemed necessary, or such a review is requested, by any IRB member or the Institutional Official.
• When the investigator reports no change or a decrease in risk, the Board reserves the right to use an administrative review process.
• When the investigator reports an increase in risk, a member of the Board conducts a review to determine whether the risks associated with a protocol remain acceptable or whether a change is necessary in the consent form or protocol.
• The IRB carefully evaluates the relationship of the AE to the research interventions and interactions and determines whether the AE represents an unanticipated problem.
• The IRB follows appropriate procedures for ensuring that any AE determined to be an unanticipated problem is reported per HHS regulations.
• The IRB determines whether the research or informed consent document(s) require modification.

19. STATEMENT ON COLLABORATIVE RESEARCH

When collaborating on human research activities with researchers outside of the FWA institutions, the EVMS IRB and the IRB of the collaborator's institution must review the research project, unless an appropriate IRB Authorization Agreement or Reliance Agreement is in place with the institutions. The IRB Director can assist with this process. Without an EVMS IRB review or an IRB Authorization Agreement or Reliance Agreement signed by the EVMS Institutional Official and collaborating institution, EVMS faculty, staff and students cannot collaborate on a human subject research project.

20. PROTOCOL DEVIATION AND/OR UNANTICIPATED PROBLEMS

Any protocol deviation that results in a change to the risk/benefit ratio or affects the integrity of the study must be promptly reported to the IRB by the investigator. In addition, the deviation must be reported to any other required entity (such as the FDA, etc.) by the investigator. It is the responsibility of the investigator to promptly inform the IRB of any unanticipated problems involving risks to human subjects or others.

21. AUDITING

Periodic auditing of IRB studies is conducted by an audit team and/or the EVMS Compliance Director to:
• Determine adherence to IRB policies and the approved protocol;
• Verify that no material changes have occurred since previous IRB review; and
• Further educate study staff and investigators about the IRB Standard Operating Procedures.

An audit occurs when there is:
• Suspicion or report of noncompliance;
• A concern about possible material changes occurring without IRB approval;
• Concern about the safety and welfare of subjects currently participating in a study; and/or
• Concern about a research team member's (faculty, trainee or staff) academic, research or other activities.

Periodic "no-cause" audits may also occur for studies selected on a random basis.

In certain circumstances, the IRB members may request that the IRB staff conduct some audits.

22. MONITORING OF STUDIES AND/OR REPORTING NONCOMPLIANCE

The Institutional Official or an IRB Chair(s) of one of the EVMS IRBs reviews initial allegations of noncompliance. A determination will be made as to whether the alleged practices appear to: (1) cause injury or any other anticipated problems involving risks to subjects or others; or, (2) constitutes serious or continuing non-compliance with IRB regulations. The IO or IRB Chair(s) may consult with additional Board members to discuss the need for a suspension. Following the consultation, the IO or IRB Chair(s) could suspend the study (or all studies of an investigator) until a timely investigation and review is completed by the convened IRB.

The IRB and/or EVMS authorities have the authority to suspend or terminate protocols or research activities that are found to be non-compliant with institutional policies and procedures, state laws, and/or Federal laws or regulations. Other sanctions imposed by the Institution or an EVMS IRB may include, but are not limited to, compliance audits, destruction of data collected without appropriate approval, letters of reprimand, and restrictions on serving as an investigator on human subjects protocols.

The Institutional Official is responsible for reporting to appropriate officials, the FDA (if appropriate), and OHRP (if appropriate) within 5 working says of his/her receipt of the report of:
• Any unanticipated problems involving risks to human subjects or others.
• Any instances of serious or continuing noncompliance with regulations or determinations of the IRB.
• Any suspensions or termination of IRB approval other than study terminations due to a lapse in Continuing Review.

23. RESPONSIBILITIES OF KEY INDIVIDUALS

The following are responsibilities of individuals who conduct research using human subjects and their department chairs.

23.1 INVESTIGATORS

Responsibilities of Investigators
OBTAIN WRITTEN IRB APPROVAL BEFORE INITIATING ANY RESEARCH PROCEDURES OR ACTIVITY. For EVMS faculty, trainees and staff, approval must be through an EVMS IRB or an IRB approved by the Research Subjects' Protections office via a signed IRB Authorization Agreement (IAA) or Reliance Agreement. The agreement must be routed through the RSP office to be signed by the EVMS Institutional Official. Obtaining another IRB approval without a signed IAA or Reliance Agreement is not acceptable.
TRAINING: • Complete required human subjects training (CITI) and provide verification of completion *before* submitting protocols for IRB review. • Complete HIPAA research training (included in CITI online training modules). • Assure that human subjects training verification is submitted for all personnel directly associated with a human subjects research study *before* including those individuals on any research study. Investigators are not allowed to remove already approved team members for lack of training and then seek to add them later. Team members must be current and if not, can be removed but no longer assist with the study. • Review training materials and all relevant Federal and State regulations, and all EVMS policies regarding the protection of human research subjects. • Attend training sessions when provided by the institution. • Have a current Investigator Assurance (IA) on file with the EVMS IRB. The IA must be renewed every three years.
STANDARD OPERATING PROCEDURES AND FEDERAL REGULATIONS: • Submit and receive an EVMS IRB approval before initiating any human subjects research. If using an IRB other than EVMS, investigator must ensure an IAA is in place between EVMS and the other IRB before initiating ANY study activity. The IAA must be processed through the Research Subjects' Protections office. • Distribute current IRB policies and procedures to staff members. • Use the most current version of IRB forms. • Review relevant State and Federal regulations, legislation, and institutional assurance documents relevant to the proper conduct of research in human subjects, particularly those that are pertinent to subject populations involved in investigator's

Responsibilities of Investigators
research studies (e.g., children, cognitively impaired individuals, pregnant women, fetuses and others). • Comply with all EVMS SOPs and federal, state and local regulations for human subject research. • Comply with the EVMS Federalwide Assurance.
PROTOCOL DOCUMENTATION: • Maintain active research protocols in an approved status for ongoing human subjects research. • Assure the accuracy and completeness of all documents submitted to the IRBs. • Each principal investigator and Department Chair must verify the scientific merit of a new study before submitting the study for IRB review. Based on information submitted by the principal investigator, the appropriate department chair (or designee) certifies the scientific merit of the study for his/her department. If the PI has any EVMS faculty appointment, the EVMS Department Chair must sign. • Submit timely IRB documentation required for Federal grants or other funding sources.
PROTOCOL MANAGEMENT: • Ensure that changes in approved research are not initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to subjects. Any changes implemented for subject safety must be submitted to the IRB immediately as an amendment. • Provide written notification of a change in association with a research study or with the institution. These changes are recorded in the Board Minutes.
CONTINUING REVIEW: • Provide timely submission of Continuing Review reports, at least two months prior to the anniversary of the previous approval date. • Submission of the Continuing Review is the responsibility of the PI and should not be dependent of receiving any reminder notices. If a study expires, the PI must stop all study activities immediately until a review and renewal is conducted by the IRB. • Any data collected during a period where IRB approval was halted cannot be saved.
COMMUNICATION: • Promptly notify the IRB of protocol deviations that affect the risk/benefit ratio to subjects or the integrity of the research study. • Promptly inform the IRB of unanticipated problems and Adverse Events involving risks to human subjects or others. • Promptly communicate the results of ALL outside audits to the IRB. • Communicate IRB approvals and other communications to sponsors • Serve as the link between the IRBs and sponsors. The IRB or its representatives will not discuss studies directly with sponsors because it is important the PI is aware of and involved in all discussions.

REPRESENTATION: • All full-time EVMS faculty, trainee or staff engaging in human subject research must utilize an EVMS IRB or an IRB approved with via an IRB Authorization Agreement (IAA) or Reliance Agreement processed through the Research Subjects Protections office. • All EVMS faculty who are NOT full-time but using their EVMS credentials or referencing EVMS in the publication of human subjects research must use an EVMS IRB or an IRB approved with via an IRB Authorization Agreement (IAA) or Reliance Agreement processed through the Research Subjects Protections office. .

23.2 DEPARTMENT CHAIRS

Responsibilities of Department Chairs
• Provide scientific review of research studies or delegate this review to appropriately experienced and trained scientific investigators. Review of scientific merit is the responsibility of the Chairman. The IRB reviews scientific merit only from the perspective of the ethics of the research and use of human subjects in fulfilling the study objectives.
• Provide signature, indicating approval of scientific merit for research studies.
• Provide the IRB with written authorization for a designated alternate for the signature of a Department Chair.
• Ensure the availability of faculty members to be appointed to the IRB, especially when the department utilizes the IRB services extensively, as well as support the member's attendance at meetings.

24. FINDER'S FEES FOR RESEARCH SUBJECTS

Finder's fees (cash or non-monetary payment) for the referral of subjects to investigators are considered unethical. This practice has the potential to violate the subject's trust in the referring entity, the investigator and in the process of research.

25. HHS SUBPART C CERTIFICATION FORM

The HHS Subpart C Certification Form is used to verify that a study has been reviewed by an IRB that has an assurance on file with the appropriate Federal agency. When necessary, it is the investigator's responsibility to provide the IRB with a completed copy of the HHS Subpart C Certification Form for signature by the IRB Chair. A copy of this form will be maintained in the IRB file.

26. RESEARCH - USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

DEFINITIONS:

Research

Research is defined as systematic investigation, including the research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR § 160.501.)

Treatment

Treatment is defined as the provision, coordination, or management of health care and related services by one or more health care providers, including the coordination or management of health care by a health care provider with a third party; consultation between health care providers relating to a patient; or the referral of a patient for health care from one health care provider to another.

26.1 POLICY

It is the policy of Eastern Virginia Medical School to abide by the use and disclosure rules set forth by the Health Insurance Portability and Accountability Act (HIPAA) of 1996, with revisions of August 14, 2002. Under the Privacy Rule, EVMS researchers are permitted to use and/or disclose individually identifiable health information in the course of conducting research with an individual authorization, or without individual authorization under limited circumstances.

26.2 PROCEDURES

26.2.1 RESEARCH USE/DISCLOSURE WITHOUT AUTHORIZATION:

To use or disclose protected health information without proper authorization by the research participant, EVMS must obtain one of the following:

a) Documentation that an alteration or waiver of authorization has been approved by an Institutional Review Board (IRB).

b) Attestation from the researcher, in writing, that the use or disclosure of PHI is solely to prepare a research protocol or purposes preparatory to research, that PHI will not be removed, and representation that access sought is necessary for research purposes.

c) Attestation from the researcher, in writing, that the use or disclosure being sought is solely for research on the PHI of decedents, that the PHI being sought is necessary for research, and documentation of the death of the individuals.

d) An EVMS IRB determines that the data is recorded in such a manner that it meets the criteria for "de-identified data" or a "limited data set".

EVMS may also disclose PHI without subject authorization or a waiver of authorization if the disclosure is to a:

a) Public health authority that is authorized by law to collect or receive PHI for the purpose of preventing or controlling disease, injury, or disability;
b) Public health authority or other appropriate government authority authorized by law to receive reports of child abuse or neglect;
c) Person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to a FDA-regulated product or activity for which that person has responsibility, for the purposes of activities related to the quality, safety, or effectiveness of such FDA-regulated product or activity. Such purposes include to:
    1. Collect or report adverse events (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations;
    2. Track FDA-regulated products;
    3. Enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
    4. Conduct post marketing surveillance.

26.2.2 WAIVER OF AUTHORIZATION

EVMS and/or EVMS Medical Group will release or permit access to PHI for research purposes pursuant to a waiver of authorization by an EVMS IRB, provided it has obtained documentation of all of the following:

1. A statement that the alteration or waiver was approved by the IRB, as stipulated by the Privacy Rule.
2. A statement identifying the IRB and the date on which the alteration or waiver was approved;
3. A statement that the IRB has determined that the alteration or waiver satisfies the following criteria:
    a) The use and disclosure of PHI involves no more than minimal risk to the privacy of an individual, based on, at least, the presence of the following elements:
    b) an adequate plan to protect the identifiers from improper uses and disclosures;
    c) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law;
    d) an adequate written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for

authorized oversight of the research project, for other research for which the use or disclosure of PHI would not be permitted by this subpart;

e) The research could not practicably be conducted without the waiver or alteration; and
f) The research could not practicably be conducted without access to and use of the PHI.

4. A brief description of the PHI for which use or access has been determined to be necessary by the IRB;
5. A statement that the alteration or waiver or authorization has been reviewed and approved under either convened Privacy Board review or expedited review procedures as stipulated by the Privacy Rule; and
6. The signature of the chair or other designee of the IRB.

26.2.3 PREPARATORY TO RESEARCH

Disclosure is permitted without a patient authorization or a waiver of authorization for review of PHI, when necessary to prepare a research protocol or for similar purposes preparatory to research.

A Researcher must provide representations to an EVMS IRB that:

a) Use or disclosure is sought solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research;
b) No PHI will be removed from EVMS by the researcher in the course of the review; and
c) The PHI for which use or access is sought is necessary for the research purposes.

EVMS requires that researchers submit an application to the IRB with representation that all of the above criteria apply to the project using the Waiver of Authorization for PHI form.

26.2.4 DECEDENT RESEARCH

A Researcher must provide representations to an EVMS IRB that:

a) use or disclosure sought is solely for research on the PHI of decedents;
b) documentation, at the request of EVMS, of the death of the such individuals; and
c) the PHI for which use or disclosure is sought is necessary for the research purposes.

EVMS requires researchers to include this information in a written protocol to the IRB for decedent research.

26.2.5 DE-IDENTIFIED INFORMATION OR LIMITED DATA SET

De-Identified Information (Safe Harbor) may be used and disclosed without being subject to the HIPAA Privacy Rule.

a) *De-Identified Information*. In order for information to be considered "de-identified", it must not include the following direct identifiers of the individual or the relatives, employers, or household members of the individual:
   1) names;
   2) all geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
      i. the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
      ii. the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000;
   3) all elements of dates (except year) for dates relating directly to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;"
   1) telephone numbers;
   2) fax numbers;
   3) electronic mail addresses;
   4) social security numbers;
   5) medical record numbers;
   6) health plan beneficiary numbers;
   7) account numbers;
   8) certificate/license numbers;
   9) vehicle identifiers and serial numbers, including license plate numbers;
   10) device identifiers and serial numbers;
   11) Web Universal Resource Locators (URLS);
   12) Internet Protocol (IP) address numbers
   13) biometric identifiers, including finger and voice prints;
   14) full face photographic images and any comparable images; and
   15) any other unique identifying number, characteristic, or code.

b) EVMS may assign a code or other means of record identification to allow de-identified information to be re-identified by EVMS, as long as the code is not derived from or related to, information about the subject. HMAC code cannot be used as a re-identification code.

c) Privacy Rule does not restrict linkage of PHI inside EVMS.

Information may also be considered as de-identified only if:

a) a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable;

b) applying such principles and methods, determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information; and

c) ii) documents the methods and results of the analysis that justify such determination.

26.2.6 LIMITED DATA SETS

Limited Data Sets for research, public health, or health care operations may be used or disclosed if:

a) EVMS uses and discloses only a limited data set;

b) EVMS obtains a Data Use Agreement from the data recipient; and

c) The data used or disclosed does not include the following direct identifiers of the individual or the relatives, employers, or household members of the individual:

1) name;
2) postal address information, other than town, city, state, or zip code;
3) fax numbers;
4) electronic mail addresses;
5) social security numbers;
6) medical record numbers;
7) health plan beneficiary numbers;
8) account numbers;
9) certificate/license numbers;
10) vehicle identifiers and serial numbers, including license plate numbers;
11) Web Universal Resource Locators (URLs);
12) Internet Protocol (IP) address numbers;
13) biometric identifiers, including finger and voice prints; and
14) full face photographic images and any comparable images.

When using or disclosing PHI in a limited data set, a Data Use Agreement is required. The Data Use Agreement establishes:

a) Who is permitted to use or receive the limited data set;

b) That the recipient of the limited data set may not further use or disclose the limited data set outside of the Data Use Agreement;

1) the recipient must use appropriate safeguards to prevent further use or disclosure;
2) the recipient must report to EVMS any use or disclosure of the limited data set that is not provided for in the Data Use Agreement;
3) the recipient must ensure EVMS that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions of the recipient as outlined in the Data Use Agreement; and,

4) the recipient will not identify or contact the individuals who are subjects of the limited data set.

26.2.7 RESEARCH USE/DISCLOSURE WITH INDIVIDUAL AUTHORIZATION:

The Privacy rule permits EVMS to use and disclose PHI for research purposes when a research participant authorizes the use and disclosure of his or her information.

a) The authorization must be written and include the following elements:
   1) A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion;
   2) The name or other specific identification of the person(s) or class of persons authorized to make the use or disclosure of PHI;
   3) The name of the person(s) or class of persons to whom EVMS is authorized to make the disclosure;

b) A description of each purpose of the use or disclosure;
   1) An expiration date or an expiration event that relates to the individual or the stated purpose of the use or disclosure. The statement "end of research study", "none", or similar language is sufficient if the authorization is for a use or disclosure of PHI for research, including the creation and maintenance of a research database or research repository;
   2) The individual's signature and date; and
   3) If signed by a legally authorized representative, a description of his or her authority to act for the individual.

c) The authorization must also include statements concerning:
   1) The individual's right to revoke the authorization in writing and either:
      i. the exceptions to the right to revoke and a description of how the individual may revoke the authorization; or
      ii. reference to the EVMS Privacy Notice.
   2) The consequences to the individual of a refusal to sign the authorization for use or disclosure of PHI for research purposes. EVMS may condition the provision of research-related treatment on the provision of authorization by a subject.
   3) The potential for information covered by an authorization to be re-disclosed by the recipient and no longer protected by the Privacy Rule.

- At EVMS, the authorization for research purposes may be incorporated into the Subject Consent Form and submitted to the IRB or Privacy Board for review and approval.
- The authorization must be written in plain language.
- EVMS must provide the individual with a copy of their signed authorization.

26.2.8 ACCOUNTING FOR DISCLOSURES

EVMS researchers must keep an accounting of disclosures made of a research subject's PHI and provide that information to the subject when requested by the subject. There are some exceptions to this accounting of disclosures requirement. The following situations DO NOT require researchers to keep an accounting of disclosures when disclosure of PHI is:

1) Made to carry out non-research-related treatment, payment and health care operations.
2) Within a limited data set with an approved Data Use Agreement.
3) Made with the authorization of subject.
4) Made incidental to another permissible disclosure or use.
5) Made prior to the compliance date of April 14, 2003.

An accounting of disclosures MUST be kept when the disclosure of PHI is made:

1) With a waiver of authorization
2) For disclosures to a Business Associates, even when there is a Business Associates Agreement in place.
3) Preparatory to research

The required elements of an accounting of disclosures are:

1) Disclosures that occurred during the six year period prior to the request (a shorter period may be permitted at the request of the subject);
2) Date(s) of the disclosures;
3) Name of entity or person(s) who received the PHI, and if known, their address;
4) Brief description of the PHI disclosed; and
5) Brief description of the purpose of the disclosure(s).

When requested by a research subject, EVMS will assist in contacting those researchers to whom it is likely that the individual's PHI was actually disclosed.

Researchers must provide to the subject an accounting of disclosures within 60 days of the request but a 30-day extension may be possible, if necessary. A subject has the right to receive one free accounting in a 12-month period. EVMS has the right to charge a reasonable cost-based fee for additional requests from the same patient within the same 12-month period. The individual making the request must be notified in advance of the fees and be provided an opportunity to withdraw or amend their request.

26.2.9 MINIMUM NECESSARY

When using or disclosing PHI or when requesting PHI from another covered entity, EVMS researchers must make reasonable efforts to limit PHI to the minimum necessary to accomplish the intend purpose. The minimum necessary standard DOES NOT apply to research for which a subject has signed an authorization to use or disclose the PHI.

Minimum necessary standards DO apply to:

1) Research conducted with a waiver of authorization;
2) Research involving PHI of decedents;
3) Use of PHI preparatory to research;
4) Limited data set research