POLICIES AND PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS 1INVOLVED IN FEDERALLY FUNDED OR SPONSORED RESEARCH

Approved By

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Commissioner
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History of Changes to this Document

Section	Section Title	Revision History	Effective Date of Change
	Edited document formatting and section numbering throughout manual.		12/28/05
III, C	Principal Investigator Responsibilities, Initial Review Submissions.	Added "13. Complete Conflict of Interest Disclosure Form H" to list.	4/30/2007 dwf
FORMS	FORMS	Added Form H and Form H Supplement to "FORMS' section. Added "Conflict of Interest Disclosure Statement *(and Supplement if applicable)"* to Form A Application Checklist.	4/30/2007 dwf
I, A	Edited document formatting and section numbering throughout manual.	Updated administrator information	2/4/2009
COVER	COVER	Updated FWA expiration date from renewal to 6/30/2014	12/22/11
I, A	Regulation Overview	Updated Chairperson and Administrator contact information – Phone and fax #'s	12/22/11

Section I. Overview and Statement of Principles

A. Regulation Overview

Title 45 Part 46 of the U.S. Code of Federal Regulations (CFR) -- Protection of Human Subjects establishes the application of *Belmont Report* principles and provides the process necessary to protect the rights of human subjects involved in research. Federal funds may not be expended for research involving human subjects unless the requirements of *Title 45 Part 46* have been satisfied (§46.122).

To eliminate confusion and promote uniformity, 17 federal departments and agencies have adopted as regulation a common Federal Policy for the Protection of Human Research Subjects (*Common Rule*). One of the programs that the Virginia Department of Rehabilitative Services (DRS) operates is the vocational rehabilitation (VR) program which receives funding and oversight from the Rehabilitation Services Administration, Office of Special Education and Rehabilitative Services, U.S. Department of Education (DOE). DOE has codified the *Common Rule* (Federal Policy for the Protection of Human Research Subjects) at 34 CFR Part 97.

The U.S. Department of Health and Human Services (DHHS) regulations incorporate the *Common Rule* as Subpart A of 45 CFR 46. Additionally, DOE has adopted Subpart D of 45 CFR 46, *Protections for Children Who Are Subjects in Research*. Therefore, all federally funded or sponsored human subjects research involving VR consumers who are minors must comply with both Subpart A and Subpart D of 45 CFR 46.

DRS also operates the Disability Determination Services (DDS) program which is fully funded by the Social Security Administration (SSA). SSA has not codified the *Common Rule*. Any research involving DDS employees, clients and/or personally identifiable data, must be approved by SSA.

The Food and Drug Administration (FDA) has concurred with the *Common Rule*, but has not adopted the Policy in its entirety. Instead, the FDA has made selected changes to its Institutional Review Board and informed consent regulations that correspond to the *Common Rule*. Where a research project is subject to FDA and *Common Rule* review, the requirements of each set of regulations must be met. This situation may arise, for example, when applying the provisions on waiver of documentation of informed consent, in cases where both the FDA and DHHS have jurisdiction over the research.

For the purposes of this policy and procedures document, the term DRS or "institution" means all DRS divisions, programs, offices or other units to include the Woodrow Wilson Rehabilitation Center, but does not include DDS.

Research covered by this policy that has been approved by the Human Research Review Committee (HRRC) may be subject to further appropriate review and approval or disapproval by the DRS Commissioner. However, the Commissioner may not approve the research if it has not been approved by the HRRC. (45 CFR §46.112)

Compliance with this policy and procedures document requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects. (45 CFR §46.101(e)) In the case of any discrepancy between DRS regulations, policies and procedures and current federal rules, regulations and policies for the conduct of human subject research, the federal guidance takes precedence.

Any Institutional Review Board (IRB) reviewing federally-funded or sponsored research that involves DRS employees, clients, facilities, or other resources must have a Federalwide Assurance. (45 CFR §46.122)

This document fulfills terms of DRS's Federalwide Assurance (FWA) on file with the U.S. Department of Health and Human Services (DHHS) to have written procedures for the conduct of human subject research.

The FWA is a binding written agreement between DRS and DHHS. It states that DRS is guided by the ethical principles of the *Belmont Report*, and will comply with federal regulations (45 CFR 46) for federally funded human subjects research.

Non-federally funded research activities involving DRS clients or employees will be conducted in compliance with Sections 32.1-162.16 et seq. and 51.5-14.01 of the *Code of Virginia* which is the basis for DRS regulations (22 VAC 30-40-10 et seq.) and *Procedures for Review of Research with Human Participants.*

Non-therapeutic research is prohibited unless the HRRC determines that such research will not present greater than minimal risk to the subject.

This policy and procedures document is intended to be an electronic resource. Please return to this electronic document to ensure that you are using the most recently updated version. The Signature copy of this document is maintained by the DRS Policy and Planning Division. An electronic copy of this document can be obtained from the HRRC web site. (http://www.vadrs.org/hrrc)

To report possible areas or incidences of research non-compliance with federal or state regulations which involve DRS employees, clients, and/or financial or other resources please contact the DRS Policy and Planning Director.

Please submit compliance concerns to:	Please submit HRRC research applications to:
Elizabeth E. Smith, JD, MS Policy and Planning Director Department of Rehabilitative Services 8004 Franklin Farms Drive Richmond, Virginia 23229 (804) 662-7071 Email: Elizabeth.Smith@drs.virginia.gov Toll Free: 1-800-552-5019 TTY Toll Free: 800-464-9950 FAX (804) 662-7663	DiVette M. Brisco HRRC Administrator Policy and Planning Division Department of Rehabilitative Services 8004 Franklin Farms Drive Richmond, Virginia 23229 (804) 840-0250 Email: DiVette.Brisco@drs.virginia.gov Or Elizabeth E. Smith, JD, MS HRRC Chairperson Department of Rehabilitative Services 8004 Franklin Farms Drive Richmond, Virginia 23229 (804) 662-7071 Email: Elizabeth.Smith@drs.virginia.gov Toll Free: 1-800-552-5019 TTY Toll Free: 800-464-9950 FAX (804) 662-7663

B. Statement of Principles

The Department of Rehabilitative Services (DRS) is responsible for safeguarding the rights and welfare of clients and employees of DRS and the Woodrow Wilson Rehabilitation Center (WWRC) who volunteer to participate in human subject research. As such, DRS assures that no human subject research will be conducted, authorized, funded or sponsored by DRS or WWRC unless the DRS Human Research Review Committee (HRRC) has reviewed and approved such research.

The National Research Act of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1979, the Commission published its report, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research,* commonly called the *Belmont Report*. Today's federal regulations for the protection of human subjects are based on the ethical principles of the *Belmont Report*. The *Belmont Report* identifies three basic principles as particularly relevant to the ethics of research involving human subjects:

(1) Respect for Persons,
(2) Beneficence and
(3) Justice.

DRS assures that all human subjects research will comply with the terms of its Federalwide Assurance (FWA).

Section II. Activities that Require HRRC Approval (45 CFR §46.102) and Types of HRRC Review and Approval

A. Definitions

i. **Research** means "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

ii. **Human subject** means "a living individual about whom an investigator (whether professional or student) conducting research obtains:
a. data through intervention or interaction with the individual, or
b. identifiable private information."

For the purposes of this policy and procedures document, the term "subject" means any and all subjects and/or participants involved in the research project.

iii. **Client,** for the purposes of this policy and procedures document, means any and all clients and/or consumers of services provided by DRS.

iv. **Intervention** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. **Interaction** includes communication or interpersonal contact between investigator and subject.

v. **Private information** includes 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, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) to constitute research involving human subjects.

The research project must meet both of the above definitions (i.e., research and human subject). If it does not, then it does not need to be submitted to the HRRC. Questions as to whether or not activities constitute human subjects research may be directed to the Chairperson or the Administrator of the DRS HRRC. (See Appendix A of this document for the research decision tree.)

B. Types of HRRC Review and Approval

There are three types of reviews: Exempt, Expedited and Full Committee. All applications for proposed research projects are assigned to a Full Committee review unless they meet the criteria for Exempt or Expedited Review. All research projects involving the use of investigational devices will be reviewed by the Full Committee.

1. Exempt Review 45 CFR §46.101(b)

    1. What Exempt Means: "Exempt" review as used in this document means exempt from the requirements set forth in Regulations for the Protection of Human Subjects (Title 45 Part 46 of the Code of Federal Regulations), such as the requirement for a written informed consent document. A determination of exempt can only be made by the HRRC, and investigators must submit an Exempt Review application. (See Appendix B for explanations and decision trees for the three types of HRRC reviews.)

    2. What Exempt Does Not Mean: "Exempt" does not mean that the research activity is exempt from the laws of the Commonwealth of Virginia, and it does not mean that the research need not conform to the canons of sound research ethics.

    3. Notes about Exempt Review:

1. If a consent form is used, the research project cannot qualify as exempt.
2. Any research in which the subjects are filmed or videotaped cannot qualify as exempt and must undergo Expedited or Full Committee Review.

3. Focus group research projects are not exempt.
    Children can be subjects of exempt research unless: a) it involves surveys or interviews; or b) it comes under the provisions of exemption categories 5 or 6. (See Appendix B)

4. Expedited Review 45 CFR §46.110

1. *What Expedited Means:* Research activities that (a) present no more than minimal risk to human subjects, ***and*** (b) involve only procedures listed in one or more of the nine Expedited Review categories (Appendix B).

2. General criteria for determining when to use Expedited Review:

1. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

2. The categories in this list apply regardless of the age of subjects, except as noted.

3. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

4. The expedited review procedure may not be used for classified research involving human subjects.

5. The HRRC and researchers are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the HRRC.

6. Categories one (1) through seven (7) for expedited reviews (see Appendix B) pertain to both initial and continuing HRRC review.

7. The DRS Commissioner may restrict, suspend, terminate, or choose not to authorize the HRRC's use of the expedited review procedure. (§46.110(d))

8. Full Committee Review

   If the research project does not meet the criteria for exempt or expedited review, then it must be submitted for Full Committee review. Full Committee review and approval is conducted at convened meetings of the HRRC in which a quorum of members is present.

Section III. Principal Investigator Responsibilities

A. General Responsibilities

The Principal Investigator (PI) is ultimately responsible for the safety and welfare of research subjects and the conduct of the research project. The PI must:

1. ensure that all research personnel (employees, co-investigators, research project coordinators or students) have been adequately trained to carry out their responsibilities,
2. report all research project violations and subject complaints to the HRRC,
3. report research project closures,
4. obtain HRRC approval prior to making non-emergency changes or revisions to the research project,
5. provide progress reports at the request of the HRRC (at least annually),
6. report promptly to the HRRC all unanticipated problems or serious adverse events, and
7. submit application for continuing review and approval 60 days before current approval expires.

B. Letter of Agreement to Participate in the Proposed Research Project

For research projects that involve DRS facilities, clients and/or employees, the PI must obtain a letter of agreement from DRS. This agreement is separate from the HRRC process and approval, and must be obtained and submitted with the DRS HRRC application. The HRRC application will be considered incomplete without this letter of agreement. PIs are encouraged to contact the HRRC Administrator or HRRC Chairperson if they need assistance in facilitating the process of obtaining division level and commissioner level agreements. The DRS Commissioner has ultimate approval authority regarding agency participation in research projects.

C. Initial Review Submissions

All initial review submissions (new applications) for HRRC review are screened by the HRRC Administrator for complete documentation. The Application Form A for new research projects is available through the HRRC website. Please submit one signed copy **and** one electronic copy of all application materials. A complete submission for HRRC initial review includes:

1. DRS HRRC Application Form A
2. Research Project Approval Letter from another IRB to include the full application as submitted to the approving IRB (if applicable)

3. Principal Investigator's Request for Exempt Review (Supplement 1) or Principal Investigator's Request for Expedited Review (Supplement 2), (if applicable)
4. Informed Consent form(s), Assent form(s) (if applicable)
5. All recruitment materials (if applicable)
6. Photograph, video and/or audio recording permission form (if applicable)
7. Complete grant/research project application as submitted to funding source (if applicable)
8. Letter of Agreement to participate in the research project from the DRS division(s) or WWRC that will be involved in the research project (if applicable)
9. Each survey, interview questions, tests and/or other tools/instruments used for the research project (if applicable)
10. Investigator(s)/Research Project Coordinator Proof of Training in federal requirements for Human Research Protections
11. A list of all fields/elements that will be included in the data set OR the original instrument from which the data were obtained (if an archival data set is being used)
12. Other materials specific to the proposed research project (e.g., documentation related to cooperative research projects, individual investigator agreement(s), etc. (if applicable).
13. Complete Conflict of Interest Disclosure Statement, Form H

If the application is incomplete or otherwise not fully prepared for review, the HRRC Administrator or HRRC Chairperson will contact the investigator by phone or e-mail requesting clarification, additional information or revisions to document(s) prior to review by the HRRC.

D. Steps for Filing an Initial HRRC Application

1. Exempt Review Procedures for Investigators

   If the investigator thinks that the research project is eligible for an Exempt Review, in addition to the Application (Form A), submit Supplement 1 form to the HRRC for final determination of the appropriate research category and/or approval. Investigators must have an approval letter from the HRRC Chairperson ***before*** beginning any research activities.

2. Expedited or Full Committee Review Procedures for Investigators

   The application process is the same for both Expedited and Full Committee Review. However, if the investigator thinks that the research project is eligible for Expedited Review, submit Supplement 2 form in addition to Application Form A. The HRRC Administrator screens all applications to determine completeness and to assign the application to either Expedited or Full Committee Review. The Administrator then either conducts the Expedited

Review or schedules a review by the Full Committee. Investigators must have a written approval letter from the HRRC ***before*** enrolling subjects in the research project. All consent forms, letters, and recruitment ads to be used must have the HRRC approval stamp before they can be used in the research project. The approval is valid for a maximum time period of one year. If not re-approved by the anniversary date, the investigator must close the research project. Note that approval of an addendum ***does not*** constitute re-approval for another year. No consent documents (consent forms/assent forms/cover letters/ads) may be used after the expiration date stamped on the form.

E. The Informed Consent Process

The first step in the informed consent process is detailing the specifics of the research project that are important to communicate to subjects and to the HRRC. (Please refer to Appendix C of this document for the required contents of the informed consent document.) Remember that obtaining subject consent is an on-going process. Potential human subjects must understand the nature of the research project and the risks and benefits involved if they are to make an informed decision about their participation in the research project.

The details should be presented in simple language by someone who is knowledgeable about both the research project and informed consent. This process requires a "consent document" that explains the nature of the research and any risks and benefits to prospective human subjects. A copy of the consent document is reviewed and approved by the HRRC ***before*** it is presented to prospective human subjects. 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 research project. The consent document is only a confirmation of the consent process.

Informed consent involves educating prospective subjects, not merely disclosing information. Providing information is part of the process. Discussions with prospective subjects should take place with sufficient time for them to consider participation. Approaching them on the same day the research project would take place may not be sufficient. Prospective subjects may need time to think about their decision or to discuss their involvement with family, friends, or individuals. For best results, prospective subjects should be approached when they are willing to listen, and are open and ready to consider consenting. The process of obtaining consent should include time for both discussion and reflection, as shown in the following steps:

1. Obtain HRRC approval of the consent document.
2. Present the prospective subject with the consent document.
3. Read through the document together, taking time to explain significant or difficult points about the research or participation. Answer any questions. Be certain to discuss risks, benefits, and alternative therapies in addition to purposes and procedures.
4. Give the prospective subjects a copy of the consent document.

5. Allow the prospective subject time to take the document home and discuss participation, if desired, with family or friends.
6. Conduct follow-up conversations with the prospective subjects and ask open-ended questions about the nature of the research project and participation to make certain he or she understands correctly.
7. If the prospective subject is willing to volunteer, have that individual or her/his legally authorized representative sign the consent document.
8. If the prospective subject is a minor, obtain assent from the minor and parental consent.
9. The witness shall also sign the consent and/or assent forms. The PI shall ensure that the witness is not a member of the research staff.

F. Readability of the Consent Document

Readability of the consent document is an important component of the process. The consent document information should be presented in non-technical terms and at a reading level that the potential subjects/audience can understand. If the document is not understandable, a claim could be made that the prospective subject did not understand what was signed. The consent document must be made readable but without compromising the content. When the consent document is completed, ask a lay person to read and explain it. A reader who has no association with the research project can often help to identify difficult or confusing areas in the document.

a. Direct it at an appropriate reading level based on cognitive ability and/or education level of likely subjects.
b. Use simple, straightforward sentences.
c. Use commonly recognizable terms and measurement amounts.
d. Avoid the use of jargon or technical language, and explain terms that may not be easily understood.

G. Assessing Prospective Subjects' Understanding of the Consent Document

It is the responsibility of the PI to ensure that prospective subjects understand the extent of their role in the research project. Read through the consent document with them and discuss participation prior to their involvement in the research project. During these discussions, the PI 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 "how would you describe." A few of the questions to ask potential subjects are:

a. Could you describe in your own words the purpose of the research project?
b. What more would you like to know?
c. Would you please explain to me what you think we're going to ask you to do?
d. What are your concerns?

However, the idea is not to quiz prospective subjects. Foster an open exchange of information and encourage them to ask questions. Remind them to continue to ask questions as they occur during their participation. Their willingness to be proactive and ask questions does not release the investigator from the responsibility to provide the necessary information on which the subjects make their decisions.

H. Selecting Research Project Subjects

1. Counselor/healthcare provider/case manager/client relationships between the investigator and prospective subjects should be avoided, when possible, to eliminate any power-based coercion. Clients can say “no” to someone they do not expect to see in the future, but it is very difficult for them to say “no” when they rely on someone for on-going care. Prospective research subjects often depend on the counselor, healthcare provider, or case manager to make recommendations, and then they defer to the counselor/healthcare provider/case manager’s professional knowledge and judgment. They may not read the consent document fully because the counselor/healthcare provider/case manager has already explained the procedure orally, and they consider this professional the primary source for information. There is a need to clearly distinguish the ongoing professional relationship from involvement in the research project and to exercise caution that the professional's influence does not dictate the subject's consent decision.

2. In justifying using children in the research project, the PI must document the specific benefits the child will receive. A parent or guardian must act as the proxy for the child and complete a parental consent document. Children also need to give their "assent." Assent is the affirmative agreement to participate in the research project if the child is able to comprehend aspects of the research. The PI must develop a separate assent form. Tailor the assent document to a level appropriate for the ages of likely child subjects. Reasonable descriptions of discomfort should be included. Children cannot give consent to research that entails risks that surpass the benefits.

I. Research Involving Non-English Speaking Prospective Subjects

Prospective subjects cannot be excluded based on language barriers. If the prospective subject pool includes individuals who do not speak English, the PI must obtain HRRC approval of translated consent document(s) in the native language(s) of each prospective subject prior to enrolling such subjects. In addition, the PI must arrange for a qualified interpreter to translate an oral explanation of the research project and translate any questions that prospective subjects may ask.

When the investigator anticipates enrolling non-English speaking subjects, the HRRC reviews and approves a translated version of the Informed Consent Document. The

credentials of the person who did the translation must be provided to the HRRC. It is the responsibility of the PI to anticipate non-English speaking subjects and to make every effort to ensure legally effective consent if such subjects are enrolled in the research project.

Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective. The HRRC must receive a translated consent document (s) (with the qualifications of the translator) following approval of the original English version of the consent form, for review and approval prior to enrolling non-English speaking subjects. The PI must provide the translated consent document(s) in a timely manner to preclude the possibility that subject enrollment closes before the HRRC approval process can be completed. Following HRRC approval, the prospective subject(s) must be provided with a copy of the translated Informed Consent Document for signature.

If one or more prospective subject (s) is/are deaf or hard of hearing, “qualified interpreter” (*Code of Virginia* (§51.5-113) services must be provided. The PI must accommodate the prospective subject’s desired communication method(s).

J. Subject Compensation

Compensation for participation in research may not be offered to the subject as a means of coercive persuasion. Rather, it should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Accordingly, compensation may not be withheld contingent on the subject's completion of the research project. In most cases involving continued participation, compensation should be given on a reasonable prorated basis to avoid the impression that the investigator is coercing the subject to continue in a research project or is punishing the subject for non-compliance.

K. Continuing Review

The PI shall submit continuing review applications (Form B) as specified by the HRRC in the initial research project approval letter. The purpose of continuing review is to analyze a research project and to determine if the anticipated risks and benefits are reflected in the actual experience of the subjects. It is also designed to make certain that the safeguards that were in place at the original approval phase are indeed adequate to ensure the safety of the subjects. The initial HRRC approval is based on the researcher’s best estimate of the anticipated risks and benefits to the subjects. It is only after research has begun that the real risk is established and the actual risk/benefit ratio can be calculated. Researchers shall stay involved in continuous re-evaluation of a research project since risks and benefits are always better understood after the research has begun.

The continuing review process involves the completion of the Continuing Review Form B. The investigator submits periodic reports as specified by the HRRC in the initial research project approval letter. There must also be "ongoing monitoring" that the researcher

performs. This is intended to alert investigators to changes in the research project that may affect the subject's decision to continue involvement in the research project. The responsibility of ongoing monitoring is just as important as continuing review by the HRRC. Both types of review are an ongoing process and not a one-time step. Procedures need to be established for the continuous monitoring of the research activity.

1. **Unanticipated Developments** mean the development of new findings that may affect the balance of risks and benefits, including any unanticipated risks or benefits. For example, are the risks and benefits the same as when they were first established? If not, have the proper steps been taken to reduce the occurrence of risks and increase the occurrence of benefits?

   Another point to consider is the development of unexpected findings. Unexpected results can affect the research project itself. The PI is responsible for informing the HRRC of unexpected findings that can affect the risk/benefit ratio. In addition, new knowledge attributable to other research projects can also affect the risk/benefit balance. These instances raise important questions for subjects that should be addressed during a continuous monitoring process. Establishment of a system to monitor research project feedback will alert investigators to unexpected findings that will need to be corrected or controlled. New findings, new knowledge, and adverse effects may need to be communicated to the subjects to determine whether their effects will change the subjects' willingness to participate. Consideration should be given to whether or not the findings need to be shared with past subjects. Strategies for discussing this with subjects should be developed.

2. **Adverse Events** mean any unexpected problems or events whose nature, severity, or frequency is not described accurately in the research project. It is the PI's responsibility to analyze the impact of an adverse event. Is this an isolated event or is it more common? Does this event have severe consequences or is the outcome unaffected? What is the appropriate ethical action to be taken? Incidents where subjects have been seriously harmed should be reported to the HRRC immediately. The HRRC should always be informed of any problems or accidents in the research project. The death of a subject, whether related to the research project or not, should also be reported to the HRRC immediately.

3. **Consent Document Revisions**: Research project subjects need to be informed of any new and important information that might affect their willingness to participate. If new information, knowledge, or an adverse event has been discovered, it should be communicated to the subjects. This may require a revised consent document. New information will require that the investigator evaluate the facts to decide on a revised consent document for future subjects as well as what information should be given to former or current subjects. Unexpected complications, adverse events, or breaches in confidentiality all signify developments that may require a revised consent form. Consult the HRRC to establish if a revised document is required. All revisions to a consent

document must receive HRRC approval prior to presenting the document to subjects**.**

L. Inquiries/Concerns Addressed to Investigators

The PI must provide an environment that welcomes inquiries, comments, and concerns from human research subjects, the community, and others. At the time of continuing review, the HRRC will request a summary of all inquiries and/or concerns.
The following guidance is provided:

a. All inquiries and/or concerns presented by human research subjects must be documented as part of the research project file (Report of Inquires, Comments, Concerns Form C), addressed using all reasonable measures, and presented to the HRRC.
b. Any issue raised must be heard as a valid concern and addressed/researched by the investigator and fully documented in writing. A valid, efficient, and careful inquiry is always warranted.
c. Every effort must be made to ensure that the matter is addressed or brought to the attention of the HRRC (if unable to address/resolve or additional risk might be posed). The Principal Investigator should reinforce to all persons who raise concerns or inquire about human subject protections that reports and inquiries can also be made to the DRS Commissioner.
d. Research subjects who raise an issue about their safety or unwillingness to participate in further research must be reminded of their right to report their concerns and discontinue their involvement in the research, without penalty.
e. For concerns regarding potential non-compliance with HRRC approval, federal, state, or local laws, or other serious concerns, investigators must immediately report the issue to the HRRC and respond verbally and in writing.

Section IV. Training

A. Investigators and key research project personnel must have completed training on protection of human research subjects before submitting an application for HRRC review and approval. In addition, if the research involves medical procedures, investigators and key research project personnel must also complete training in bioethics. Proof of training must be included with the application for research approval.

B. It is the responsibility of the DRS Policy and Planning Director to plan for and implement educational and training programs for human subjects protections for the HRRC and for DRS employees who propose to conduct human subjects research. DRS employees and contract staff must complete the DRS HRRC on-line training prior to engaging in human subjects research.

Section V. The Human Research Review Committee (HRRC)

A. HRRC Mission and Purpose

The mission and purpose of the DRS HRRC is to assure that the rights and welfare of the humans who volunteer to participate in research are adequately protected. To achieve this, the HRRC advises investigators in design of research projects in a manner to minimize potential harm to human volunteers, reviews all planned research involving human subjects prior to initiation of the research, approves research that meets established criteria for protection of human subjects, and monitors approved research to ascertain that human subjects are indeed protected.

The HRRC also informs and assists DRS and its researchers on ethical and procedural issues related to the use of research volunteers to facilitate compliance with relevant regulations of the United States Government and to provide a framework suitable for continued support by government agencies for research involving human subjects at DRS and WWRC.

Primary responsibility for assuring that the rights and welfare of the individuals involved are protected continues to rest with the Principal Investigator(s) conducting the research. Others engaged in the conduct of the research share this responsibility. Supervisors of employees who propose to conduct research have an obligation to consider carefully whether those individuals are qualified to safeguard adequately the rights and welfare of prospective research volunteers.

In fulfillment of its mission and purpose, the HRRC exercises the authority to protect all humans who volunteer to participate in research where activities are involved that meet the definition of ***'human subjects'*** and ***'research'*** (both exempt and nonexempt), where one or more of the following apply:

a. The research is sponsored by the institution, or

b. The research is conducted by or under the direction of any employee or agent of the institution in connection with his or her institutional responsibilities, or

c. The research is conducted by or under the direction of any employee or agent of the institution using any property or facility of the institution or

d. The research involves the use of the institution's non-public information to identify or contact human research subjects or prospective subjects.

B. HRRC Membership (45 CFR §46.107)

a. The HRRC shall have at least five members and all members must be appointed by the DRS Commissioner. Members shall have varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The HRRC shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the HRRC shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The HRRC shall, therefore, include persons knowledgeable in these areas. If the HRRC regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or persons with disabilities, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

b. Every nondiscriminatory effort will be made to ensure that the HRRC does not consist entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the HRRC on the basis of gender. The HRRC may not consist entirely of members of one profession.

c. The HRRC shall include at least one member whose primary concern is in scientific areas and at least one member whose primary concern is in nonscientific areas.

d. The HRRC shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

e. The HRRC may not have a member participate in the HRRC's initial or continuing review of any research project in which the member has a conflicting interest, except to provide information requested by the HRRC.

f. At its discretion, the HRRC may invite scientists or non-scientists from within or outside DRS, who have special expertise, to function as consultants and ad hoc reviewers of a research project application. These individuals have access to all documents submitted to the HRRC relevant to the specific research project under review, may participate at the deliberations and make recommendations on the research project, but may not vote.

g. Non-voting members of the Committee are not included in determining or establishing a quorum at the meetings. HRRC meeting minutes reflect the presence of non-voting members.

h. Term of membership commences with the date of the appointment letter and may be unlimited.

i. Officers shall include the Chairperson and the Human Protections Administrator. (See Appendix E of this document for responsibilities.)

C. HRRC Functions and Operations (45 CFR §46.108)

1. Within 45 days of receiving a complete application, the HRRC must complete its review.

1. The HRRC Administrator will screen all applications for completeness.

2. Under an *Expedited Review* procedure, the review may be carried out by the HRRC Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the HRRC. In reviewing the research, the reviewers may exercise all of the authorities of the HRRC except that the reviewers may not disapprove the research. A research activity may be disapproved only after full Committee review. (45 CFR 46.110)

3. When an Expedited Review procedure is used, the HRRC Chairperson shall advise members during the next meeting of the Full Committee of research projects that have been approved since the last meeting of the Full Committee. The DRS Commissioner may restrict, suspend, terminate, or choose not to authorize the HRRC's use of the Expedited Review procedure.

1. Meetings

The HRRC shall:

1. Meet at least once per month (meetings will be held the first Monday of the month at 10:00 a.m.). Individual meetings may be cancelled by the Chairperson due to (a) insufficient applications requiring Full Committee review, (b) inability to secure a quorum for attendance, or (c) other reasons (such as inclement weather) that make a scheduled meeting unnecessary or otherwise inappropriate. In the event of a State holiday, the Committee will meet the second Monday of that month.

2. Follow written procedures.

3. Except when an expedited review procedure is used, review proposed research at convened meetings at which a majority of the members of the HRRC is present. In order for the research project to be approved, it shall receive the approval of a majority of those members present at the meeting.

4. Agendas will be included in the official record to assist with the location of a specific item or action in the minutes of the meeting. The agenda will identify each research project by HRRC control number, Principal Investigator name, and title of research project. A copy of the final agenda may be placed with the minutes in order to assist in the location of items within the minutes. The agenda is not considered a required document as per regulation, but rather a tool for organizing meetings and preparation of minutes.

D. Order/Quorum

1. The HRRC meeting is called to order by the Chairperson when a quorum of members is in attendance. The meeting ends or is suspended whenever a quorum of members is no longer present for deliberations. A quorum is required to review research and vote.

2. A quorum requires a majority of the voting members. Alternates with appropriate backgrounds may serve in the place of regular members and count toward quorum if materials were presented to them in advance of the meeting.

3. At the discretion of the Chairperson and/or primary reviewer, the PI may be invited to attend the meeting for the purpose of additional clarification or discussion. The investigator(s) is(are) required to leave the meeting for subsequent discussion and voting.

4. At the discretion of the Chairperson, voting may be by written ballot or show of hands. The official meeting minutes record, without individual identification, the number of votes to approve, disapprove, table, or abstain. In the event a member of the HRRC elects to abstain, the minutes record the abstention (and the identity of the individual who did not vote).

5. Conditions of Quorum.
   The following conditions apply to votes and achieving a quorum.

   <u>Members Present</u>:
   At least one scientific and one non-scientific member must be present at all meetings in which research activities are being considered. It is recommended that at least one physician be present when research activities involving drugs, biologics or medical devices are being considered.

Voting Conditions and Process:
A vote must follow a motion proposed by a voting member of the HRRC. A second member of the HRRC must second the motion. The Chairperson will call for a vote if no further discussion is raised. Only members and alternates may vote. No one may vote who has a conflict of interest with respect to the research under consideration. A favorable vote of the majority of the members/alternates present is required to approve research activities. Votes by proxy are not allowed.

E. Guest Attendance Policy for HRRC Meetings

Persons may be permitted to observe HRRC meetings as guests under the following conditions:

i. Guest attendance is at the discretion of the Chairperson.
ii. Guests may be asked to leave at any time.
iii. Guests must not be in attendance during the review of research in which they serve as PI or co-investigator.
iv. Guests may be asked to sign an HRRC Confidentiality Certificate Form G.
v. Guests must reveal any conflicts of interest prior to attendance and/or must excuse themselves if a potential conflict reveals itself.
vi. Guests must sign in and may be asked to document the purpose of their visit.

F. Teleconferencing

If necessary, HRRC meetings may be conducted via telephone conference call provided each participating member has received all pertinent material prior to the meeting, and can actively and equally participate in the discussion of all research projects. Minutes of such meetings will clearly document that these two conditions have been satisfied in addition to the usual regulatory requirements.

G. Committee Motions

During a convened meeting of the HRRC, any member may make a motion using one of the following procedures:

1. Approved
   Defined as approved as is, with no further action requested or required.

2. Approved on condition that required scripted changes are made
   (NOT TO BE USED AT TIME OF CONTINUING REVIEW) Defined as approved on condition that scripted changes are made to documents and returned for verification via expedited review – not returned to the Full HRRC.

3. Tabled

   (NOT TO BE USED AT TIME OF CONTINUING REVIEW) Defined as the requirement that additional information must be provided and/or more than scripted changes to documents must be made and returned to the Full HRRC for further review.

4. Disapproved

   Defined as not approved by the HRRC for reasons specified in a Letter of Disapproval.

5. Suspended

   Defined as the suspension of approval of the research project for any reason the HRRC deems appropriate.

6. Termination

   Defined as the termination of approval of the research project for any reason the HRRC deems appropriate.

7. Approved/Short Term-a

   (CONTINUING REVIEW USE ONLY) Allow for continuing review to proceed to approval where SCRIPTED CHANGES have been requested by the HRRC, a delay in implementing the changes will not place subjects at increased risk of harm, **and** the HRRC will not have time to approve the changes before HRRC approval expires. All scripted changes to documents must be made and returned for verification via expedited review as detailed in the approval letter. Under this motion to approve, expiration of approval is on the last day of the second month from the HRRC meeting (e.g. HRRC meeting date is December 6, 2005, and approval will expire February 28, 2006). Once the supplemental information/modifications (scripted only) have been made and are verified by expedited review, the continuing review cycle will be reset (not to exceed one year from full committer continuing review). The HRRC is using this process at the time of continuing review in order to ensure that scripted changes requested by HRRC members are given valid and thorough consideration, and not overlooked simply due to concerns about the impact of an interruption in HRRC approval.

8. Approved/Short Term-b

   (CONTINUING REVIEW USE ONLY) Allow for continuing review to proceed to approval where SUPPLEMENTAL INFORMATION OR NON-SCRIPTED CHANGES have been requested by the HRRC, a delay in reviewing the information or implementing the changes will not place subjects at increased risk of harm, **and** the HRRC will not have time to approve the changes before HRRC approval expires. The HRRC is using this process at the time of continuing review in order to ensure that

supplemental information or non-scripted changes requested by HRRC members are given valid and thorough consideration, and not overlooked.

H. Criteria for HRRC Approval of Research

In order to approve research covered by this policy, the HRRC shall determine that all of the following requirements are satisfied:

1. Risks to subjects are minimized:
   a. by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
   b. whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the HRRC should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The HRRC should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of subjects is equitable. In making this assessment, the HRRC should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, persons with mental disabilities, or economically or educationally disadvantaged persons.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Informed Consent section of this document.

5. Informed consent will be appropriately documented, in accordance with, and to the extent required by the Informed Consent section of this document.

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with

mental disabilities, or economically or educationally disadvantaged persons, additional safeguards have been included in the research project to protect the rights and welfare of these subjects.

I. HRRC Review of Research (45 CFR §46.109)

The HRRC shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

1. The HRRC may require that information, in addition to that specifically mentioned in the Informed Consent section of this document be given to the subjects when in the HRRC's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

2. The HRRC shall require documentation of informed consent or may waive documentation in accordance with the Informed Consent section of this document.

3. The HRRC shall notify investigators in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure HRRC approval of the research activity. If the HRRC decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

4. The HRRC shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

5. The HRRC considers certain groups of human subjects to be particularly vulnerable in a research setting. The HRRC considers additional protections for research activities involving children, pregnant females, and/or individuals with cognitive impairments. In reviewing these research projects, the HRRC ascertains that the inclusion of the vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to each population. The HRRC considers for approval research projects involving vulnerable populations if one of the following conditions is met:

    1. the research does not involve more than minimal risk to the subject;
    2. the research is likely to benefit the subject directly, even if the risks are considered to be more than minimal; or
    3. the research involves greater than minimal risk with no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition.

Requests for approval of any research that exposes vulnerable populations to risks that do not meet one of the above criteria must be submitted to the United States Secretary of Health and Human Services for review and approval.

J. Continuing Review

1. Substantive and Meaningful Continuing Review

   Continuing review of research must be substantive and meaningful. The convened HRRC, with record, votes on each continuing review unless the research is otherwise appropriate for expedited review. Furthermore, Section V, Subpart H of this manual sets forth the criteria that must be satisfied in order for the HRRC to approve research. These criteria include, among other things, determinations by the HRRC regarding risks, potential benefits, informed consent, and safeguards for human subjects. The HRRC must ensure that these criteria are satisfied at the time of both initial and continuing review. The procedures for continuing review by the convened HRRC may include a primary reviewer system. In conducting continuing review of research not eligible for expedited review, all HRRC members should at least receive and review a research project summary and a status report on the progress of the research, including:

   a) The number of subjects accrued;
   b) A summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last HRRC review;
   c) A summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review;
   d) Any relevant multi-center trial reports;
   e) Any new advertisement or changes to advertisement(s)
   f) Any other relevant information, especially information about risks associated with the research; and
   g) A copy of the current informed consent document and any newly proposed consent document.

   At least one member of the HRRC (i.e., a primary reviewer) also should receive a copy of the complete research project including any modifications previously approved by the HRRC. Furthermore, upon request, any HRRC member also should have access to the complete HRRC research project file and relevant HRRC minutes prior to or during the convened HRRC meeting.

   When reviewing the current informed consent document(s), the HRRC should ensure the following:

1. The currently approved or proposed consent document is still accurate and complete;

2. Any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with the Informed Consent section of this document.

   Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the HRRC, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

   Furthermore, the minutes of HRRC meetings should document separate deliberations, actions, and votes for each research project undergoing continuing review by the convened HRRC. When reviewing research under an expedited review procedure, the HRRC Chairperson (or designated HRRC member(s)) should receive and review all of the above-referenced documentation, including the complete research project.

2. Expedited Review Procedures for Continuing Review (45 CFR 46.110(b)(1))

   Expedited review procedures are limited to specific research categories published in the Federal Register at 63 FR 60364-60367 and made available in Appendix B of this document and to the review of minor changes in previously approved research during the period (of one year or less) for which approval is authorized. The HRRC is permitted to use expedited review for the continuing review of research that involves solely one or more of the activities published at 63 FR 60364-60367.

   Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by Expedited Review Categories (8) and (9) (see below). It is also possible that research activities that previously qualified for expedited review have changed or will change, such that expedited review would no longer be permitted for continuing review.

1. Expedited Review Category (8):

   An expedited review procedure may be used for the continuing review of research previously approved by the convened HRRC where:

   1. the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; OR
   2. no subjects have been enrolled and no additional risks have been identified; OR
   3. the remaining research activities are limited to data analysis.

Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened HRRC may undergo subsequent continuing review by the expedited review procedure.
For a multi-center research project, an expedited review procedure may be used by the HRRC at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the HRRC at a particular site has identified any additional risks from any site or other relevant source.

2. Expedited Review Category (9):

An expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) (see Appendix B) do not apply but the HRRC has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened HRRC.

3. Continuing Review Date Determination (45 CFR 46.108(b) and 109(e))

    1. Except when an expedited review procedure is used, the HRRC must review proposed research at convened meetings at which a majority of the members of the HRRC are present, including at least one member whose primary concerns are in nonscientific areas; and

    2. The HRRC must conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once per year. The HRRC should decide the frequency of continuing review for each research project necessary to ensure the continued protection of the rights and welfare of research subjects.

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

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

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

Scenario 3: The HRRC reviews a research project at a convened meeting on October 1, 2002, and has serious concerns or lacks significant information that requires HRRC review of the research project at subsequent convened meetings on October 15 and October 29, 2002. At their October 29, 2002 meeting, the HRRC completes its review and approves the research project. Continuing review must occur within 1 year of the date of the convened meeting at which the HRRC reviewed and approved the research project, that is, by October 29, 2003.

Scenario 4: The HRRC reviews a research project that has been approved by another institution's IRB and that institution has a currently active FWA. The HRRC continuing review date will be the same as the review date established by the other institution.

4. Expedited Review

For a research project approved under expedited review, continuing review must occur within 1 year of the date the HRRC Chairperson or HRRC member(s) designated by the Chairperson gives final approval to the research project. Review of a change in a research project ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full research project, not simply a change to it. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of HRRC approval. Therefore, continuing review and re-approval of research must occur on or before the date when HRRC approval expires.

The logistical advantages of keeping the HRRC approval period constant from year to year throughout the life of each research project is recognized. When continuing review occurs annually and the HRRC performs continuing review within 30 days before the HRRC approval period expires, the HRRC may retain the anniversary date as the date by which the continuing review must occur. This would be, for example, October 1, 2003, in the above Scenarios 1 and 2, and October 29, 2003, in Scenario 3, even if the continuing reviews took place up to 30 days prior to these dates.

5. Lapse in Continuing Review

The HRRC and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the HRRC or the HRRC has not reviewed and approved a research project by the continuing review date specified by the HRRC, the research must stop, unless the HRRC finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of HRRC approval.

When continuing review of a research project does not occur prior to the end of the approval period specified by the HRRC, HRRC approval expires automatically. Such expiration of HRRC approval does not need to be reported to OHRP as a suspension of HRRC approval under DHHS regulations.

K. General Requirements for Informed Consent (45 CFR §46.116)

Except as provided elsewhere in this policy and procedures document, no investigator may involve a human being as a subject in research covered by this policy and procedures document unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

a. Basic elements of informed consent.

Except as provided in paragraph 3 (Wavier or Alteration of Informed Consent) of this section, in seeking informed consent the following information shall be provided to each subject:

1. a statement that the project 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;
2. a description of any reasonably foreseeable risks or discomforts to the subject;
3. a description of any benefits to the subject or to others which may reasonably be expected from the research;
4. a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

5. a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. 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, if so, what they consist of, or where further information may be obtained;
7. an explanation of who to contact for answers to pertinent questions about the research and research subjects' rights, and who to contact in the event of a research-related injury to the subject; and
8. 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.

b. Additional elements of informed consent.

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

A. 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;
B. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
C. 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;
D. 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; and
E. The approximate number of subjects involved in the research project.

c. Wavier or Alteration of Informed Consent

The HRRC 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 HRRC finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state government officials and is designed to study, evaluate, or otherwise examine:

i. Public benefit or service programs;
ii. Procedures for obtaining benefits or services under those programs;

iii. Possible changes in or alternatives to those programs or procedures; or
iv. Possible changes in methods or levels of payment for benefits or services under those programs; and
v. The research could not practicably be carried out without the waiver or alteration. (45 CFR §46.116c) (See Appendix E for the decision tree to aid in determining if informed consent can be waived or consent elements altered.)

2. The HRRC may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

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; or
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.

d. In cases in which the documentation requirement is waived, the HRRC may require the investigator to provide subjects with a written statement regarding the research. (45 CFR §46. 117c)

e. The informed consent requirements in this policy are not intended to preempt any applicable Federal or State laws which require additional information to be disclosed in order for informed consent to be legally effective.

f. Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

L. Documentation of Informed Consent. (45 CFR §46.117)

Except as provided in Paragraph 3 of this section, informed consent shall be documented by the use of a written consent form approved by the HRRC and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

Except as provided in Paragraph 3 of this section, the consent form may be either of the following:

C. A written consent document that embodies the elements of informed consent required by the policy and procedures document. 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; or

D. A short form written consent document stating that the elements of informed consent required by policy and procedures document 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 HRRC 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 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.

The HRRC may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

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; 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.

In cases in which the documentation requirement is waived, the HRRC may require the investigator to provide subjects with a written statement regarding the research.

M. HRRC Records (45 CFR §46.115)

i. The HRRC shall prepare and maintain adequate documentation of HRRC activities, including the following:

Copies of all research project applications reviewed, scientific evaluations, if any, that accompany the research project applications, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
Minutes of HRRC meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the HRRC; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controversial issues and their resolution.
Records of continuing review activities.
Copies of all correspondence between the HRRC and the investigators.
A list of HRRC members in the same detail as described in §46.103(b)(3).
Written procedures for the HRRC in the same detail as described in §46.103(b)(4) and §46.103(b)(5).
Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

ii. The records required by this policy and procedures document shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the OHRP at reasonable times and in a reasonable manner.

N. HRRC Site Visits

Site visits will serve as the HRRC's proactive method of ensuring that investigators understand HRRC policies and procedures and to ensure the rights and welfare of the humans who have volunteered to participate in research projects are being protected. In addition, these visits are intended to nurture a productive partnership between the HRRC and research investigators.

During the initial review of an application and for each continuing review, the HRRC will determine whether it will schedule a site visit and designate the team that will conduct the visit. The topics covered during the site visit will be tailored to the research project and approved by the Full HRRC prior to the visit. Topics may include but are not limited to the following: compliance with the HRRC approved research project, conflict of interest, data and safety monitoring and the informed consent process. As part of the site visit, members of the HRRC may contact a random sample of human subjects who have consented to participate in the research project or may observe the consent process.

O. Conflict of Interest

Neither the sponsor, nor the investigator, or any individual involved in the conduct of the research activity under review will participate in the HRRC review or approval processes, except to provide information. No member may participate in the HRRC's initial or continuing review of any research project in which the member has a conflicting interest, except to provide information requested by the HRRC. It is the responsibility of all HRRC members to announce any potential conflict of interest regarding the discharging of duties as voting HRRC members. Members having a conflict of interest shall:

1. Announce the conflict and disqualify themselves from participation during review of that research project, except to provide information on request.

2. Leave the meeting during the discussion and the vote on any motion to approve or disapprove the research in question (Note: When a person with a conflict of interest leaves the room, he/she cannot be counted towards a quorum. If the quorum is lost, the research project will be tabled.).

P. Cooperative Research (45 CFR §46.114)

Cooperative research projects are those research projects covered by this policy and procedures document which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy and procedures document. With the approval of the Federal Department or Agency head, an institution participating in a cooperative research project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

The DRS Commissioner is the only person who can approve a request for the DRS HRRC to 'Defer' to an External IRB to serve as the IRB of record for the research project. The following information must be prepared in a written request (letter) submitted to the HRRC Chairperson:

Provide the name of the institution that would provide the IRB oversight for this research. Also list the institution's FWA (Federalwide Assurance) number and IRB Registration number(s).

Is the proposed activity conducted by or under the direction of a DRS employee? If YES, does the activity involve DRS facilities (e.g., WWRC, DRS offices, etc.)?

Does the proposed activity involve the use of DRS clients or employees (including non-public information, registries, administrative databases, etc.) for the purpose of research or in order to identify or contact human research subjects or prospective subjects?

Is the proposed activity funded fully or in part with funds administered by DRS?

Is the proposed activity funded fully or in part by an external sponsor through a grant, contract, or cooperative agreement? If YES, is DRS currently managing the external sponsorship of this activity? Was DRS the original recipient of the external sponsorship?

Q. Applications Lacking Definite Plans for Involvement of Human Subjects (45 CFR §46.118)

Certain types of applications for grants, cooperative agreements, or contracts are submitted to awarding federal departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application. These include activities such as institutional type grants when selection of specific research projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and research projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by the HRRC before an award may be made. However, except for research exempted or waived under §46.101 (b) or (i), no human subjects may be

involved in any research project supported by these awards until the research project has been reviewed and approved by the HRRC, as provided in this policy and procedures document, and certification submitted, by DRS, to the Federal Department or Agency that awarded the grant, cooperative agreement, or contact.

R. Research Undertaken Without the Intention of Involving Human Subjects (45 CFR §46.119)

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by the HRRC, as provided in this policy and procedures document, a certification submitted by DRS to the awarding Federal Department or Agency, and final approval given to the proposed change by the awarding Department or Agency.

S. Suspension or Termination of HRRC Approval of Research (45 CFR 46.113)

a. The HRRC shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the procedures as stated in the application as approved by the HRRC. Additionally, the HRRC shall suspend or terminate a research project when there has been an unexpected serious harm to a subject(s). Any suspension or termination of approval shall include a statement of the reasons for the HRRC's action and shall be reported promptly to the investigator and the appropriate institutional officials. Any suspension or termination as a result of serious harm to a subject(s) shall also be reported to the Federal Office for Human Subjects Protection.
b. All suspensions or terminations resulting from (1) potential or actual injury or any other unanticipated problems involving risks to subjects or others or (2) serious or continuing noncompliance are reported to the Office for Human Subjects Protection in accordance with the terms of the DRS FWA. (Note: Administrative suspensions/terminations resulting from incidental noncompliance (i.e., missed deadline) are NOT reported to OHRP unless determined to be serious or continuing noncompliance.)

Office for Human Research Protections	For Medical Devices
Department of Health and Human Services The Tower Building 1101 Wootton Parkway, Suite 200 Rockville, MD 20852 866-447-4777 240-453-6900 240-453-6909 fax **e-mail: ohrp@osophs.dhhs.gov**	Division of Bioresearch Monitoring (HFZ-310) Office of Compliance Center for Device and Radiological Health (CDRH) 2094 Gaither Road Rockville, MD 20850 Phone: 301-594-4718 Fax: 301-827-6748

Section VI. Additional Protections for Children Involved as Subjects in Research

A. Requirements for Permission by Parents or Guardians and for Assent by Children (§46.401 through §46.409)

Without a waiver of assent, assent must be obtained from all DRS clients who have not reached the age of 18. If the investigator does not believe assent is appropriate for some or all of the children eligible for the research project, the investigator must apply to the HRRC for a waiver of assent.

The regulations pertaining to assent require the HRRC to consider several factors and allow for several options. These protections for children are IN ADDITION to all informed consent requirements.

The HRRC (and the Principal Investigator, in planning the research) will consider:

Obtaining assent from the child as appropriate to the age, maturity, and psychological state of the child,

a. requiring both parents to give consent/permission when:

1. The research involves greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition; or
2. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (Note: BOTH parents are required to consent unless one is deceased, unknown, incompetent, or only one parent has legal responsibility for care and custody.)

The biggest challenge in writing assent forms is keeping the language and concepts appropriately simple. The target language level is a 4th grade reading level.

Although there are very formal requirements for the elements that must be present in a consent form, no such requirements exist for assents. This means that the investigator can propose assent content that he/she believes will best inform prospective subjects about the research project.

The HRRC Assent Template Form E offers suggested headings and content; however, the investigator is encouraged to delete or add content as appropriate to the project. The length of the assent form should be proportional to the complexity of the research project. For most minimal risk studies, much of the information in the template can be deleted.

The HRRC encourages the use of topic headings (those suggested in the template or others) with the belief that they improve readability. The sentences under each topic should be in a single paragraph.

The signature block only needs lines for the child to write his/her name and the person obtaining assent to sign his/her name. The person obtaining assent must be someone who is approved to obtain consent for the research project.

If the child is not able to read the assent form, and verbal assent is obtained using the content in the assent form, the person obtaining assent should place in the chart or research record a statement with the following content. *"I have discussed this research project with _____ using language which is understandable and appropriate. I believe I have fully informed him/her of the nature of the research project and its possible risks and benefits. I believe the participant understood this explanation and assented to participate in this project."*

B. Wards §46.409

The regulations state the following:

> (*a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:*
>
> > *(1) related to their status as wards; or*
> >
> > *(2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.*
>
> *(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.*

C. Emancipated Minors

Emancipated minors are consented as adults. In accordance with the *Code of Virginia*, Section, 16.1-333 an "emancipated minor" is a person 16 or 17 years of age who has a *court order* declaring him or her to be such based upon one or more of the following factors:

2. Legitimately married or divorced;
3. On active duty in a branch of the U.S. Armed Forces; or
4. Willingly living separate and apart from a parent or guardian with consent and acquiescence of parents or guardian and supporting him or herself and competently managing his or her own financial affairs.

Section VII. Definitions

A. *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (45 CFR 46.402(b) & 34 CFR 97.402(b))

B. *Assurance* means a document negotiated between an institution and the Department of Health and Human Services (DHHS) assuring that the institution conducting research supported by DHHS will comply with its regulations (45 CFR 46) for the protection of human subjects.

C. *Business Associate* means "a person who on behalf of DRS, but other than in the capacity of a member of the workforce: (1) performs or assists in the performance of a function or activity involving the use or disclosure of individually identifiable health information, including claims processing or administration, data analysis, processing or administration, utilization review, quality assurance, billing, benefit management, practice management, and re-pricing; or (2) provides legal, actuarial, accounting, consulting, data aggregation, management, administrative, accreditation, or financial services where the provision of the service involves the disclosure of individually identifiable health information." (45 CFR, Subpart A, 160.103)

D. *Children* are 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 (see definition of minors). (45 CFR 46.402(a) & 34 CFR 97.402(a))

E. *Code Set* means "any set of codes used for encoding data elements, such as tables of terms, medical concepts, medical diagnostic codes, or medical procedure codes."(Public Law 104-191, Section 1171(1))

F. *De-identified* refers to information that is not Individually Identifiable Health Information or Protected Health Information. To be considered de-identified, data must be free of the following:
    1. Names
    2. Geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes (an exception exists for the first three digits of a zip code meeting specific requirements)
    3. All elements of dates (except year) directly related to the individual; and all ages over 89 and all elements of dates (including year) indicative of such age; may aggregate over 90 into single category
    4. Telephone numbers
    5. Fax numbers
    6. Electronic mail addresses
    7. Social security numbers
    8. Medical record numbers
    9. Health plan beneficiary numbers
    10. Account numbers

11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code

G. *Department or Agency head* means the head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated. (45 CFR 46.102(a))
H. *Designated Record Set* means a group of records maintained by or for DRS that is "(i) the medical records and billing records about individuals maintained by or for a covered health care provider; (ii) the enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (iii) used, in whole or in part, by or for the covered entity to make decisions about individuals." For purposes of this definition, the term *record* means any item, collection, or grouping of information that includes protected health information and is maintained, collected, used or disseminated by or for DRS.
I. *Disclosure* means "the release, transfer, provision of access to, or divulgence in any manner of information outside the entity holding the information."
J. *Exculpatory* means "clearing of guilt or blame." (WordNet ® 2.0, © 2003 *Princeton University)*
K. *Existing Data* are constitutive of retrospective research. An item is considered to exist if it was previously collected for another purpose. Information is considered to be existing if it is already contained in a system of files or records, or a data bank at the time that the research is submitted to the HRRC. Data are not existing, (for regulatory purposes), if it is to be collected during the course of the research project. (DHHS guidance document)
L. *Guardian* means "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care." (45 CFR 46.402(e) & 34 CFR 97.402(e))
M. *HRRC* means an Institutional Review Board established in accord with and for the purposes expressed in this policy (45 CFR 46 §46.102(q)). Also see Human Research Review Committee (HRRC).
N. *HRRC approval* means the determination of the HRRC that the research has been reviewed and may be conducted at an institution within the constraints set forth by the HRRC and by other institutional and Federal requirements. (45 CFR 46 §46.102(h))
O. *Human Research Review Committee (HRRC)* means the DRS HRRC.
P. *Human subject* means "a living individual, about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." For purposes of these procedures, the term human participant is *practically equivalent* to human subject.
Q. *Hybrid entity* means "a single legal entity that is a covered entity and whose covered functions are not its primary functions."

R. *IRB* Each institution that conducts research subject to Federal Regulations for the Protection of Human Subjects is required to establish an Institutional Review Board (IRB) to review and approve research prior to its initiation and at appropriate intervals thereafter. A research project must be reviewed no less than once per year. The IRB's primary obligation is to exercise oversight of research to protect the rights and the well being of research subjects. The IRB is charged to: protect the autonomy of subjects; to minimize risks to subjects and maximize benefits to the subjects and/or to society as a whole; and to assure that the risks and benefits of research are equitably distributed across all segments of society. The IRB has additional responsibilities to protect vulnerable populations including human fetuses, prisoners, children, and the cognitively impaired. The IRB has responsibility to minimize physical, psychological or social risks to subjects, and to maximize benefits to the subjects and to society. The DRS IRB is called the Human Research Review Committee (HRRC).

S. *Individually Identifiable Health Information* means (also referred to as Protected Health Information) "information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (i) that identifies the individual; or (ii) with respect to which there is a reasonable basis to believe the information can be used to identify the individual." (Public Law 104-191, Section 1171(6))

T. *Institution* means all DRS divisions, programs, offices or other units to include the Woodrow Wilson Rehabilitation Center but does not include the Disability Determination Services (DDS) program.

U. *Interaction* includes "communication or interpersonal contact between investigator and subject.

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

W. *Legally authorized representative* means, in the following specified order of priority, (i) the parent or parents having custody of a prospective subject who is a minor, (ii) the agent appointed under an advance directive, as defined in §54.1-2982, executed by the prospective subject, provided the advance directive authorizes the agent to make decisions regarding the prospective subject's participation in human research, (iii) the legal guardian of a prospective subject, (iv) the spouse of the prospective subject, except where a suit for divorce has been filed and the divorce decree is not yet final, (v) an adult child of the prospective subject, (vi) a parent of the prospective subject when the subject is an adult, (vii) an adult brother or sister of the prospective subject or (viii) any person or judicial or other body authorized by law or regulation to consent on behalf of a prospective subject to such subject's participation in the particular human research. For the purposes of this chapter, any person authorized by law or regulation to consent on behalf of a prospective subject to such subject's participation in the particular human research shall include an attorney in fact appointed under a durable power of attorney, to the extent the power grants the authority to make such a decision. The attorney in fact shall not be employed by the person, institution, or agency

conducting the human research. No official or employee of the institution or agency conducting or authorizing the research shall be qualified to act as a legally authorized representative. (*Code of Virginia* §32.1-162.16)

X. *Minimal risk* means "the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (45 CFR 46 §46.102(i))

Y. *Minor* means "an individual who is less than 18 years of age." (Section 1-13.42 *Code of Virginia*) The federal regulations do not dictate an age at which assent should be sought from minors, but rather dictate that assent should be sought when, in the judgment of the HRRC, the minor is capable of providing it.

Z. *Non-therapeutic research* means "human research in which there is no reasonable expectation of direct benefit to the physical or mental condition of the participant."(Section 32.1-162.16 of the *Code of Virginia)* Note: Non-therapeutic research is prohibited unless the Committee determines that such research will not present greater than minimal risk to the subject.

AA. *Parent* means "a child's biological or adoptive parent." (45 CFR 46.402(d) & 34 CFR 97.402(d))

BB. *Permission* means "the agreement of parent(s) or guardian to the participation of their child or ward in research." (45 CFR 46.402(c) & 34 CFR 97.402(c))

CC. *Private information* means "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, a medical record). Private information must be individually identifiable (i.e., the identity of the subject 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 subjects." (45 CFR 46 §46.102(f))

DD. *Protected Health Information or PHI* (see Individually Identifiable Health Information). (Public Law 104-191, Section 1171(6))

EE. *Publicly Available information* is publicly available if any adult member of society can legally access it. For example, if the information can be found in a newspaper or magazine, in a public library, in publicly accessible data banks, in city directories or telephone books, on the internet (unless access is restricted), or in information published by federal agencies such as the Bureau of the Census or the National Center for Health Statistics. Information is not publicly available if access to it is restricted to certain individuals. Examples of information that is not public include: college registration records, education transcripts, medical records, personal files, individuals' credit card debts, private correspondence, personnel files, etc. Please note that if information such as credit card debt is not very secure, it is, nevertheless not intended to be available to any member of the public.

FF. *Qualified Interpreter* shall be one who holds at least one of the following credentials: (1) certification from any national organization whose certification process has been recognized by the Department for the Deaf and Hard-of-Hearing; or (2) a current screening level awarded by the Virginia Quality Assurance Screening Program

of the Department for the Deaf and Hard-of-Hearing; or (3) a screening level or recognized evaluation from any other state when (i) the credentials meet the minimum requirements of Virginia Quality Assurance Screening and (ii) the credentials are valid and current in the state issued.

GG. *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. (45 CFR 46, Section 46.102(d)) As defined in Section 32.1-162.16 of the *Code of Virginia,* research is "*a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to general knowledge."* Note that per the informal opinion of the Virginia Attorney General's Office, dated July 29, 2003, *"generalizable knowledge" and "generalized knowledge" are practically equivalent in meaning for the purposes of determining what activity constitutes human research. The Human Research Review Committee should therefore consider that both terms mean the same.* Note that activities that meet the above definition of research constitute research for purposes of these procedures, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

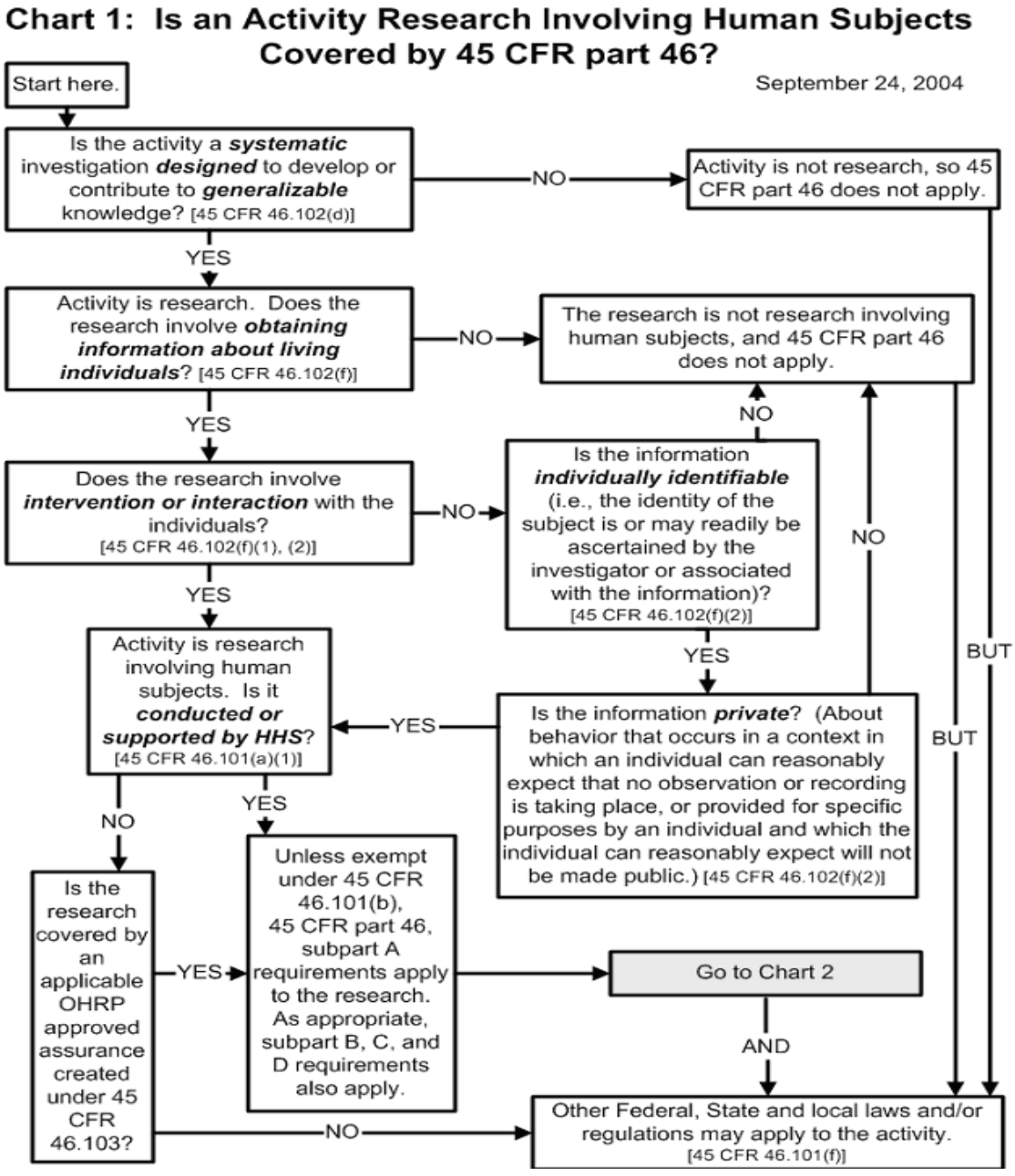
HH. *Research investigator* means "the person, whether professional or student, who conducts the research."

II. *Significant Financial Interest* means anything of monetary value, including but not limited to, salary or other payments for service (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights).

JJ. *Unanticipated Problem* is language utilized in 45 CFR 46 that encompasses complications in the research process that were unforeseen by the research project or informed consent form. Unanticipated problems, such as breaches in confidentiality or mortality of a subject, can occur in biomedical and social-behavioral research.

KK. *Use* means, with respect to individually identifiable health information, "the sharing, employment, application, utilization, examination, or analysis of such information within an entity that maintains such information."

Appendix A Decision Tree: Is an Activity Research Involving Human Subjects?



Source of Decision Trees in appendices:
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm

Appendix B Explanations and Decision Trees for the Three Types of HRRC Review and Approval

1. Exempt Review (45 CFR 46.101(b))

Certain categories of research involving human subjects qualify for exemption from federal regulations. DRS is authorized to determine whether research projects thought by the PI to be exempt from federal regulations actually qualify for exemption (45 CFR §46.101(b). Such determination is made on behalf of DRS by the HRRC. Only the HRRC has authority to make a determination that a research project is exempt from federal regulations. When the HRRC notifies a PI that a research project is Exempt, it also notifies the PI that the research project is approved for initiation or continuation.

In order to qualify for exemption, a research project must fall entirely within one or more of the six categories for exemption and it cannot place subjects at greater than minimal risk. If information obtained is recorded in such a manner that human subjects can be identified or if the research involves pregnant women, human fetuses, in vitro fertilization, or prisoners, then it does not qualify for exemption.

Additionally, any of the following three items means that the research project **does not** qualify for exemption**:**

1. a consent form is used,
4. any research project in which the subjects are filmed or videotaped, or
5. focus group research projects.

Unless otherwise required by the DRS Commissioner, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from the requirement to document informed consent. However, research investigators must submit an application for an exempt review to the HRRC. The HRRC retains the sole authority to grant an exemption.

Categories of Research That May Be Reviewed by the HRRC through an Exempt Review Procedure

Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
(ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph 2 above, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or
(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

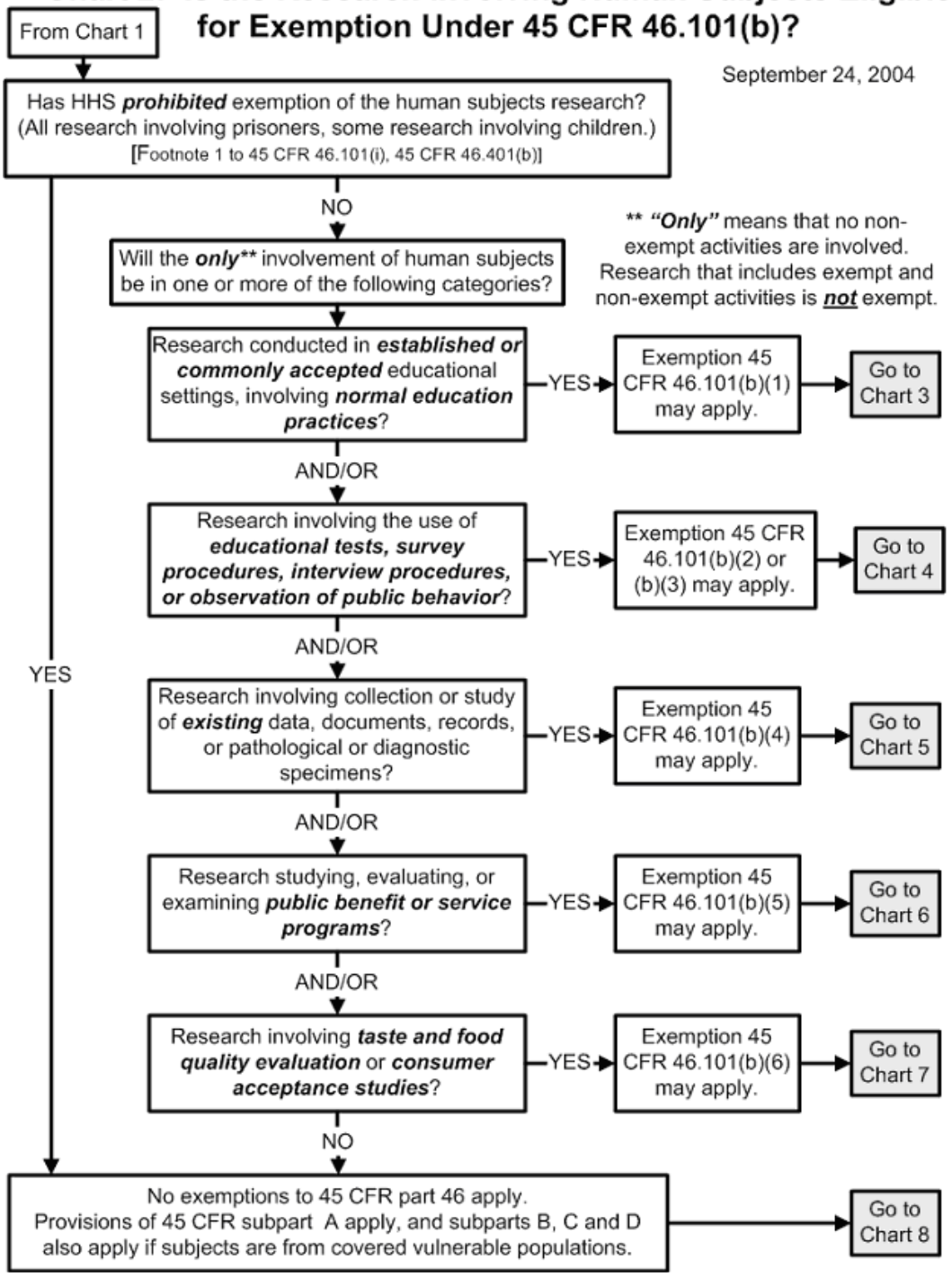
Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) public benefit or service programs;
(ii) procedures for obtaining benefits or services under those programs;
(iii) possible changes in or alternatives to those programs or procedures; or
(iv) possible changes in methods or levels of payment for benefits or services under those programs.

Taste and food quality evaluation and consumer acceptance projects,

(i) if wholesome foods without additives are consumed or
(ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Chart 2: Is the Research Involving Human Subjects Eligible for Exemption Under 45 CFR 46.101(b)?



2. Expedited Review (45 CFR 46.110 and 21 CFR 56.110)

Expedited review is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the HRRC. A list of categories of research has been established in the Federal Register that may be reviewed by the HRRC through an expedited review procedure and are cited below.

The HRRC may use the expedited review procedure to review either or both of (i) some or all of the research appearing on the list of categories of research and found by the reviewer(s) to involve no more than minimal risk, or (ii) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

The following criteria must be met in order for research to be considered for expedited review:

1. The research activities must present no more than minimal risk to human subjects. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

2. All of the research activities involve only procedures listed in one or more of the expedited review research categories. The categories in this list apply regardless of the age of subjects, except as noted. Categories one through seven pertain to both initial and continuing HRRC review.

Categories of research that may be reviewed by the HRRC through an Expedited Review Procedure

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

   (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   (b) Research on medical devices for which

      (i) an investigational device exemption application (21 CFR Part 812) is not required; or

      (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

   (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

   (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

   (a) hair and nail clippings in a non-disfiguring manner;
   (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
   (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat);
   (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
   (f) placenta removed at delivery;
   (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
   (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
   (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
   (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Research projects intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including research projects of cleared medical devices for new indications.) Examples:

   (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subjects privacy;
   (b) weighing or testing sensory acuity;

(c) magnetic resonance imaging;
(d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. [45 CFR 46.101(b)(4)] This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. [45 CFR 46.101(b)(2) and (b)(3)] This listing refers only to research that is not exempt.)

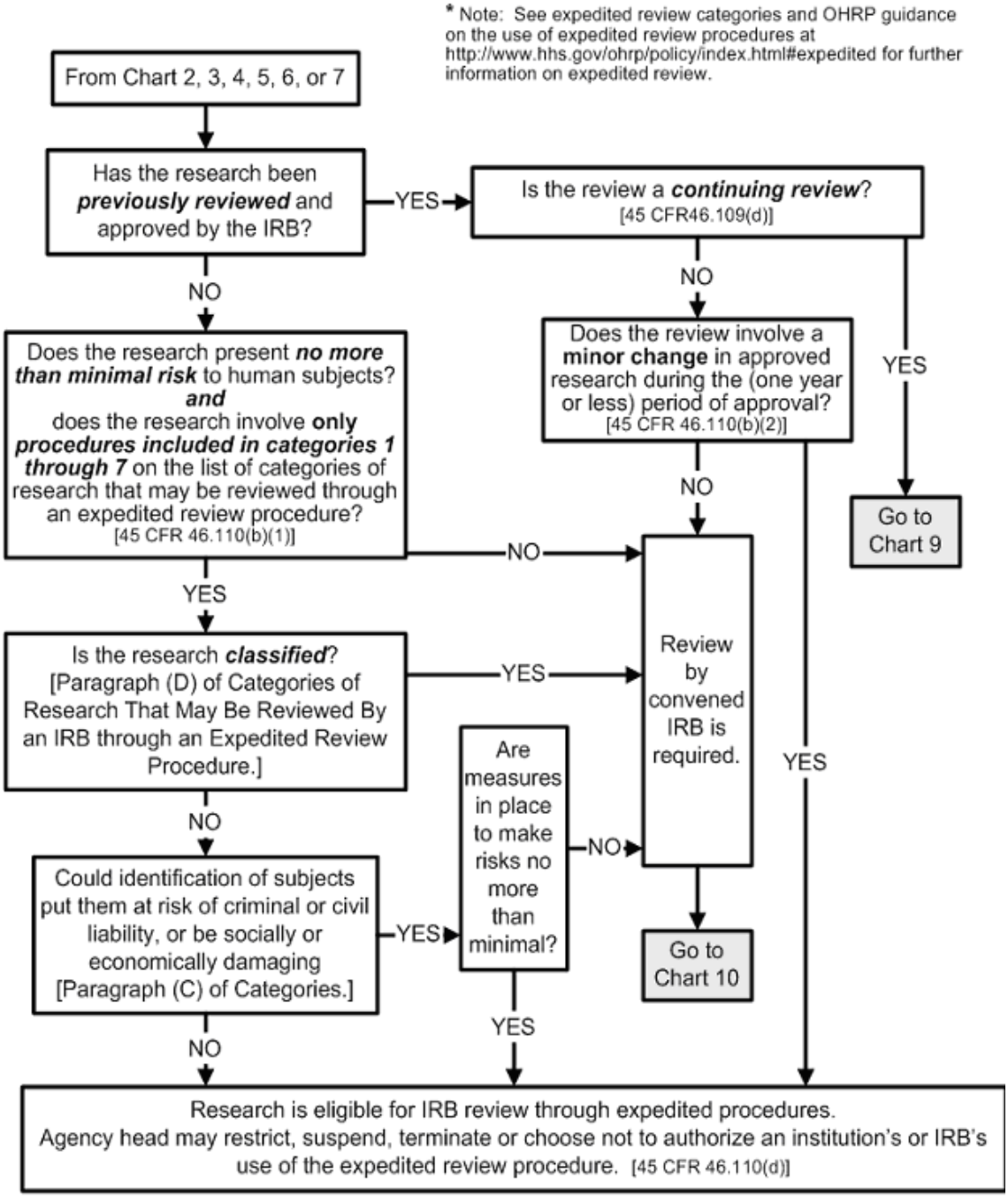
8. Continuing review of research previously approved by the convened HRRC as follows:
   (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

   (b) where no subjects have been enrolled and no additional risks have been identified; or

   (c) where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the HRRC has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Chart 8: May the IRB Review Be Done by Expedited Procedures Under 45 CFR 46.110?*



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Full Committee Review

If the research project does not meet the criteria for exempt or expedited review, then it must be submitted for Full Committee review. Full Committee review and approval is conducted at convened meetings of the HRRC in which a quorum of members is present. The following materials (as applicable) shall be distributed to all panel members at least 10 business days in advance of a meeting:

The preliminary agenda. If changes have been made after the packets have been distributed, members will receive a copy of the final agenda when they arrive for the meeting
The minutes from the previous HRRC meeting, as time permits drafting minutes between meetings
DRS HRRC Application Form A, including detailed research synopsis and specific information about how DRS employees, clients and/or resources will be used in the conduct of this research
Informed Consent Documents/Assent Forms, if appropriate
Advertisements/Recruitment Materials, if appropriate
Request for Amendments Form B, if appropriate
Report of Problems/Adverse Events/Complaints Form B, if appropriate
Grant Application, if appropriate
PI and Co-investigator(s) biographical sketch, highlighting factors indicating qualifications to conduct the proposed research to include training in the protection of human research subjects
Conflict of Interest Disclosure
For initial review, a letter of agreement from the DRS division(s) that will be involved in the research, if appropriate

Appendix C Required Content for the Informed Consent Document

Research subjects should be made aware of certain information, including:

A. **Research Purpose**: State the purpose of the research and give a fair explanation of the research procedures. Include a statement that the project is research. Experimental procedures must also be identified.

B. **Research Procedures**: Explain tasks and procedures from the subject's point of view (what will he or she be expected to do?). Estimate the total amount of time for the person involved in the research project. Explain the frequency of procedures and include any additional costs or charges for the research procedures with estimated amounts. State why the individual is eligible to participate or what criteria will be used to determine eligibility.

C. **Risks**: 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. Risks may range from inconvenience to bodily pain. Do not overlook "soft" risks such as confidentiality and embarrassment. Decisions about invasive procedures will always involve a degree of uncertainty regarding the harmful effects. Calculating the probability that these situations will occur can aid in explaining the risks. The view of the nature of a risk will vary from subject to subject. Be sensitive to the difficult task of determining if the subject is more of a risk taker, is ignoring the risk(s), or has not adequately understood the probability of the risk(s).

D. **Benefits**: Describe any benefits to the subject or others that can reasonably be expected. Benefits may range from feeling good about participation to monetary compensation to free access to an experimental drug. Be careful, however, 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. If there are no benefits, clearly state this. The consent document must describe the terms of any payments used to compensate individuals for their participation. This includes the conditions under which research subjects would receive partial payment or no payment at all.

E. **Alternatives**: State alternative procedures or courses of treatment, if any, that might be advantageous and available to the subject. Provide information on what would be considered the standard treatment(s) for the client's diagnosis. What are the subject's other options? (In non-therapeutic research projects, the alternative may simply be nonparticipation.)

F. **Confidentiality**: The informed consent process must describe the level of confidentiality of the research data and the measures that the research project plans to

take to ensure that confidentiality is maintained. Describe the steps that will be taken to protect the subject's privacy. Also describe under what circumstances records will be made available and to whom. Include any techniques that may be used for de-identifying data, such as creation of a numeric code. Subjects should be assured that their identity will not be disclosed. However, 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.

G. **Disclosure of Potential Conflict of Interest**: Researchers must inform their subjects of any conflicts of interest they have in the research, such as a stake in a company that might benefit from the research. The HRRC might require that prospective subjects be made aware of this information.

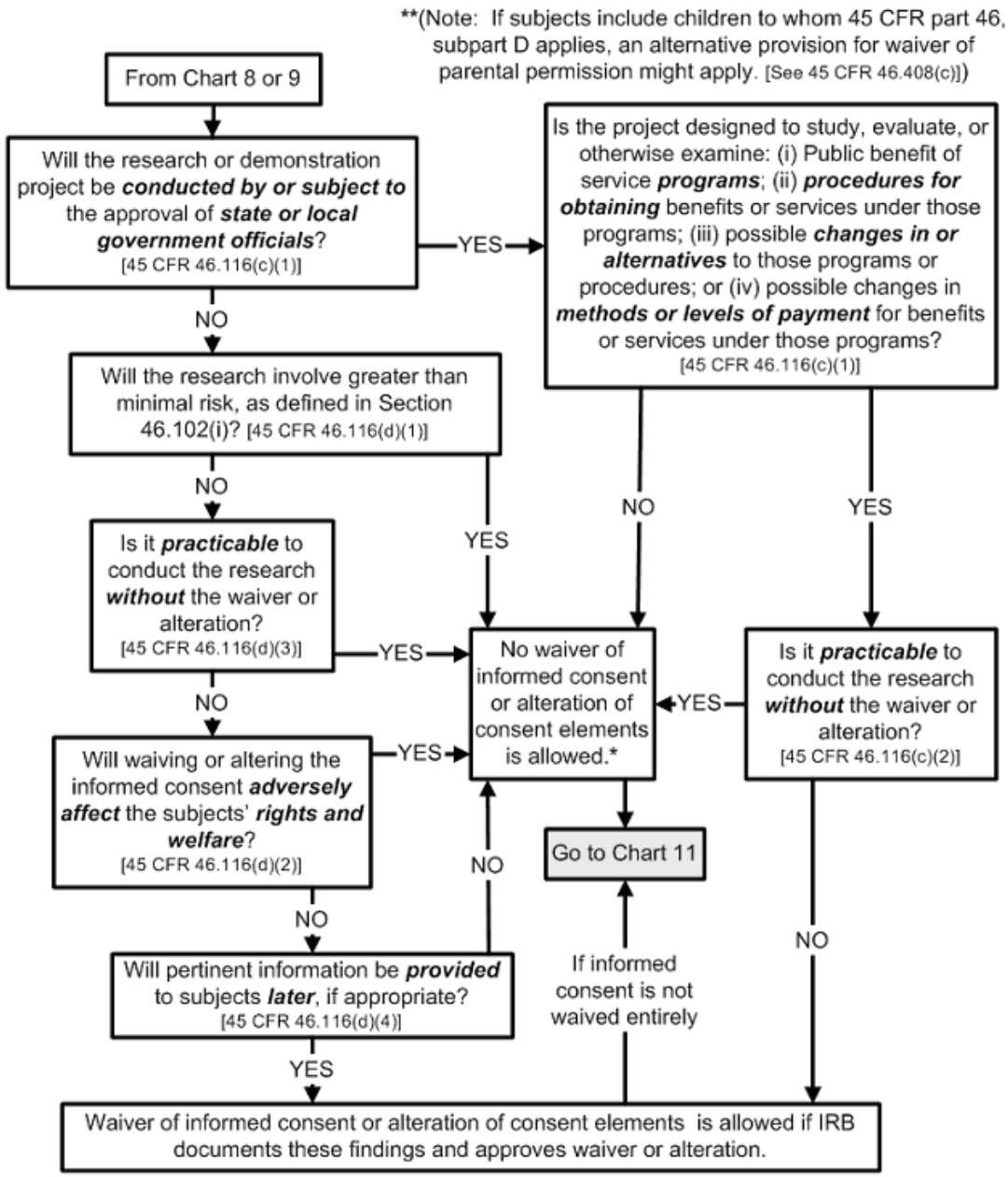
H. **Research-Related Injury**: Compensation can fall into one of these categories when this is applicable: (i) the sponsor of the research project has some funds available to pay for care for injuries resulting directly from being in the research project, (ii) the research project has not yet identified the source of payment for injuries, or (iii) there is no physical component to this research so compensation is not required. Indicate whether compensation or medical treatments will be available if the subject becomes injured. Include what the compensation/treatment consists of and where further information regarding research-related injury can be obtained (for research involving physical contact or activity).

I. **Contact Information**: Give the names of people who can answer questions about the research, including the Principal Investigator. Furnish the contact name of a neutral third party (HRRC Chairperson or Administrator) who can explain the rights of research subjects if the subject has any questions.

J. **Withdrawal**: Always stress the fact that participation is voluntary. State that refusing to participate will involve no penalty or decrease in benefits to which the subject is otherwise entitled. Emphasize that the individual may discontinue participation at any time without penalty or loss of benefits. If there are limitations or risks involved in withdrawal, such as a danger to the subject's well being, these must also be clearly explained.

Appendix D Decision Tree: Can Informed Consent Be Waived or Consent Elements Be Altered?

Chart 10: Can Informed Consent Be Waived or Consent Elements Be Altered Under 45 CFR 46.116(c) or (d)?**



* Note: See OHRP guidance on informed consent requirements in emergency research at http://www.hhs.gov/ohrp/policy/index.html#emergency for further information on emergency research informed consent waiver.

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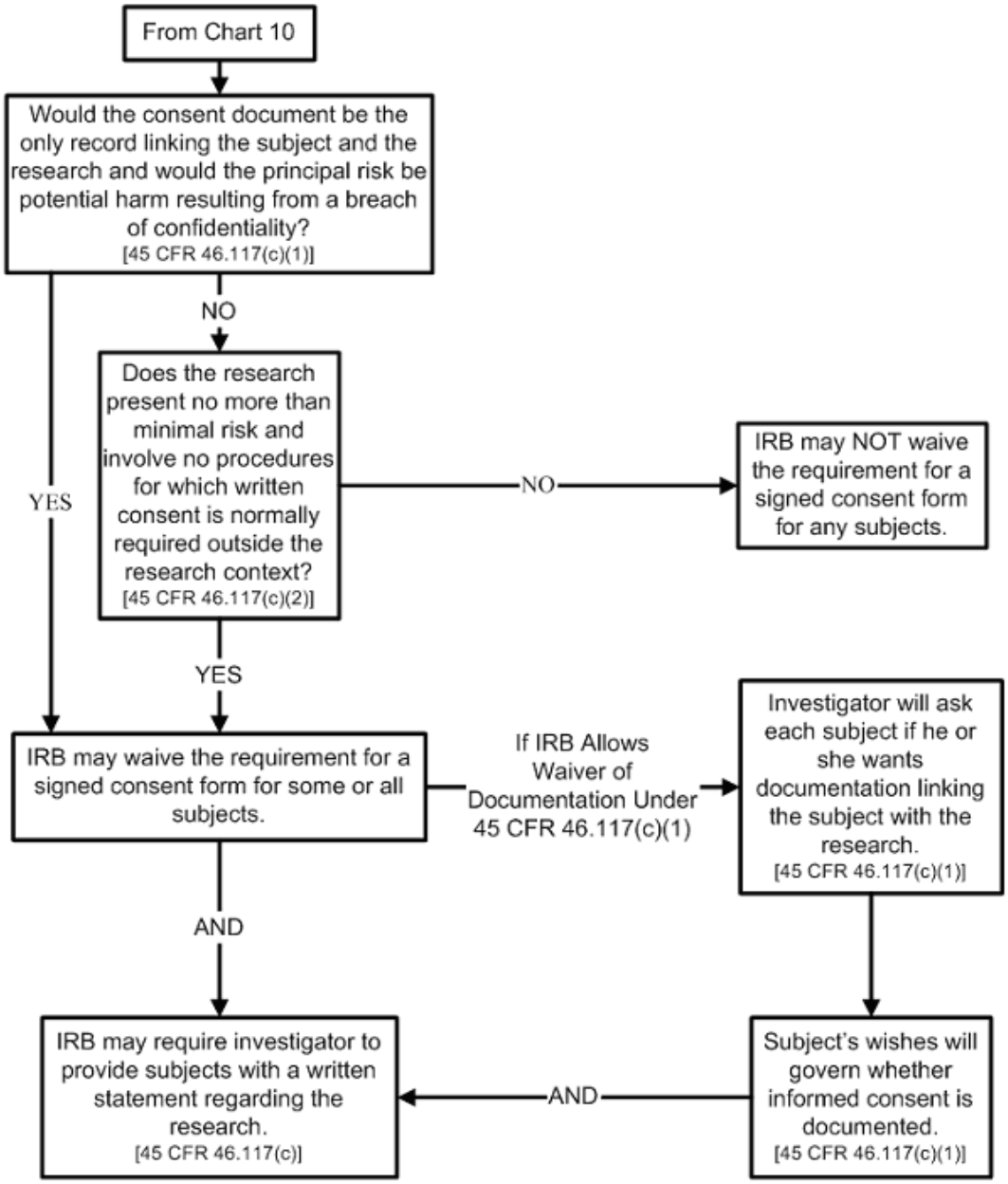
Chart 11: Can Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?



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Appendix E Responsibilities of the HRRC Chairperson, Administrator and Primary Reviewer

The **HRRC Chairperson** shall:

1. complete any education programs required by DRS's Federalwide Assurance (FWA) on file with the U.S. Department of Health and Human Services;
2. be appointed by the DRS Commissioner;
3. advise the DRS Commissioner on HRRC activities and have direct access to the Commissioner for all HRRC matters;
4. ensure that the Commissioner is providing adequate resources and support to the HRRC**;**
5. ensure the compliance of the HRRC with all federal regulations;
6. conduct the HRRC's meetings in an efficient and orderly fashion with respect given to the opinions of all members (*Robert's Rules of Order* may be used as a guidebook for conducting the meeting);
7. serve as primary signatory official for HRRC correspondence;
8. maintain a thorough understanding of federal regulations pertaining to human subject protections, federal guidance, the DRS HRRC, policies and procedures, and other applicable state, and local regulations;
9. take immediate action to address the safety of subjects and/or call meetings of the HRRC;
10. assign reviewer(s) to research projects;
11. (when an Expedited Review procedures is used) shall advise members during the next meeting of the Full Committee of research projects that have been approved since the last meeting of the Full Committee (The DRS Commissioner may restrict, suspend, terminate, or choose not to authorize the HRRC's use of the Expedited Review procedure.);
12. lead the HRRC to discuss specific findings, as required by regulation where vulnerable populations are involved, e.g., children, prisoners, pregnant women and fetuses;
13. call for a motion for HRRC action;
14. at time of the motion, request that the specific elements pertaining to the motion be clearly repeated for the record;
15. ensure that the minutes recorder has understood and documented the basis of any motion and vote of the Committee; and
16. respond to any complaints received.

The **HRRC Administrator**, identified in DRS's Federalwide Assurance (FWA) on file with the U.S. Department of Health and Human Services, shall:

17. assist HRRC Chairperson in preparing for and monitoring HRRC meetings;
18. maintain files on all human subjects research, including copies of all correspondence between the HRRC and investigators;
19. maintain database for tracing research projects;
20. preside over HRRC meetings as needed in the absence of the Chairperson;
21. keep records of HRRC minutes;
22. screen research applications for completeness prior to initiating the HRRC review process;
23. determine whether application qualifies for exempt, expedited or full committee review.
24. Under an Expedited Review procedure, the review may be carried out by the HRRC Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the HRRC.
25. serve as a resource for investigators on general regulatory information, guidance with forms, and assistance in preparing and application for HRRC review;
26. provide staff support to the HRRC for all written correspondence;
27. maintain information on federal regulations relating to human subjects research;
28. facilitate education regarding the HRRC process to the DRS community;
29. maintain records of HRRC membership including training;
30. maintain HRRC meeting schedule;
31. support all logistic functions of the HRRC;
32. maintain HRRC website;
33. modify HRRC policies and procedures as necessary;
34. submit updates and reports as required by the Federalwide Assurance; and
35. serve as primary reviewer for all HRRC applications.

When an application will receive Full Committee review, the **HRRC Primary Reviewer** shall:
conduct a full review of all materials related to the assigned research project;
contact the HRRC Chairperson if additional expertise/consultation may be necessary;
conduct informal queries of the Principal Investigator and/or other experts in order to provide a thorough review;
prepare for and lead the discussion of the research project, the complete grant application (as applicable), and the risk/benefit ratio;
coordinate review comments/questions with the secondary reviewer, if appropriate; and
present specific recommendations for HRRC action, including changes and/or questions in written form (where appropriate) to the HRRC Chairperson.

D. When an application will receive exempt or expedited review, the **HRRC Primary Reviewer** shall:

i. conduct a full review of all materials related to the assigned research project;
ii. conduct informal queries of the Principal Investigator and/or other experts in order to provide a thorough review;
iii. present clear and concise requirements/recommendations for changes and/or questions in written form (by email or otherwise) to the HRRC Chairperson .

a. In reviewing the research, the reviewers may exercise all of the authorities of the HRRC except that the reviewers may not disapprove the research. A research activity may be disapproved only after full Committee review. (45 CFR 46.110)

Appendix F Steps for Arranging for/Managing a Consultation

1. Payment of consulting fees should be pre-arranged through the Policy and Planning Director.

2. It should be determined if the consultant needs to sign a confidentiality agreement.

3. If the consultation will include a review of the research project, the consulting reviewer should receive these materials in a timely manner.

4. A timeline for the consultation should be included, so that the consulting reviewer will have enough time before the scheduled presentation for discussion of the review with the HRRC.

5. The consulting reviewer may be invited to attend the HRRC meeting as a guest and/or may provide written comments prior to the convened meeting of the HRRC.

6. The HRRC is not obligated to follow a consultant recommendation, but the meeting minutes must include an explanation of why the recommendations were not adopted.

7. If a consulting reviewer requests contact with the sponsor or investigator for more information, this request must be managed by the HRRC Chairperson.

8. The consulting reviewer should not have independent contact with either the investigator or the research project sponsor.

Appendix G Investigations of Alleged Research Non-Compliance

ALL allegations of research non-compliance are officially investigated by the DRS Policy and Planning Director with the involvement or consultation of the HRRC. The following points outline the recommended procedures to be used for resolving alleged noncompliance.

When made aware of a potential problem, the Policy and Planning Director compiles file information and any other documentation. The Policy and Planning Director makes a determination as to whether to pursue the matter with the Principal Investigator via telephone call, e-mail, paper memo, or in person. The purpose of such contact is fact-finding, i.e., to determine whether the problem is intentional, unintentional and/or the result of mistake or oversight and to ensure that appropriate corrective actions are taken.

If a meeting is held, other HRRC members may be permitted to attend. Care is taken to maintain confidentiality when leaving messages for the Principal Investigator via voice mail or with secretarial and support staff. The Policy and Planning Director documents the outcome of any and all communications and discussions in writing, by either e-mail or paper memo with a copy to the HRRC files. Such documentation should be factual and objective, and include timelines for resolution (e.g., meeting dates, response deadlines, etc.). Any discussions and effort to achieve resolution are documented in the HRRC files, and presented at the next HRRC meeting by the Chairperson.

When a review of relevant documents and meetings as described above do not lead to resolution, the Policy and Planning Director schedules a review by the full HRRC at the next available meeting. If a quorum of HRRC members is present, and after discussion, the HRRC shall vote recommended actions. Other sanctions imposed by the DRS Commissioner and/or the HRRC may include but are not limited to compliance audits, letters of reprimand, and restrictions on serving as an investigator on human subjects research projects.

Appendix H Guidance on When Previously Approved Research May be Voluntarily Terminated by the Investigator

I. Purpose

To provide HRRC members and staff as well as investigators and their staff guidance on when previously approved research may be voluntarily terminated by the investigator, thereby ending further HRRC oversight of a research project.

II. Background

Regulations 45 CFR 46.109(e) and 21 CFR 56.109(e) require that HRRCs conduct continuing review of ongoing research involving human subjects at intervals appropriate to the degree of risk, but not less than once per year. During a January 2004 quality assurance visit, representative from the Office of Human Research Protections (OHRP) noted that HRRC oversight must continue through the data analysis phase if the analysis work involves identifiable data. Acknowledging that data analysis can take years to complete and is often accomplished by external parties, this policy was developed to meet the regulatory requirements and provide adequate protection to subjects while minimizing the burden to the HRRC and investigators.

III. Definitions

For purposes of this policy and procedures document direct identifier means any data that, either alone or when combined with other data available at the same institution, would allow a person without access to additional information to establish the identity of an individual. External Party means any organization or individual outside of DRS including WWRC.

IV. Guidance

A notification to close a research project must be received by the HRRC on an "HRRC Research Project Closure Form F." The report must be signed by the Principal Investigator (PI) attesting to the accuracy and comprehensiveness of the information provided.

A Research Project Closure Form F must be submitted to the HRRC and must provide a summary of results for local subjects. If data will be retained with direct identifiers or links/codes, the Research Project Closure Form F must provide the following explanations:

a. why direct or non-direct identifiers/links must be retained;
b. the length of time data with direct and non-direct identifiers/links will be retained;

c. who will have access to data with direct identifiers;
d. where data with direct or non-direct identifiers or links/codes will be stored (if more than one location, each should be noted); and
e. how data will be secured/how subject privacy will be protected (for each location).

In determining whether the research project may be closed, the HRRC will use the following guidance:

V. Need for continuing oversight

HRRC oversight of previously approved research must continue if any of the following activities are ongoing:

1. Subjects are being screened.
2. Subjects are being recruited/enrolled.
3. Subjects are receiving treatment/intervention.
4. Subjects are being followed/data are being collected.
5. Data analysis, which includes direct or non-direct identifiers or link to identifiers, is ongoing (see exceptions in next section).

VI. Circumstances under which HRRC oversight may end

HRRC oversight may end under the following circumstances and conditions:

1. All activity is complete, including data analysis.
2. All research project activity is complete, including data analysis, and no external party is involved in the research.
3. All research project activity is complete and any external party(ies) has/have or will be given only de-identified data.
4. All subjects at sites for which HRRC serves as the HRRC of record are deceased.
5. All local subjects are deceased.
6. Activity is limited to analysis of data containing no direct or non-direct identifiers/codes/links; research project activity is limited to data analysis; data at all sites are stripped of direct and non-direct identifiers, codes, and links.
7. Activity is limited to analysis of data by an external party with only non-direct direct identifiers/codes/links.
8. Data are stripped of direct and non-direct identifiers, including codes and links, or the HRRC has reviewed and approved justification for retaining identifiers locally and externally, as applicable, and accepted a plan for securing the data locally and externally, as applicable.
9. Data held by external party contains only non-direct identifiers or a link/code (held by the local investigator) to direct identifiers.
10. HRRC has reviewed and approved a justification for retaining identifiers locally, if applicable.
11. HRRC has reviewed and approved a justification for retaining direct and non-direct identifiers locally, if applicable.
12. HRRC has reviewed and approved a plan for securing data at the local site, if applicable.

13. HRRC has reviewed and approved a plan to secure data at the local site, if applicable. The investigator has filed a representation stating that a code to direct identifiers will not be shared with any external party, excluding audits, without reactivating HRRC approval.
14. HRRC has reviewed and approved the investigator's justification for retaining direct and non-direct identifiers locally and for securing data locally, as applicable. Investigator has filed a representation stating that the code to direct identifiers will not be shared with any external party without reactivating HRRC's approval.

Appendix I Individual Investigator Agreement (OHRP Guidance Document dated, January 31, 2005)

There are two types of collaborating individual investigators:

1. A collaborating independent investigator is:
    a. not otherwise an employee or agent of DRS;
    b. conducting collaborative research activities outside of DRS facilities; and
    c. not acting as an employee of **any** institution with respect to his or her involvement in the research being conducted by DRS.
2. A collaborating institutional investigator is:
    a. not otherwise an employee or agent of DRS;
    b. conducting collaborative research activities outside DRS facilities;
    c. acting as an employee or agent of an institution that does not have a Federalwide Assurance (FWA) with respect to his or her involvement in the research being conducted by DRS; and
    d. employed by, or acting as an agent of, an institution that does not **routinely** conduct human subjects research.

DRS may extend its FWA to cover a collaborating independent or institutional investigator provided all of the following conditions are satisfied and the individual investigator has completed and submitted an Individual Investigator Agreement Form D:

A. The DRS PI directs and appropriately supervises all of the collaborative research activities to be performed by the collaborating individual investigator.
B. The extension of the coverage of the FWA is put in place by use of an appropriate written agreement for each collaborating individual investigator who will be engaged in the research being conducted by DRS. DRS must maintain the Individual Investigator Agreement on file and provide copies to Office of Human Research Protections (OHRP) upon request.
C. For collaborating institutional investigators, the appropriate authorities at the institution that does not have an FWA state in writing that the conduct of the research is permitted at their institution.
D. DRS and the HRRC designated under the FWA approve the extension of the assurance through either the Individual Investigator Agreement or other written agreement used by DRS.
E. The following documents are made available to the collaborating individual investigator:
    a. The *Belmont Report* or other internationally recognized equivalent (see section B.1. of the Terms of the Federalwide Assurance;
    b. The DHHS regulations for the protection of human subjects at 45 CFR part 46;
    c. the FWA and applicable Terms of the FWA for DRS; and

d. the relevant DRS policies and procedures for the protection of human subjects.

F. The collaborating individual investigator understands and accepts the responsibility to comply with the standards and requirements stipulated in the documents referenced in the preceding paragraph and to protect the rights and welfare of human subjects involved in research conducted under the Individual Investigator Agreement.
G. The collaborating individual investigator agrees to comply with all other applicable federal, international, and state laws, regulations, and policies that may provide additional protections for human subjects participating in research conducted under the Individual Investigator Agreement.
H. The collaborating individual investigator agrees to abide by all determinations of the HRRC as designated under the DRS FWA and agrees to accept the final authority and decisions of the HRRC, including but not limited to directives to terminate participation in designated research activities conducted under the Individual Investigator Agreement.
I. The collaborating individual investigator agrees to complete any educational training required by the DRS and the HRRC prior to initiating research covered under the Individual Investigator Agreement.
J. The collaborating individual investigator agrees to report promptly to the HRRC any proposed changes in the research conducted under the Individual Investigator Agreement.
K. The collaborating institutional investigator agrees not to initiate changes in the research without prior HRRC review and approval, except where necessary to eliminate apparent immediate hazards to subjects.
L. The collaborating individual investigator agrees to report immediately to the HRRC any unanticipated problems involving risks to subjects or others in research covered under the Individual Investigator Agreement.
M. The collaborating individual investigator, when responsible for enrolling subjects, agrees to obtain, document, and maintain records of informed consent for each such subject or each subject's legally authorized representative as required under this policy and procedures manual and stipulated by the HRRC.
N. The collaborating individual investigator acknowledges and agrees to cooperate with the HRRC in its initial and continuing review, record keeping, reporting, and certification for the research covered by the Individual Investigator Agreement, or other agreement used by the assured institution. The collaborating institutional investigator agrees to provide all information requested by the HRRC in a timely fashion.
O. The collaborating individual investigator agrees not to enroll subjects in research under the Individual Investigator Agreement, prior to the research being reviewed and approved by the HRRC.

Appendix J Certificate of Confidentiality

PIs engaged in biomedical, behavioral, clinical, or other research (including research on mental health and the use and effect of alcohol and other psychoactive drugs) should obtain a Certificate of Confidentiality. The Certificate of Confidentiality protects the privacy of individuals who are the subjects of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.

The Certificate of Confidentiality provides protection against compelled disclosure of identifying information about subjects enrolled in sensitive biomedical, behavioral, clinical, or other research. This protection is not limited to federally supported research.

For more information on Certificates of Confidentiality and their limitations, see http://grants.nih.gov/grants/policy/coc/index.htm.

For Certificate of Confidentiality contacts at the National Institutes of Health, see http://grants.nih.gov/grants/policy/coc/contacts.htm.

For information on obtaining a Certificate of Confidentiality for research supported by other DHHS agencies, please contact the appropriate program official.

Appendix K Health Information Portability and Accountability Act (HIPAA)

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides various national health insurance protections. One part of this legislation mandated that if Congress did not pass a law on national patient privacy standards, the DHHS would move to establish such standards through regulation. The final Privacy Rule was published on August 14, 2002. The implementation date for compliance with these regulations was April 14, 2003 (except for some small health plans for which the compliance date was delayed until April 14, 2004). DRS is a hybrid HIPAA entity and the Privacy Rule and its concepts as they apply to research involving human subjects that is conducted, sponsored, reviewed or managed by DRS is outlined in this section.

Data Covered

The Privacy Rule covers one type of data–protected health information (PHI). PHI is health information that directly identifies the person who is the subject of the information or contains data with respect to which there is a reasonable basis to believe that the information can be used to identify the individual. Health information that has been de-identified is not protected by the Privacy Rule. However, the definition of identifiers which must be eliminated from data to qualify as de-identified is more explicitly established under the Privacy Rule than in previous regulations such as the *Common Rule* (45 CFR 46). This is discussed in more detail below.

Conditions Under Which PHI Can be Used

Because the authority for the Privacy Rule came from the HIPAA legislation identified above, the Rule regulates conditions of using PHI that is created, maintained, or transmitted by certain health care providers, health plans, and health care clearinghouses. These groups are collectively called covered entities. The Rule does not regulate other forms of health information, including information obtained directly from individuals or from other entities.

Most, if not all, of DRS programs and activities do not meet the definition of a covered entity, although some of these programs may be covered entities as constituted at the State level. However, the HIPAA requirements do apply to the Woodrow Wilson Rehabilitation Center. A decision tree from the Center for Medicare and Medicaid Services (CMS) provides a framework which can be useful to decide if a provider, health plan, clearinghouse, or program is a covered entity. (See http://www.cms.hhs.gov/hipaa/hipaa2/support/tools/decisionsupport/default.asp)

Use of PHI in Research

Beginning on April 14, 2003, researchers who enroll subjects in research projects that require access to (or who otherwise seek to obtain) data that includes PHI from covered entities will need to:

1. obtain a signed authorization of disclosure from each research subject to use his or her PHI or to have it disclosed from the covered entity,
2. receive a waiver of authorization of disclosure from an IRB or Privacy Board, or
3. sign a data use agreement with the covered entity and agree to receive a limited data set (a data set with some enhanced detail of certain identifiers).

In each case, the researcher may receive only the "minimal data" necessary to conduct the research. The requirement for staff disclosure of minimal data necessary for research is discussed in further detail at: http://privacyruleandresearch.nih.gov/pr_02.asp and http://privacyruleandresearch.nih.gov/.

Authorization of disclosure is separate from the informed consent process. Although the authorization can be included in or combined with the informed consent form, there are specific requirements for the content of the authorization which may best be dealt with in a separate form. In addition, the wording of the form may vary somewhat by institution, complicating the consent form review process for multi-site research projects when authorization is included in the informed consent form. OHRP agreed that the authorization form itself will not need to be reviewed by the IRB if separate from the informed consent form. The authorization form must contain specific language and will be reviewed by the covered entity for compliance with the regulations prior to release of or access to the PHI. Additional guidance about the required content of the authorization form is available at http://privacyruleandresearch.nih.gov/authorization.asp .

The Privacy Board or IRB can grant a waiver of authorization of disclosure if the request is justified by addressing certain criteria established in the Privacy Rule. In general, these criteria are similar to those in the 45 CFR 46 for granting a waiver of informed consent. Additional guidance on how to request a waiver of authorization of disclosure is available at http://privacyruleandresearch.nih.gov/pr_08.asp#8c . The waiver of authorization would seem to be appropriate for research projects in which a waiver of informed consent is used or is being requested, but the investigator will need to separately request the waiver of authorization from the IRB or Privacy Board.

In addition, the Privacy Rule allows the use or disclosure of PHI without patient authorization for research on decedents and for "preparatory research," that is, preliminary work to assess if the data can be used for research purposes, provided that the PHI does not leave the covered entity.

Research in Progress

All research that is in progress on the HIPAA implementation date will need to comply with the Privacy Rule requirement of signed authorization of disclosure for all subjects who enroll on or after April 14, 2003. Authorization or waiver of authorization of disclosure will also be required for those research projects (including research projects exempt from 45 CFR 46) in which PHI is requested or obtained from a covered entity after that date. It also appears that subsequent data sharing or secondary analyses of research projects using PHI obtained after the implementation date will likely require separate authorization or a waiver of authorization for each research project.

Non-exempt research that collects PHI from a covered entity on persons enrolled prior to April 14, 2003 will be able to continue to do so after the implementation date provided that a signed informed consent document which outlines continuing data collection has been obtained, or a waiver of informed consent has been granted by an IRB prior to the compliance date. The “grandfather” provision does not apply to new enrollees or to “new” information collection on subjects in continuing research projects. “New” information is information collected from the covered entity after the implementation date that is different in some way that has yet to be specified from that which was previously being collected as outlined in the consent form or research project. The grandfather provision extends general or blanket permission to collect unspecified future information, although such general permission must be documented in the consent form or the research project. In addition, if subjects need to be re-consented for other reasons after the compliance date, the grandfather provision would no longer apply and authorization or waiver of authorization of disclosure would be required.

Therefore, those non-exempt research projects which currently conduct follow-up on a continuing basis or plan to collect information from medical records of subjects enrolled prior to April 14, 2003 should not necessarily face disruption in this circumstance, provided that this continuing collection is covered in the consent form or under a waiver of consent obtained from an IRB prior to the compliance date. However, collection of information that is not similar to that previously collected would not be permitted without authorization of disclosure or waiver of such authorization. Exempt research projects in progress on or after the compliance date will need to address the issues discussed below.

Definition of Identifiers

The Privacy Rule provides the first definition in Federal regulations of identifiability in terms of a list of personal identifiers which must be removed to de-identify the data. The following are considered identifiers under the Privacy Rule, and the presence of any of these items in data from a covered entity on the health status of the individual would be sufficient to make it protected health information.

1. Names

2. All geographic subdivisions smaller than a State, including ZIP code and geocodes (except for the initial three digits of the ZIP code under certain circumstances)
3. All elements of dates except year for dates directly related to an individual, including birth date, admission date, date of service, date of discharge, date of death; and all ages over 89 years, including all elements of dates including birth year indicative of such age (except that there may be a category of age 90 or older)
4. Telephone numbers
5. Facsimile numbers
6. Electronic mail addresses
7. Social Security numbers
8. Medical record and prescription numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers, including serial numbers and license plate numbers
13. Device identifier and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including fingerprints and voiceprints
17. Full face photographic images
18. Any other unique identifying numbers, characteristic or code.

The complete elimination of all these identifiers from health data to be disclosed is called the “Safe Harbor” approach to de-identification which is designed to preclude release of data which could be used alone or in combination with other information to identify an individual who is the subject of the information. Alternatively, a covered entity could release additional information if it can document that the data were adapted by a person with statistical expertise to decrease the risk of identification of an individual. The Federal Committee on Statistical Methodology has guidance on this latter process, but there is concern that covered entities may for legal reasons choose only the Safe Harbor approach for release of de-identified data.

For more information on HIPAA, updates, and official guidance for its implementation, visit the web site of the Office for Civil Rights (OCR) at http://www.hhs.gov/ocr/hipaa .