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RESEARCH INFORMED CONSENT GUIDEBOOK
(HRP 03.01G)

Veteran Affairs Maryland Health Care System
(VAMHCS)

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Section I: Informed Consent Overview

A. Introduction

Research involving human subjects in the social, behavioral, and medical sciences poses complex ethical issues. It requires careful thought and consideration on the part of both researchers and research participants. Prospective participants must be given adequate information on both the possible risks and the potential benefits of their involvement to allow them to make informed decisions.

As a researcher, it is your responsibility to educate participants about risks, benefits, and rights, obtain their consent before involving them in research, and keep them informed. This is the "informed consent process."

The Informed Consent Guidebook is intended to be a comprehensive, digestible, educational, up-to-date treatment of the topic of informed consent. It includes practical tips on how to fulfill campus requirements (VAMHCS, IRB, CICERO). It begins with a brief description of the ethical and historical foundations of the informed consent process and continues with very specific advice on such topics as writing VA-specific informed consent documents, submitting an informed consent document to CICERO with the VAMHCS specifically in mind, obtaining and documenting informed consent, types of research & research participants, assessing decision-making capacity, and others. This guidebook is meant specifically for VAMHS studies, even though many aspects are generalizable to the UMB campus and are consistent with national standards. Throughout the guidebook, there are references to other R&D Service standard operating procedures and guidances as well as UMB IRB and federal policies. Both experienced and new investigators and staff should regard the Guidebook as a master reference for performing research at the VAMHCS.

B. The Process[1]

Obtaining a signature on a consent document is important, but it is just one step in the informed consent process.

Informed consent is about people's understanding and willingness to participate in a study; it is not limited to obtaining their signature on the consent form. Prospective participants in a research study must understand the purpose, the procedures, the potential risks and benefits of their involvement, alternatives to participation, that they do not have to volunteer, and that they can withdraw at any time. While a consent document that provides this information is a vital part of the process, the opportunity to discuss any questions or concerns with a

[1] Based upon: "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research", published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979), a seminal document expounding the principles of the informed consent process.

knowledgeable research team member is also essential. In addition, prospective participants may need time to think about their decision and to discuss it with family, friends, physician, therapist, or religious advisors.

Making an informed decision about participating in research includes the participant's having a clear understanding of the possible risks and benefits to their involvement and knowing that they do not have to volunteer and can withdraw at any time.

Be mindful of these concepts when you answer the Consent Procedure questions in your CICERO submission.

The informed consent process starts before enrollment and continues throughout the trial. During the trial, subjects are told of new findings regarding the study or the study entity, are encouraged to ask questions, and are continually assessed for their understanding of the study and their voluntary participation.

C. Basic Principles

To discern the key components of informed consent, it is important to understand the ethical issues of research involving human subjects. The principles of autonomy, beneficence, and justice are basic to these ethical issues and merit consideration.

1. Autonomy: Autonomy means that each person should be given the respect, time, and opportunity to make their own decisions. Prospective participants must be given the information they will need to decide to enter a study or not to participate. There should be no pressure to participate. "From the Nuremburg Code on, the right of a subject to say "no" is the first right of a subject." (Conley, 2003)

   The principle of autonomy requires that protection be given to potentially vulnerable populations such as children, the elderly, the mentally ill, or prisoners. Individuals in these groups may be incapable of understanding information that would enable them to make an informed decision about study participation. They are considered potentially "vulnerable." Consequently, careful consideration of their situation and needs is required and extra care must be taken to protect them. For example, how will you assess the diminished capacity of an elderly individual, who will be the guardian, and how and when will you involve another individual as guardian in the process?

Be mindful of this concept when you answer Vulnerable Subjects Consent Procedure sections in your CICERO submission.

2. Beneficence: Beneficence obligates the researcher to ensure the well being of all study participants. It is your responsibility to protect participants from harm, as well as make certain that they experience the possible benefits of involvement.

Balancing risks and benefits is an important consideration. The key, according to the 1979 Belmont Report on the protection of human subjects, is to "maximize possible benefits and minimize possible harms."

When do the benefits to society outweigh the possible risks of research? This is an ethical question that researchers face. The peer review process and the principle of beneficence help you answer this question and protect your research participant's rights.

Be mindful of this concept when you answer the Justification, Potential Risks & Discomforts and Benefits sections in your CICERO submission.

3. Justice: The ethical considerations of risks versus benefits raise the question of justice. Who should bear the risk of a study, and who should receive its benefits? The concept of justice may be questioned when we attempt to decide who will be given an opportunity to participate and who (and for what reason) will be excluded. Are some classes or persons being selected simply because of their availability, their compromised position, or their manipulability while others are not? Keep the following tips in mind when selecting prospective participants:

   - Participants should not be selected due to age, gender, class, socioeconomic status, or race unless justified by study objectives.
   - Women have been underrepresented in certain research studies because of the risks associated with child bearing. Now researchers must justify why women are not included in a study population. Failure to provide scientifically sound arguments for the exclusion of one gender is grounds for denial of approval.
   - An existing counselor-client relationship requires consideration of the potential for power-based coercion when expanding that relationship to include investigator-subject. Provision, or adjustments, might need to be made to attempt to equalize the roles.
   - Teacher-student relationships always carry a perception of inequality in roles. The informed consent process should reflect the precautions taken to balance the relationship and guard against even the perception of coercion.

   Justice is a difficult and complex ethical issue. However, attempt at all times in your study to distribute the risks and benefits fairly and without bias.

Be mindful of this concept when you answer the Justification, Vulnerable Subjects, Potential Risks & Discomforts and Benefits sections in your CICERO submission.

Keep the principles of autonomy, beneficence, and justice in mind when you are selecting participants, obtaining consent, and conducting your study. The responsibility to protect and inform research participants is ultimately yours and cannot be ignored or delegated.

Although various tasks may be delegated to certain team members, the PI cannot delegate the responsibility of protecting and informing participants of their rights.

Remember these points when you are designing and conducting research studies:

- Other people and their private information don't belong to the PI.
- The sheer value of research does not automatically trump the rights of people.
- Ask before you take unless the IRB approves. (Conley, 2003)

D. A Brief History of Human Subjects Rights and Protections

Here are some significant dates in the development and history of informed consent.

1947: Twenty-six Nazi physicians are tried at Nuremberg, Germany, for research atrocities performed on prisoners of war. This results in the Nuremberg Code, the first internationally recognized code of research ethics, issued by the Nazi War Crimes Tribunal (a prototype for later codes of ethics).

1940s: A series of research abuses starts in Tuskegee, Alabama. In one study on the natural history of untreated syphilis, poor, black males are uninformed of their disease and denied treatment even after a treatment is found in 1947. The abuses are revealed in 1972.

1962: The Kefauver-Harris Bill is passed to ensure greater drug safety in the United States after thalidomide (a new sleeping pill at the time) is found to have caused birth defects in thousands of babies born in Western Europe.

1964: The 18th World Medical Assembly meets in Helsinki, Finland, and issues recommendations to guide physicians in biomedical research involving human subjects.

1974: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research is established, and the National Research Act is passed by Congress. This Act prompted the establishment of IRB's at the local level and required IRB review and approval of all federally funded research involving human participants.

1979: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research publishes The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research -- a guide for U.S. research with human subjects.

1993: The Albuquerque Tribune publicizes 1940s experiments involving plutonium injection of human research subjects and secret radiation experiments. Indigent patients and mentally retarded children were deceived about the nature of their treatment.

1994: President Clinton creates the National Bioethics Advisory Commission (NBAC).

1995: The President's Advisory Committee on Human Radiation Experiments concludes that some of the radiation experiments from the 1940s were unethical.

These events and more recent ones have prompted increased federal action to protect human subjects involved in all types of research.

Proposed research designs from VA staff and affiliate university faculty, staff, and students must be reviewed by the University of Maryland, Baltimore (UMB) IRB and the VAMHCS Research & Development Committee. The IRB is charged with reviewing plans for the protection of research participants in VAMHCS studies. The IRB ensures that human subjects do not bear any inappropriate risk and that consent documents accurately reflect the description of the study and other elements of informed consent. Along with the protection of human subjects, the VAMHCS R&D Committee is also concerned with regulatory criteria specific to the VA and utilization of VA resources.

The IRB consists of representatives of VA staff, veterans, and the local community. The IRB and the R&D Committee review all research involving human subjects, irrespective of the funding source. This includes research that is funded by federal agencies, state government, foundations, internal grants, departmental funds, etc.

E. Definitions of "Human Subject" and "Research"

VA regulations at 38 CFR 16.102(d) and the Common Rule define **research** as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

VA regulations at 38 CFR 16.102(f) and the Common Rule define **human subject** as "a living individual about whom an Investigator (whether professional or student) conducting research obtains either: data through intervention or interaction with the individual or identifiable private information. These individuals could be patients, healthy volunteers, students, employees, and/or members of the community.

- **Interaction:** Includes communication or interpersonal contact between an Investigator or his/her research staff and the research participant or the participant's private identifiable information.
- **Intervention:** This includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes.
- **Private Information:** Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example,

medical records). Private information must be individually identifiable (i.e., the identity of the participant is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human participants.

If an FDA-regulated test article is involved, the FDA regulations will also apply. It is important to note that the definitions of human subject and research in the FDA regulations differ from the VA regulations and the Common Rule. An activity is FDA-regulated research when:

- It involves any use of a drug other than the use of an approved drug in the course of medical practice. (21 CFR 312.3(b)) This is the meaning of "experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act" in the definition of "clinical investigation".
- It evaluates the safety or effectiveness of a medical device (21 CFR 812.2(a)) This is the meaning of "experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act".
- The results of the activity are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

21 CFR 56.102(e) defines **human subject** as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient." The FDA further defines "human subject" as an individual on whose specimen a device was used.

VA policy highlights that the definition of human subject includes investigators, technicians, and other assisting investigators when they serve a "subject" role by being observed, manipulated, or sampled.

More extensive definitions of human participant and research can be found in the IRB P&P Glossary and the R&D Service "Human Research Protections Plan" (HRP 01.02).

Examples of Human Subject Research. The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research conducted in VA. They may be done at one VAMC or may be conducted as multi-center projects (viz: Cooperative Studies Program).

1. **Clinical Research.** Clinical research involves research: (a) to increase scientific understanding about normal or abnormal physiology, disease states, or development and (b) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of

clinical research. As defined in the FDA regulations, clinical investigation means any experiment that involves a test article and one or more human subjects. (21 CFR 56.102) The terms research, clinical research, clinical study, and clinical investigation are generally considered to be synonymous.

2. **Behavioral and Social Sciences Research.** The goal of social and behavioral research is similar to that of clinical research — to establish a body of knowledge and to evaluate interventions — but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.

3. **Epidemiological Research.** Epidemiological research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, efficiency, interventions, or delivery of services to affected populations. Some epidemiological research is conducted through surveillance, monitoring, and reporting programs — such as those employed by the Centers for Disease Control and Prevention (CDC) — whereas other epidemiological research may employ retrospective review of medical, public health, and/or other records. Because epidemiological research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. Epidemiologic studies may not even be "research" according to the definitions above. However, the VAMHCS policy is that the IRB must determine whether a project is "research", whether it is expeditable, or whether it is exempt from regulations. The PI should contact the IRB for guidance in this area.

4. **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB should review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with or without IRB review of individual research protocols. The VA has specific requirements for repository research. See also I.F.2h-j (p.8-9) and II.D. Essential element #5.

5. **Quality Assurance/Quality Improvement Activities.** Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities may constitute human subject research (and therefore require IRB review) if they are designed or intended to contribute to generalizable knowledge. Quality assurance activities that are designed solely

for internal program evaluation purposes, with no external application or generalization, will probably not require IRB review or will qualify for an exemption. It is VAMHCS policy that the IRB must determine whether a project is "research", whether it is expeditable, or (especially in the case of some QA projects) whether it is exempt from regulations. The PI should contact the IRB for guidance in this area. If in doubt, the IRB, not the individual investigator, should determine when IRB review of such activities is required.

6. **Pilot Studies.** Pilot studies involving human subjects are considered human subject research and require IRB review. See also I.F.2.f (p.8)

7. **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. OHRP representatives have advised that "third parties," about whom identifiable and private information is collected in the course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRBs can consider if informed consent from third parties can be waived in accordance with Section.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate. See also I.F.2.j (p.9)

F. What Research Must Be Reviewed

All research at the VAMHCS involving humans, human tissue, or records gathered on human subjects requires IRB and R&D review. This is true regardless of the funding source or area of research.

1. VAMHCS human subjects research that must undergo IRB review includes that which:

- It is conducted completely or partially in VA facilities or at approved off-site locations/facilities;
- It is conducted by researchers with VA appointments while on official VA duty (including those with WOC status);
- The research directly involves recruitment of or interactions with veterans associated with the VAMHCS or its satellites;
- The research is VA-funded;
- It is research that involves VAMHCS medical records or VAMHCS databases, or otherwise derives data from intervention or interaction with VAMHCS subjects or tissues.

2. In addition, the following circumstances will require IRB review:

   a. Research conducted at another institution: "Research involving human subjects that is conducted completely or partially in VA facilities, conducted in approved off-site locations/facilities and/or conducted by VA researchers or staff while on VA official duty time. This also includes recruitment of VA patients to research protocols conducted elsewhere by VA investigators while on duty at VA facilities or approved off-site locations. The research may be VA funded, funded from extra-VA sources, or conducted without direct funding." (VHA 1200.05)

   b. Research that is part of multi-center clinical trials: Approval of a document at the national level is not sufficient to bypass approval at the local level. Therefore, proposals and consent forms must also be submitted for IRB review.

   c. Research in foreign countries: Research conducted by VA researchers in foreign countries falls under VA guidelines. Although they cannot be imposed on other cultures, the standards for ethical conduct cannot be lowered. Human subjects in foreign countries deserve the same level of protection as subjects in the United States.

   d. Research conducted in courses: Courses in research methods and class assignments involving research with human subjects require IRB approval.

   e. Faculty-supervised student research: Faculty must take an active role in ensuring that research projects are conducted in accordance with the IRB's requirements.

f. Research at a pilot or feasibility stage: Pilot and feasibility studies, even those with only one human subject, require the same review as full-scale research projects. Applications to the IRB for pilot studies should be identified as such, and subjects must be told during the consent process that the study is a pilot study.

g. Research involving secondary use of data: Projects that use data on human subjects gathered in earlier projects and in which individual identifiers are present require IRB review (See IRB P&P). If, however, someone who has legitimate access to the records gathers the data and who gives the investigator only "blinded" data (meaning the investigator is unable to identify the subjects), the research project may qualify for an exemption from full review.

h. Research using "waste" and "extra" material: Research conducted on "waste" or "extra" human tissue or fluids[2] must be submitted for review.
   - "Waste" material is defined as material that is collected originally for clinical or diagnostic purposes but is no longer needed.
   - "Extra" material is defined as material that is collected above and beyond what is needed for a clinical or diagnostic procedure but for investigational purposes.

NOTE: If the original consent for the clinical procedure contains permission for the use of "waste" material for research, the IRB may not require another consent form. Collection and use of "extra" material will need IRB review.

i. Research involving biological tissue[3]: The VA has recently published a directive that covers this topic in detail (VHA Directive 1200, "Banking of Human Biological Specimens Collected from Veterans for Research", 3/31/03). However, this directive is very detailed and very far-reaching. If you or your sponsor plans to store *any kind of biological specimen or related biomaterial such as DNA* for the purposes of the study or for future uses, *even if it is "left-over" or waste material*, you MUST get IRB approval, you MUST use a VA or a VA-approved storage facility, and you should read the directive. *In addition, the VA requires additional language in the consent form. See section II.F.5 (p. 27).*

   Also, even if you send *non-banked* specimens to a non-VA institution for analysis (as in the sponsor's central lab), the remainder of the specimens must

[2] "Human biological specimens" are defined as materials derived from human subjects, such as blood, urine, tissue, organs, hair, nail clippings, saliva, sputum, buccal swabs, excreta and external secretions (including sweat), teeth, dental plaque and calculus, or any other materials that are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.
[3] See footnote 2 above.

be returned to you for destruction or the non-VA institution must certify in writing that the specimens or biomaterial have been destroyed.

The IRB requires that approval be obtained for any research studies using specimens or data collected prospectively or used retrospectively. In some cases, approval for a specific "research repository" may need to be obtained. See UMB HRPP Policies & procedures.

See also I.E.4 (p.9).

j. Genetic research: The greatest risk to subjects participating in genetic research is the inappropriate release of personal and private information. Therefore, the manner in which confidentiality of the data and specimens collected during the study is a primary concern. The CICERO submission and consent form should address the following points:
    - That all study information is coded and personal identifiers maintained securely;
    - That the consent form includes information about who will receive the information (i.e. the subject, family members, family physician, other physicians or investigators);
    - Whether clinically relevant information may be uncovered during the study and give participants the opportunity to decline receiving this information;
    - Will genetic counseling be made available;
    - Study data should not be recorded in the subject's medical record;
    - Inform subjects of any special risks associated with their participation (i.e. changes in family relationships, risks to privacy, confidentiality, insurability, employability, paternity suits);
    - Indicate whether study results will be made available to subjects;
    - Indicate the length of time the specimens will be retained and at what point they will be discarded (see "Tissue Banking" section);
    - Provide a contact (the investigator) in the consent form so subjects can request that their sample be destroyed;
    - Should there be a potential commercial value derived from the research, the subject must be informed as to whether they will be asked to waive their rights or control over the tissue;
    - When the genetics study is part of a larger study, subjects must be told that they can decline participation in the genetics study and still participate in the primary study.

    See Sections I.E.7, I.F.2j and II.F.6-7.

k. The following categories of research are prohibited at the VA:

- Projects involving fetuses, *in utero* or e*x utero* (including human fetal tissue)
- Projects involving *in vitro* fertilization
- Projects involving embryonic stem cells
- Research that is "planned emergency research" such that the investigator is seeking a waiver of prospective informed consent
- Projects involving a recruitment strategy that requires "cold calls" to veterans and/or asking veterans for social security numbers during a phone call.

l. The following categories of research require a waiver from the Chief Research and Development Officer (CRADO) or other special requirements
   - Research involving children
   - Research involving prisoners
   - International research
   - Research involving pregnant women
   - Research involving participants with impaired decision making capacity
   - Research involving banking of human biological specimens

G. Special Circumstances for Informed Consent

Special Circumstance	**Description**	**Regulation/ Reference**	**VA / IRB[4]**
1 Exempt from IRB Approval	The protocol does not need IRB approval at all. Does not need informed consent.	21 CFR 56.104.d 38 CFR 16.101(b) VHA Handbook 1200.5, page A-1	Must fall within a specific list of types of studies; must submit the protocol to the IRB and answer questions in CICERO See IRB policy

[4] VAMHCS SOPs are available through the Research Service www.maryland.research.va.gov. IRB SOPs are at http://www.hrpo.umaryland.edu/policies.asp.

Special Circumstance	Description	Regulation/ Reference	VA / IRB[4]
2a[5] Waiver of documentation of informed consent [Waiver of need for a signed informed consent form]	The IRB may waive the requirement to obtain a signed ICF for some or all subjects e.g. concern over confidentiality	21 CFR 56.109(c)(1) 45 CFR 46.117(c) 38.CFR16.116(c), (d) 38CFR17(c) (VHA Handbook 1200.5, Par 7i(2)(e), Appendix C par3f) See Appendix B-2a	Must fit either of 2 requirements; Complete CICERO See IRB policy
2b[6] Exempt from informed consent [Waiver of or change in informed consent procedure]	No need for informed consent at all (public health, minimal risk)	45 CFR 46.116(c)(d), 38 CFR 16,116(c),(d) (VHA Handbook 1200.5, Par 7i(2)(e), Appendix C par3f) See Appendix B-2b	Must fit 2 requirements; Complete CICERO See IRB policy
3a Exception from general requirements "Emergency Consent" [Investigator may proceed without informed consent in special circumstances; MUST obtain consent if/when it becomes possible]	If consent cannot be obtained in a life threatening situation	21 CFR 50.23 (VHA Handbook 1200.5, Par 14f See Appendix B-3	Must meet 5 criteria which must be validated in writing by independent physicians; IRB must be notified within 5 working days. See IRB policy
3b Exception for requirements for informed consent in Emergency Research [the IRB prospectively grants a waiver from	The nature of the study is such that it couldn't practicably be done without a waiver (e.g. research on	21 CFR 50.24 21 CFR 56.109(k) **NOT ALLOWED AT THE VA**	**NOT ALLOWED AT THE VA**

[5] 2a and 2b may appear to overlap significantly. See the policies and regulations cited.
[6] See footnote 5 above.

Special Circumstance	Description	Regulation/ Reference	VA / IRB[4]
obtaining informed consent] **NOT ALLOWED AT THE VA**	emergencies or traumas)		
3c Emergency use of a test article (prior to IRB approval) "Emergency Exemption from Prospective IRB Approval"	Immediate life-threatening situation, no standard treatment available, and no time to get IRB approval; **data *cannot* be used for research.**	21 CFR 56.104(c) 21 CFR 56.102(d) See Appendix B-3c	Must meet specific criteria; IRB must be notified within 5 working days. See IRB policy **NOT ALLOWED AT THE VA**
4 Oral Presentation Using "Short Form" *(not to be confused with "verbal consent" which is NOT allowed by UMB or VA policies)*	Used if the standard written informed consent cannot be obtained e.g. the subject/legal representative cannot read or is visually impaired.	21 CFR 50.27(b)(2), 45 CFR 46.117(b)(2) 38 CFR 16.117(a)(2) VHA Handbook 1200.5 Appendix C Par 3.d(2) See Appendix B-4	Submit a summary of the oral presentation and a "short form" that contains the elements of informed consent; both must be approved by the IRB. See IRB policy

Section II: Informed Consent Process

A. Introduction

Federal code states "[a]ny research project utilizing human subjects requires the informed consent of those subjects." The first step in the process is gathering the specific details of the study that are important to communicate to participants and to the IRB.

Potential participants must understand the nature of the study and the risks and benefits involved if they are to make an informed decision about their participation. The details should be presented in simple language by someone who is knowledgeable about both the study and informed consent.

This process requires a "consent document" that explains the nature of the research, any risks and benefits to the participant, and the voluntary nature of participation. A copy of the consent document is reviewed and approved by the R&D Committee and the IRB before it can be presented to prospective participants.

Because informed consent is an ongoing process, it starts before any forms are signed, and it continues through the completion of the subject's involvement in the study. The consent document is only a confirmation of the consent process.

The VA requires that the consent document is signed and dated by the subject or the subject's legally authorized representative (see section II.B.8). The VA also requires the signature/date of the investigator or the person obtaining consent. The 10-1086 provides signature lines for these signatures. A consent form is not considered valid unless all required signatures (and dates) are present.

The VA DOES NOT require that each page be initialed by the subject. The VA DOES require that subject identifiers are placed on each page of the ICF (the 10-1086 prompts this in the header).

NO RESEARCH PROCEDURE, ***EVEN NON-INVASIVE ONES***, MAY BE DONE UNTIL THE CONSENT DOCUMENT HAS BEEN SIGNED[7][8]

B. Selecting Participants: Special Populations

Recruitment of participants needs to be done in an unbiased, non-coercive manner. It is important that none of the participants ever feel that they will be penalized if they do not participate in the study. Convenience should not be the sole factor in the selection of participants. All avenues of recruiting participants should be investigated. The following relationships that involve ongoing care or a clear imbalance of power can be potentially troublesome for obtaining ethical informed consent.

1. Therapist-Client or Physician-Patient

[7] An exception to this is a study that has been granted a HIPPA waiver or a partial privacy waiver. ***Only the IRB may grant these waivers***.

[8] A research procedure is one that is done purely because of participation in the study protocol. It is a test, measurement, intervention or procedure that would not be done at all or at that time or frequency except for being in a study. Procedures that are done for standard clinical care but also happen to be part of the research protocol may be performed as they are required for the clinical care of the patient. For example, routine blood work that would have been done whether or not the patient was in the study is acceptable before research consent is obtained, but additional tests are not.

When possible, investigators should avoid recruiting participants with whom they have an established therapist-client or physician-patient relationship to eliminate any power-based coercion. Clients and patients may find it easy to say no to someone they do not expect to see in the future, but it may be difficult for people to say no when they rely on someone for on-going care.

Participants often depend on therapists and physicians to make recommendations, and may sometimes defer to professional knowledge and judgment. They may not read the consent document fully because the therapist or physician has already explained the procedure orally, and they consider the therapist or physician the primary source for information.

There is a need to clearly distinguish the treatment from the research involvement and to exercise caution that the professional's influence does not dictate the subject's consent decision.

2. Teacher-Student

Special consideration of recruitment is also needed for instances when an instructor wants to include his or her students in a research study. The teacher cannot assume that everyone in the class wants to be involved in the study. Students must be assured that their grade is not affected by their participation, and they should be able to decline participation without penalty.

Researchers may fail to identify the need for informed consent if the study is not perceived to have physical or psychological risks. Students may not see it this way. Participants, including students, have the right to refuse involvement in a research project, even if there is no identified risk.

3. Employees as participants

Colleagues, subordinates, or peers should never be placed in a compromising situation with perceived retribution for not being a research participant. Recruiting through advertisements or a third party is a better strategy for avoiding coercion.

4. Prisoners

Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer (CRADO)**.** If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as

research subjects (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). ***NOTE:*** *Requirements for requesting a waiver may be obtained by contacting the Office of Research and Development at VA Central Office or by accessing the VA research web site at http://www.va.gov/resdev.*

If you feel that the inclusion of prisoners is an important aspect of your study (for example, studies of incarcerated veterans), contact the VAMHCS Research Compliance Officer about the possibility of a CRADO exception.

You will also be required to follow UMB HRPP Policies & procedures

5. Children

"The VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans and is not authorized to care for the offspring of veterans. Therefore, research involving children cannot be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the CRADO." (VHA Handbook 1200.05 Par 48)

The VA defines children as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." In the state of Maryland, the legal age for consent is 18.

If you feel that the inclusion of children is an important aspect of your study (for example, studies of children of veterans), contact the VAMHCS Research Compliance Officer about the possibility of a CRADO exception. You will also need to follow the procedures stated in UMB HRPP Policies & procedures.

6. Elderly

Participants that have diminished vision or hearing can oftentimes overcome the problems and can give consent themselves. If the person is determined to be incompetent (such as in the case of Alzheimer's disease or other brain diseases), or of "impaired decision making capacity" (IDMC), the investigator must seek the consent of a proxy, *but the research must also meet the criteria in #7 below*.

7. Mentally Disabled Persons or Those with "Impaired Decision Making Capacity" (IDMC)

Research involving subjects who are mentally ill or subjects with impaired decision making capacity (IDMC) warrants special attention.

*Within the VA, research involving persons with IDMC may only be approved when **all** of the following apply*:

a. Only incompetent persons or persons with IDMC are suitable as research subjects; competent persons are not suitable as subjects (for example, if the purpose of the research is to examine some aspect of IDMC subjects); ***or*** the disorder (e.g., Alzheimer's) leading to the individual's lack of decision-making capacity is being studied, whether or not the lack of decision-making itself is being evaluated (e.g., an individual who lacks decision-making capacity as the result of a stroke can participate in a study of cardiovascular effects of a stroke), but only if the study cannot be performed with only persons who have decision-making capability; ***or*** the subject of the study is not directly related to the individual's lack of decision-making capacity, but the investigator can make a compelling argument for including individuals who lack decision-making capacity in the study (e.g., transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in a nursing home where both individuals with, and those without, decision-making capacity are affected).

b. The proposed research entails no greater than minimal risk (as determined by the IRB), ***or*** if the research presents some probability of harm, there must be at least a greater probability of **direct** benefit to the participant ***or*** if the research is greater than minimal risk and has no prospect of direct benefit to the participant, is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

Basically, the investigator must demonstrate to the IRB that there is a compelling reason to include incompetent persons or persons with IDMC as subjects. *Incompetent persons or persons with IDMC must not be subjects in research simply because they are readily available.*

In addition, procedures must be devised to ensure appropriate procedures for respecting dissent, procedures for obtaining assent (if required by the IRB), and, if required by the IRB, any additional safeguards that need to be used (e.g., consent monitoring).

Participant's representatives must be well informed regarding their roles and obligations to protect incompetent subjects or persons with IDMC. Surrogates (see II.C-D) must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent or, if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

If you plan to recruit IDMC participants you must describe the consent process to include legally authorized representatives (LAR)[10] in CICERO at the time of submission for

[10] See Section II.D

approvals. You should also consider the possibility to apply for a waiver or alteration of HIPAA authorization in the event that a suitable "personal representative" for signing the HIPAA authorization is not available (see section II.D.4). The plan must also include consent of the patient in the eventuality of temporary or fluctuating lack of decision-making capacity (1200.05 Par 49.c).

C. Determination of IDMC[11]

Decision-making capacity for health care decisions has four major components: understanding, appreciating, formulating, and communicating. The first two components represent the patient's ability to understand and appreciate the nature and expected consequences of each health care decision. The latter two components represent the ability to formulate a judgment and communicate a clear decision concerning health care.

One way of determining the decision-making capacity of a person is by looking for evidence of one or more of the following:

1. The ability to make a choice;
2. The ability to understand relevant information;
3. The ability to appreciate the situation and its likely consequences; and
4. The ability to manipulate information rationally.

In practice, the use of assessment instruments (see appendix H) that directly evaluate the research subject's understanding of the risks and benefits of the study, whether they understand that their participation is voluntary and that they can withdraw at any time is advocated. The IRB has a standard questionnaire in the HRPO website investigator tool kit that can be used.

Patients are presumed to have decision-making capacity unless an appropriate clinical evaluation determines that the patient lacks decision-making capacity, or the patient is a minor, or the patient has been ruled incompetent by a court of law.

Investigators and staff must be aware that some subjects' decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity (such as those with delirium) or those with decreasing capacity to give consent, a re-consenting process with surrogate consent is recommended. This process should be documented in source documents. If appropriate, the informed consent process should be repeated periodically and informed consent forms re-signed by the subject or the proxy (see Section II.K).

Some IDMC persons may <u>resist</u> participating in a research protocol approved by their representatives, i.e. subject dissents. If a participant dissents, the research may not continue

[11] See VHA Handbook 1200.05 Par 49

for that participant. *Even if the participant has been judged incompetent to provide informed consent, the person should be considered competent to refuse or to withdraw*.

The determination of incompetence or IDMC must be made in accordance with the following requirements and documented in the person's **medical record** in a signed and dated progress note by the physicians making the certification. According to VHA Handbook 1200.05 [par 49b], an individual is presumed to have decision-making capacity unless any of the following apply:

a. It has been documented by a qualified practitioner in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study. ***NOTE:*** *The qualified practitioner may be a member of the research team*;

b. The individual has been ruled incompetent by a court of law.

If there is any question as to whether or not a potential adult subject has decision-making capacity, and there is no documentation in the medical record that the individual lacks decision-making capacity, and the individual has not been ruled incompetent by a court of law, the investigator must consult with a qualified practitioner (who may be a member of the research team) about the individual's decision-making capacity before proceeding with the informed consent process.

In addition, the IRB requires the following documentation by the attending physician, consulting physician(s), and other members of the health care team when an LAR is consulted as to research participation;

a. The basis for their determination that the patient is incapable of making an informed decision regarding medical treatment and capacity to consent to research;
b. The identity of the legally authorized representative and the rationale for the selection of the individual, which shall be documented on the Legally Authorized Representative Identification Documentation Form (a copy shall be maintained in the research records); and
c. The process by which the patient was enrolled or declined to be enrolled in the clinical research.

Orientation to person, place and time and physical ability alone is not adequate to determine capacity to give consent. Cognitive assessment tools such as those in Appendix D or one designed by you specifically for your study or your subject population can be indicators of capacity to provide informed consent. See also Sections II.H and II.I for detailed information on and tools for testing subject understanding.

D. Proxy/Surrogate Consent[12]

1. Definitions and Distinctions

A "health care proxy" is the catchall word for anyone who makes medical decisions on behalf of a patient. The IRB uses the term "legally authorized representative" instead of "proxy".

Under Maryland law, there are three kinds of health care proxies:

- a **health care agent**.
- a **surrogate**.
- a **guardian**.

A ***health care agent*** is someone appointed by an individual to make health care decisions for the individual. Usually, the health care agent is appointed by the individual through an advance directive, a durable power of attorney for health care, or some other means. The health care agent steps in after the individual has lost the ability to make these decisions personally.

If no health care agent is available and the patient can no longer make health care decisions, Maryland law has established a hierarchy of which family member or friend can make health care decisions. This person (or sometimes more than one) is called a ***surrogate decision maker***, or ***surrogate*** for short.

Sometimes a court names a ***guardian of the person***, or ***guardian*** for short, to make health care and other decisions for individuals. Guardianship might be necessary to get consent for a specific medical procedure, for ongoing medical care, or for research.

The roles of proxies are different from each other:

- A ***health care agent's*** authority depends on what the person's advance directive says. A health care agent's duties begin when the individual loses the ability to make health care decisions on his or her own (or, rarely, when the person wants to let the agent decide even though he or she still could). This is determined by a process outlined in the advance directive. If no process is identified, two physicians must certify that the person is incapable of making decisions concerning his or her own health care. (If the person is unconscious or unable to communicate, the certification of a second physician is not required.). See IDMC (section (II.C).

  Most advance directives give the health care agent authority to make any and all

[12] A large part of this section is adapted from "Who Can Make Health Care Decisions for Another? Defining Health Care Proxies Under Maryland State Law", Office of the Maryland State Attorney General, 3/06.

decisions the patient would make, if able. However, if the advance directive did not specifically state the patient's wishes regarding research (or other wishes, if known to the legally authorized representative), then even the health care agent cannot enroll a patient in research not directly related to medical care and treatment required due to the patient's medical condition (this is generally interpreted to mean studies that are greater than minimal risk that offer no direct benefit). If the patient has not given a health care agent specific authority to enroll the patient in research that may not offer medical benefit for the patient, and the patient's specific wishes are unknown or unclear, decisions are to be made by the agent solely in accordance with the determination of the patient's best interest, and not with regard to the agent's or patient's interest in research. The PI should seek guidance from the IRB or VA regional counsel on enrollment of decisionally impaired subjects in greater than minimal risk studies with no direct benefit as there may be societal benefit (advancement of medical knowledge that might help others with the same condition) that might justify enrollment of these subjects.

- A ***guardian's*** duties depend on the court's order and on Maryland law. A guardian often is responsible for making health care decisions generally and assuring that the person is living in a safe environment, but the court may limit this authority. A guardian may need to seek court approval for medical procedures that involve a substantial risk to the person's life, including a decision to withhold or withdraw life sustaining procedures. A guardian must file an annual report with the court about how the patient is doing, whether the patient's condition has changed, and whether any changes in the court order are necessary.

In general, however, the proxy's role is to carry out the patient's stated wishes (substituted judgement). If the proxy does not know the wishes of the participant regarding research studies, the proxy should try their best to act according to section the subject's best interests and IRB policies. Investigators should ask proxies if they think the participant would have decided in the same manner if s/he were competent.

For proxy consent for research not directly related to the participant's medical condition, it is prudent for investigators to seek guidance from the ORC, the IRB, VA regional counsel,

2. Hierarchy of Proxy Consent

Under appropriate conditions (see II.C above) ***and*** a VAMHCS study specifically approved to include IDMC participants), investigators may obtain consent from the legally authorized representative of a subject. Such consent may be obtained from (in order of hierarchy):

a) a health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) or similar document;
b) court-appointed guardians of the person;
c) surrogate in the following order of priority:
    a. the patient's spouse

b. an adult child (18 years or older) of the patient
c. a parent of the patient
d. adult sibling (18 years or older) of the patient
e. an adult grandparent or grandchild (in that order of preference) of the patient (but no other relative or
f. close friend.

"Adult" in this section means a person at least 18 years old.

These are the only surrogate entities who are allowed to provide consent for research purposes for VAMHCS studies.[13] Be aware that this hierarchy is slightly different for UM studies who must use the LAR hierarchy as defined by Maryland law.

3. Proxy Consent for Research Studies (v. "Standard Health Care")

There is also a very important distinction for you to keep in mind: ***you are asking for consent for a research study, not standard medical care***. The Maryland state law, the "Health Care Decisions Act" (HCDA), never specifically states the circumstance of research, but instead speaks of "health care to [the] individual, or the withholding or withdrawal of health care from [the] individual".

In general, legally authorized representatives may consent only to health care research which provides medical treatment for a participant; **therapeutic research *may*** qualify as health care[14]. Participation in a clinical trial might be in the patient's best interest if the net additional risk caused by the participation is small, and there is scientific evidence that participation is reasonably likely to offer benefits over standard treatment or no treatment, if none exists.

The VHA and the IRB have additional criteria for determining eligibility, roles, and responsibilities of proxies/legally authorized representatives for research decisions. Some criteria, for example, the certification of IDMC, is even more stringent than state law. ***The VHA even restricts the types of research that can be done using impaired (IDMC) participants (see II.B.7, p.18).***

When the IRB reviews research involving decisionally impaired persons, it must decide:

- whether the study involves greater than minimal risk for participants, or
- ***if*** the proposed study involves greater than minimal risk, does it offer the prospect of direct benefit to each study participant.

As noted above, the IRB may need to seek legal advice for greater tha minimal risk studies

[13] See VHA Handbook 1200.05, Par 36.c,
[14] "**Therapeutic research**" may qualify as health care if there is an articulable link between the research and a possible improvement in the patient's condition (IRB P&P II.4.C.4).

with no prospect of direct benefit..

Therefore, the rules that you are used to using for proxy consent in clinical care are somewhat different for research consent and it is important for you to check VAMHCS and IRB SOPs and the VAMHCS Research Service or Office of Research Compliance (ORC) and VHA Handbook 1200.05 when you are confronted with a patient with impaired decision making capacity (IDMC).

4. Proxy Consent for HIPAA Authorizations

VHA Handbook 1200.05 states that:

> An individual who is qualified to be a [legally authorized representative] LAR for research purposes may not always qualify as a personal representative for purposes of consenting to use or disclose a living subject's PHI (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a subject's PHI, the investigator must ensure the LAR meets the requirements of a personal representative in HIPAA and the Privacy Act of 1974 (legal guardian or power of attorney) prior to the LAR's signing a HIPAA authorization (see VHA Handbook 1605.1).[15]

Therefore, VA protocols that enroll decisionally impaired subjects may need two different individuals as signatories for the research informed consent form and the HIPAA Authorization.

- The **Legally Authorized Representative**[16] (LAR) can be any individual in the hierarchy listed in II.D.2 above. LARs sign *informed consents* on behalf of decisionally impaired participants.
- In VA, only a **Personal Representative**[17] may sign the *HIPAA authorizations* for decisionally impaired participants. The ***only individuals who can be personal representatives for this purpose are***: a health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) or similar document, a court-appointed guardian of the person, or other person authorized under applicable law. ***Family members, friends or others allowed to be LARs might not be personal representatives for the purpose of signing HIPAA authorizations***.

[15] See Appendix A

[16] **Legally Authorized Representative**. Legally Authorized Representative (LAR) means an individual or judicial or other body authorized under applicable law to **consent** on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102(c)). LARs allow for a hierarchy of family members and significant others to sign research informed consent documents.

[17] **Personal Representative.** A Personal Representative is a person, who under applicable law, has authority to act on behalf of the individual. This may include Durable Power of Attorney (DPA) for Health Care, legal guardianship of an individual, the executor of the estate of a deceased individual, or someone under Federal, state, local or tribal law with such authority (e.g., parent of a minor). *A personal representative for the purposes of VHA Handbook 1605.1 does not necessarily equate to a surrogate for the informed consent process (see 38 CFR Section 17.32(e) for authorized surrogates for informed consent).*

- Therefore, some but not all LARs may also be qualified to sign HIPAA authorizations. If the LAR and Personal Representative are one in the same (i.e. the LAR is a DPA or a legal guardian), then that individual may sign both the Informed Consent and HIPAA Authorization.

If you believe your study could involve participation of decisionally impaired individuals, ***and*** if use or disclosure of PHI is required for your project, ***and*** if you will not be able to guarantee that you will always have a DPA or legal guardian who is the LAR, then you should request a waiver or alteration of HIPAA authorization from the IRB for your study.

The PI is strongly encouraged to discuss these issues with the VA privacy officer before they submit their protocol to the IRB for review.

E. Who can get consent

The VAMHCS is very strict as to who can get consent from potential subjects. The details of these requirements are in the R&D Service SOP, "Research Personnel Education and Training" (HRP 04.02).

In summary, the requirements for staff to be qualified to obtain consent from potential subjects are:

- S/he must maintain employment status at the VA, either as a VA employee or a without compensation (WOC) appointment, provide documentation of degrees earned, provide current license(s);
- S/he must have a signed Research Scope of Practice on file in the Research Service;
- S/he must complete a training course on the VA Privacy Policy training;
- S/he must complete human research protections training and Good Clinical Practices (GCP) training (CITI) biannually via online or the equivalent;
- The PI must delegate this duty (obtaining informed consent) in writing in the study protocol or CICERO application. The delegation may be to the individual or to the category, e.g. 'study coordinator', research assistant', etc.

See the "Trainings" page of the R&D Service website for the most current procedures for accessing mandatory trainings: www.maryland.research.va.gov.

All of the above training and credentialing requirements must be on file in the R&D Service Office. It is possible that the IRB or the VAMHCS may change the specific criteria for research staff. Check with the R&D Service to check current requirements.

Additionally, anyone who discusses the research study with a potential subject must be knowledgeable about the study and the condition for which the study is being performed.

They must also be able to contact the Principal Investigator or other senior study staff in order to answer the subject's or the family's questions.

F. Describing Research: The Informed Consent Form and CICERO

Your participants should be made aware of certain information about the study and their rights. Federal regulations require some information to be included on consent documents and the IRB and the VA also require some specific text.

When you select the VAMHCS as a study site in CICERO, CICERO, you must choose the "VAMHCS Informed Consent Template" and complete it using the same content as the UMB form (except for the VA injury statement). The elements below designated with an asterisk are "**essential elements of informed consent**" and are mandated by federal regulations. Depending on your study, it may be appropriate to also include federally mandated "**additional elements of informed consent**". The elements in CICERO are consistent with Maryland state law. Appendix E contains a Self-Assessment Tool for the content of your informed consent document.

Essential Elements of Informed Consent

1. Description: Use this section to differentiate between various versions of the consent form(s) such as "Version #__", "Healthy Volunteers", "Pilot", etc. This description appears as a title below the VA header on page 1 of the consent form, so be sure to phrase and punctuate it in a form suitable for a title. If there is only one consent form, this field may be left blank.

   The actual protocol title, and the PI name are automatically entered by CICERO into the VA 10-1086 header box based on the information entered in CICERO Sections A1 and A2.

2. Background: Begin this section with the statement "You are invited to participate in a research study being conducted by <PI>." Explain the nature of the condition being studied, the nature of the research, why the subject is being approached, and/or other general aspects of the study. Include the name of the Sponsor.

   If there is any potential conflict of interest for you regarding your relationship with the Sponsor this should be revealed here. The IRB will review this COI during the approval process and will inform you of conditions for managing the COI if the study is approved. Using the IRB's conditions (if any), inform participants of any conflicts of interest, such as a stake in a company that might benefit from the research.

It is essential that you specifically mention that the subject is being invited to enroll in a ***research*** study*. This is a federally mandated element of an informed consent form,.

3. Research Purpose*: State the goal(s) of the research and give a fair explanation of the context within which the study appears to be a feasible undertaking, a continuation of prior studies, etc. (if not already covered in "Background"). Explain how/why the patient/volunteer qualifies for the study. It is highly recommended to restate the concept of being a "research study" as often as appropriate in this section.

4. Demographics questions: Enter the required information. "This study will be Single center Trial / Multi Center Trial; Total subjects; Number of institutions; Subjects per institution.

5. Procedures*: Explain tasks and procedures *from the subject's point of view* (what will he or she be expected to do? How is the study organized, i.e. study visits, periods, etc? How much time will each visit take? How often? How many?). Specify which procedures would be done as routine medical care and which are experimental or done purely for the purpose of the study (a standard procedure which is done more frequently or for a different reason than usual because of the study). Estimate the total amount of time the person will be involved in the study (duration*). State what criteria will be used to determine eligibility and the probability of assignment, randomization, controls and placebos. What types, frequencies and amounts (Tsp/Tbsp) of specimens will be collected? Discuss any testing that may involve sensitive issues (drug screens, mental health questionnaires, etc.). Also see the extensive instructions provided on the CICERO screen.

   If the study entails the storage of any biological specimens or related biomaterial (such as DNA) for future or other use, the following information needs to be included in this or other appropriate section of the consent form:
   - Will the collected specimen be used for future research and if so, a statement about the area of research for which they will be used;
   - Will the specimen be used to generate a cell line or for genetic testing.
   - Will the specimen be stored without any identifier (deidentified) and if so, will it be a linked specimen or unlinked specimen (able to be traced back to donor);
   - A statement of who other than UMB researchers will have access to them;
   - Will the research results be conveyed to the subject and/or health care provider;
   - Will the subject be contacted after the completion of the original study;
   - Will the specimens and all links to clinical data be destroyed or removed from the bank upon the subject's request.
   - The disposition of the specimen after completion of the study or at the end of the banking period.
   - Any potential conflict of interest or financial gains for the investigators or the participating institution;

- A statement describing the participant's rights to profits made from products derived from their samples;
- A separate sign off for the storage and/or genetic testing allowing the participant to initial to whether or not he/she provides his/her consent;
- A separate sign off requesting permission to re-contact the participant if the Investigator anticipates a need to verify information;
- A statement that the participant can decline permission for future use and still participate in the primary study; and
- An individual name and number to contact should participants wish to have their samples destroyed and withdrawn from future study.

Be sure that all the information in the consent form accurately reflects the information you submitted in CICERO. Also be sure that information in CICERO matches information you submit to the VAMHCS Subcommittee for Research Safety (SRS). SRS review is one component of R&D Committee review.

For further details on this topic, see UMB HRPP policies & procedures.

See item #6 below to see additional language that should be included if genetic studies or potential cell lines are features of the study. See also I.E.7 (p.10) and I.F.2j (p.13).

6. Potential Risks and Discomforts*: Describe any foreseeable risks or discomforts the subject will bear. Include all reasonably common risks as well as potentially serious risks and, if possible, indicate the likelihood of occurrence (‘very likely’, ‘less likely’, ‘rare’; or compare the risks with natural risks that are understood by most patients). Risks may range from inconvenience to bodily pain. Do not overlook "soft" risks such as breaches in confidentiality, embarrassment or psychological, legal, or socioeconomic impacts. Decisions about invasive procedures will always involve a degree of uncertainty regarding the harmful effects. Calculating the probability that harmful situations might occur can aid in explaining the risks.

   Do not include the risks associated with standard medical therapy that would be delivered regardless of participation in the clinical trial *unless such inclusion would clarify*: (1) the distinction between the standard and investigational therapies and/or (2) the cumulative or additional risks associated with the trial (for example the cumulative risk of research-related x-rays when they are in addition to standard care). Information about the risks of standard medical procedures should continue to be provided in separate informed consent documents as part of usual (non-research) medical care.

   In the “Subject’s Rights” section later in the consent form, consider adding text concerning confidentiality. However, in some studies, it might be appropriate to discuss this issue in more detail here. In special circumstances, such as for reportable conditions like child abuse, absolute confidentiality may not be possible. If this or a similar

possibility exists, then explain the circumstances under which information must be disclosed and to whom.

Consider describing the level of confidentiality of the research data and the measures that you plan to take to ensure that confidentiality is maintained. Describe the steps that will be taken to protect the participant's privacy. Also describe under what circumstances records will be made available and to whom. Include any techniques you may use for identifying data, such as creation of a numeric code. Subjects should be assured that their identity will not be disclosed, or the circumstances under which it might be disclosed.

Participants will vary in their view of the nature of the risk involved. Be sensitive to the difficult task of determining if the participant is more of a risk taker, is ignoring the risk(s), or has not adequately understood the probability of the risk(s).

Regarding studies that include genetic testing, study participants should be informed of the following items, either in this section or in another appropriate section of the informed consent form:

- the kind of information they will be provided (e.g. that they will receive only information the investigator feels is significant and reliable, or that no genetic information will be provided) and at what point in the study they will receive information;
- that they may find out things about themselves or their family that they did may not really want to know, or that they may be uncomfortable knowing;
- that information about themselves may be learned by others in their family;
- whether information they learn or information generated about them during the study may compromise their insurability;
- that actions they may take as a result of their participation may expose them to risks (e.g. submitting insurance claim forms for reimbursement for costs of genetic counseling or procedures whose costs are not covered by the protocol);
- about what assurance can be given to protect confidentiality;
- about the rights they retain and the rights they must give up regarding control over what can be done with tissue they donate (e.g. blood samples);
- what the consequences of withdrawal form the study will be; and
- any costs associated with participation (including, for example, the cost of genetic and/or psychological counseling, if those costs will not be covered by the investigator or the institution).

Be sure that all the information in the consent form accurately reflects the information you submitted in CICERO.

Again, as above, participants will vary in their view of the nature of the risk involved.

<u>Potential Benefits*</u>:

Describe any benefits to the participant or others that can reasonably be expected. Benefits may range from feeling good about participation to free access to an experimental drug to knowledge that may be useful for society to direct care/cure for the subject's condition. However, be careful not to oversell any benefits. Calculate the probability that these beneficial effects will occur. This will aid in determining the weight given to the benefits.

Or state: "You will receive no direct benefit from participation in this study. However, your participation may help the investigators better understand (ENTER WHAT INVESTIGATORS WILL LEARN BELOW)." This is the place to describe any collateral benefits for studies that have no potential direct benefit to subjects. Payment is not considered a benefit in any category to research subjects, as it is meant to be compensation for time.

7. Alternatives*: Describe alternative procedures or treatments that are available to the individual (and their important benefits and risks) if the individual chooses not to participate in the study. Provide information on what would be considered the standard treatment(s) for the patient's diagnosis and the option of no treatment. What are the participant's other options? Specifically, state what treatment will be offered or recommended if patient declines to participate.

   In non-therapeutic studies, the alternative may simply be nonparticipation. State: "This is not a treatment study. Your alternative is to not participate."

8. Additional Signatures: Complete the section if necessary.

9. Subject Costs and Payments: The consent document must describe the terms of any payments used to compensate individuals for their participation (e.g., time, travel, etc). This includes the conditions under which research participants would receive partial payment or no payment at all. If this is an industry study, the statements must match or be consistent with the Sponsor contract.

   Describe the type of payment (money, gift certificates, coupons, etc.), the dollar amount, and the distribution plan (one payment, pro-rated payment, paid upon completion, etc.). If this study includes compensation to subjects for their participation in the study which is in excess of $600 in a calendar year, include a statement that informs subjects that they will be responsible to report this income to the IRS. If no compensation is to be offered, then state that subjects will not be paid.

   The descriptions of payments must coincide with the statements made in the initial CICERO application. See also UMB HRPP policies & procedures.

Detail all costs to the subjects that may result as a consequence of their participation in the study. For studies that involve a treatment intervention, this section should clearly state that subjects will not be responsible for any costs that are conducted solely for the purpose of the research, i.e. more frequent tests and additional visits that would not be occurring if the subject was not in a research study but receiving the standard of care.

For VA patients, it must be made clear to them that their co-pays will continue for any procedures not research-related (Title 38 United states Code [USC] 1710[f] and 1710[g]). Suggested wording follows: "Some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payments requirements will continue to apply to medical care and services provided by the VA that are not part of this study." The VAMHCS ICF template contains template language.

If the investigator does not anticipate any financial support, and the project involves clinical procedures conducted primarily for research purposes, provide an explanation of the expected source of payment for these procedures (specifically state who will pay or whether the subject will be responsible for payment). The IRB seeks reassurance that subjects will not be put to financial risks from participation in the research study

If there is a possibility that cell lines may be developed from subjects' samples which may potentially be commercially profitable, this should be disclosed here, along with a statement as to whether or not subject(s) will have any rights regarding possible cell lines.

11. Subject's Rights: Use the template language.

    A VAMHCS contact and phone number MUST be included here, even if UMMS contacts are also included. Give the names of people who can answer questions about the research, including the principal investigator. If the researcher is a student, include the names and phone numbers of the principal investigator and, where applicable, the faculty supervisor for questions.

Additional Elements of Informed Consent

One or more of the following elements of information must also be provided to each subject when appropriate. This information can be inserted into appropriate sections of the CICERO informed consent submission.

1. A statement that the particular treatment or procedure may involve currently unforeseeable risks to the subject, or to the embryo or fetus, if the subject is or becomes pregnant. Please review the CICERO language to make sure it conforms with your protocol. If changes need to be made, submit them as an amendment.

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without the subject's consent.

3. Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5. A statement that significant new findings developed during the course of the research which may relate to this subject's willingness to continue participation will be provided to the subject.

6. The approximate number of subjects involved in the study.

7. If the investigators believe that the human biologic specimens obtained could be part of, or lead to the development of a commercially valuable product, or if the specimens are to be retained after the end of the study, current VA policy and Veterans Health Administration (VHA) regulations must be followed. ***NOTE:*** *If genetic testing is to be done, VA requirements pertaining to genetic testing must also be met.* See I.E.7 (p.9), I.F.2.h-j (p.12-13), and II.F.5 (p.26).

8. As appropriate, a statement regarding any payment the subject is to receive and how payment will be made.

G. Ensuring Readability

Readability of the consent document is an important component of the process. Your consent document information should be presented in non-technical terms at a level that your audience can understand. If your document is not understandable, a claim could be made that the participant did not understand what he or she was consenting to when they signed the form. **The Nuremberg Code, the Declaration of Helsinki, and 45 CFR 46 all emphasize that the consent form should be in understandable language comprehensible to the participant.** A consent document must be made readable but without compromising the content.

Sponsors usually provide a consent form that they wish you to use. Because these consent templates have been already been approved within the company and because any changes will have to go through another approval process within the company, they often frown upon you making any changes except those required by the IRB. Therefore, changes that are made

purely for the purpose of readability are often not accepted by the sponsor unless the IRB has requested them.

In this case (and in general), consider other ways to inform your potential subjects, such as:

- A separate summary chart about the conduct of the research study, participant's rights, etc. (see Appendix G for an example)
- A separate information sheet about the disease, the drug, the study, etc.
- A glossary
- A diagram or chart of study activities (a version, "Study Schedule", is now required by CICERO; it might be possible to use it or an adapted version)
- Diagrams or pictures of body organs or anatomy, or of equipment (especially if the patient will use it), etc.
- Encourage note-taking in the margins of or on the back of the actual informed consent form itself
- A video or demonstration

NOTE: all informational materials directed towards subjects should be submitted to the IRB CICERO.

Some suggestions for ensuring the readability of the consent form:

- Direct it at a reading level appropriate to your subject population (in general, 7th-8th grade).
- Use simple, straightforward sentences.
- Use active voice.
- Use commonly recognizable terms and measurement indices.
- Avoid the use of jargon or technical language, and explain terms that may not be easily understood. (See Appendix F for some lay terms.)
- Be aware of overall readability and understandability…just substituting simple words does not necessarily improve comprehension.
- Take into account your subject population (age, intelligence, culture, education, ethnicity, etc.)

Ask someone with no expertise in the area of the study to read the consent form and other informational materials and explain it to you. A reader who has no association with the study can often help you to identify difficult or confusing areas in the document.

Study participants should not be excluded based on language barriers. If you have a participant who does not speak English, the IRB prefers that you have an IRB-approved translated consent document and arrange for a qualified interpreter to translate your explanation and questions for the participant. Alternatively, the IRB allows an oral presentation in a language understandable to the participant by a person fluent in the language. Read IRB policy for details.

H. Discussing Participation

Informed consent involves educating prospective participants, not merely disclosing information. The factual elements to be conveyed are discussed in the previous section (Section F), "Describing the Research". Discussions with prospective participants should expand upon the facts in the informed consent document, giving participants a more detailed picture of the study. The prospective participants and their families should be given sufficient time to consider participation. Approaching them on the day the study will take place may not be sufficient. Participants may need time to think about their decision or to discuss their involvement with family, friends, or religious advisors. For best results, participants should be approached when they are willing to listen, and are open and ready to consider consenting.

Be aware of "information overload". It is known that an average individual's short-term memory can only retain 3-5 pieces of information at a time. A typical consent form and discussion entails many more facts than that, many of which can be very complex. For many participants, even the basic concept of a research study is an unfamiliar topic. Many participants are dealing with a new diagnosis about which they have little knowledge. Many may be experiencing a high level of stress.

It is therefore not surprising that participants have a difficult time digesting all the facts involved with a research study. This points out the importance of thorough discussion, often repeating key concepts, often using aids such as written instructional materials, pictures and diagrams.

Investigators are required to have a written plan for distribution of the VA pamphlet, "I'm A Veteran. Should I Participate in Research?" during recruitment activities. The pamphlet is available in the R&D Service Office to assist you and your potential participants during the informed consent discussion.

For some studies there is a short time window for enrollment after a sentinel incident (e.g., 'within 12 hours of first antibiotic dose', 'within 24 hours of admission to the hospital', etc.) In this case, take *very great care* to inform the subject and family of the urgency involved with the opportunity to enroll *but without coercing* them to make quick decisions. Particular care should be taken to inform them of options to withdraw from the study without penalty if they should change their minds later.

Key components of the informed consent process include:

- information,
- comprehension,
- voluntariness, and
- time to think.

The process of obtaining consent should emphasize these components and should include time for both discussion and reflection, as shown in the following steps:

1. Present the prospective participant with the approved consent document.
2. Read through the document together, taking time to explain significant or difficult points about the research or participation.
3. Explain the research using simple terms, in language that is understandable to the subject.
4. Describe what is going to happen.
5. Be clear about what aspects of the study are investigational, which are standard therapies, and which are "research-related" (standard therapies or interventions that are being done purely as part of the research protocol). Consider providing a chart or written material that illustrates this.
6. Be aware of "information overload": the participant might not be retaining key concepts.
7. Be clear that participating is voluntary. Explain what might be the medical consequences of a decision to withdraw and what would be the procedures for orderly termination.
8. State benefits without exaggerating.
9. Do not minimize statement of risks.
10. Explain all alternatives
11. Do not assume that the participant has remembered everything you discussed or even very much of what you discussed ("information overload"). Repeat, review, repeat, review…
12. Use visual aids, written materials. Encourage the participant/family to take notes, write down questions *and the answers*, underline, circle or otherwise mark-up their copy of the consent form, etc.
13. Do not use exculpatory (inducing subjects to give up rights) or coercive (threat of harm or reprisal) language. Do not apply undue influence (offer of excessive or improper reward; another form of coercion).
14. Answer any questions.
15. Allow the participant time to take the document home and discuss participation, if desired, with family, friends or medical advisors.
16. Meet with the participant again and ask open-ended questions about the nature of the study and participation to make certain he or she understands correctly. (See Assessing Participant Understanding and Decisional Capacity on page 39).
17. If the participant is willing, have him or her sign the consent document.
18. Give the participant a copy of the signed consent document.
19. Document the process and subject enrollment in CPRS and in study files (see Section J).

At any point in this process, representatives of the IRB or the VAMHCS Research Compliance Office may be present in order to evaluate the quality of the process.

Short Form:

In some circumstances, the VHA and the UMB IRB allow for the use of a short form of the informed consent form, such as with an illiterate or visually impaired participant or subject population.

The CICERO submission to the IRB must then include a "short form" version of the full ICF AND a written summary of the oral presentation to be given (see the IRB's policy on this, IRB P&P. The IRB and R&D Committee must approve these forms.

The "short form" must state that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there ***must*** be a witness to the oral presentation.

Make the oral presentation to the subject/representative ***with a witness present***, then:

- the subject or the subject's legally-authorized representative signs and dates the short form;
- the witness signs and dates both the short form and a copy of the summary;
- the person actually obtaining the consent signs and dates a copy of the summary (this person cannot also be the witness to the consent);
- the original short form and summary must be filed in study files and copies sent to the R&D Service to be scanned into CPRS;.
- a copy of the summary must be given to the subject or the subject's legally-authorized representative, in addition to a copy of the signed short form.
- If a person is illiterate but understands English, s/he may have the consent form read to her/him and then make her/his mark.
- If a person does not understand English, see Section H above and IRB P& P.

All other aspects of documentation of informed consent must then be carried out: the enrollment note (containing a statement about the short form presentation), the scanning of the forms by the R&D Service, etc.

I. Assessing Participant Understanding and Decisional Capacity

Understanding or comprehension is a key component of decision-making capacity. One cannot make a decision if one does not understand what is being asked.

It is your responsibility as a researcher to ensure that prospective participants understand the extent of their role in your research. Read through the consent document with them and discuss participation prior to their involvement in your research. During these discussions you should answer questions and ask questions, too. Use open-ended and nondirective questions. Open-ended questions often begin with words such as "what," "where," "how often," "when," and "please describe."

A few of the questions you may want to ask are:

- What questions do you have?
- Tell me the purpose of the study…the risks…etc.
- What else would you like to know?

- Would you please explain to me what you think we're going to ask you to do?
- What questions do you have?
- What are your concerns?
- What would you do if you decided you didn't want to stay in the study?

The idea is not to quiz the individual, but rather to foster an open exchange of information and encourage them to ask questions. Remind them to continue to ask questions throughout the study. However, a subject's hesitancy to be proactive or to ask questions does not release you from the responsibility to provide the necessary information on which his/her decision should be made and on which his/her voluntariness throughout the study should be based.

A subject's basic ability to comprehend is based on factors such as intelligence, rationality, maturity, and grasp of language. However, keep in mind that, based on factors such as disability, illness, consciousness, medications, etc., a subject's level of cognition and level of decisional capacity may be temporary, fluctuating, declining or permanently impaired. For this reason, it is *highly recommended to continually assess a subject's consent to continue in the study*. As a subject's level of comprehension changes, so may his/her desire to continue with the study. Thus applies to "healthy" subjects as well as impaired subjects!

There is no gold standard for assessing comprehension or decisional capacity. However, in some instances (for example, a vulnerable population) the IRB may require a formal test of comprehension or decisional capacity. Several tools are available to asses understanding (such as the "Evaluation to Sign Consent Form" available on the HRPO website and Appendix H, or the Dartmouth evaluation tool) and decisional capacity (such as the Mini-Mental State Examination [MMSE] or the MacArthur Competence Assessment Tool-Clinical Research [MacCAT-CR]) (See Appendix H for all these tools).

Or you may wish to develop your own tool as a simple way to assess and document understanding (you must submit the tool to the IRB in CICERO, and describe the use of the tool including scoring). You will see from looking at some of the tools above that they do not need to be complicated. They can even be used as prompters for conversational points.

Whatever tool you use, it should be attached in CICERO at the time of protocol submission.

Yet in most instances, your professional experience and judgment are what come into play when evaluating a subject's state of mind. The following or similar questions may be helpful when you evaluate a subject's/representative's decisional capacity:

- Can the subject/representative engage in meaningful conversation?
- Can the subject/representative grasp relevant facts and repeat them (see above)?
- Does the subject/representative realize that the proposed research is different from personalized clinical care?
- Can the subject/representative make personal decisions?

- Is the subject/representative's reasoning not dominated by a hope for a cure?

Whether a formal tool or personal interactions are used to assess decisional capacity, the following elements are always kept in mind: understanding, reasoning, appreciation, choice, and communication.

It is important to document your method of assessment of the subject's/representative's understanding. State whether there a written quiz or tool was used, whether the subject could verbally state the nature of the study, etc**.**

J. Documenting Informed Consent

After all the discussing, answering of questions, and assessment of understanding, if the recruit does agree to participate in the study, the informed consent form must be signed. *No study-related procedure may be done until the consent form has been signed and dated.*

The VA requires the following signatures with dates:

- Subject (or the subject's proxy if the provisions discussed in earlier sections have been fulfilled),
- and
- The person obtaining the informed consent.(who MUST be the PI or other staff who meets the qualifications outlined in II.E [p.24]).

The IRB may require a witness signature.

The person obtaining consent must write an enrollment note in CPRS documenting at least the following:

- The name of the study,
- The person obtaining the subject's consent,
- A statement that the subject or the subject's legally-authorized representative was capable of understanding the consent process,
- A statement that the study was explained to the subject, and
- A statement that the subject was given the opportunity to ask questions.

The R&D Service has additional requirements which are contained in the "Enrollment Note template" below. This template, as well as other important details for entering research notes into CPRS and establishing your own template, is found in the R&D Service SOP, (HRP 07.01) "Establishing a Patient into CPRS".

Protocol Title:
Principal Investigator:
IRB #:
IRB Validation Dates:
Date the Informed Consent form was signed:

Time the Informed Consent form was signed:
Person Obtaining Consent:

Participant was enrolled in above-mentioned protocol. Participant/legal guardian has been fully informed about the study including procedures, risks and benefits. Participant/legal guardian has read the consent form or had it read to them and was given the opportunity to have questions answered prior to signing the informed consent document. Participant/legal guardian was [*description of participant's/guardian's mental capacity and the type(s) of assessments used*]. Participant/legal guardian agreed to comply with all follow-up procedures including the length of participation. The participant/legal guardian was given a copy of the informed consent document and study contact information.

STUDY-SPECIFIC COMMENTS (If applicable):
- Specific aspects of the study's consent process
- Combine with an entry note* if applicable

Additionally, when the subject actually enters the study, a "Research Subject Clinical Warning" must be entered into CPRS if the participant's participation in the study involves:

- Any invasive research procedure;
- Interventions that will be used in the medical care of the subject, or that could interfere with other care the subject is receiving or may receive (e.g., administration of a medication, treatment, or use of an investigational device);
- Clinical services that will be used in the medical care of the subject (e.g., orders for laboratory tests or x-rays ordered as a part of the study), or that could interfere with other care the subject is receiving or may receive; or
- The use of a survey or questionnaire that may provoke undue stress or anxiety unless the IRB determines that mandatory flagging is not in the best interests of the subject (e.g., an interview study of victims of sexual assault).

In other situations, the IRB determines if flagging is necessary.

Details on how to do a "Research Subject Clinical Warning" are found in the R&D Service SOP, (HRP 07.01) "Enrollment Notes for Research Participants".

The R&D Service will scan the ICF into CPRS and "attach" it to the enrollment note. You must bring a copy of the signed ICF to the R&D Service in order for the scanning to take place. You should place a copy of the enrollment note as well as all research notes into the source documents file (see the R&D Service Guidance on source documentation).

Finally, the investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not IRB granted a waiver of documentation of informed consent. Investigators must not add a subject's name to the master list of all

subjects until after: informed consent has been obtained from that subject, and, when appropriate, informed consent has been documented using an IRB-approved informed consent form. The investigator must secure the master list appropriately in compliance with all VA confidentiality and information security requirements in the investigator's file for each study. The IRB may waive the requirement for the master list for a given study if both of the following conditions are met:

(a) There is a waiver of documentation of informed consent, and

(b) The IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.

K. Continual Assessment of Willingness to Participate

At each interaction you must reassess whether a subject continues to understand their participation in the study and whether they remain willing to remain in the study. Use study visits to remind them of what to expect in upcoming visits and to remind them of their right to withdraw. Be sensitive to signals (both verbal and non-verbal) that a subject may be wavering in their willingness or may be at a decreased level of capacity to understand or to make decisions.

Some investigators and study units routinely administer tests of understanding at each/periodic study visits in order to assess and document subjects' decisional capacity. Whether you administer a test or whether you simply discuss the study with the participant, be sure to document this aspect of the study visit in your progress note for that visit.

L. Reconsent

Reconsent is required when significant changes are made to the research and/or changes are made to an approved informed consent form. These changes may only occur through a formal request for an amendment made to the IRB via CICERO. In some instances (such as new benefits or follow-up procedures) you might have to make an effort to reconsent all enrolled individuals, including those who have completed their study involvement. In others, it might be adequate to reconsent individuals who are still active in the study as they are seen for study visits. Check with the IRB or the VAMHCS Research Compliance Office to determine what should be your reconsent procedure.

M. Final Thoughts

From designing a study to submitting a CICERO consent form for approval to following through on the consent process with participants to documenting informed consent, the process of informed consent can be a long and intense process. However, if you continually keep in mind that the process is meant to protect basic human rights and if you perhaps even put yourself in the shoes of a participant, it might be easier to juggle all the balls you are asked to keep in the air.

Besides protecting your patients and study participants, you have a personal stake in the process as well:

- Rules that protect the subjects also protect the investigators, staff and institution.
- The Principal Investigator's (PI) integrity is measured by compliance.
- The reputation of the PI's institution is at stake.
- Future funding can be jeopardized.
- Funding authority credibility can be questioned.
- All research must be ethically defensible.
- As goes the public's trust, so goes the research. (Conley, 2003)

Finally, the bonds that form between subject and staff during the informed consent process can lay groundwork for a rewarding experience for all, and insight into communications issues, compliance issues, and perceptions.

N. References

(The following and other VHA publications can be found at: www1.va.gov/vhapublications/)
VHA Directive 1004.1, "VHA Informed Consent for Clinical Treatment & Procedures"
VHA Directive 1200, "Banking of Human Biological Specimens Collected from Veterans for Research", 3/31/03
VHA Handbook 1200.05, "Requirements for the Protection of Human Subjects in Research"

Federal Regulations: 38 CFR 16, 45 CFR 46, 21 CFR 50, 21 CFR 56

R&D Service website: www.maryland.research.va.gov
R&D Service SOP, "Research Personnel Education and Training" (HRP 04.02)
R&D Service SOP, "Enrollment Notes for Research Participants" (HRP 07.01)
R&D Service SOP, "Writing a VAMHCS Informed Consent Form" (HRP 03.02)
R&D Service SOP, "Obtaining and Documenting Informed consent" (HRP 03.03)
HRPO website (including CICERO logon): http://www.hrpo.umaryland.edu/default.asp
"Research Ethics Informed Consent", talk by William T. Carpenter, MD; Maryland Psychiatric Research Center
Defining a Patient's Capacity to Provide Consent", talk by Robert Conley, MD; Maryland Psychiatric Research Center
"Informed Consent: It's in the Process", talk by Kathleen Palmer, RN, CCRC; General Clinical Research Center
"Research Informed Consent Guidebook"; Manchester (NH) VA Medical Center

Appendix A-1

APPENDIX A: VHA Handbook 1200.05, Par 30-33

30. GENERAL REQUIREMENTS FOR INFORMED CONSENT
Except as provided in Paragraph 35 of this Handbook, no investigator may involve a human being as a subject in research covered by this Handbook unless the investigator has obtained the legally effective informed consent of the subject or the subject's LAR (38 CFR 16.116). An individual who is qualified to be a LAR for research purposes may not always qualify as a personal representative for purposes of consenting to use or disclose a living subject's PHI (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a subject's PHI, the investigator must ensure the LAR meets the requirements of a personal representative in HIPAA and the Privacy Act of 1974 (legal guardian or power of attorney) prior to the LAR's signing a HIPAA authorization (see VHA Handbook 1605.1).

a. **Circumstances Under Which Informed Consent May Be Sought.** The Common Rule requires (38 CFR 16.116):
(1) The investigator to seek informed consent only under circumstances that:
(a) Provide the prospective subject or the subject's LAR sufficient opportunity to read the informed consent document when applicable,
(b) Provide the prospective subject, or the subject's LAR, sufficient opportunity to consider whether or not to participate, and
(c) Minimize the possibility of coercion or undue influence.
(2) The information that is given to the subject or the subject's LAR must be in language understandable to the subject or the subject's LAR.
(3) No informed consent, whether oral or written, may include any exculpatory language through which the subject or the subject's LAR:
(a) Is made to waive, or appear to waive, any of the subject's legal rights; or
(b) Releases, or appears to release, the investigator, the sponsor, the institution, or its agents from liability for negligence

b. **Person Obtaining Informed Consent.** If someone other than the investigator conducts the informed consent process and obtains informed consent from a subject or the subject's representative, the investigator must formally and prospectively designate in writing in the protocol or the application for IRB approval, the individual who will have this responsibility (see subpar. 9j(1)). The person so designated must have received appropriate training to perform this activity. This person must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

c. **Observing the Process.** The IRB has the authority to observe or have a third party observe the informed consent process.

d. **Informed Consent Form.** The most current IRB-approved version of VA Form 10-1086, Research Consent Form, for each study (or the most current IRB-approved electronic version of VA Form 10-1086) must be used as the informed consent form.

(1) All required elements must be completed (see par. 31) as well as any additional elements required by the IRB which may include, but not be limited to those in Paragraph 32.
(2) The informed consent form must contain a designated block for each required signature (e.g., subject, person obtaining the informed consent, and witness when applicable) and for the date of each signature (see subpar. 33c). ***NOTE:*** *For the purposes of the informed consent form, a "block" may be a labeled line, window of a table, or other format that clearly indicates what type of signatures and dates the IRB specifically requires for that study's informed consent form.*

31. REQUIRED ELEMENTS OF INFORMED CONSENT
a. **Elements of Informed Consent Required by the Common Rule.** Except as provided in Paragraphs 34, 35 and 36 of this Handbook, 38 CFR 16.116(a) requires the following elements of informed consent be provided to each subject:
(1) **A Statement That the Study Involves Research.**
(2) **An Explanation of the Purposes of the Research.**
(3) **The Expected Duration of the Subject's Participation.** A description of the expected length of the subject's commitment to active participation in the interventions or interactions of the study, including long-term follow-up. This does not include the time after all interventions and interactions with the subject have ended and the study activities include only analysis of specimens and/or data, and/or preparations for publication of results.
(4) **A Description of the Procedures to be Followed.**
(5) **Experimental Procedures.** Identification of any procedures that are experimental (38 CFR 16.116(a)(1)).
(6) **Risks or Discomforts.** A description of any reasonably foreseeable risks or discomforts to the subject (38 CFR 16.116(a)(2)).

(a) This description is to include, but not be limited to, physical, social, legal, economic, and psychological risks.
(b) Risks that do not result from the research, but that result solely from treatments or services that have been designated in the IRB-approved protocol to be the responsibility of the health care provider, should not be described in the consent form. The informed consent process is to include language advising subjects to review the risks of such clinical treatments or services with their health care provider(s).

(7) **Benefits.** A description of any benefits to the subject or to others that may reasonably be expected from the research (38 CFR 16.116(a)(3)).
(8) **Alternatives.** A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (38 CFR 16.116(a)(4)).
(9) **Confidentiality.** A statement describing the extent to which confidentiality of records identifying the subject will be maintained (38 CFR 16.116(a)(5)). If appropriate, a statement that Federal agencies including, but not limited to, the FDA, OHRP, ORO, and the VA Office of the Inspector General (OIG) may have access to the records. If an FDA-regulated test article is involved, FDA requires a statement that the FDA may choose to inspect research records that include the subject's individual medical records.
(10) **Research-Related Injury**

(a) For research involving more than minimal risk, a statement that includes:

1. An explanation as to whether any compensation is available if injury occurs, and

2. An explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained (38 CFR 16.116(a)(6) and see par. 59).

(b) Although the Common Rule at 38 CFR 16.116(a)(6) only requires that the informed consent contain information on research-related injury if the study is more than minimal risk, VA regulations (38 CFR 17.85) require the VA to provide care for all research-related injuries including those studies that are considered minimal risk.

(11) **Contact Information.** An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject (38 CFR 16.116(a)(7). There must be at least one contact other than the investigator or study personnel.

(12) **Participation is Voluntary.** A statement that participation is voluntary, refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (38 CFR 16.116(a)(8).

b. **Other Elements of Informed Consent Required by VA.** In addition to the elements for informed consent required by the 38 CFR Part 16, VA requires the following elements of informed consent:

(1) **The Name of the Study.**

(2) **The Name of the PI.** The name of the PI and, in multi-site studies, the name of the LSI.

(3) **The Sponsor of the Study.**

32. ADDITIONAL ELEMENTS OF INFORMED CONSENT

a. **Additional Elements of Informed Consent Required by the Common Rule.** When appropriate, the Common Rule requires one or more of the following elements of information be provided to each subject (38 CFR 16.116(b). Also, when any of these additional elements are appropriate, VA requires them to be documented in the IRB-approved informed consent form unless documentation of informed consent is waived.

(1) **Unforeseeable Risks.** A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or becomes pregnant) which are currently unforeseeable (38 CFR 16.116(b)(1)).

(2) **Termination of Subject's Participation.** Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent (38 CFR 16.116(b)(2)).

(3) **Additional Costs.** Any additional costs to the subject that may result from participation in the research (38 CFR 16.116(b)(3)).

(a) Pursuant to 38 CFR 17.102, subjects in VA-approved research cannot be charged, nor can their insurance be billed, for research-related interventions or procedures (e.g., tests, drugs, clinic visits, hospital admissions, transportation) that are required by the protocol. If medical services are furnished to a person who is not eligible for medical services as a Veteran, the medical care appropriation will be reimbursed from the research appropriation.

(b) When appropriate for the informed consent for VA-approved research to include information on additional costs to the subject that may result from participation in the

research, the informed consent must contain a statement that a Veteran subject or a non-Veteran subject will not be required to pay for medical services received as a subject in an approved VA research study. The only exception is that certain Veterans are required to pay applicable co-payments for medical care and services provided by VA that are not rendered as part of the VA-approved research study (see 38 U.S.C. 1710(f) and 1710(g)). An example of language that may be appropriate for the informed consent form is "Some Veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to VA-provided medical care and services that are not part of this study."

(4) **Consequences of Withdrawal From Study.** The consequences of a subject's decision to withdraw from the research and procedures for orderly and safe termination of participation by the subject (38 CFR 16.116(b)(4)).

(5) **New Findings.** A statement that any significant new findings which may relate to the subject's willingness to continue participation, developed during the course of the research, will be provided to the subject (38 CFR 16.116(b)(5)).

(6) **Number of Subjects.** The approximate number of subjects involved in the study (38 CFR 16.116(b)(6)).

b. **Additional Elements of Informed Consent Required by VA.** When appropriate, VA requires one or more of the following elements of information be provided to each subject. Also, when any of these additional elements are appropriate, VA requires them to be documented in the IRB-approved informed consent form, unless documentation of informed consent is waived.

(1) **Commercial Product.** If applicable, that the investigator believes that the human biologic specimens obtained could be part of, or lead to the development of, a commercially valuable product.

(2) **Future Use of Specimens.** If the specimens are to be retained after the end of the study for future research, where the specimens will be retained, who will have access to them, and how long they will be retained. Current applicable institutional, VA and other Federal requirements must be met for handling, use and storage of biologic specimens and data (see VHA Handbook 1200.12).

(3) **Future Use of Data.** If any of the data will be retained after the study for future research, where the data will be stored, and who will have access to the data (see VHA Handbook 1200.12). Current applicable institutional, VA and other Federal requirements must be met for use and storage of data (see VHA Handbook 1200.12).

(4) **Re-contact.** If the subject will be re-contacted for future research whether within VA or outside VA.

(5) **Payment for Participating in the Study.** If appropriate, a statement regarding any payment the subject is to receive for participating in the study and how the payment is to be made (see par. 59).

(6) **Disclosure of Results.** If the subject will receive a report of the aggregate results or any results specific to the subject.

33. DOCUMENTATION OF INFORMED CONSENT

Informed consent must be documented prospectively by the use of a written consent form approved by the IRB (38 CFR 16.117(a), unless documentation of informed consent has been

explicitly waived by the IRB (38 CFR 16.117(c)). ***NOTE:*** *Email communications do not constitute documentation of informed consent.*

a. **Consent Form.** VA Form 10-1086, Research Consent Form, must be used as the consent form for VA research. The only exception is that a DoD informed consent form may be employed for active duty military personnel participating in VA research at DoD sites when VA-specific language is not necessary (e.g., when language for treatment of research related-injury is not needed because active duty military personnel are covered by DoD). The informed consent form must be the most recent IRB-approved informed consent form that includes all the required elements and, as appropriate, additional elements (see pars. 31 and 32).
(1) The requirement to utilize VA Form 10-1086 to document informed consent applies to all VA-approved research including, but not limited to, studies in which VA investigators working on VA Research enroll subjects at the affiliate hospital or other sites outside VA (e.g., community centers or shopping malls).
(2) The "most recent" IRB-approved version of the informed consent form contains the date of the version of the informed consent form most recently approved by the IRB (e.g., in a header or footer). For instance, if the most recent version of the informed consent sent for approval by the IRB was the June 14, 2009, version, and the IRB approved it on July 1, 2009, the investigator must ensure the informed consent form contains the date June 14, 2009, on each page. The June 14, 2009, version would continue to be the most recent version even after approved by the IRB during the continuing review process (i.e., if there is no change in the informed consent form at the time of continuing review, it is not considered a new version).

b. **IRB Approval Date.** The IRB approval must be documented in the IRB minutes or IRB protocol files for those studies reviewed by the expedited process. IRB correspondence with the investigator must clearly indicate which version of the informed consent form has been approved (e.g., see the example in subpar. 33a(2)). The IRB approval date must be documented by the use of a stamp or preprinted box on each page of the informed consent form. This stamp or preprinted box must indicate the most recent date of IRB approval of the informed consent form. The IRB must maintain a copy of the approved informed consent form in its records.

c. **Signatures and Dates.** The informed consent form must be signed and dated by:
(1) The subject or the subject's LAR (38 CFR 16.117(a)),
(2) The person obtaining the informed consent, and
(3) A witness, if required by IRB (e.g., the IRB may require a witness if the study involves an invasive intervention or an investigational drug or device). A witness is always required when a short form consent is employed (see subpar. 33f(2)).

(a) The witness is required to witness only the subject's or subject's LAR's signature, not the informed consent process (e.g., if the subject does not want the witness to know the nature of the research study), unless the sponsor or IRB requires the witness to witness the informed consent process.
(b) The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member.

d. **Original Signed Consent Form.** The original signed and dated informed consent form (see subpar. 30d(2)) must be filed in the investigator's research file for that subject so that it is readily accessible for auditing. If the subject submits the signed and dated informed consent form to the investigator or designee by facsimile, the person who obtains informed consent must sign and date the facsimile, and then the facsimile can serve as the original informed consent document. If facsimile is used for the informed consent document, measures must be employed to ensure the confidentiality of the information, and the privacy of the subject.

e. **Copies of Signed Consent Form**
(1) A copy of the signed and dated informed consent form must be provided to the subject or the subject's LAR (38 CFR 16.117(a)).
(2) Where applicable, a copy of the signed and dated informed consent form must be placed in the medical record in accordance with VHA Handbook 1907.01.

f. **Consent Documents.** Except as provided in Paragraph 34 the informed consent form may be either of the following (38 CFR 16.117):
(1) **Written Informed Consent With All Required Elements**. The consent may be in the form of a written consent document that embodies the elements of informed consent required by 38 CFR 16.116. This form may be read to the subject or the subject's LAR, but in any event, the investigator must give either the subject or the representative adequate opportunity to read it before it is signed (38 CFR 16.117(b)(1)); or
(2) **Short Form Consent.** The consent may be in the form of a short form written consent document stating that the elements of informed consent required by 38 CFR 16.116 have been presented orally to the subject or the subject's LAR (38 CFR 16.117(b)(2)). When this method is used:

(a) There must be a witness to the oral presentation (38 CFR 16.117(b)(2)).
(b) The IRB must approve a written summary of what is to be said to the subject or the LAR (38 CFR 16.117(b)(2)).
(c) Signatures are to be obtained as follows:

1. The short form is to be signed by the witness, and the subject or LAR (38 CFR 16.117(b)(2)).
2. The copy of the summary is to be signed by the witness and the person actually obtaining consent (38 CFR 16.117(b)(2)).

NOTE: *The IRB cannot waive the requirement for a witness or witness signature when the short form consent is employed.*

(d) A copy of the summary and a copy of the short form are to be given to the subject or the LAR (38 CFR 16.117(b)(2)).
(e) The original signed short form and summary must be filed in the investigator's research file for that subject.
(f) Where applicable (see VHA Handbook 1907.01), a copy of the signed short form informed consent form must be placed in the medical record in accordance with VHA Handbook 1907.01).
(g) The investigator must file all original, signed and dated, short form informed consent forms in the investigator's research file for that subject, so that they are readily accessible for auditing.

Appendix B

Special Circumstances for Informed Consent

B-2a, 2b: Waiver of Requirement for a Signed Informed Consent, Exempt from Informed Consent, Waiver of Need for Informed Consent

B-3: Emergency Consent

B-4: Emergency Use of a Test Article ("Emergency Exemption from Prospective IRB Approval")

B-5: Oral Informed Consent / "Short Form"

B-2a

WAIVER OF REQUIREMENT FOR A SIGNED INFORMED CONSENT
[from VHA Handbook 1200.05 Par 34]

a. **Criteria for Waiver.** The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds and documents either (38 CFR 16.117(c)):
(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (38 CFR 16.117(c)(1)); or
(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (38 CFR 16.117(c)(2)).
b. **Written Statement.** In cases in which the documentation requirement is waived, IRB may require the investigator to provide subjects with a written statement regarding the research (38 CFR 16.117(c)(2)).
c. **IRB Documentation.** IRB must document its determinations regarding a waiver of documentation of informed consent in the IRB minutes or in the protocol file (see par. 28).
d. **Informed Consent Process.** Unless IRB has granted a waiver of informed consent (see par. 35), even if IRB has granted a waiver of documentation of informed consent, the investigator, or designee, must still perform an adequate informed consent process.

B-2b

EXEMPT FROM INFORMED CONSENT "Waiver of Informed Consent"

[from 1200.05 Par 35]

35. WAIVER OF INFORMED CONSENT
a. **Government Research and Informed Consent is Not Practicable.** The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent; or waive the requirement to obtain informed consent, provided the IRB finds and documents that (38 CFR 16.116(c)):
(1) The research is to be conducted by, or is subject to, the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (38 CFR 16.116(c)(1)):
(a) Public benefit of service programs;
(b) Procedures for obtaining benefits or services under those programs;
(c) Possible changes in or alternatives to those programs or procedures; or
(d) Possible changes in methods or levels of payment for benefits or services under those programs.
(2) The research could not practicably be carried out without the waiver or alteration

(38 CFR 16.116(d)(3)); and
(4) Whenever appropriate, the subjects are provided with additional pertinent information after participation (38 CFR 16.116(d)(4)).
c. **Other Applicable Federal, State, or Local Laws.** The informed consent requirements in this Handbook are not intended to preempt any applicable Federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective (38 CFR 16.116(e)).
d. **IRB Documentation.** The IRB must document its determinations regarding a waiver of informed consent in the IRB minutes or in the protocol file.

B-3a

EXCEPTION FROM GENERAL REQUIREMENTS
"Emergency Consent"

See the UMB "Investigator Manual" for crucial details on executing this type of consent on the VAMHCS/UMB campus. The "Investigator Manual" is available on the UMB HRPO website: http://www.hrpo.umaryland.edu/default.asp.

[FDA requirement 21 CFR 50.23]

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the

use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation

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B-3c

EMERGENCY EXEMPTION FROM PROSPECTIVE IRB APPROVAL

FDA defines emergency use as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized. Informed consent is required unless the conditions for exemption are met. The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review.

B-4

DOCUMENTATION OF INFORMED CONSENT
"Oral Consent"/ "Short Form"

See IRB policy for crucial details on executing this type of consent on the VAMHCS/UMB campus.

[VHA Handbook 1200.05 par 33f.2]

(2) **Short Form Consent.** The consent may be in the form of a short form written consent document stating that the elements of informed consent required by 38 CFR 16.116 have been presented orally to the subject or the subject's LAR (38 CFR 16.117(b)(2)). When this method is used:
(a) There must be a witness to the oral presentation (38 CFR 16.117(b)(2)).
(b) The IRB must approve a written summary of what is to be said to the subject or the LAR (38 CFR 16.117(b)(2)).
(c) Signatures are to be obtained as follows:
1. The short form is to be signed by the witness, and the subject or LAR (38 CFR 16.117(b)(2)).
2. The copy of the summary is to be signed by the witness and the person actually obtaining consent (38 CFR 16.117(b)(2)).
NOTE: *The IRB cannot waive the requirement for a witness or witness signature when the short form consent is employed.*
(d) A copy of the summary and a copy of the short form are to be given to the subject or the LAR (38 CFR 16.117(b)(2)).

(e) The original signed short form and summary must be filed in the investigator's research file for that subject.
(f) Where applicable (see VHA Handbook 1907.01), a copy of the signed short form informed consent form must be placed in the medical record in accordance with VHA Handbook 1907.01).
(g) The investigator must file all original, signed and dated, short form informed consent forms in the investigator's research file for that subject, so that they are readily accessible for auditing.

[FDA requirement 21 CFR 50.27]

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A *short form* written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

[DHHS Requirement 46.117]

The investigator may, as an alternative, give the participant or the representative a short written consent form which documents that the elements of the informed consent were presented orally to the participant or representative. The short written consent form is signed by the participant or representative. When this method is used, a witness should observe the oral presentation and a written summary of what is to be said to the participant or representative should be used. The witness should sign the short written consent form and the summary. The person actually obtaining consent should sign the summary. A copy of the summary should be given to the participant or the representative, in addition to a copy of the short written consent form.

APPENDIX C: Copy of VAMHCS form 10-1086

(See hard copy in the R&D Service Office or at the following website(s):
www1.va.gov/resdev/funding/process/forms/10-1086.doc

APPENDIX D: Selected Definitions Regarding Impaired Decision Making Capacity (IDMC)

- **Capacity to Consent to Research**: The capacity to consent to research is the ability to give informed consent for participation in research. When research involves health care procedures, having capacity to consent not a means that a person is able to make an informed decision about the provision, withholding, or withdrawal of a specific treatment or course of treatment. A person is not able to make an informed decision if the person is unable to understand the nature, extent, or probable consequences of the proposed treatment or course of treatment, is unable to make a rational evaluation of the burdens, risks, and benefits of the treatment or course of treatment, or is unable to communicate a decision by speech or other means. A person may be able to make decisions about medical care, but lack capacity to consent to research. The fact that a guardian has been appointed for a person does not mean that the person is unable to make decisions about medical care, or lacks capacity to consent to research.
- **Cognitively Impaired:** Having a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorder), an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and individuals with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interest. A person who is cognitively impaired is not deemed to be incapable of making informed health care decisions or deemed to lack capacity to consent to research. A person who is cognitively impaired may be able to make informed health care decisions but unable to give informed consent to research participation. A person who is cognitively impaired may consent to participation in research, yet may not assent to participation, or dissent to participation.
- **Competent Individual**: A person at least 18 years of age, or an Emancipated Minor/LAC, who has not been determined to be incapable of making an informed decision about health care. A competent individual may consent to medical treatment (subject to the limitation of the Minor/LAC's authority; see the definition of Minor/LAC in the master Glossary). A competent individual may have capacity to consent to research, but a determination of capacity should be made, especially in the case of an Emancipated Minor, Minor/LAC, or a cognitively impaired person.
- **Guardian of the Person**: A guardian of the person may be named by court order for an adult in Maryland. For an adult, a guardian of the person is the person's legally authorized representative for research unless (a) the participant has appointed a health care agent, in which case the agent is the legally authorized representative or (b) the order appointing a guardian of the person limits the guardian's authority for health care decisions generally, or in relation to research.

- **Health Care Agent:** An agent appointed by a person under an advance directive to make health care decisions for the person, should the person be incapable of making such decisions. The authorities of the Health Care Agent are described fully in the Health Care Decision Act, but may be modified by an advance directive or power of attorney document. Emancipated Minors can appoint health care agents; other minors cannot do so. The term "agent" or "health care agent" means the health care agent.
- **Health Care Decision**: A decision made by or on behalf of a patient regarding the patient's health care, including but not limited to:
  - The selection and discharge of health care providers and institution;
  - Approval or disapproval of diagnostic tests, medical treatments, surgical procedures, programs of administration of medication, and orders not to resuscitate;
  - Directions to provide, withhold or withdraw artificial nutrition and hydration and all other forms of health care; and/or
  - Transfer to other health care facilities.
- **Health Care Decision Act, or HCDA**: The Health Care Decisions Act of Maryland, which applies to questions of consent to medical treatment, including treatment involved in research, in Maryland. The HCDA is applied to determine who has legal authority to consent to medical treatment for a research participant who is an adult or Emancipated Minor. The person who has authority to consent to medical treatment is the participant's legally authorized representative for research involving medical treatment.
- **Incapable of making an informed decision**: This phrase, defined in the HCDA, means the inability of an adult patient or competent individual to make an informed decision about the provision, withholding, or withdrawal of a specific medical treatment or course of treatment because the patient is unable to understand the nature, extent, or probable consequences of the proposed treatment or course of treatment, is unable to make a rational evaluation of the burdens, risks and benefits of the treatment or course of treatment, or is unable to communicate a decision.
- **Incompetent**: As used in III.C or other sections pertaining to VAMHCS, this means being unable to make informed decisions about health care and lacking capacity to consent to research. The term is not used in the HCDA.
- **Informed Consent:** An individual's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. The consent process begins when a potential research participant is initially contacted.
- **Legal Guardian:** An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.
- **Legally Authorized Representative (LAR):** An individual or a judicial or other body authorized under applicable law to consent on behalf of a prospective participant for that person's participation in the procedures involved in research. LARs allow for a hierarchy of family members and significant others to sign research

informed consent documents. In Maryland, a legally authorized representative for an adult or an Emancipated Minor for medical research is one of the following persons who is determined, consistent with the HCDA, to have health care decision-making authority for the participant: a health care agent; a guardian of the person who is serving as a surrogate under the HCDA; or one of the other surrogates named in the HCDA. For a minor other than an Emancipated Minor, the legally authorized representative for medical research is the parent or parents or the guardian of the minor. A legally authorized representative for an adult for non-medical research is only a person who holds a specific power of attorney addressing research, if there is not an appointed guardian of the person, or the guardian of the person. For VA research, see the definition of "Surrogate" regarding VA limitations on the relatives and other persons who can consent to research for another person.

- **Personal representative (for HIPAA authorizations):** A Personal Representative is a person, who under applicable law, has authority to act on behalf of the individual. This may include Durable Power of Attorney (DPA) for Health Care, legal guardianship of an individual, the executor of the estate of a deceased individual, or someone under Federal, state, local or tribal law with such authority (e.g., parent of a minor). *A personal representative for the purposes of VHA Handbook 1605.1 does not necessarily equate to a surrogate for the informed consent process (see 38 CFR Section 17.32(e) for authorized surrogates for informed consent).*
- **Surrogate:** In the case of an adult or Emancipated Minor who is incapable of making an informed decision about medical treatment, and has not appointed a Health Care Agent, one of the following, in order of priority, is the individual's surrogate for medical treatment decisions, and is the legally authorized representative of the individual for decisions related to research participation that provides medical treatment: the individual's guardian of the person, spouse, adult son or daughter, parent, adult brother or sister, or a friend or other relative who meets special requirements discussed in the HCDA. Note that for VA research not all persons allowed by Maryland law to act as surrogates can serve as leally authorized representatives. The surrogates permitted to serve as legally authorized representatives in VA research are the spouse, adult son or daughter, parent, adult sibling, grandparent, adult grandchild, or close personal friend of the research participant. A grandparent or grandchild must meet the HCDA special requirements in order to act as a surrogate and legally authorized representative. An "adult" is a person 18 years of age or older.

Appendix E

Informed Consent Form Review Checklists:

E1: "Elements of an Informed Consent Document" (federal requirements)

E2: "Informed Consent Requirements and Written Documentation of Informed Consent" (a combination of UMB IRB checklists 9 and 10; a more comprehensive checklist of informed consent process plus CICERO submission)
(http://medschool.umaryland.edu/orags/hrpo/checklist9.pdf)

E-1: "Elements of an Informed Consent Document"
(useful for a quick check of compliance)

The basic **(essential)** elements of informed consent shall be provided to each subject:

Y	N/A	Essential elements of informed consent
		A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
		A description of any reasonably foreseeable risks or discomforts to the subject;
		A description of any benefits to the subject or to others, which may reasonably, be expected from the research;
		A disclosure of appropriate alternative procedures of courses of treatment, if any, that might be advantageous to the subject;
		A statement describing the extent if any, to which confidentiality of records identifying the subject will be maintained;
		For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, is so, what they consist of, or where further information may be obtained;
		An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights and whom to contact in the event of a research-related injury to the subject;
		A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

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

Y	N/A	Additional elements of informed consent
		A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
		Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
		Any additional costs to the subject that may result from participation in the research;
		The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
		A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
		The approximate number of subjects involved in the study.

E-2: "Informed Consent Requirements and Written Documentation of Informed Consent"
(a combination of UMB IRB checklists 9 and 10; a more comprehensive checklist of informed consent process plus CICERO submission)

Please go to the HRPO website:
(*http://medschool.umaryland.edu/orags/hrpo/checklist9.pdf*)

Appendix F: Lay Language for Informed Consent

Term	Definition
acute	new, recent, sudden
adverse effect	negative side effect
assay	lab test
benign	not malignant, usually without serious consequences
bolus	an amount given all at once
carcinogenic	Capable of causing cancer
catheter	a tube for withdrawing or introducing fluids
chronic	continuing for a long time
clinical trial	an experiment with patients
controlled trial	a study in which the experimental procedures are compared to standard (accepted) treatments or procedures
culture	test for infection, or organisms that could cause infection
double blind	study in which neither the investigators nor the subjects know which intervention the subject is receiving
dysplasia	abnormal cells
edema	increased fluid
efficacy	Effectiveness
extravasate	to leak outside of a blood vessel
hematoma	a bruise, a black and blue mark
heparin lock	needle placed in the arm with blood thinner to keep the blood from clotting
monitor	check on, keep track of, watch carefully
morbidity	undesired result or complication
mortality	death or death rate
necrosis	death of tissue
oncology	the study of tumors or cancer
percutaneous	through the skin
placebo	a substance of no medical value, an inactive substance
PRN	as needed
protocol	plan of study
random	by chance, like the flip of a coin
relapse	the return of a disease
retrospective	looking back over past experience

Appendix G: Example of Supplemental Instructions to Research Participants on the Subject of a Research Study (Summary of ICF)

INSTRUCTIONS TO STAFF:
Remember that this is meant to be an assist for your participants. The information here should be as brief as possible *while remaining scrupulously faithful to the information in the consent form*. The finished product should be only 1-2 pages long and should be a helpful distillation of the pages of details in the consent form. Refer participants to the consent form for details. Adapt the wording of this form in any way that fits your needs but be sure to keep it in plain language understandable to your research population.

Remember that this DOES NOT REPLACE discussion of the consent form itself, questions & answers with research staff, or any other part of the informed consent process.

This chart should be submitted for approval to the IRB via Section S of CICERO.

****

Dear Participant,

This is a summary of the information in your consent form. It does not take the place of the actual consent form. If you have any questions or problems about the study, please read through the details of the consent form or call me or my staff.

Thank you for thinking about taking part in this research study.

Dr. _____ and the Research Staff

Element	Comment
This is research	This [drug/procedure/intervention] is experimental. We are not sure if it will work and whether you could have any unexpected bad effects.
Why we think it might work	[brief explanation]
This is voluntary	You can leave the study at any time. There will be NO penalty to you if you do, except that we would ask you to do some final tests mainly to make sure that you are OK.
What you will be asked to do	[short list of procedures/visits; use bullets to help make it visually easy; refer to the study schedule chart if that might be helpful] Details about these procedures/visits are in the consent form.
The things that are experimental are	[list]
Some uncomfortable things that could happen are:	[list the main, most probable]. Other things are possible but seem rare at this

	time. They are listed in the consent form.
Some good things that could happen are:	[list]
If you decide not to participate in this study, this is what your doctor could do instead:	[summary of alternative treatments]
We will keep your identity private as much as possible, but it is possible that the following individuals or groups might need to see your information:	[list]
If you get injured because of taking part in this study…	[explain in everyday language]
If you have any questions about the study	[contacts for study staff]
If you have a complaint or want to talk to someone not connected with the study	[VAMHCS Research Compliance Office (605-7000 x6512), UMB HRPO, (410-706-5037)]
You CAN leave the study at any time. If you decide to leave the study, this is what could happen to you	[List of reasonable risks]
You CAN leave the study at any time. If you decide to leave the study, this is what we might ask you to do	For your safety, we would ask for some final [tests/measurements] to make sure you are OK. There is NO penalty to you if you decide to leave the study.
This is how you will be compensated if you take part in this study	Short description of payments and distribution schedule
Pregnancy/embryo/fetus	(If applicable)
Why we might stop the study for you	(If applicable)
These are some possible costs for you	(If applicable)
If we find out information that could affect you decision to stay in the study, this is what we'll do	(If applicable)

Appendix H: Tests of Understanding and Decisional Capacity

H-1: Mini-Mental State Examination (MMSE)

The MMSE is a standardized paper-and-pencil assessment for which one purchases a kit (http://www.minimental.com).

> "The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment" (from the webpage)

On the MMSE, a score of 24 is the minimum score for an educated person. However, other factors should be taken into account when using the Mini-Mental exam as an indicator for mental capacity. In some cases, a score of 24 may be too low; in others, lower scores may still allow an individual to be included. Consult the publisher for further information.

H-2: MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR)

The MacCAT-CR is a standardized, commercial product available through its publisher at: www.prpress.com/mactcrset-fr.html.

> "The MacCAT-CR provides a structured format for capacity assessment that is adaptable to the particulars of any given research project. With the introduction of the MacCAT-CR, researchers enrolling human participants in their studies have available for the first time a reliable and valid means of assessing their potential subject's capacity to consent to participation. The MacCAT-CR can typically be administered in 15-20 minutes.
>
> Beginning with project-specific disclosures to potential participants, the MacCAT-CR measures the four generally accepted components of decision-making competence: understanding, appreciation, reasoning, and the ability to express a choice. Quantification of subjects' responses permits comparisons across subject and age groups, and allows the MacCAT-CR to be used for not only screening individual participants but also for conducting research on the characteristics of subject populations and for assessing the effectiveness of interventions designed to increase subjects' capacities" (from the webpage)

H-3: Dartmouth Informed Consent Evaluation Feedback Tool (ICE ET)

This tool was developed by Elizabeth Bankert at the Dartmouth Committee for the Protection of Human Subjects. It can be seen at: http://www4.od.nih.gov/oba/rac/pdfs/IC_Evaluation_Tool_Dartmouth_CPHS.pdf.

H-4: Evaluation to Sign Consent Form (ESC)

This tool (on the following page) has been designed by and used in the UMB MPRC by Dr. Robert Conley and his staff. It can be used as is or adapted to the specifics of your study or your study population. It can be downloaded from the HRPO website at: www.medschool.umaryland.edu/orags/hrpo/eval.pdf.

Appendix I: EVALUATION TO SIGN CONSENT FORM

See the HRPO website for the most recent version of an acceptable evaluation to sign consent

http://www.hrpo.umaryland.edu/toolkit_additional_docs.asp