INFORMED CONSENT FOR HUMAN SUBJECTS RESEARCH

A Primer

Management Decision and Research Center

Health Services Research and Development Service

Office of Research and Development

Department of Veterans Affairs

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The Health Services Research and Development Service (HSR&D) is a program within the Veterans Health Administration's Office of Research and Development. HSR&D provides expertise in health services research, a field that examines the effects of organization, financing, and management on a wide range of problems in health care delivery – quality of care, access, cost, and patient outcomes. Its programs span the continuum of health care research and delivery, from basic research to the dissemination of research results, and ultimately to the application of these findings to clinical, managerial, and policy decisions.

Informed Consent for Human Subjects Research

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Informed Consent for Human Subjects Research

Purpose of Primer series:
To help bridge the gaps between health services researchers, policy makers, managers, and clinicians in an effort to improve the quality and cost-effectiveness of health care for veterans. The Primer series is part of a larger set of dissemination initiatives developed by VHA's Office of Research and Development through the Management Decision and Research Center, a program within the Health Services Research and Development Service.

Purpose of the Informed Consent for Human Subjects Research Primer:
To provide an overview of informed consent for research within VA, from regulations to the content and process of obtaining consent from potential research participants. The Primer provides a framework for understanding the basics of informed consent, incorporating the responsibilities of everyone involved, from researchers to senior managers. More in-depth readings and other resources are listed in the appendices.

Suggested audience:
VA professionals, clinicians, managers, front line supervisors, researchers, and staff involved in health care delivery in all parts of the Veterans Health Administration.

Suggested uses:
Individual study, orientation for professional staff and health care providers, management training programs in Veterans Integrated Service Networks and within VA facilities, and continuing medical education courses and other medical and health professional training programs.

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Preface

Providing veterans with the highest quality, most cost-effective health care is the mission of the Veterans Health Administration (VHA). Within VHA's Office of Research and Development, we conduct research that provides us with new knowledge or evidence we need to make system decisions that insure best health care practices and outcomes. Veterans help us in this quest to continuously improve the quality of the health care we provide through their willingness to participate in research studies. It is our honor and privilege to serve our veterans, and it is our duty to protect their rights and guarantee their safety in research.

Informed consent is the cornerstone for providing protections for human subjects in research studies. By law, participants recruited into research studies must be informed about the risks and benefits of the study and voluntarily consent to participate. While this sounds logical and easy enough to implement, there are many potential hurdles in achieving true informed consent. For example, what if a prospective research participant is very ill or homeless and vulnerable? How does one decide if a research candidate is competent to provide voluntary consent? And who is ultimately responsible for insuring appropriate and meaningful consent in VHA?

VHA is committed to conducting the highest quality research in areas that are important to veterans' health. Our research efforts must follow all federal regulations and meet exemplary ethical standards. This Primer is designed as an educational tool for VHA managers, clinicians, researchers, and others who are responsible for obtaining or overseeing appropriate informed consent, or are in some other way involved in the process. It provides an overview and informational resources for learning more about this very important topic.

Robert H. Roswell, MD
Under Secretary for Health

Introduction

During the 1990's, public interest focused on several well-publicized cases that illustrated some significant gaps in research study safety and administration, some with tragic results. These cases raised questions about the processes used to insure the rights and safety of research participants.

Informed consent, the major tenet for insuring understanding and voluntariness of participation in research, justifiably came under intense scrutiny. One important consideration is whether a research participant's signature on a consent form provides enough assurance that the participant truly understands the risks and benefits of a study and is competent to voluntarily agree to participate. There is also the issue of impartiality and responsibility of those obtaining consent from the participants. Informed consent is intended to protect the dignity and safety of research participants, but how best to confidently implement it in today's fast-paced, high technology health care environment can be complex.

Within VA this is of particular importance because the agency bears a public trust to provide the best possible care for veterans. Accordingly, VA took quick action to shore up all aspects of compliance, safety, and protections of research participants as well as improvements in the administration of research studies. VA's compliance structures and research policies were reviewed and updated, and new systems were developed to improve education and accountability. VA's Office of Research and Development initiated a State of the Art Conference (SOTA) on "Making Informed Consent Meaningful" that brought together VA and non-VA clinicians, researchers, ethicists, and managers with the goal of identifying what could be done to improve the theory and practice of informed consent.

This Primer is an outgrowth of the Informed Consent SOTA conference. It was developed to provide a broad audience within and outside of VA with a clear definition of informed consent and the regulations that govern it, as well as the roles and responsibilities of all those involved, directly or indirectly, in the consent process in VA. It is presented in a question and answer format for easy reading and accessibility. The appendices provide definitions, further reading, and other training and informational resources.

What is informed consent for research?

Informed consent is the process through which the research team obtains – and maintains – the legally effective permission of a person or a person's authorized representative to participate in a research study. Informed consent is achieved when a prospective subject receives full disclosure of the research plan and intent, understands all of the information that is disclosed to him or her, voluntarily consents to participate in the study, and is competent to do so.

The concept of informed consent originated in the clinical care setting, and has become a cornerstone for the ethical conduct of human subjects research. Although sometimes thought of as a rote reading of rights ending in the participant's signature on the dotted line of a consent form, informed consent is not merely a formality. Nor is it simply a bureaucratic policy. Informed consent is a legal and moral responsibility to uphold the individual autonomy and personal dignity of all people who consider participating in research.

The concept of informed consent originated in the clinical care setting, and has become a cornerstone for the ethical conduct of human subjects research.

The Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research identifies three basic ethical principles that should serve as guideposts for human subjects research: respect for persons, beneficence, and justice. Truly informed consent upholds all three of these basic ethical principles.

Why is informed consent important to VA?

VA is a world leader in research, and, as such, is committed to upholding the principles for the ethical conduct of research. VA's clinical research enterprise depends on the voluntary and informed participation of thousands of human subjects who deserve to be treated with respect and dignity.

Because it is the right thing to do, and VA is subject to federal regulations for the protection of all human research participants, no VA research may involve a person as a participant without first obtaining

his or her legally effective informed consent. The only exceptions are those cases in which the Institutional Review Board (IRB), with oversight responsibility for a given study, approves a waiver of informed consent.

In addition, VA patients tend to be very trusting of their clinicians, particularly their nurses. Many VA patients who are candidates for research participation are quite sick; still others are vulnerable because they are demented, mentally ill, or substance-abusing. As a result, these patients may give their consent to participate without fully understanding the intent, risks, and other aspects of the research study. In these circumstances, research team members have an even greater responsibility to fully explain research opportunities to patients or their legally authorized representatives in an impartial manner and to ensure that they understand the explanation.

VA…agreed to follow the …Common Rule. VA facilities are responsible for developing their own standard operating procedures for addressing all aspects of human subjects protection, including informed consent.

An array of laws, regulations, and policy statements emphasize the need for obtaining meaningful informed consent and address how this should be done in accordance with the basic ethical principles of human subjects research. The federal government has developed uniform standards on informed consent for federally funded research. However, some groups, such as the National Bioethics Advisory Commission, have cited a need to develop uniform standards on informed consent for research that is not federally funded as well.

VA is one of 17 federal departments and agencies that have agreed to follow the *Federal Policy for the Protection of Human Subjects*, more familiarly known as the Common Rule, effective June 18, 1991. This policy is described in the *Code of Federal Regulations (CFR), Title 45, Part 46* (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm). VA's incorporation of this policy can be found at *38 CFR 16*.

Investigators receiving support from other federal agencies, such as the National Institutes of Health, must meet the human subjects requirements of those funding sources in addition to those of VA.

Generally, the requirements are similar, because those agencies are also governed by the Common Rule. Where Food and Drug Administration (FDA) regulated test articles are used, FDA regulations also apply, regardless of funding source (http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr50_00.html). Finally, investigators must meet applicable local and state regulations.

VA facilities are responsible for developing their own standard operating procedures for addressing all aspects of human subjects protection, including informed consent. The Institutional Review Board (IRB) with oversight responsibility for a given study may toughen a research protocol, making the informed consent process more rigorous if it feels this is necessary to protect the rights and welfare of subjects. (See "Who is responsible for ensuring informed consent in VA research?" on page 4.) VA's policies and procedures for informed consent may be found in VHA Handbook 1200.5, Appendix C: The Informed Consent (http://www.va.gov/resdev/directive/RevisedHandbookProtectionHumanSubjectsInResearch.doc).

What are the elements of informed consent?

Federal regulations and VA policy govern the content of informed consent for VA-approved research, defining a number of *basic* elements that must be explained to the prospective subject as part of the informed consent process. Depending on the nature of the research, several *additional* elements may also be required.

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Following is a brief description of the basic elements of informed consent. A more detailed description of both the basic and additional elements of informed consent may be found in Appendix A of this primer.

Basic Elements of Informed Consent

Purpose and Description: *Explain the purpose of the study, the length of time expected for the subjects' participation, the process to be followed during the study, and any experimental procedures.*

Risks: *Describe any reasonably foreseeable harms, inconvenience, or discomforts to the participant.*

Benefits: *Describe any benefits to the prospective participant or to others that may reasonably be expected to result from the research.*

Alternatives: *Disclose any appropriate alternative treatments that might benefit the prospective participant.*

Confidentiality: *Tell the prospective participant whether his or her individual record will be kept confidential and explain the level of confidentiality to be maintained.*

Greater Than Minimal Risk: *For research involving more than minimal risk, provide an explanation of whether any compensation is available and whether medical treatments are available if injury occurs.*

Contact Information: *Provide information about whom the subject may contact with questions about the research.*

Voluntary Participation: *Explain that participation is voluntary.*

No Payment Required: *Inform the prospective participant that he or she will not be required to pay for treatment received as a subject in a VA research project.*

There are several layers of responsibility for ensuring informed consent in VA research.

There are several layers of responsibility for ensuring informed consent in VA research. VA leaders, including facility and network directors, chiefs of staff, service chiefs, associate chiefs of staff for research and development, and other managers, clinicians, investigators, and research staff all share responsibility for maintaining proper informed consent procedures.

Within the VA system, the facility director has oversight responsibility for all research conducted at that facility and for ensuring that all human subjects protection regulations are implemented correctly. Part of that responsibility has to do with fostering an institutional culture of respect for human subjects protection, assuring access to information on human subjects protection, and seeing to it that investigators fulfill their responsibilities. The facility director is also responsible for ensuring that the facility has its own written standard operating procedures (SOPs) for human subjects protection,

including the manner in which informed consent sessions are to be conducted, and that all SOPs are followed.

The facility director also establishes oversight to ensure compliance with regulations and effective administration of the facility's human subjects research protection program. The facility director appoints IRB members upon recommendation from the R&D Committee, provides the IRB with needed resources and staff, and supports the IRB's authority and decisions.

In facilities with sizable research programs, the facility director delegates responsibility to administer the program to the Research Service, headed by the associate chief of staff for research and development (ACOS for R&D). In smaller facilities, a research and development coordinator replaces the ACOS. The IRB is a subcommittee of the R&D Committee, and the ACOS for R&D is the executive secretary of the R&D Committee. For a study involving human subjects to proceed, the study protocol, including the consent forms, must be approved by both the IRB and the parent R&D Committee. Neither committee can overturn a disapproval by the other, providing a double layer of protection to research subjects.

At the research study level, the principal investigator is responsible for ensuring that effective informed consent is obtained and documented correctly for all study participants before participants may enter a study. In some instances, the principal investigator does not personally obtain informed consent from prospective participants, but delegates that responsibility to another member of the research team (usually a research nurse or a research assistant). However, the principal investigator still bears responsibility for ensuring that informed consent is obtained properly. In addition, the principal investigator must make sure that the person obtaining informed consent fully understands what needs to be done and has adequate training to carry out this task.

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Is there a difference between informed consent in clinical research versus informed consent in standard medical treatment?

When a research participant confuses the goals of research with those of treatment, this gives rise to what is called "therapeutic misconception."

As mentioned, the concept of informed consent originated and developed in the clinical care setting before becoming an important issue in the research setting. As a result, the conceptual and ethical framework of informed consent for medical treatment is similar in many ways to that of informed consent for research. There is one major difference, though. Whereas medical treatment has as its primary and overriding goal the successful treatment of the individual patient, the primary goal of research is to produce generalizable knowledge. This new knowledge may or may not help the individual research participant.

Sometimes, a prospective research participant may not understand this key difference in goals between research and treatment, and may enter a research trial believing that the research intervention will help him or her directly. The prospective participant views participation in the research study as a form of treatment and expects better health as a result. Frequently, research participants in this situation assume that they have the same relationship with the study researchers as they would with their own doctors. But these expectations and assumptions are simply not true. When a research participant confuses the goals of research with those of treatment, this gives rise to what is called "therapeutic misconception."

Therapeutic misconception can seriously impair the ability of an otherwise competent person to give legally effective informed consent. As a result, researchers must be careful to ensure that prospective participants fully understand the goals of research, as well as the difference between receiving medical care in a research study versus receiving medical care from a personal physician.

Are there subsets of patients with whom we need to be particularly careful when obtaining informed consent?

There are several subsets of patients who have characteristics or problems that may make them particularly vulnerable to decision-making that is not fully competent or voluntary. Research team members must make special efforts to recognize these vulnerable patients and assure that when they give consent to participate in research, their decisions are fully competent and voluntary.

These subsets of vulnerable patients include:

- *Some people with mental illness, including certain elderly patients suffering from dementia. These patients may need a legally authorized surrogate decision-maker – usually a family member – to act on their behalf.*
- *Substance abusers, who may be vulnerable to coercion.*
- *Homeless patients, who may perceive a benefit to participating in a research study, such as being able to sleep in a hospital.*
- *Patients who are desperately ill and particularly vulnerable to therapeutic misconception.*

How is informed consent obtained?

Meaningful informed consent is obtained by having a conversation with the prospective participant. Once obtained, informed consent is maintained through an ongoing process to keep the participant informed of any developments that may affect his or her decision to continue in the study.

Meaningful informed consent is obtained by having a conversation with the prospective participant.

Several things need to happen during the initial conversation. First, the research team member obtaining consent must disclose to the prospective participant everything he or she needs to know about the research study in order to make a fully informed decision about whether to participate. The consent form spells out the information

The consent form spells out the information that must be disclosed – including the purpose of the study, risks, benefits, alternative treatments, and other elements of informed consent.

that must be disclosed – including the purpose of the study, risks, benefits, alternative treatments, and other elements of informed consent.

However, the research team member must be careful not to focus exclusively on the consent form. The consent form is a tool. It serves as a guide for how to conduct the conversation and as a receipt, once it has been signed by the participant, that the participant has given informed consent to be in the study.

The consent form is not the only means for the research team member to inform the prospective participant. Informed consent is obtained through a thoughtful dialogue that respects the individuality of each prospective participant and allows ample opportunity for the prospective participant to ask questions, which the research team member must answer fully. The goal is to ensure that the prospective participant truly understands everything he or she needs to know about the study before making a decision, that the decision to participate is completely voluntary, and that he or she is competent to make this decision.

This may actually require more than one conversation, depending on the nature of the research. In fact, some researchers believe that, especially for more complicated studies or those with unusual risks, prospective participants should be informed in stages on several occasions, so that they have time to reflect on what they have been told before receiving more information.

In addition, research team members may want to encourage prospective participants to talk with their families before reaching a decision. They may also want to give prospective participants written materials on the study and on participation in VA research to help guide their decisions. (See the Office of Research Compliance and Assurance web site at www.va.gov/orca for the brochure, "I'm a veteran. Should I participate in research?")

There is no single best way to obtain informed consent. Research studies vary widely – obtaining informed consent for a trial of a

highly experimental therapy is a very different matter from obtaining informed consent for a survey study. Researchers are experimenting with different tools for administering informed consent. For example, some studies indicate that informational videotapes or audiotapes may help improve prospective participants' understanding of a research study. Other researchers have focused on ways to simplify the language used to inform prospective participants so that complex information is more easily understood.

It is very important for research team members to keep in mind that informed consent is a process, not something obtained simply by having a prospective participant sign a consent form. And getting a participant's signature on the consent form does not end the process. The research team must keep participants informed of any significant new findings developed during the study that may affect participants' willingness to continue in the study.

It is very important for research team members to keep in mind that informed consent is a process, not something obtained simply by having a prospective participant sign a consent form.

What are some tips for providing prospective research participants with the information they need and ensuring that they understand it?

Plain speaking – both verbally and in writing – is critical to obtaining informed consent. Prospective participants must understand the nature of their involvement in a study before they can give meaningful informed consent. Because VA patients tend to be very trusting of their clinicians, they may give their consent without fully understanding what they are doing. For this reason, research team members must make a special effort to communicate simply and directly with prospective participants and ensure their understanding. Here are some tips for doing this:

Write to your audience. When developing a consent form or an oral script, write at a level that matches the reading ability of your prospective participants, generally at or below the 8th grade level.

Use active voice, short words. Whether in writing or in conversation with a prospective participant, use active voice and short, simple words. For example, "we note" is better than "it is noted," and "pay" or "repay" is better than "compensate."

Prospective participants must understand the nature of their involvement in a study before they can give meaningful informed consent.

Speak plainly. Get rid of jargon and use descriptive phrases to convey information. For example, instead of "researchers," use the phrase "people doing the study."

Make it simple. Keep your sentences short. Limit your ideas to one per sentence.

Don't dictate. When developing a consent form, don't put words in patients' mouths by using the first person singular construction. Consent forms that read along the lines of "I understand that I will be asked…" or "I recognize that I may be at some risk for…" may be intimidating to prospective participants. In fact, many IRB experts view this construction as coercive. It is better to write *to* your prospective participants. "You will be asked to…" or "You may be at risk for…" are good constructions.

Break it down. Organize the information you are providing into discrete "chunks" that are easier for people to understand. The elements of informed consent (see Appendix A) provide a good framework for organizing your information.

Be straightforward. Do not overstate the possible benefits of your research. On the flip side, do not understate the risks. The information you present must be full and objective, if true informed consent is to be obtained.

Quiz the patient. Ask the prospective participant several times during the conversation whether he or she remembers and understands what you have just told him. Ask the person to explain that information back to you in his or her own words.

Don't rush a decision. Give the person time to think the matter over. You may need to have several conversations over a period of days. Encourage the prospective participant to talk with his or her family members before reaching a decision.

A written consent form that embodies the required elements of informed consent serves as documentation that informed consent was obtained prior to a subject's enrollment in a study. Both the IRB and the R&D Committee of the institution where the research is being conducted must approve this form before any prospective research participants are approached.

When a prospective participant has agreed to give informed consent to participate in a study, he or she or a legally authorized representative signs and dates the consent form. A witness to the participant's signature must also sign and date the form. The original signed consent form is then filed in the participant's case history. A copy of the signed form must be provided to the participant or their legal representative.

A written consent form that embodies the required elements of informed consent serves as documentation that informed consent was obtained prior to a subject's enrollment in a study.

Under some conditions, the IRB may approve a short form written consent. The content of this informed consent form may be presented orally to prospective participants who can't read. A written summary of what is to be said to the prospective participant must be approved in advance by the IRB. In addition, there must be a witness to the oral presentation. After the presentation, the participant signs a short written statement attesting that the elements of informed consent have been presented to him or her orally. The witness and the person obtaining the consent must also sign this statement, as well as a copy of the summary that was read to the participant.

What is the role of the IRB in informed consent?

The IRB is a subcommittee of the R&D Committee. For a study involving human subjects to proceed, both these committees must approve the study protocol, including the informed consent form. Neither committee can overturn a disapproval by the other.

Prior to reviewing the informed consent form, the IRB examines the research protocol closely, particularly with respect to the potential risks and benefits, to ensure that the risk-benefit ratio is acceptable.

The IRB must also ensure that the informed consent process, as performed by the research staff, has been properly documented…

This becomes an important issue when the IRB assesses the consent form, which must accurately reflect the study's risks and benefits and provide the prospective participant with all the information needed to give fully informed consent.

Once the IRB has approved an informed consent form, the form must be used to obtain legally effective informed consent for the study. It cannot be modified without approval from the IRB.

IRB meeting minutes, including approval of consent forms, are reviewed by the R&D Committee, which must approve the minutes before they are sent to the facility director for final concurrence. Although approval by the R&D Committee is generally routine, they may flag controversial issues regarding research protocols or consent forms and ask the IRB to review them again. The R&D Committee, as well as higher authorities (facility director, ORD) may also add other modifications or strengthen requirements that must be met before approval of the protocol or consent form.

The IRB must also ensure that the informed consent process, as performed by the research staff, has been properly documented, including filing the original executed informed consent form in the subject's case history. In addition, IRB members may choose to observe the process of obtaining consent, to ensure that prospective participants are being adequately and effectively informed. Under certain circumstances, the IRB may approve an amended consent procedure or waive the requirements for documentation of informed consent.

VA managers should keep in mind that protection of human research subjects is a shared responsibility and make sure that the lines of communication are always open between the IRB and others involved in informed consent. In particular, facility directors should maintain an ongoing dialogue with their IRBs, R&D committees,

ACOS for R&D, and others involved in ensuring and maintaining informed consent.

Facility directors have ultimate responsibility to and for their facilities' IRBs. They must ensure that investigators conducting research at their facilities comply with the IRBs' rulings, as well as ensuring that the IRB does its job properly, carries the required accreditation, and operates in compliance with the facility's standard operating procedures for human subjects protection. Facility directors must also see to it that IRB members have adequate training in informed consent procedures and requirements. Finally, they must ensure that adequate administrative support, including personnel and space sufficient to provide privacy for conducting sensitive duties and storing records, is provided for IRB activities.

What data protection issues apply to informed consent for clinical research?

Ensuring the privacy and confidentiality of all patient data used for human subjects research is of paramount importance to VA. Key here is whether individual patients whose data are being used in research will be identifiable as a result of the research. The IRB examines this issue when reviewing the study protocol. If concerns arise over patient privacy and confidentiality, the IRB will direct the research team to strengthen the protocol so that it addresses these concerns appropriately.

In addition, effective in April 2003 are new patient privacy protections under the Health Insurance Portability and Accountability Act (HIPAA) of 1996. These rules guide uses and disclosures of protected health information at health care facilities that are covered under HIPAA, including VA facilities. Researchers and others involved in human subjects research should familiarize themselves with the new HIPAA privacy rules. Good resources include the Health Privacy Project at the Georgetown University Institute for Health Care Research and Policy (www.healthprivacy.org), and the Department of Health and Human Services Office of Civil Rights

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(www.hhs.gov/ocr/index.html). VA privacy regulations can be found in VA Manual M-1, Part 1, Chapter 9.

The Institute of Medicine recommends that all research organizations work with their IRBs to develop specific guidance and examples for interpreting and applying key aspects of the new federal regulations and make such guidance and examples available to all investigators submitting proposals for review. VA managers may want to consider working with their IRBs to identify and develop best practices for protecting privacy and confidentiality in research. (See "Protecting Data Privacy in Health Services Research," Committee on the Role of Institutional Review Boards in Health Services Research Data Privacy Protection, Institute of Medicine, National Academy Press 2000, http://www.nap.edu/catalog/9952.html.)

Both the federal Office for Human Research Protections (OHRP) and VA strongly recommend training related to human subjects research. All who are involved in the informed consent process must be sufficiently knowledgeable, either through training or experience.

Within VA, network directors, facility managers, IRB chairs, human research protection administrators, and research investigators all should have appropriate training in human subjects protection, including informed consent. Investigators, in particular, must provide documentation of completion of approved training to the local research office prior to conducting any research in VA. The Office of Research Compliance and Assurance (ORCA) has arranged for VA system-wide access to a comprehensive web-based training program on the protection of human research subjects. The CITI (Collaborative IRB Training Initiative) Course in the Protection of Human Research Subjects was developed by a multi-institutional collaboration that includes VHA participation through ORCA. This is an optional training vehicle that will assist facility managers, IRB members and staff, research administrative staff, and investigators to

fulfill training and education requirements. VA employees wishing to use the module should go to the CITI-VA registration site at www.miami.edu/bb/vareg.

For more information on VA training and education regarding informed consent, visit ORCA's web site, www.va.gov/orca/. Also, see Appendix C for a list of training resources for research staff and IRB members.

The CITI training module is one example of how VA is working to improve informed consent by training and educating VA managers and research staff.

In addition, VA is working with the National Committee for Quality Assurance (NCQA), a private, non-profit accreditation organization, to establish an accreditation program for human subjects research. In 2000, VA signed a 5-year contract with NCQA to develop accreditation standards, survey all VA facilities conducting research with human subjects every three years, and determine the accreditation status for each facility. In creating this accreditation program, VA is raising the bar for protecting human subjects enrolled in research and setting an example for the rest of the research community to follow. For details, visit www.ncqa.org/pages/programs/QSG/VAHRPAP/vahrpap.htm.

Finally, VA is looking to its own research for insights on how to improve informed consent. For example, a VA Cooperative Studies Program project – Enhancing the Quality of Informed Consent, otherwise known as EQUIC, is underway to test innovations in informed consent. VA researchers will conduct structured interviews with VA research participants to determine whether key elements of informed consent were achieved, how satisfied they were with the process, how much information they retained, and whether they understood the information they were given. EQUIC will try to identify ways that the process can be improved. VA's Office of Research and Development also expects to fund additional research in the area of informed consent.

. . . VA is raising the bar for protecting human subjects enrolled in research and setting an example for the rest of the research community to follow.

People who participate in clinical research make a tremendous contribution to medical science. The VA research enterprise has both a moral and a legal obligation to respect the rights and autonomy of all people who consider participating in VA research. VA is a world leader in research, striving for excellence in all its research programs. Key to achieving that goal is ensuring the protection of all VA research participants through a thoughtful and deliberate informed consent process.

Many questions remain to be answered about how best to achieve fully informed consent. VA will continue to explore innovations in informed consent, and will adopt and disseminate those techniques that improve patient protection.

Appendix A: Elements of Informed Consent

What are the elements of informed consent?

Following are the basic elements of informed consent. For more detail, please refer to VHA Handbook 1200.5, Appendix C.

Purpose and Description: Tell the prospective participant that the study involves research, explain the purpose of the study and the length of time expected for participation, describe the process to be followed during the study, and identify any experimental procedures or other procedures being done only for the research. For example, the researcher should say whether the study involves a new drug, extra tests, separate research records, or nonstandard means of management, such as random assignment. VA policy specifies that the following information must be provided to the prospective participant:

- *Name of the study*
- *Name of the principal investigator*
- *A statement that the study involves research*
- *An explanation of the purposes of the research and expected duration of the subject's participation*
- *A description of the procedures to be followed and identification of those being done for research purposes*
- *Identification of any procedures that are experimental*

Risks: Describe any reasonably foreseeable harms, inconvenience, or discomforts to the participant. If additional risks are identified during the study, the consent process and documentation will require revision to inform continuing, as well as new participants of these risks.

Benefits: Describe any benefits to the prospective participant or to others that may reasonably be expected to result from the research. There may be none, other than a sense of helping society at large.

Alternatives: Disclose any appropriate alternative treatments that might benefit the prospective participant. For example, a medication in a drug study may be available through the participant's family doctor or clinic.

Confidentiality: Tell the prospective participant whether his individual record will be kept confidential and explain the level of confidentiality to be maintained. For example, some studies require disclosure of information to study sponsors, the FDA, or other federal agencies.

Greater Than Minimal Risk: For research involving more than minimal risk, provide an explanation of whether any compensation is available and whether medical treatments are available if injury occurs, and, if so, what they consist of and where further information may be obtained.

Contact Information: Tell the prospective participant whom to contact if he has questions about the research and his rights as a study participant, and whom to contact if he has an injury that may be related to the research.

Voluntary Participation: Explain that participation is voluntary, that refusal to participate will result in no penalty or loss of benefits to which the prospective participant would otherwise be entitled, and that the participant may withdraw from participating in the study at any time without penalty.

No Payment Required: Inform the prospective participant that he or she will not be required to pay for treatment received as a subject in a VA research project. However, he or she may be required to pay usual co-payments for VA care and services that are not part of the study.

When appropriate, the following *additional* elements of consent should be included:

Unforeseeable Risk: Explain that the study treatment or procedures may have risks for the prospective participant (or to an embryo or fetus, if the participant is or may become pregnant) that the researcher cannot currently foresee.

Termination of Participation Without Consent: State the circumstances under which the participant's further involvement in the study may be terminated without that person's consent.

Additional Costs: Disclose any additional costs to the prospective participant that may result from participation in the study.

Consequences and Process of Withdrawal: Explain how a participant can leave the study and what may happen to him if he chooses to withdraw.

Impact of Significant New Findings: Tell the participant that he will be informed of any significant new findings developed during the research that may relate to his willingness to continue in the study.

Number of Participants: Inform the prospective participant of the approximate number of people involved in the study.

Human Biologic Specimens: Follow the VHA Handbook on Banking of Human Biological Specimens, if specimens obtained in the study might lead to the development of a valuable product or will be retained after the study ends.

Payment: Include a statement regarding any payment the participant is to receive and how payment will be made. If payment is given to participants, it must not be coercive in amount or method of distribution. (VA permits payment to human research participants under specific circumstances; payment must be approved in advance by the IRB.)

Appendix B: Resources

What VA and non-VA resources are available to managers, investigators, and other research staff?

There is an abundance of bioethics, research compliance, and other human subjects protection information available from government, academic, and private sources, much of it accessible via the Internet. A sampling of several different types of resources is presented here. These resources can provide information and assistance in a variety of ethics, policy, and compliance areas. Many of the resources listed here also provide extensive additional resource listings on their web sites. First are listed some important VA offices and contacts for guidance on a variety of issues related to informed consent. Next is a listing of other government resources, as well as some additional non-government sites of interest.

WITHIN VA

National Center for Ethics

The National Center for Ethics is VHA's primary office for addressing the complex ethical issues that arise in patient care, health care management, and research. It is distinctive in serving the nation's largest integrated health care delivery system and supports the development of integrated ethics programs at the local, regional, and national levels. The Center's mission is to clarify and promote ethical health care practices within VHA and beyond, and it serves as the primary advisor on ethical issues to the Under Secretary for Health.

Telephone: (802) 296-5145
Email: vhaethics@med.va.gov

Web Link
http://www.va.gov/vhaethics/index.cfm

Office of Research Compliance and Assurance (ORCA)

The Office of Research Compliance and Assurance serves as the primary Veterans Health Administration component in advising the Under Secretary for Health on all matters affecting the integrity of research in the protection of human subjects and the welfare of laboratory animals. ORCA promotes enhancements in the ethical conduct of research in conformance with regulations and policies, and investigates any allegations of research improprieties and scientific misconduct.

Telephone: (202) 565-9080

Web Link
http://www.va.gov/orca/

Office of Research and Development

The Office of Research and Development is committed to ensuring that VA funded research and all VA researchers comply with statutory and regulatory requirements for the protection of human research participants. As such, it is continually reviewing its research policies, issuing appropriate guidance, and developing new systems to improve education, accountability, and adherence to the research assurance requirements.

Telephone: (202) 565-8440

Web Link
http://www.va.gov/resdev/default.cfm

OTHER GOVERNMENT RESOURCES

Office for Human Research Protections (OHRP)

The Office for Human Research Protections, part of the Department of Health and Human Services (DHHS), monitors programs for the protections of human subjects at universities, hospitals, and other medical and behavioral research institutions in the United States and abroad. OHRP is responsible for leading efforts to protect human subjects in biomedical and behavioral research and carrying out patient protection initiatives issued by DHHS.

Web Link
http://ohrp.osophs.dhhs.gov/

U.S. Food and Drug Administration (FDA)

FDA's mission is to promote and protect the public health by helping safe and effective products reach the market in a timely way, and monitoring products for continued safety after they are in use. It maintains enforcement authority to ensure that researchers carrying out FDA-authorized drug and medical device clinical trials are complying with Department of Health and Human Services patient protection and consent requirements through its inspection and auditing of the conduct and reporting of clinical trials.

- **Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators**
  http://www.fda.gov/oc/ohrt/irbs/default.htm

- **Center for Drug Evaluation and Research**
  http://www.fda.gov/cder/about/smallbiz/clinical_investigator.htm

National Institutes of Health (NIH)

NIH is committed to the ethical conduct of research and the protection of human subjects. As part of this commitment, it has produced documents to provide guidance for researchers and IRB members who have an obligation to safeguard the rights and welfare of research participants and has developed a bioethics resource web site. *Bioethics Resources on the Web* is designed to facilitate research, scholarly activities, and training. The web site provides information about bioethics initiatives at NIH Institutes and Centers and other government offices and programs, publications, reports, guidelines, and regulations related to bioethics.

- **Bioethics Resources on the Web**
  http://www.nih.gov/sigs/bioethics/

The President's Council on Bioethics

The newly established President's Council on Bioethics advises the President on bioethical issues that may emerge as a consequence of advances in biomedical science and technology. The Council's web site also includes a link to the archived site of the National Bioethics Advisory Commission, established by the previous administration.

Web Link
http://www.bioethics.gov/

NON-GOVERNMENT RESOURCES

National Committee for Quality Assurance (NCQA)

NCQA is a not-for-profit organization dedicated to improving health quality. Working with VA, it is operating an accreditation program to ensure that VA medical centers are complying with VA and other relevant federal regulations designed to protect human subjects of research.

Web Link
http://www.ncqa.org/programs/accreditation/vahrpap/vahrpap.htm

Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP)

AAHRPP is a nonprofit organization working to protect the rights and welfare of research participants by fostering and advancing the ethical and professional conduct of persons and organizations that engage in research with human participants. It offers accreditation to institutions engaged in research involving human participants using a voluntary, peer-driven educational model.

Web Link
http://www.aahrpp.org/

Association of American Medical Colleges (AAMC)

The AAMC has as its purpose the improvement of the nation's health through the advancement of medical schools and teaching hospitals. As an association of medical schools, teaching hospitals, and academic societies, the AAMC works with its members to set a national agenda for medical education, biomedical research, and health care, and assists its members by providing services at the national level that facilitate the accomplishment of their missions.

Web Link
http://www.aamc.org/research/start.htm

- **AAMC Research Compliance Resources**
  http://www.aamc.org/research/dbr/compliance/startcom.htm

Public Responsibility in Medicine & Research (PRIM&R)

PRIM&R is committed to the advancement of strong research programs and to the consistent application of ethical precepts in both medicine and research. Through national conferences and published reports, it has addressed a broad range of issues in research, clinical practice, ethics, and the law.

Web Link
http://www.primr.org/index.html

Applied Research Ethics National Association (ARENA)

ARENA is a national service organization for professionals interested in bioethics, researchers, administrators, and members of Institutional Review Boards, hospital ethics committees, patient advocacy groups, and Institutional Animal Care and Use Committees. Its function is to promote educational activities, networking, resolution and/or amelioration of mutual problems, and the professional advancement of its members.

Web Link
http://www.primr.org/arena.html

The Hastings Center

The Hastings Center is an independent, nonpartisan, interdisciplinary research institute that addresses fundamental ethical issues in the areas of health, medicine, and the environment as they affect individuals, communities, and societies. Their publications include the *Hastings Center Report* (and special supplements to this journal), *IRB: Ethics & Human Research*, and other publications addressing issues related to human subjects research.

Web Link
http://www.thehastingscenter.org/

RESOURCES FOR SIMPLIFYING INFORMED CONSENT LANGUAGE AND FORMS

University of Michigan
Medical School Institutional Review Board: Simplification Guide to Medical Terms
http://www.med.umich.edu/irbmed/InformationalDocuments/consent/synonym.html

University of California-Davis
Office of Human Research Protection: Glossary of Human Subjects Terminology (Glossary of Lay Terms for Use in Preparing Consent Forms for Human Subjects)
http://ovcr.ucdavis.edu/HumanSubjects/HSDefinitions/HSGlossary.htm

What training resources are available for investigators, IRB members, and other research staff?

Training and certification in human subjects protection is a requirement for all VA investigators, and training is equally important for IRB members and research staff. A selection of online training resources is provided here, as well as contact information for organizations providing more formal training courses. Numerous other resources exist, and local medical schools and academic medical centers can also be excellent resources for training in a variety of areas of human subjects protection and informed consent.

CITI (Collaborative IRB Training Initiative) Course: The Protection of Human Research Subjects
Includes special registration site and training module for VA staff
www.miami.edu/bb/vareg

Association of American Medical Colleges (AAMC)
AAMC Research Compliance Resources: Computer-Based Instruction and On-Line Resources for Human Subjects Protection
http://www.aamc.org/research/dbr/compliance/curricula.htm

Public Responsibility in Medicine & Research (PRIM&R)
http://www.primr.org/training.html

National Institutes of Health
Tutorials, Case Studies and Courses
http://www.nih.gov/sigs/bioethics/casestudies.html

Office for Human Research Protections (OHRP)
Educational Materials
http://ohrp.osophs.dhhs.gov/educmat.htm
Workshops
http://ohrp.osophs.dhhs.gov/wrkshp.htm

VA New Jersey Health Care System
Protection of Human Research Subjects Training Module
http://pws.prserv.net/vanjhcs_research/VAT1/first.htm

Dunn CM and Chadwick G.
Protecting Study Volunteers in Research: a comprehensive manual designed to assist clinical research professionals in providing the highest standards of safety and ethical treatment for their study volunteers. Developed in accordance with ACCME standards, readers can apply for CME credits and Nursing Contact Hours. An exam is provided with each manual.
http://www.centerwatch.com/bookstore/pubs_profs_protect.html

What reading materials are available to provide more information on informed consent, research ethics, and the protection of human subjects in research?

Informed consent has been the subject of numerous publications, from entire books and journals devoted to the topic to individual articles and literature reviews. The list below provides an extensive, but by no means complete guide to a variety of published articles and journals covering research ethics and human subjects protection, as well as specific aspects of informed consent and the regulations which govern it.

JOURNALS

IRB: Ethics & Human Research
Includes articles and features that help clarify fundamental ethical concerns, explore regulatory developments, and share insights and experiences, as resources not only for IRB members, but also for investigators, sponsors, research administrators, participant-subjects, and others actively involved in research with human subjects.
http://www.thehastingscenter.org/Membership/IRBdefault.asp

The Hastings Center Report
The premiere publication of the Hastings Center, the *Hastings Center Report* was the first periodical devoted specifically to ethical issues in medicine, the life sciences, and the professions. This journal offers a public forum in which the many disciplines and professions that contribute to bioethics - philosophy, medicine, law, the natural and social sciences, theology - can join in mutually enriching discussion. Its goal is to stimulate the moral imagination of its diverse readers in articles that are both intellectually rigorous and generally accessible.
http://www.thehastingscenter.org/Membership/memberdefault.asp

REGULATIONS/CODES

Ethical Principles and Guidelines for the Protection of Human Subjects of Research (*The Belmont Report*). *The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. April 18, 1979.*
http://www.fda.gov/oc/ohrt/irbs/belmont.html

Federal Policy for the Protection of Human Subjects (*Common Rule)*
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

VHA Handbook 1200.5: Requirements for the Protection of Human Subjects in Research
http://www.va.gov/resdev/directive/RevisedHandbookProtectionHumanSubjects InResearch.doc

VA Human Research Protection Accreditation Program Accreditation Standards
National Committee for Quality Assurance (NCQA)
http://www.ncqa.org/Programs/QSG/VAHRPAP/vahrpap.htm

BOOKS

Berg JW, Appelbaum PS, Parker LS, Lidz CW. ***Informed Consent: Legal Theory and Clinical Practice. 2nd ed.*** New York: Oxford University Press;2001.

Doyal L, Tobias JS, editors. ***Informed Consent in Medical Research.*** London: BMJ Books;2001.

Dunn CM, Chadwick G. ***Protecting Study Volunteers in Research:*** *A comprehensive manual designed to assist clinical research professionals in providing the highest standards of safety and ethical treatment for their study volunteers.*
http://www.centerwatch.com/bookstore/pubs_profs_protect.html

Faden R, Beauchamp TL; in collaboration with: King NMP. ***A History and Theory of Informed Consent.*** New York: Oxford University Press;1986.

Hartnett T, editor. ***The Complete Guide to Informed Consent in Clinical Trials.*** Springfield (VA): PharmSource Information Services, Inc.;2000.

Kahn JP, Mastroianni AC, Sugarman J, editors. ***Beyond Consent: Seeking Justice in Research.*** New York: Oxford University Press;1998.

Levine RJ. ***Ethics and Regulation of Clinical Research. 2nd ed.*** New Haven: Yale University Press;1988.

Mazur DJ. ***Medical Risk and the Right to an Informed Consent in Clinical Care and Clinical Research.*** Tampa (FL): American College of Physician Executives;1998.

ARTICLES

VA's Office of Research and Development, in collaboration with the Hastings Center, has made available on the web a searchable annotated bibliography of empirical research on informed consent.
http://www.va.gov/resdev/fr/informed_consent

Appendix E: Glossary

Glossary of Informed Consent Terms

Adverse Event (AE): Any untoward physical or psychological occurrence in a human subject participating in research. An adverse event does not necessarily have a causal relationship with the research treatment or intervention. See also Serious Adverse Event and Unexpected Adverse Event.

Assurance: Also called an Assurance of Compliance or Federalwide Assurance (FWA). It is obtained from the Office for Human Research Protections (OHRP) and constitutes a written commitment by an institution to protect human subjects participating in research. Any institution conducting or engaged in federally supported research involving human subjects must obtain an Assurance.

Belmont Report: A statement of basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects, and guidelines to assure that this research is conducted in accordance with such principles.

Case History: A record of all observations and other data pertinent to the investigation on each research subject. Case histories include the case report forms and supporting data, including the original signed and dated consent form documenting that informed consent was obtained prior to participation in the study.

Common Rule: The Federal Policy for the Protection of Human Subjects which VA and 16 other federal agencies and departments have agreed to follow. It is described in the Code of Federal Regulations (CFR) at 45 CFR 46, and VA has incorporated its subscription to this policy at 38 CFR 16.

Consent Form: An Institutional Review Board (IRB) approved document containing all relevant information to be communicated to potential research participants; a participant's signature on this form is intended to document their voluntary consent to participate in a research study. In VA research, VA form 10-1086 must be used as the consent form. The consent form is only one part of the consent process.

Human Subject: A living individual about whom a research investigator obtains data. Data may be obtained through intervention or interaction with the individual, or through identifiable private information.

Institutional Review Board (IRB): A committee of scientific and non-scientific individuals, established according to federal requirements, with responsibility for review and approval of human subjects research protocols and consent forms used in those protocols.

Institutional Review Board Records: These may include but are not limited to all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, investigator brochures, supplemental information, consent forms, information submitted for continuing review, all correspondence, and IRB membership, including a resume for each member.

Investigator: An individual who conducts some or all aspects of a research investigation.

Legally Authorized Representative: An individual or body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in a procedure(s) involved in research, when the subject is incapable of providing consent.

Principal Investigator: An individual with primary responsibility for the design and conduct of an investigation, and under whose immediate direction research is conducted. In the event of an investigation conducted by a team of individuals, the principal investigator is the responsible leader of the team.

Research Records: Records that consist of both IRB records and case histories, or any data gathered for research purposes.

Researcher: A principal investigator and/or investigator.

Serious Adverse Event (SAE): Death, a life threatening experience, hospitalization (for a person not already hospitalized), prolongation of hospitalization (for a patient already hospitalized), persistent or significant disability/incapacity, congenital anomaly/birth defects, or other event that jeopardizes the research subject and may require medical or surgical treatment to prevent one of the above outcomes.

Unexpected Adverse Event (UAE): Any adverse event/reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure, product labeling, or the risk information described in the general investigational plan or proposal.

Vulnerable Subjects: Individuals whose willingness to volunteer for a research study may be more easily influenced or coerced, or who may be less able to make an informed decision to participate. These individuals may include: pregnant women and fetuses, prisoners, the mentally ill and those with impaired decision-making capacity, children, and economically and/or educationally disadvantaged persons.

Notes

Notes

Informed Consent for Human Subjects Research: A Primer is available in electronic and printed formats. Additional copies may be obtained from the sources listed below.

Electronic copies (PDF format) can be downloaded from the VA HSR&D web site. Point your browser to http://www.hsrd.research.va.gov/publications/primer/

Print copies may be requested from:
Special Projects Office (512A5/152)
VA Maryland Health Care System
Telephone: (410) 642-1092
Email: rainelle.holcomb@med.va.gov

Other primers in the series include:

Primary Care in VA
Health Technology Assessment in VA
Using Outcomes to Improve Healthcare Decision Making
Program Evaluation for Managers
Risk Adjustment: A Tool for Leveling the Playing Field
Clinical Practice Guidelines
Organizational Change

Office of Research and Development
Veterans Health Administration
Department of Veterans Affairs

Produced by the Information Dissemination Program
Management Decision and Resource Center
VA Boston Health Care System (152-M)
150 South Huntington Avenue
Boston, MA 02130
617-278-4433
MDRC.Boston@med.va.gov

http://www.hsrd.research.va.gov